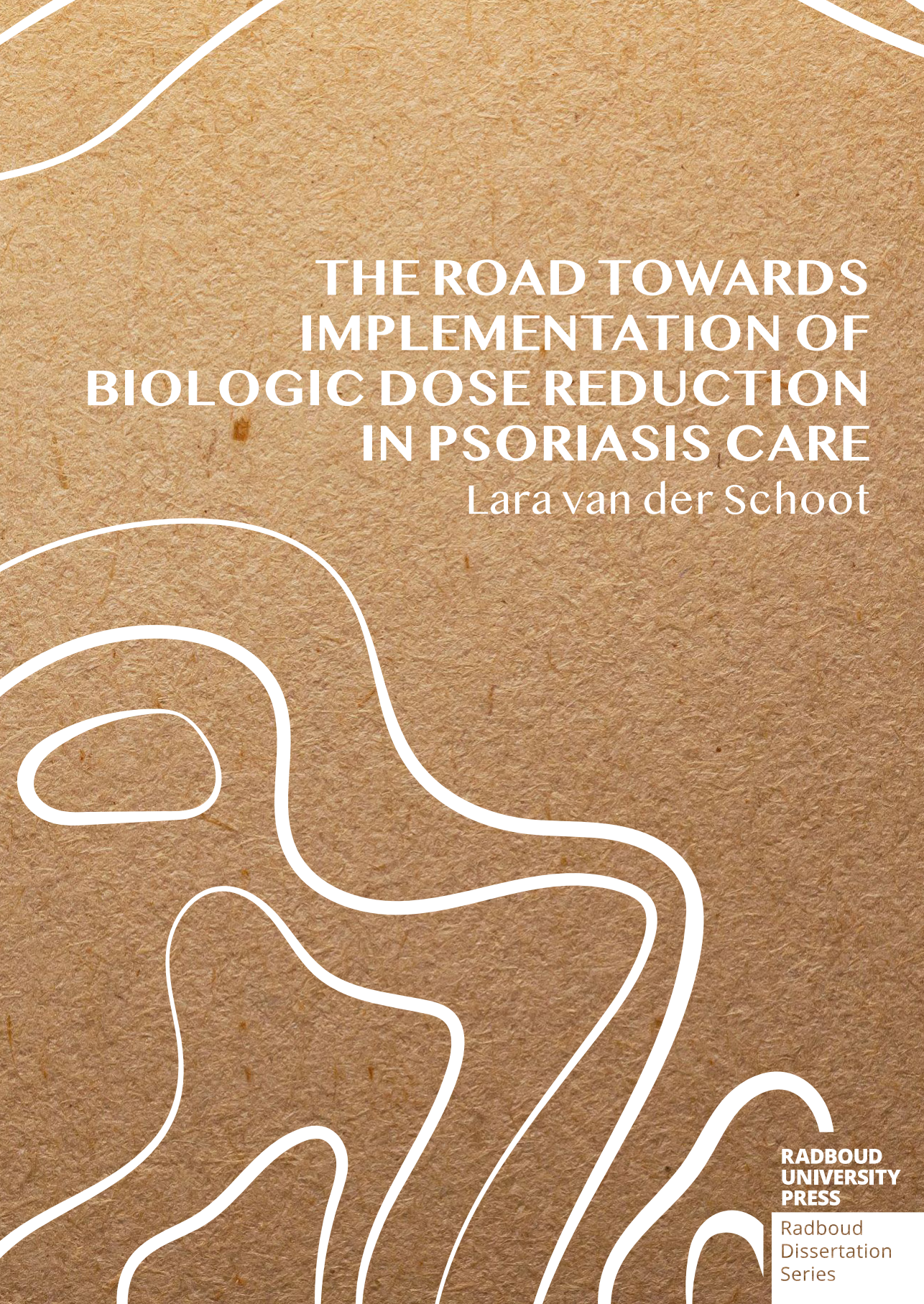


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THE ROAD TOWARDS IMPLEMENTATION OF BIOLOGIC DOSE REDUCTION IN PSORIASIS CARE

Lara van der Schoot

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**THE ROAD TOWARDS
IMPLEMENTATION
OF BIOLOGIC DOSE REDUCTION
IN PSORIASIS CARE**

Lara S. van der Schoot

Author: **Lara Sophie van der Schoot**

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The road towards implementation of biologic dose reduction in psoriasis care

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
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volgens besluit van het college voor promoties
in het openbaar te verdedigen op

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CHAPTER 1

General introduction and thesis outline

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by red, scaly, and itchy plaques. Psoriasis can significantly alter patients' quality of life and is associated with important comorbidities such as psoriatic arthritis (PsA) and cardiovascular disease.¹⁻³

The estimated prevalence of psoriasis in the western population is 2-3%, which corresponds with approximately 500.000 patients in the Netherlands.⁴⁻⁶ Psoriasis onset can occur at any age, with incidence peaks in young adulthood and middle age.^{7,8} Its prevalence is equal for women and men, although it has been reported that men have more severe disease.^{9,10} This thesis will mainly focus on the most common psoriasis phenotype, which is 'plaque psoriasis' or 'psoriasis vulgaris'.¹¹

Although there is no cure, insights into the pathogenesis of psoriasis have led to the development of cytokine-based therapies that have revolutionized the management of psoriasis: biologics.^{12,13} Biologics for psoriasis have become available since 2003. Besides their effectiveness, biologics are expensive and impose a high burden on national healthcare budgets.¹⁴ Effective and efficient use of biologics is therefore warranted.

Although many biologics have entered the market since their introduction and the arsenal is still growing, selecting the optimal biologic for the individual patient is not always possible yet.¹⁵ Hence, choosing the right option sometimes comprises a process of trial-and-error. Therefore, research focusing on personalized treatment with biologics is still needed. Furthermore, lifelong treatment with biologics is mostly needed for long term disease control. Treatment with a fixed dose may however not be necessary in patients with good treatment responses.¹⁶ Dose reduction (DR) of biologics for psoriasis is a solution for more efficient use in patients with low disease activity. Overtreatment can be prevented and healthcare costs will decrease when striving for the lowest effective dose. Guidance is however needed, as DR could theoretically lead to disease exacerbations.

In this thesis, we investigated further implementation of biologic DR for psoriasis. In addition, possibilities for more personalized treatment with biologics were explored, focusing on differences between male and female patients, risk of respiratory tract infections, and patients of older age.

Clinical features

Psoriasis has different clinical phenotypes, of which plaque psoriasis is the most common phenotype. Plaque psoriasis is present in 90% of cases.¹¹ Plaque psoriasis is characterized by well demarcated, red plaques covered with white to grey scales, causing itching, painful, bleeding or burning sensations.¹⁷ Plaques may vary in size and thickness and may enlarge or show central clearing. Although any skin surface can be affected, common sites of occurrence are extensor sites of the elbows and knees, the lumbosacral region, and the scalp. Plaques may occur in a symmetrical pattern. Lesions can occur at sites of trauma, which is known as the Koebner phenomenon.¹⁸ Anatomical variants of plaque psoriasis include scalp psoriasis, palmoplantar psoriasis, inverse psoriasis (affecting the skin folds), genital psoriasis, and nail psoriasis. See **Figure 1**.

Other less common subtypes include erythrodermic, guttate, and pustular psoriasis.¹⁸ In erythrodermic psoriasis, the entire skin is involved. Guttate psoriasis is characterized by many small, red and scaly 'droplet-like' papules disseminated over the body.¹⁹ Pustular psoriasis is uncommon and presents with sterile pustules and erythema, either generalized or localized to palms and/or soles (palmoplantar pustulosis).²⁰ Psoriasis is usually diagnosed by visual inspection. In case of atypical presentation, a skin biopsy may be performed.

Psoriasis is considered to be a systemic inflammatory disease, not only limited to the skin.²¹ Patients with psoriasis can as such have important comorbidities. Approximately 25% of patients with moderate-to-severe psoriasis will develop PsA versus 16% of patients with mild psoriasis, respectively.²² PsA is a seronegative inflammatory arthritis which comprises peripheral arthritis, enthesitis or dactylitis. As psoriasis and PsA share some immunological and pathophysiological features, some therapies are registered for both diseases.²³ Besides PsA, psoriasis is associated with several other diseases such as cardiovascular disease, depression, Crohn's disease, and metabolic syndrome. However, direction of causality remains unclear.²⁴⁻²⁸ Psoriasis is associated with a significant physical and psychological burden, and it has been described that this impact can be cumulative which results in failure of patients to achieve a 'full life potential'. This concept is also referred to as 'cumulative life course impairment'.^{3, 29}



Figure 1. Different clinical presentations of psoriasis.

A-C. Plaque psoriasis, D. Guttate psoriasis, E. Erythroderma, F. Generalized pustular psoriasis, G. Palmoplantar pustulosis, H. Inverse psoriasis, I. Nail psoriasis, J. Psoriatic arthritis with dactylitis and nail psoriasis. Reprinted from *The Lancet*, Vol. 397, C.E.M. Griffiths, A.W. Armstrong, J.E. Gudjonsson and J.N.W.N. Barker, 'Psoriasis', Pages 1301-1315, Copyright (2021), with permission from Elsevier.

Histologic features

Histology of psoriasis includes acanthosis (epidermal thickening), hyperkeratosis (stratum corneum thickening), and parakeratosis (retention of nuclei in the stratum corneum). Other features are downward elongations of rete ridges, a thinned or absent granular layer, and changes to vasculature including elongated and dilated capillaries. Furthermore, an inflammatory infiltrate of predominantly T-cells is present in the dermis and epidermis, and sometimes clusters of neutrophils are present in the parakeratotic scale. Neutrophils can cluster into pustules (Kogoj spongiform micropustules) or accumulate to form micro abscesses of Munro in the stratum corneum.^{11, 18, 30}

Pathogenesis

Psoriasis pathogenesis is considered to be multifactorial and involves genetic risk factors, environmental triggers, and components of the innate and adaptive immune system.^{18, 31, 32} An immunological crosstalk between the innate and adaptive immune system is thought to be responsible for sustained inflammation in psoriasis, caused by gene-environment interaction. Several pro-inflammatory cytokines which drive this crosstalk are relevant therapeutic targets, such as tumour necrosis factor (TNF) alpha (α), interleukin (IL)-23 and IL-17 (**Figure 2**).

Genetic predisposition is a main risk determinant for development of psoriasis. Various genetic variants can lead to an increased risk to develop psoriasis.^{33, 34} The major psoriasis susceptibility gene for early-onset psoriasis is HLA-C*06:02.³⁵ Other psoriasis susceptibility genes are predominantly involved in innate and adaptive immune responses.^{33, 34, 36} Depending on gene-environment interaction, psoriasis develops with participation of different innate immune cells including plasmacytoid dendritic cells, Natural Killer T-cells, keratinocytes, macrophages, and type I interferons (IFN).¹⁸ These innate immune cells secrete several pro-inflammatory cytokines (TNF- α , IFN- γ , IFN- α , IL-1 β). Activated keratinocytes also start to produce antimicrobial peptides (LL-37 cathelicidin and β -defensins), and chemokines (CXCL8-11, CCL20) which play a role in attracting neutrophils into the skin.³² By the secretion of pro-inflammatory cytokines, antimicrobial peptides, and self-DNA released by activated keratinocytes, myeloid dendritic cells become active. Activated myeloid dendritic cells in turn secrete cytokines (IL-12, IL-23, TNF- α) which induce differentiation of T-helper (Th) cells into IL-17 producing cells. Activated Th17, IL-17-producing CD8+ T (Tc17) cells, IFN- γ secreting Th1 and Tc1 cells, mast cells and neutrophils are drawn into the skin. Neutrophils can form specialized structures to release IL-17, so called neutrophil extracellular traps (NETs). A special subset of neutrophils with features of aged cells (e.g., 'aged neutrophils') is involved in psoriasis. These aged neutrophils have as such a pro-inflammatory effect on

T-cells, mediated by NET formation.³⁷⁻³⁹ Involving skin-draining lymph nodes, the involved T-cells in turn produce TNF- α , IL-17 and IL-22. Hence, a self-sustaining cycle of inflammation is created leading to altered keratinocyte proliferation and differentiation, skin thickening, erythema and angiogenesis.^{18, 31, 32, 40} NET formation is increased in psoriasis lesional skin and peripheral blood, and correlates with disease severity.⁴¹ NETs also induce the production of the antimicrobial peptide human β -defensin-2 (HBD-2), which is overexpressed in psoriasis epidermis and can be used as surrogate biomarker for disease activity.⁴² Thus, the typical gene expression profile and histopathology of psoriasis are predominantly enhanced by activation of the IL-23/17 pathway. A subset of T-cells, tissue-resident memory T-cells (TRMs), persist in epithelial tissues on the long term. When aberrantly activated due to responses to auto-antigens, they contribute to immune-mediated diseases such as psoriasis.⁴³ The chronic course of the disease and the characteristic recurrence of psoriasis at previous sites may be explained by the presence of these cells.^{44, 45}

Disease severity and outcome measures

In order to measure disease activity in patients with psoriasis, many outcome measures have been developed. Some of these measures are well-established and frequently used in clinical practice and research, but others are not used on a large scale or have not been validated.⁴⁶ Outcome measures related to this thesis are discussed below.

The Psoriasis Area and Severity Index (PASI) is the most frequently used tool for measuring psoriasis disease severity.^{46, 47} PASI combines severity scores for erythema, induration, and scaling with assessment of the affected body surface area for four major body sites (head, trunk, arms, legs). The total score ranges from 0 (no visible lesions) to 72, with PASI scores >10 indicating moderate-to-severe disease.⁴⁸ Although PASI is frequently used, it can be considered to be complex and time-consuming which makes it less feasible for performance in daily practice. Moreover, PASI can be difficult to assess at lower score levels, as it loses sensitivity in mild psoriasis with limited affected surface.^{49, 50} In research settings, percentage of PASI improvement compared to baseline PASI score is often expressed. As such, PASI75, PASI90 or even PASI100, which correspond with 75%, 95% and 100% improvement from baseline, are used to describe treatment effects in clinical trials.⁵¹ A possible disadvantage of the use of relative PASI is the dependence on the baseline score, as patients with low PASI scores at baseline will not be able to achieve 75% or 90% reductions even though treatment responses are adequate. Hence, it has been shown that the possibility of reaching PASI75 or PASI90 is lower for patients who are treated in a real-world setting compared to patients in randomized controlled trials.⁵² Also incorporated in the PASI is the Body Surface Area (BSA), which is the percentage of

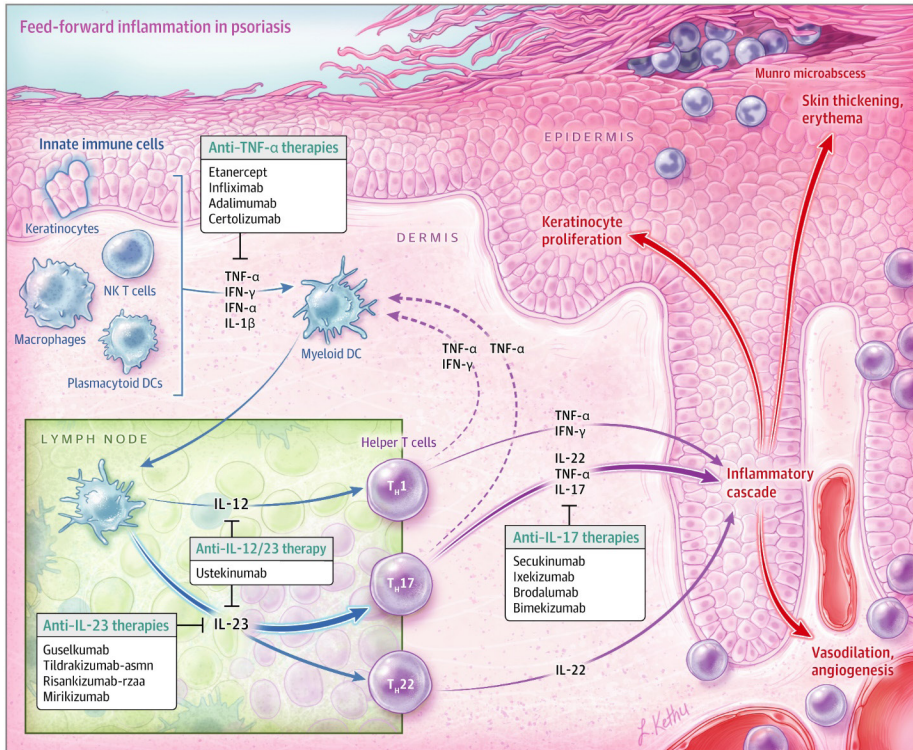


Figure 2. Pathophysiology of psoriasis including biologics and their respective targets.

The pathophysiology of psoriasis involves excessive feed-forward activation of the adaptive immune system. Depending on gene-environment interaction, psoriasis initiation begins. Different innate immune cells become activated and secrete pro-inflammatory cytokines. Various immune cell populations and keratinocytes respond to downstream effects of increased IL-23 and IL-17 signaling. This results in an inflammatory cascade that leads to psoriatic disease manifestations. Reproduced with permission from JAMA. 2020;323(19):1945-1960. Copyright©(2020) American Medical Association. All rights reserved.

the body affected by psoriasis. Based on the number of handprints of the patient, including palms and extended digits, fitting in the affected area, the BSA is calculated. The patients' own handprint equals approximately 1% of the body surface area.⁵³

Another more practical tool to assess disease severity which is frequently used in research settings, is the Physician's Global Assessment (PGA).^{54, 55} A subjective overall evaluation of disease severity is made by the physician. Although there are several variants, disease severity is typically rated on a 5- to 7-point rating scale that ranges from 'clear' to 'very severe'. Possible advantages are that it is less time consuming compared to PASI and it resembles the normal assessment of physicians in clinical practice.^{56, 57}

Besides clinical parameters, patient reported outcomes (PROs) are used in healthcare, but also in health policy making and clinical research, in order to provide more patient-centered care. PROs are reported by patients themselves without interpretation by a healthcare provider. As such, they provide insight in physical or psychological complaints that might otherwise be missed, they enhance better communication between patients and healthcare providers, and can be used for monitoring of treatment responses.⁵⁸

One of the most important PROs is health-related quality of life (HRQoL). HRQoL reflects the patients' evaluation of effects of a disease and/or treatment on their physical, psychological, and social functioning and well-being.⁵⁹ For psoriasis, it has been extensively reported that having the disease has a large impact on patients' quality of life.^{1, 60, 61} Although different measures for dermatology-related quality of life exist, the Dermatology Life Quality Index (DLQI) is a frequently used PRO in research and in clinical practice.⁶²⁻⁶⁴ The DLQI consists of 10 questions and comprises several categories: symptoms and feelings, leisure, work/school, personal relationships, and treatment. It evaluates impact of the skin disease over the past week. Scores range from 0-30, with higher scores indicating a larger impact on patients' quality of life. A DLQI ≤ 5 can be considered as a minimal impact of the disease on patients' HRQoL.⁶⁴

Another PRO used for measuring impact of dermatologic diseases on patients' quality of life is the Skindex-29.^{65, 66} Skindex is a 29-item questionnaire which comprises eight scales: cognitive effects, social effects, depression, fear, embarrassment, anger, physical discomfort, and physical limitations. The higher the score, the larger the impact on HRQoL. As Skindex is longer than DLQI it can be considered to be less practical for daily use.

For the evaluation of treatments according to patients, the Treatment Satisfaction Questionnaire for Medication (TSQM) can be used. It provides insight into treatment satisfaction.⁶⁷ Aiming for high treatment satisfaction is important, as it relates to drug adherence.⁶⁸ The TSQM (version II) is a generic and validated questionnaire developed for different patients and medications. It covers four domains: effectiveness, convenience, global satisfaction and side-effects, with scores for every domain ranging from 0 (extremely dissatisfied) to 100 (extremely satisfied).⁶⁷

Treatment goals

The use of outcome measures for measuring disease severity in clinical practice is encouraged, as outcome measures can be incorporated in clinical treatment guidelines and used to define treatment goals.

In the current European treatment guidelines for psoriasis (2020), definitions for disease severity and corresponding treatment goals are based on a European consensus from 2011.^{48, 69, 70} Mild disease was defined as PASI ≤ 10 and BSA ≤ 10 and DLQI ≤ 10 , and moderate-to-severe psoriasis as (PASI or BSA > 10) and DLQI > 10 . Special localizations of psoriasis, such as nail psoriasis, genital lesions or visible areas, could upgrade mild psoriasis to severe psoriasis.⁶⁹ In accordance with these classifications, treatment goals were defined. Here, treatment success was defined as PASI75, and treatment failure as not achieving PASI50. In case of PASI50-75, DLQI ≤ 5 was considered as treatment success whereas DLQI > 5 was considered treatment failure.⁴⁸

As treatment options have expanded since the consensus from 2011, with the newest biologics allowing some patients even to achieve complete clearance,⁷¹ new definitions and targets or goals have been defined in recent years.⁷² As such, the International Psoriasis Council performed a consensus in 2020 in which patients were categorized into candidates for topical or systemic therapy. Candidates for systemic therapy were patients with BSA $> 10\%$ and/or involvement of special areas.⁷³ Other more strict treatment goals or targets are for example a BSA of 1% or less as therapeutic goal defined by the National Psoriasis Foundation (USA),⁷⁴ or a PASI90 or PGA ≤ 1 , with a DLQI ≤ 1 and prolonged remission as defined by a Spanish group.⁷⁵ In Belgium, a multidimensional target was defined, including disease activity, itch, DLQI, daily functioning and safety.⁷⁶ British authors concluded that PASI ≤ 2 and PGA clear/almost clear are relevant treatment targets.⁷⁷ In the Netherlands, no new definitions for disease severity and treatment goals have been defined yet at the time of writing this thesis.

Treatment options

Treatment options for psoriasis include topical therapies (topical corticosteroids, coal tar, vitamin D analogues, dithranol, topical calcineurin inhibitors), phototherapy (narrowband ultraviolet B (UVB), ultraviolet A combined with psoralens (PUVA)), conventional systemic therapies (acitretin, cyclosporin, fumaric acid esters, methotrexate) and biologics and small molecule inhibitors (e.g., apremilast) (**Figure 3**). Treatment choice depends on multiple factors, such as disease severity, patient preferences, comorbidities, disease phenotype and localizations, treatment history, age and conception plans. This thesis mainly focuses on biologics, which are described below.

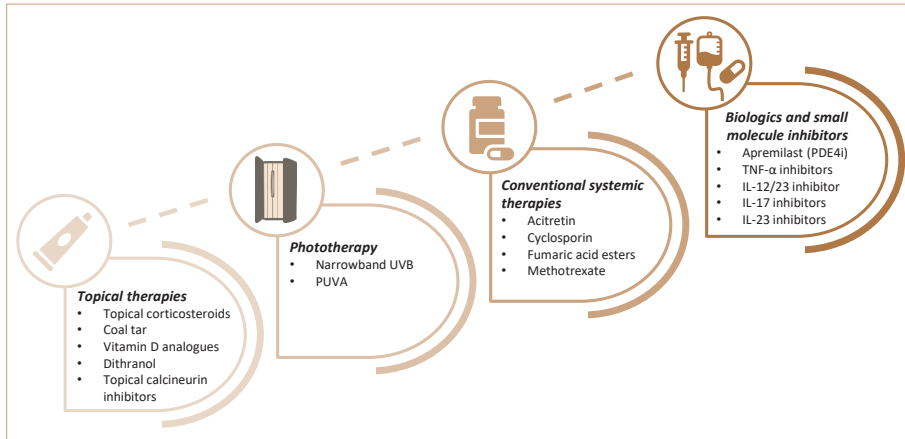


Figure 3. Treatment options for psoriasis.

Biologics

Biologics are targeted treatments which selectively interfere in the psoriasis pathogenesis pathway by blocking relevant cytokines or their receptors.⁷⁸ They have become available for the treatment of psoriasis since 2003. Biologics used in psoriasis treatment are proteins derived from living organisms, produced by recombinant DNA techniques. The composition of biologics can be derived from their names, with receptor fusion proteins indicated with the suffix ‘-cept’, and monoclonal antibodies with ‘-mab’. Fully human monoclonal antibodies have the suffix ‘-umab’, and combined antibodies have ‘-ximab’ as common stem for chimeric antibodies, and ‘-zumab’ for humanized antibodies.⁷⁹ Biologics are given by injections or infusions, as oral administration would lead to degradation in the gastro-intestinal tract.

Based on their target, currently available biologics (2022) can be divided into four groups: TNF- α inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors. An overview is presented in **Table 1**. The first biologics which were approved for treatment of psoriasis had other targets. These were efalizumab (CD11a inhibiting monoclonal IgG1-antibody) which was marketed in 2003, and alefacept (T-cell CD2 receptor blocker) which was never introduced on the European market. Efalizumab was withdrawn from the market in 2009 due to safety concerns.⁸⁰ Alefacept was available in the US from 2003 to 2011, but was then withdrawn by the sponsor as more effective biologics had become available.⁸¹ The biologics infliximab, etanercept, adalimumab, and ustekinumab entered the European market between 2004 and 2009, and are sometimes referred to as the first generation biologics for psoriasis. From 2015, biologics targeting IL-17 (secukinumab, ixekizumab, brodalumab, bimekizumab) were introduced, followed by IL-23 inhibiting biologics (guselkumab,

risankizumab, tildrakizumab) from 2017. In 2018, the TNF- α inhibitor (certolizumab pegol) was marketed for psoriasis. Certolizumab pegol was developed in a way that it does not undergo transfer across the placenta in pregnant women. Development of new biologics and small molecule inhibitors is still ongoing, with a new oral drug inhibiting tyrosine kinase 2 (TYK2) in the JAK/STAT pathway (deucravacitinib) being investigated in phase 3 trials,⁸² and phase 2 studies being published regarding a trivalent nanobody (which is smaller than a monoclonal antibody) targeting IL17A/F (sonelokinumab).⁸³ For patients with pustular psoriasis, a new biologic targeting IL-36 is currently being investigated in phase 2 trials (spesolimab).^{84, 85}

In general, biologics are prescribed to patients with moderate-to-severe psoriasis. When the first biologics became available, they could be prescribed only when conventional systemic treatments and phototherapy had failed or when patients had contra-indications for conventional systemics or phototherapy. For the newer biologics, treatment labels allow their use in patients with moderate-to-severe psoriasis who are candidates for systemic therapy despite their treatment history. For some 'first generation biologics' the label has been adapted as well. Currently, less stringent labels are present for the biologics adalimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, risankizumab, and tildrakizumab. The current European guideline indicated however that conventional systemic therapies should be considered as first line treatment. Biologic treatment could be initiated in patients with severe disease where treatment success cannot be expected with use of conventional systemics.⁷⁰

Despite their high effectiveness rates,¹² biologics are expensive and impose a high burden on national healthcare budgets.¹⁴ The manufacturing process of biologics is complex, leading to high development costs. Market prices can rise up to €23.000,- per patient per year in the Netherlands. When patents of the original biologics expire, biosimilars can be marketed. These are biological products highly similar to the originator. For biosimilars, there should be no clinically meaningful difference with regard to quality, efficacy and safety compared to the originator.⁸⁶ By use of biosimilars, costs are often reduced.

In general, biologics are considered to be safe in the treatment of patients with psoriasis.^{87, 88} There are however some downsides and several contra-indications for which patients should be screened before treatment start.⁷⁰ Due to their mechanism of action, biologics may increase risk of infections. Cytokines which are targeted by the different biologics play a role in immune defense against infections. As such, TNF- α is involved in defense against intracellular infections, including viral infections.⁸⁹

Table 1. Overview of available biologics for psoriasis

Target	Biologic	Year of approval ^a	Mode of action	Dose ^b
TNF- α	Etanercept ¹⁰⁴	2004	Human TNF receptor p75 Fc fusion protein binding TNF, thereby acting as a competitive inhibitor of endogenous TNF- α	50 mg s.c. twice weekly for 12 weeks, followed by 50 mg every week
	Infliximab ¹⁰⁵	2005	Chimeric IgG1 κ monoclonal antibody binding TNF- α	5 mg/kg i.v. at week 0, 2 and 6, followed by every 8 weeks
	Adalimumab ¹⁰⁶	2007	Human IgG1 monoclonal antibody binding TNF- α	80 mg s.c. initial dose, followed by 40 mg at week 1, and ever (other) week thereafter
	Certolizumab pegol ¹⁰⁷	2018	PEGylated Fab'fragment of a humanized IgG1 monoclonal antibody targeting TNF- α	400 mg s.c. at week 0, 2 and 4, followed by 200 mg or 400 mg every 2 weeks
IL-12/23	Ustekinumab ¹⁰⁸	2009	Human IgG1 κ monoclonal antibody, targeting the shared p40 subunit of IL-12 and IL-23	45 mg or 90 mg s.c. (depending on body weight, ≤ 100 kg vs >100 kg) at week 0 and 4, followed by ever 12 weeks
IL-17	Secukinumab ¹⁰⁹	2015	Human IgG1 monoclonal antibody selectively binding IL-17a	300 mg s.c. at week 0, 1, 2, 3 and 4, followed by every 4 weeks
	Ixekizumab ¹¹⁰	2016	Human IgG4 monoclonal antibody, selectively binding IL-17a	160 mg s.c. initial dose, followed by 80 mg at week 2, 4, 6, 8, 10 and 12, followed by 80 mg every 4 weeks
	Brodalumab ¹¹¹	2017	Human IgG2 monoclonal antibody binding IL-17RA, thereby blocking IL-17a, IL-17a/f, IL-17F, IL-17c, and IL-17e (IL-25)	210 mg s.c. at week 0, 1 and 2, followed by every 2 weeks
	Bimekizumab ¹¹²	2021	Humanized IgG1 monoclonal antibody targeting IL-17a and IL-17f	320 mg s.c. at week 0, 4, 8, 12, 16, followed by every 8 weeks ^c
IL-23	Guselkumab ¹¹³	2017	Human IgG1 λ monoclonal antibody targeting the p19 subunit of IL-23	100 mg s.c. at week 0 and 4, followed by every 8 weeks
	Tildrakizumab ¹¹⁴	2018	Humanized IgG1 κ monoclonal antibody targeting the p19 subunit of IL-23	100 or 200 mg s.c. (depending on body weight ≥ 90 kg or severe disease) at week 0 and 4, followed by every 12 weeks
	Risankizumab ¹¹⁵	2019	Humanized IgG1 monoclonal antibody targeting the p19 subunit of IL-23	150 s.c. at week 0 and 4, followed by every 12 weeks

^aYear of approval by European Medicine Agency. ^bDosing regimen for adult patients with plaque psoriasis according to the label. ^cIn case of insufficient response at week 16, bimekizumab can be administered as 320 mg every 4 weeks in patients weighing ≥ 120 kg, who are not free from psoriasis at 16 weeks. Abbreviations: IgG, immunoglobulin G; IL, interleukin; i.v., intravenous; kg, kilograms; mg, milligrams; s.c., subcutaneous; TNF, tumour necrosis factor.

IL-12 regulates T-cell mediated immunity by production of IFN- γ .⁹⁰ In addition, IL-17 is involved in defense against fungal infections,⁹¹ and use of IL-17 inhibitors is associated with increased risk of *Candida* infections.⁹² Both IL-17 and IL-23 are involved in regulation of Th17 cells, providing cellular immunity,⁹³ and seem important in mucosal immunity, with antagonizing resulting in a potentially increased risk of respiratory tract infections.⁹⁴ Among most frequently reported adverse events among biologic users in clinical trials and daily practice are respiratory tract infections, other infections and headache.⁹⁵⁻¹⁰³

Real word evidence

Efficacy and safety of biologics for psoriasis have been established in randomized controlled trials (RCTs). RCTs are considered as the gold standard to investigate efficacy of drugs compared to placebo or other drugs, as by design potential forms of bias can be handled.^{116, 117} By randomizing participants between groups that are being compared, differences in outcomes can be attributed to the studied intervention. Therefore, selection bias and confounding are minimized by randomization and allocation concealment. Besides these advantages, there are however some shortcomings. Outcomes from RCTs cannot always be translated to the real-world situation, due to short-term observations and strict in- and exclusion criteria. Hence, patients included in RCTs may differ from the real-world population with regard to age, comedication use and comorbidities.¹¹⁷⁻¹¹⁹ As such, RCTs have a high internal validity but a low external validity. Therefore, it is widely acknowledged that real-world observational studies are needed alongside RCTs.¹²⁰ Real-world data can provide more insight in real-world effectiveness, safety, and PROs. Results from real-world studies are more generalizable to the general patient population as they comprise actual patients who are treated based on prevailing guidelines, personal preferences, or local policies.¹²¹

Many real-world registries are nowadays available in order to evaluate treatment with biologics.¹²²⁻¹²⁶ Results from such registries showed that female sex is a predictor for earlier treatment discontinuation with biologics, but actual reasons remain unclear.¹²³⁻¹²⁹ Although there is no difference in the male-to-female prevalence ratio for psoriasis,¹³⁰ it has been reported that male patients receive treatment with biologics more often and might have more severe disease compared to females.^{9, 131} More generally, it has been observed that sex differences exist in the presentation of symptoms, communication and treatment outcomes.^{132, 133} In this thesis, differences in treatment satisfaction with biologics between male and female patients were explored (**chapter 5.1**).

This thesis is partly based on data collected in the observational, prospective, multicenter, long-term Continuous Assessment of Psoriasis Treatment Use REgistry with Biologics (BioCAPTURE). BioCAPTURE contains daily practice data on patients treatment with biologics in daily practice since 2005 (www.biocapture.nl). In 2022, 23 centers in the Netherlands were included in the registry, and this number is still growing. Collected data includes patient- and treatment characteristics, effectiveness measures, safety data, and PROs (dermatology related quality of life, treatment satisfaction, work-related impact of the disease).

Biologic dose reduction

For patients with moderate-to-severe psoriasis, lifelong treatment with biologics is mostly needed for long term disease control. This results in treatment with biologics in fixed dosages during many years. The possibility of achieving very good treatment responses, or even complete clearance, poses the question how these patients should be treated over the long term. Continuous treatment with a fixed dose may not be necessary in patients with good treatment responses.¹⁶ Moreover, due to the high costs of biologics, sustainable use is warranted.

Dose reduction (DR) of biologics for psoriasis patients with low disease activity is a solution for more efficient use. Overtreatment can be prevented and healthcare costs will decrease when striving for the lowest effective dose. Guidance is however needed, as DR could theoretically lead to reduced effectiveness of lower doses, and there might be concerns related to not achieving adequate responses after resuming the standard dose. DR of biologics, also referred to as 'dose tapering', can be achieved by administration of a lower dose (e.g., in mg) per administration or by prolongation of the regular dosing interval (e.g, injection interval), after initial treatment according to the registered dose.

For the first generation biologics, it was demonstrated that treatment withdrawal resulted in psoriasis exacerbations.¹³⁴ At that time, few alternatives were available in case of treatment failure. As such, DR was not an attractive option. In the field of rheumatology however, studies demonstrated feasibility of DR of TNF- α inhibitors in patients with low disease activity.¹³⁵ Approximately 10 years after the introduction of biologics for psoriasis, the possibility of lowering biologic dosages for psoriasis was explored.

Evidence regarding biologic DR for psoriasis indicates that DR is possible in patients with low disease activity without losing disease control, but reported success rates differ due to variations in success definitions, used DR strategies, and

study designs.^{136, 137} A review of the literature in 2021 showed that most studies on biologic DR for psoriasis included the first generation biologics (e.g., TNF- α inhibitors and IL-12/23 inhibitor). Although uniform criteria for application of DR were not defined, most studies described a minimal treatment duration and/or stable low disease activity of 6 to 12 months prior to DR, and the biologic dose was mostly reduced gradually in fixed steps leading to respectively 67% and 50% of the original dose.¹³⁶ Regaining adequate treatment responses after resumption of the standard dose in case of relapse due to DR was described in a few small retrospective studies.^{138, 139} Knowledge gaps identified in the review included lack of long-term data, limited knowledge on predictors for successful DR, and little insight in DR of the newer biologics (IL-17 and IL-23 inhibitors).¹³⁶ As results from previous DR studies regarding the first generation biologics might not be directly translated to the newer generations, a novel randomized, controlled, non-inferiority trial on DR of IL-17 and IL-23 inhibitors in patients with psoriasis was designed and is currently being performed in Belgium and the Netherlands. The study protocol for this trial is described in **chapter 4**.

In 2020, results of the first RCT regarding biologic DR of adalimumab, etanercept or ustekinumab in psoriasis patients with stable and low disease activity, were presented: the CONDOR trial.^{140, 141} In this trial, stepwise DR by means of injection interval prolongation leading to 67% and 50% of the standard dose, guided by disease activity (PASI) and impact on patients' HRQoL (DLQI), was compared to the standard maintenance dose. Although non-inferiority with regard to disease activity (PASI) was not demonstrated, no differences in persistent disease flares were observed between groups. In total, 53% of patients successfully lowered their dose, and the strategy resulted in substantial cost savings.^{140, 142} DR was considered safe, and no differences regarding formation of neutralizing anti-drug antibodies against adalimumab or ustekinumab were observed between groups.¹⁴³ In this thesis, further implementation of the used DR strategy from the trial in daily clinical practice will be described.

As stated before, stopping biologic treatment will lead to disease flares in the majority of patients and is therefore not advised.¹⁴⁴ It should as such be emphasized that the goal of DR is not to withdraw the biologic, but to strive for the lowest effective dose. In this thesis, DR by tight control of disease activity without discontinuation of the biologic is studied. With the use of a tightly controlled strategy, guided by disease activity and a PRO such as impact on patients' HRQoL, timely dose adjustments can lead to regaining adequate treatment responses, hence limiting long term safety risks for patients.

Implementation

Although several studies investigated clinical effects of biologic DR,¹³⁶ criteria for performing DR have not been elaborated in treatment guidelines and insight in actual practice on performance of biologic DR is lacking. Adoption of evidence-based DR strategies into practice seems important, as this may result in limiting unwanted practice variations and risks for patients. As publication of new insights in medical journals or guidelines will not guarantee actual uptake of these insights in clinical practice, factors which might hamper or facilitate implementation should be investigated.^{145, 146} Hence, implementation studies designed to develop and/or evaluate implementation strategies in a specific context could contribute to better uptake of innovations.¹⁴⁷ For the development of so called implementation strategies, different frameworks exist of which constructs relevant for the specific context can be selected.^{146, 148-150} These theoretical frameworks help to identify barriers for change and to develop a strategy with components targeting these barriers. Barriers could for example lie at the healthcare providers' level, organizational level or patients' level.^{145, 146, 151} For instance, at the healthcare providers level, barriers against implementation of biologic DR may include fear of risking disease flares and limited knowledge on how to perform DR. At the organizational level, it is conceivable that practical issues may arise such as lack of guidelines or protocols and lack of time to install DR. Patients themselves may fear disease flares, which has previously been reported for patients with inflammatory arthritis.^{152, 153} Further insight in these factors is important to enhance implementation of biologic DR in psoriasis care.

Aims and outline of this thesis

This thesis addresses personalized treatment with biologics for patients with psoriasis, with a special focus on dose reduction. Specifically, the following aims were defined:

1. To gain insight in current practice and in perspectives of patients and healthcare providers towards biologic dose reduction in psoriasis.
2. To investigate implementation of dose reduction of the first generation biologics for psoriasis in daily practice.
3. To generate evidence on tightly controlled disease activity guided dose reduction for the newer biologics for psoriasis (IL-17 and IL-23 inhibitors).
4. To explore possibilities for more personalized treatment with biologics, with focus on differences in treatment satisfaction between male and female patients, differences in risk of respiratory tract infections among biologics, and effectiveness and safety of biologics in patients of older age.

In **chapter 2**, insight into current practice of biologic DR was investigated through surveys among dermatologists in the Netherlands (**chapter 2.1**) and worldwide (**chapter 2.2**), focusing on their attitudes and behaviour regarding application of biologic DR. The patient perspective regarding biologic DR was explored in a qualitative interview study in **chapter 2.3**.

Regarding further implementation of DR of the first generation biologics, the DR strategy from the previously conducted RCT was adapted and evaluated in clinical practice.¹⁴⁰ Results are described in **chapter 3.1**. Follow-up data from this daily practice evaluation study and data from the previously conducted randomized trial were analysed in order to investigate treatment responses of patients who resumed the standard dose after DR failure (**chapter 3.2**). In **chapter 3.3**, results of a pilot implementation study designed to investigate implementation of a protocolized biologic DR strategy in daily dermatological practice are described. By using a multicomponent implementation strategy, healthcare providers in 3 participating centers were directed towards adoption of protocolized DR. Evaluation focused on feasibility and barriers and facilitators for implementation of DR in daily practice. Finally, steps towards defining clear criteria that can guide healthcare providers, and consequently their patients, to safe application of DR were made by performing a Delphi consensus procedure among Dutch dermatologists (**chapter 3.4**).

In order to generate robust evidence on DR for the newer generations biologics, we designed a novel RCT. The study protocol for this pragmatic, randomized, controlled, multicenter, non-inferiority trial designed to investigate DR of the newest generation biologics (IL-17 and IL-23 inhibitors) is described in **chapter 4.1**. At the time of writing this thesis, the trial was still ongoing.

Regarding the search for possibilities for providing more personalized treatment with biologics, real-world data from the BioCAPTURE registry was used to explore differences in satisfaction with biological treatment between male and female patients in **chapter 5.1**. As a result of safety questions on drug use arising during the COVID19 pandemic, differential risk of respiratory tract infections among biologics was investigated in **chapter 5.2**, also by using BioCAPTURE data. An inventory of effectiveness and safety of biologics and conventional systemic therapies in older patients with psoriasis was made by performing a systematic review of the literature. Results are described in **chapter 5.3**.

The results described in this thesis are summarized and discussed in **chapter 6**.

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CHAPTER 2

Perspectives of patients and
dermatologists towards dose
reduction of biologics
in psoriasis



CHAPTER 2.1

Attitudes and behaviour towards dose reduction of biologics in psoriasis among dermatologists in the Netherlands

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Lead

Biologics are effective but expensive therapies for the treatment of psoriasis. So far, biologics are prescribed in fixed doses as specified by their label. The Dutch Association for Dermatology and Venereology (NVDV) included the question whether each patient requires this standard dosage in their research agenda. Therefore, a survey was distributed among the members of the NVDV in order to (1) evaluate whether dose reduction is already performed by Dutch dermatologists and (2) to investigate the opinions and attitudes of Dutch dermatologists with regards to dose reduction of biologics in psoriasis.

Introduction

Biologics are effective but expensive therapies for the treatment of psoriasis. So far, biologics are prescribed in fixed doses as specified by their label. Perhaps, not every patient requires this standard dose.

Dose reduction seems a promising method to promote the efficient and safe use of biologics. By reaching the lowest effective dose, healthcare costs can be reduced and long-term drug exposure can be decreased. Recently, a prospective, randomized, multicentre trial was conducted in six Dutch hospitals, assessing dose reduction of adalimumab, etanercept, and ustekinumab.¹ Non-inferiority of dose reduction as compared to standard treatment was demonstrated with regard to quality of life, but could not be demonstrated for disease activity. Non-inferiority studies are further explained in **Frame 1**.² Dose reduction was successful in 53% of patients after one year. Successful dose reduction was defined as the use of a decreased dose and retaining Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) ≤ 5 in one year.

Besides results from clinical research, insights into current practice in the Netherlands is needed for further implementation of biologic dose reduction.³ Therefore, the aim of this survey was to assess the attitudes and behaviour of Dutch dermatologists with regard to dose reduction of biologics for psoriasis.

Methods

An anonymous online survey was distributed among 702 NVDV members on 15 October 2019. This cohort consisted of dermatologists and residents who were familiar with prescribing biologics. Responses could be returned until 26 November 2019. Data were collected through Qualtrics software (XM 2020, Provo, UT, USA).

The survey included questions related to whether dose reduction was applied by the respondents, reasons for applying or not applying dose reduction, the strategies

used, and conditions for considering dose reduction in patients. Dose reduction was defined as either increasing intervals between doses (e.g., injections) or reducing the absolute dosage (e.g., milligrams) per administration. It was also assessed whether respondents thought guidelines on dose reduction would be beneficial. The survey contained both open and closed questions using predetermined answer options. Additionally, there was the option to leave comments in a free-text field. Only completed surveys were eligible for analysis. The results of these surveys were analysed using descriptive statistics in SPSS 25 (IBM, Armonk, NY, USA).

- A non-inferiority study is designed to demonstrate that a new treatment is not substantially worse or less effective than the standard treatment (non-inferior). It does not demonstrate superiority (i.e., higher effectiveness) of the new treatment.
- Reasons to choose a non-inferiority design:
 - New treatment option with benefits other than treatment effect, such as less side effects or costs reduction;
 - Large patient groups are needed to demonstrate only a marginal difference in treatment effect;
 - Research in rare conditions, for which only a limited number of patients can be included.
- A limitation of a non-inferiority design is that the potential treatment benefits of the new treatment are often not carefully studied. In that case, a new treatment can be marketed based on a non-inferiority trial, even though it might not have a true benefit compared to the standard treatment.

Frame 1. Explanation of non-inferiority studies²

Results

In total, the survey was distributed among 570 currently practicing dermatologists and 132 dermatology residents. Out of these 702 surveys, 114 (16.2%) were fully completed. Among the 114 respondents there were 108 dermatologists and 6 residents; a total of 14 respondents (12.3%) were employed in academic hospitals. Dose reduction was already applied by 89 respondents (78.1%).

Prescription behaviour and monitoring disease activity (n=114)

The survey assessed which types of biologics were prescribed, and whether participants used a clinical score to evaluate the severity and extent of psoriasis. The absolute number of prescribers was the highest for the biologics adalimumab,

ustekinumab, secukinumab, and etanercept, which were prescribed by 106 (93.0%), 104 (91.2%), 81 (71.1%) and 77 (67.5%) respondents, respectively. Infliximab and the more recently introduced biologics (e.g., certolizumab pegol, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab) were less frequently prescribed. The most commonly used tool to assess the extent and severity of psoriasis was the PASI (n=88, 77.2%), followed by the Body Surface Area (BSA; n=15, 13.2%) and Physician Global Assessment (PGA; n=11, 9.6%). Sixteen (14%) of the respondents used multiple tools, while 22 (19.3%) respondents did not use tools.

What were reasons to apply dose reduction? (n=89)

Among the respondents that applied dose reduction, the main reason to apply dose reduction was cost savings (n=84, 94.4%). Safety/less side effects was mentioned by 53.9% (n=48) of the respondents, and 41.6% (n=37) of the respondents applied dose reduction on patients' requests. Respondents were allowed to select multiple answers. In further questions, the respondents were requested to provide an estimate of the percentage of their patients in which they would consider dose reduction, as well as an estimate of the percentage of patients that would be willing to start dose reduction. Also, the respondents were asked to provide an estimate of the percentage of successful dose reduction attempts. The answers to these questions are presented in **Table 1**.

Dose reduction: how it's done (n=89)

The numbers of respondents that applied dose reduction per biologic are presented in **Figure 1**. Adalimumab (n=73), ustekinumab (n=68 for the 45mg dose and n=63 for the 90mg dose), and etanercept (n=44) were tapered by the highest number of respondents. The used methods to achieve dose reduction for each biologic are presented in **Figure 2**. Only a small number of respondents applied dose reduction for the biologics infliximab (n=6), certolizumab pegol (n=8), brodalumab (n=4), risankizumab (n=8) and tildrakizumab (n=1). These biologics were therefore not included in Figure 2. For infliximab, four respondents tapered the standard dosage of 5mg/kg every 8 weeks to 3mg/kg per 8 weeks. Two respondents stated tapering infliximab by 'increasing the number of weeks between doses' or 'in combination with methotrexate'. However, dose reduction of infliximab is not recommended due to a potential increased risk of infusion reactions.⁴ For biologics with a long dosing interval such as ustekinumab, more conservative steps (e.g., to 80% of the standard dose) were frequently reported, while for biologics with shorter dosing intervals, such as adalimumab and etanercept, dose reduction up to 50% of the standard dose was frequently reported (**Figure 2**).

Table 1. Estimations of proportions of patients on dose reduction, patients' willingness to start dose reduction and success rates (n=89)

Question	n (%)
In how many percent of your patients do you consider dose reduction?	
<5%	11 (12.4)
5-25%	44 (49.4)
25-50%	21 (23.6)
50-75%	5 (5.6)
>75%	8 (9.0)
How often do your patients agree to start dose reduction?	
Rarely	3 (3.4)
Sometimes	20 (22.5)
Often	54 (60.7)
Always	12 (13.5)
In what percentage of your patients that underwent dose reduction, the dose reduction strategy was successful?	
<20%	5 (5.6)
20-40%	20 (22.5)
40-60%	24 (27.0)
60-80%	20 (22.5)
>80%	6 (6.7)
Unknown	14 (15.7)

Data are presented as n (%) of total respondents applying dose reduction.

For secukinumab and etanercept, dose reduction was achieved by both interval prolongation as well as halving the absolute dosage per administration. For patients with a body weight of >100 kg who receive a standard dose of 90mg ustekinumab, tapering to injections of 45mg may be possible (applied by one respondent). Secukinumab, etanercept, and ustekinumab (90mg) are currently the only treatment options for which it is possible to prescribe a lower dosage per individual administration. A considerable number of respondents used the answer option 'Other' to report a dose reduction strategy consisting of increasing the dosing interval by one week between every dose. For ustekinumab, a dosing interval of 16 weeks was reported by a number of respondents. For the more recently introduced biologics, respondents frequently reported having too little experience with these biologics to attempt dose reduction.

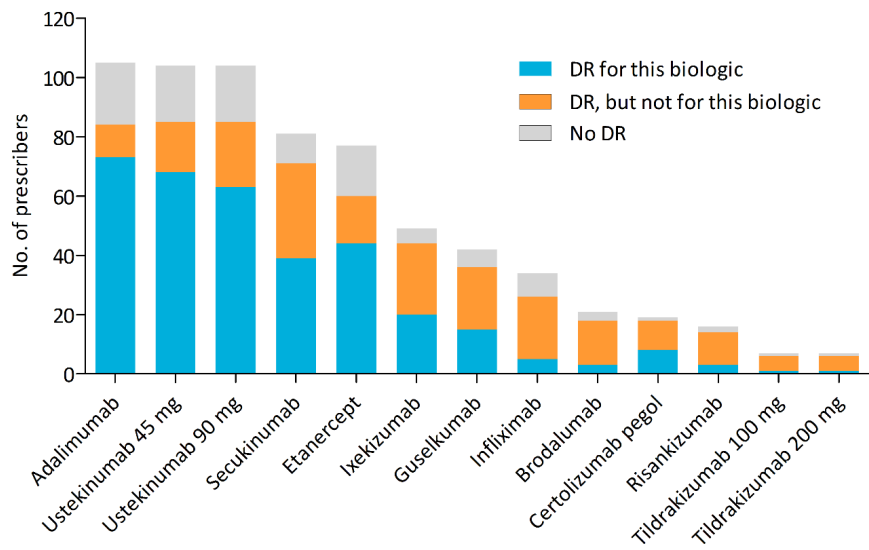


Figure 1. Dose reduction per biologic.
Results are presented as absolute number of prescribers for each biologic, and the proportion of respondents that applied dose reduction for each specific biologic.

Do’s and don’ts in dose reduction (n=89)

The survey also addressed the criteria that respondents used to determine when to start or stop dose reduction. These criteria varied widely and are presented in **Table 2**. Most respondents (n=64, 71.9%) stated that they selected patients for dose reduction based on a good clinical response. Six respondents (6.7%) reported that they did not require patients to have a long and stable low disease activity before attempting dose reduction. Sixteen (18%) respondents reported in the free text fields to involve patients’ opinions in decision-making.

Dose reduction could potentially lead to adjustments in outpatient follow-up visits. Of the respondents that applied dose reduction, 47.2% (n=42) reported not to adjust the intervals between outpatient visits. In contrast, 29 respondents (32.6%) increased the interval between visits, 11 (12.4%) respondents scheduled an additional telephone appointment, and 10 (11.2%) respondents scheduled an extra outpatient visit. None of the respondents reported determining serum drug levels of the biologic and/or assessing antibody formation after applying dose reduction.

When inquiring about reasons for re-increasing the biologic dose, most respondents

indicated that dose reduction was discontinued based upon patient request (n=65, 73%). Multiple answer options could be selected. Other reasons to increase the previously reduced dose were an assessment of the disease severity as moderate-severe (n=33, 37.1%), a PASI >3 (n=14, 15.7%), or a PASI >5 (n=15, 16.9%). Eight respondents (9%) reported having other reasons for discontinuing dose reduction, such as a combination of factors or insufficient response to topical therapies.

Dose reduction: yes or no?

Of the 89 respondents that applied dose reduction, 60.7% (n=54) wanted to apply it more often. Reasons for not discussing or attempting dose reduction were being convinced that the patient would not be interested (n=14, 25.9%), a lack of experience with newer treatment options (n=13, 24.1%), forgetting to discuss dose reduction (n=12, 22.2%), a lack of time to discuss or apply dose reduction (n=11, 20.4%), a lack of experience with dose reduction (n=9, 16.7%), a lack of available support (n=5, 9.3%), and/or concerns about financial consequences (n=1, 1.9%).

Reasons not to apply dose reduction (n=25)

Of the 114 respondents, 21.9% (n=25) did not apply dose reduction. Among these 25 respondents, the most commonly reported reasons not to apply dose reduction were not knowing how to apply it (n=12, 48%), a lack of experience with prescribing biologics (n=8, 32%), and concerns about the formation of antibodies (n=5, 20%). Other reasons were 'not having considered it before', 'being convinced that patients would not want it due to fears of exacerbations', 'a lack of scientific evidence', 'negative experiences with dose reduction attempts in the past', and 'being convinced that the pharmaceutical companies should adjust the medication costs'.

Is there a need for a guideline?

A total of 89 (78.1%) of the 114 respondents reported the need for a guideline with scientific evidence and practical advice. Among these 89 respondents, 66 (74.2%) already applied dose reduction whilst 23 (25.8%) did not.

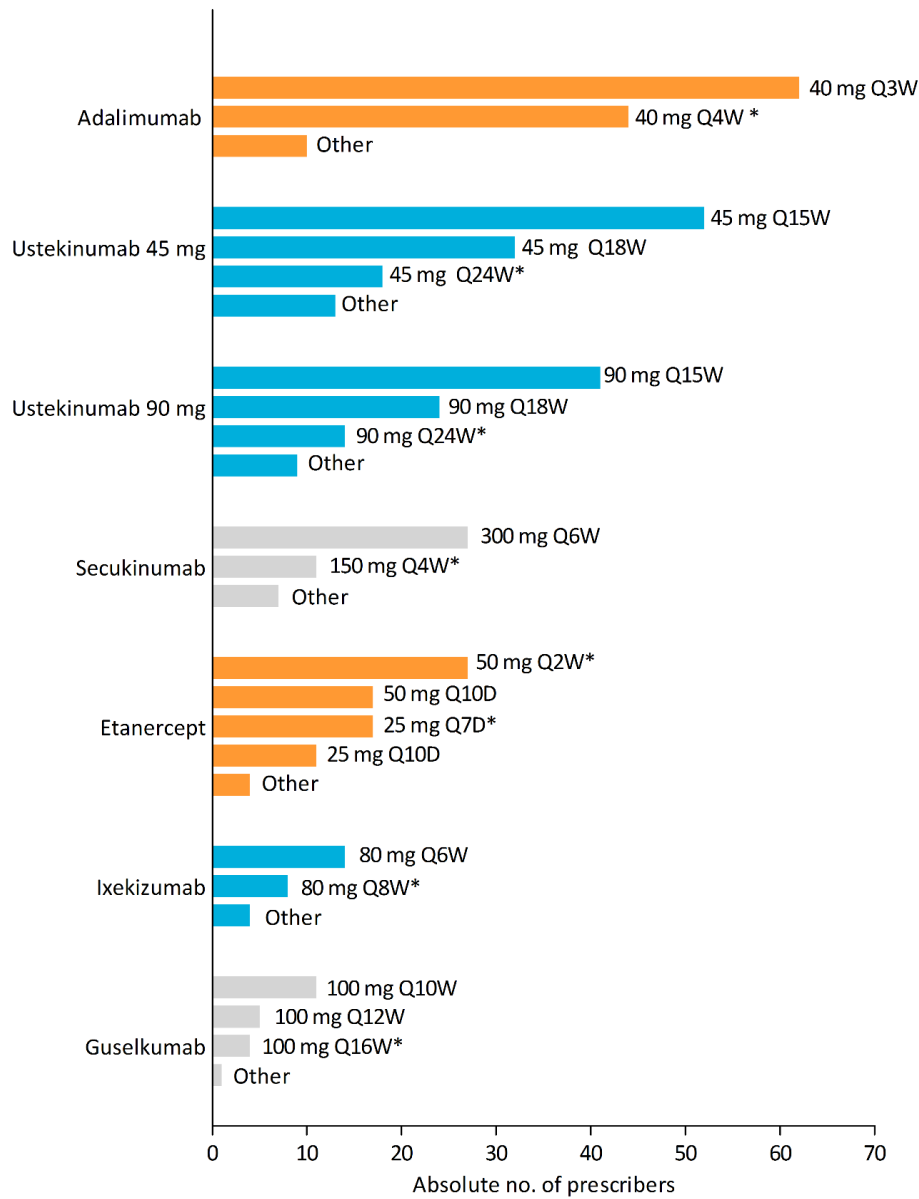


Figure 2. Dose reduction regimen per biologic.
Results are presented as absolute number of prescribers for each biologic. *50% reduction of the original dose.

Table 2. Criteria for applying dose reduction (n=89)

Question	n (%)
Criteria for starting dose reduction ^a	
Based on physicians perspective	64 (71.9)
PASI ≤1	16 (18.0)
PASI ≤3	12 (13.5)
PASI ≤5	8 (9.0)
BSA ≤10%	1 (1.1)
In case of side-effects	22 (24.7)
Other	16 (18.0)
Minimal treatment duration	
At least 1 year	27 (30.3)
At least 9 months	4 (4.5)
At least 6 months	28 (31.5)
At least 3 months	11 (12.4)
Other	4 (4.5)
Decision independent of treatment duration	15 (16.9)
Duration stable low disease activity	
At least 1 year	10 (11.2)
At least 9 months	1 (1.1)
At least 6 months	39 (43.8)
At least 3 months	27 (30.3)
At least 6 weeks	4 (4.5)
Decision independent of duration stable low disease activity	6 (6.7)
Change of outpatient visits ^a	
Prolongation of time between visits	29 (32.6)
Additional outpatient visit	10 (11.2)
Additional telephone call	11 (12.4)
No adaption	42 (47.2)
Reasons to discontinue dose reduction ^a	
At patients' request	65 (73.0)
Clinical estimation of disease activity as 'moderate'	33 (37.1)
PASI >3	14 (15.7)
PASI >5	15 (16.9)
BSA >10	1 (1.1)
Other	8 (9.0)

Results are presented as n (%) of total respondents applying dose reduction. Abbreviations: PASI, psoriasis area and severity index; BSA, body surface area. ^aMultiple answers were possible.

Discussion

In October 2019, an online survey was distributed among 702 Dutch dermatologists and dermatology residents, to assess their attitudes and behaviour regarding dose reduction for biologics in psoriasis. The results demonstrate that dose reduction is already being applied by a majority of respondents, with a total of 89 (78%) of the 114 respondents applying dose reduction in daily practice. Dose reduction was most commonly applied for the biologics adalimumab, etanercept and ustekinumab. Motivations for applying dose reduction included reducing costs, patient safety, and upon patients' requests. The response rate to the survey was low (16%). The non-respondents could potentially be physicians that prescribe biologics rarely or not at all, or residents that do not independently make treatment decisions. However, another explanation may be that the survey was less frequently completed by physicians that rarely apply dose reduction, which may have introduced selection bias.

The more recently introduced biologics (IL-17 and IL-23 inhibitors) were less frequently prescribed than biologics that were introduced earlier (TNF- α inhibitors and ustekinumab), and were also relatively less frequently subjected to dose reduction. A potential explanation for this may be the presence of literature on dose reduction in first-generation biologics and a relative lack of literature regarding dose reduction of the newer generations of biologics. Additionally, there is likely less experience with prescribing these biologics in general. Currently, a new randomized multicentre study on dose reduction of IL-17 and IL-23 inhibitors is being conducted in 17 hospitals in Belgium and the Netherlands [NCT04340076].

The wide variation in methods to achieve dose reduction was remarkable. So far, a number of studies have demonstrated that dose reduction of biologics is possible and safe in a selection of patients with low disease activity and good dermatology-related quality of life.^{1,5,6} By treating these patients with a lower dose, biologics can be used in a more efficient way, and the drug exposure can be reduced. However, more research is required with regard to the long-term effects of dose reduction, identifying patients that are eligible for dose reduction, and the optimal methods to attempt dose reduction. In combination with a clear treatment goal, this could potentially lead to comprehensive guidelines. Currently, both the Dutch and European guidelines (2015) recommend aiming to achieve PASI75, based on a consensus statement from 2011.⁷ More recent guidelines from various other countries however described more stringent treatment goals which include various other criteria besides disease activity.⁸⁻¹⁰ Seventy-eight percent of the respondents to this survey reported a need for a guideline on dose reduction, with scientific evidence and practical advice.

The most important reasons for not applying dose reduction were the conviction that patients would not be willing, forgetting to discuss it, or having insufficient time to apply dose reduction. The reasons for not applying dose reduction at all were not knowing how to apply it or an overall relative lack of experience in prescribing biologics. These concerns should be considered when further implementing biologic dose reduction. Furthermore, these concerns emphasize the need for a practical guideline on dose reduction of biologic therapies.

Besides the low response rate (16%) to the survey, another limitation of this study is the risk that the pre-programmed answer options did not completely match the current practice. To decrease the extent of this problem a free-text answer option was added to each question. Although the results of this survey have been collected prior to the COVID-19 pandemic, the pandemic has raised many questions regarding responsible application of dose reduction of biologic therapies, and in which biologics. This further demonstrated the importance of continuing research on this topic. It is possible that dermatologists have applied dose reduction more often during the pandemic.

Dose reduction of biologic therapies is a topic of interest in both dermatologists and patients, and was therefore prioritized out of 1034 research questions by the NVDV for its research agenda.¹¹ The research agenda contains the ten most pressing questions regarding dermatologic daily practice care. The results of this survey contribute to answering one of these questions, and can be used for further implementation of knowledge.

In summary, dose reduction is already applied by many Dutch dermatologists in daily practice, however their approaches to achieve dose reduction varied. There is a need for clear guidelines that are substantiated with scientific evidence. A guideline on dose reduction could potentially lead to a more uniform approach, and may be able to assist dermatologists who are currently considering the application of dose reduction. Ultimately, dose reduction could lead to more efficient and safer use of biologics in psoriasis.

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CHAPTER 2.2

Attitudes and behaviour regarding dose reduction of biologics for psoriasis: a survey among dermatologists worldwide

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Abstract

Dose reduction (DR) of biologics, where possible, seems promising for more efficient use of expensive biologics. For implementation of DR strategies, it is essential to get insight in factors that influence implementation. The objective of this study was to evaluate the attitudes and behaviour regarding DR of biologic therapies for psoriasis among psoriasis expert dermatologists worldwide. A 27-question e-survey was sent through the International Psoriasis Council (IPC) to its 114 dermatologist councilors worldwide. The survey assessed demographics, general and DR prescription behaviour, and motivations for and barriers against application of DR. Of 57 respondents, 53 respondents who prescribed biologics were included for analysis. Thirty-seven (69.8%) applied DR (i.e., 'DR dermatologists'), and 16 (30.2%) did not (i.e., 'Non-DR dermatologists'). DR strategies varied among respondents. Regarding criteria for starting DR, differences were reported in required treatment duration, and interpretation and duration of stable low disease activity. In addition, the prolongation of intervals between injections varied between respondents. For most 'DR dermatologists' (n=32/37, 86.5%), cost savings were one of the main reasons to apply DR. Fifteen out of 16 'Non-DR dermatologists' (94%) did not apply DR due to lack of scientific evidence. In conclusion, DR of biologics for psoriasis is part of clinical practice in psoriasis experts globally. Barriers for applying DR included lack of evidence or guidelines, and uncertainty on DR effects and risks. Although growing evidence shows DR feasibility, future studies are needed to accumulate and broaden evidence, along with development of (inter)national guidelines on DR strategies.

Introduction

Biologics have expanded treatment options for psoriasis in the last decades. These drugs reduce skin symptoms and improve quality of life in psoriasis patients.¹ Besides their effectiveness, biologics are expensive and impose a high burden on national health care expenditures. In addition, it is important to strive for the lowest effective dose, to reduce the risk of side effects. Therefore, personalized and efficient use of biologics is warranted. Biologics are often prescribed in a fixed, registered dose, whereas patients with a good response might not need this standard dose.

Dose reduction (DR) of biologics (also referred to as 'dose tapering'), seems, therefore, a promising way for more efficient and safer use of biologics. By striving for the lowest effective dose, overtreatment can be prevented and healthcare costs can be reduced. To date, studies on biologic DR report different strategies, but DR seems feasible and safe in a substantial part of patients with low disease activity.²⁻⁹ However, studies to date mostly focussed on TNF- α inhibitors and ustekinumab, and information on the newer biologics is sparse.¹⁰

For further implementation of DR strategies worldwide, it is essential to get more insight in factors which influence implementation.¹¹ Possible barriers which might prevent application of DR are for example knowledge and attitudes of the involved patients and dermatologists. In addition, local organization of healthcare, and availability of expertise and resources, should be taken into account. While previous studies mainly focused on clinical DR outcomes in local settings, little is known about the current daily practice and attitude towards DR of dermatologists worldwide. Therefore, in 2020, an international survey was sent via the International Psoriasis Council to its dermatologist councilors worldwide, with the aim to evaluate their thoughts and behaviour regarding biologic DR in psoriasis patients.

Materials and methods

Target population and survey methodology

A questionnaire was developed based on a previous questionnaire sent to Dutch dermatologists.¹² All questions were reviewed by the International Psoriasis Council (IPC) chief executive officer for face validity. The survey was designed using online questionnaire and data repository software Qualtrics (XM 2020, Provo, UT, USA). The target population consisted of dermatologists worldwide, affiliated with the IPC as councilor, and who prescribed biological therapies for psoriasis patients. The 27-question survey and an introduction e-mail were sent electronically via the IPC on 28 July 2020 to all IPC councilors (n=114). To maximize response rates, a

reminder was sent after 10 weeks. The online survey was closed on 30 October 2020. All participant responses were anonymously collected using unique respondent identification numbers.

This study was reviewed by the ethics committee of the region of Arnhem-Nijmegen and Radboud University Medical Center and was deemed to not fall within the remit of the Medical Research Involving Human Subjects Act (2021-13093), as we did not collect any personal data. Therefore, informed consent from participants was not mandatory. Consent to participate was assumed in case of completion of the e-survey. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Survey content

Dose reduction was defined in the survey as 'the application of injection interval prolongation' and/or 'decreasing the absolute dose in number of milligrams per administration'. The survey addressed demographics (country and place of work), prescription behaviour of biologics for psoriasis in general (numbers of patients treated with biologics, clinical scores used for measuring disease activity), application of DR (attitudes towards DR, reasons for applying or not applying DR, DR regimen per biologic, conditions for applying DR, success rates of applied DR). At last, respondents were asked for barriers which might prevent them from application of DR. Both open answers and predefined answers were used. In case of predefined answers, there was an option to add comments. Questions regarding DR were only displayed to respondents who indicated that they applied DR. For the complete questionnaire, see the online **Supplement S1**.

Analysis

Only completed surveys were included for analysis. Descriptive statistics were calculated to describe survey responses. As the number of respondents exposed to each question differed, results are presented as absolute numbers with percentages of respondents that were exposed to the question. All analyses were conducted in SPSS Statistics 25 (IBM, Armonk, NY, USA).

Results

A total of 57/114 surveys were completed, indicating a response rate of 50%. Four respondents were excluded from analyses as they did not prescribe biologics or biosimilars for psoriasis. Among 53 dermatologists (46.5%) that prescribed biologics or biosimilars for psoriasis, 35.8% were from Europe (Denmark [n=5], Germany [n=2], Italy [n=3], Portugal [n=2], Sweden [n=1], Switzerland [n=2], The Netherlands [n=1],

United Kingdom [n=3]), 24.5% from South America (Argentina [n=3], Brazil [n=2], Chile [n=3], Colombia [n=5]), 17.0% from Asia (China [n=2], Iran [n=1], Israel [n=1], Japan [n=3], Malaysia [n=1], Singapore [n=1]), 15.0% from North America (Canada [n=4], Guatemala [n=1], USA [n=3]), 5.7% from Africa (Egypt [n=3]), and 1.9% from Australia (Australia [n=1]). The majority (n=33, 62.3%) was employed in an academic hospital. The majority of respondents (n=27, 50.9%) estimated the total number of patients treated with biologics at their departments between 100 and 500. Ten respondents (18.9%) estimated this number as <100, whereas 15 respondents (28.3%) estimated that this number was >500, and 1 respondent did not know. Biosimilars were prescribed by 66.0% (n=35). Dose reduction was applied by 37 dermatologists (69.8%) (further called 'DR dermatologists'), and 16 dermatologists (30.2%) did not apply DR ('Non-DR dermatologists').

Prescription behaviour and monitoring of psoriasis disease activity (n=53)

Ustekinumab and secukinumab were prescribed by the highest absolute number of respondents (n=51, 96.2%), whereas brodalumab and tildrakizumab were prescribed least often (n=24, 45.3%, and n=14, 26.4%, respectively). Tools that were used for measurement of disease activity were PASI, Body Surface Area (BSA) and Physician Global Assessment (PGA) by, respectively, n=46 (86.8%), n=42 (79.2%), and n=28 (52.8%) of the respondents (multiple answers possible). One dermatologist (1.9%) did not use a disease activity score in daily practice. Six respondents replied 'other', and described using the DLQI (n=2), Visual Analogue Scale (VAS) itch (n=1), photo documentation (n=1), subjective impact (n=1), or a 'VAS score of the patient' (n=1).

DR eligibility criteria and regimens (n=37 'DR dermatologists')

Criteria for applying DR are presented in **Table 1**. Nine respondents (24.3%) would only consider DR if patients were free from psoriasis (PASI/BSA/PGA 0). Seventeen respondents (45.9%) indicated a 'PASI ≤ 1 or ≤ 2 , BSA ≤ 1 or ≤ 2 , or PGA ≤ 1 ' as criterium to initiate DR. Two respondents (5.4%) would consider DR in PASI ≤ 3 , n=1 (2.7%) in PASI ≤ 5 , n=2 (5.4%) in BSA ≤ 3 , and n=1 (2.7%) in BSA $\leq 5\%$. DR criteria were based solely on disease activity by 23 respondents (43.4%), whereas 14 respondents (37.8%) used a combination of disease activity measures, side effects and/or patient preferences. The majority of DR dermatologists (n=24, 64.9%) would consider DR after at least 1 year of treatment duration. Fifteen respondents (40.5%) considered stable low disease activity for the duration of at least 1 year prior to initiation of DR to be necessary. Detailed responses to questions on DR eligibility criteria are presented in supplementary **Tables S1 and S2**.

Figure 1 depicts the absolute number of prescribers for each biologic of the total number of respondents (n=53), and the proportion of respondents that applied DR for each specific biologic. Dose reduction was applied by the largest number of ‘DR dermatologists’ for adalimumab (n=28/37, 75.7%), secukinumab (n=24/37, 64.9%), ustekinumab (n=19/37, 51.4%), and etanercept (n=19/37, 51.4%). **Figure 2** displays the DR regimens applied by the absolute number of ‘DR dermatologists’ for each biologic separately. Two respondents indicated to reduce doses on individual basis without selecting predefined answer options. In general, smaller DR steps were used in biologics with long injection intervals, leading to relatively less reduction of the original dose, as opposed to biologics with shorter injection intervals.

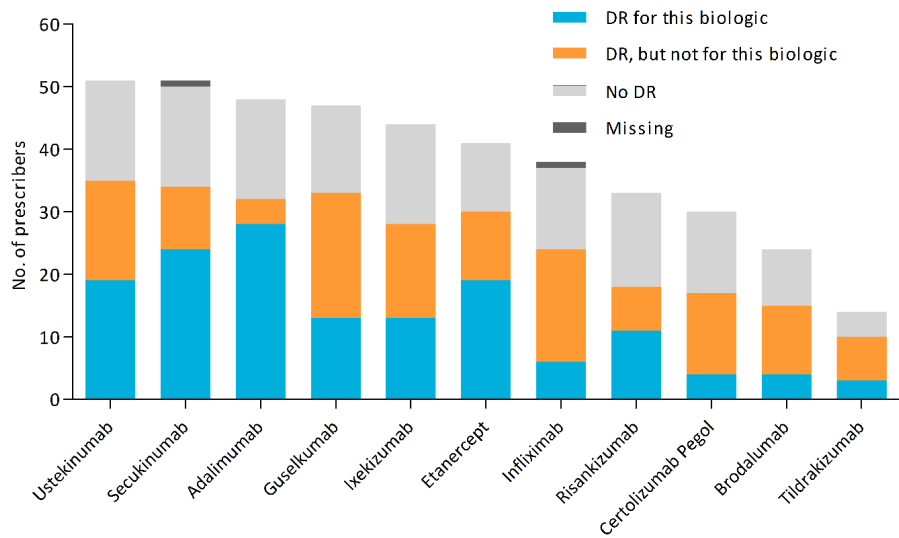


Figure 1. Dose reduction (DR) per biologic.

Results are presented as absolute number of prescribers for each biologic, and the proportion of respondents that applied DR for each specific biologic. Respondents were first asked which biologics they prescribed. Subsequently they were asked to indicate whether they applied DR for the biologics they prescribed. Respondents who indicated to prescribe a specific biologic, but did not specify if they applied DR for that biologic, were accounted as missing. Abbreviations: DR, dose reduction.

Table 1. Criteria for applying dose reduction (DR) in 'DR dermatologists' (n=37)

Question	n (%)
Criteria for starting dose reduction ^a	
In case of side effects	7 (18.9%)
At patients' request	10 (27%)
Other	2 (5.4%)
Max. disease activity score for which DR is considered ^b	
PASI 0 / BSA 0 / PGA 0	9 (24.3%)
PASI ≤1 or ≤2 / BSA ≤1 or ≤2 / PGA ≤1	17 (45.9%)
PASI ≤3 or ≤5 / BSA ≤3 or ≤5	6 (16.2%)
Estimation of disease activity (clear/almost clear)	4 (10.8%)
Other	1 (2.7%)
Treatment duration	
At least 3 months	1 (2.7%)
At least 6 months	7 (18.9%)
At least 9 months	0
At least 1 year	24 (64.9%)
At least 2 years ^b	1 (2.7%)
Independent of treatment duration	3 (8.1%)
Other	3 (8.1%)
Duration stable low disease activity	
At least 6 weeks	1 (2.7%)
At least 3 months	8 (21.6%)
At least 6 months	8 (21.6%)
At least 9 months	2 (5.4%)
At least 1 year	15 (40.5%)
At least 2 years ^b	1 (2.7%)
Independent of duration stable low disease activity	0
Other	2 (5.4%)
Change of outpatient visits ^a	
Additional outpatient visit	2 (5.4%)
Additional telephone call	3 (8.1%)
Additional e-consult ^c	1 (2.7%)
Prolongation time between visits	13 (35.1%)
No adaptation	1 (2.7%)
Only at patients' request	1 (2.7%)
Individualized per patient	2 (5.4%)

Data are presented as n (%) of total respondents applying dose reduction ('DR dermatologists'). Abbreviations: PASI, psoriasis area and severity index; BSA, body surface area.

^a More answers were possible. ^b 1 answer per respondent. ^c Answered in comment section.

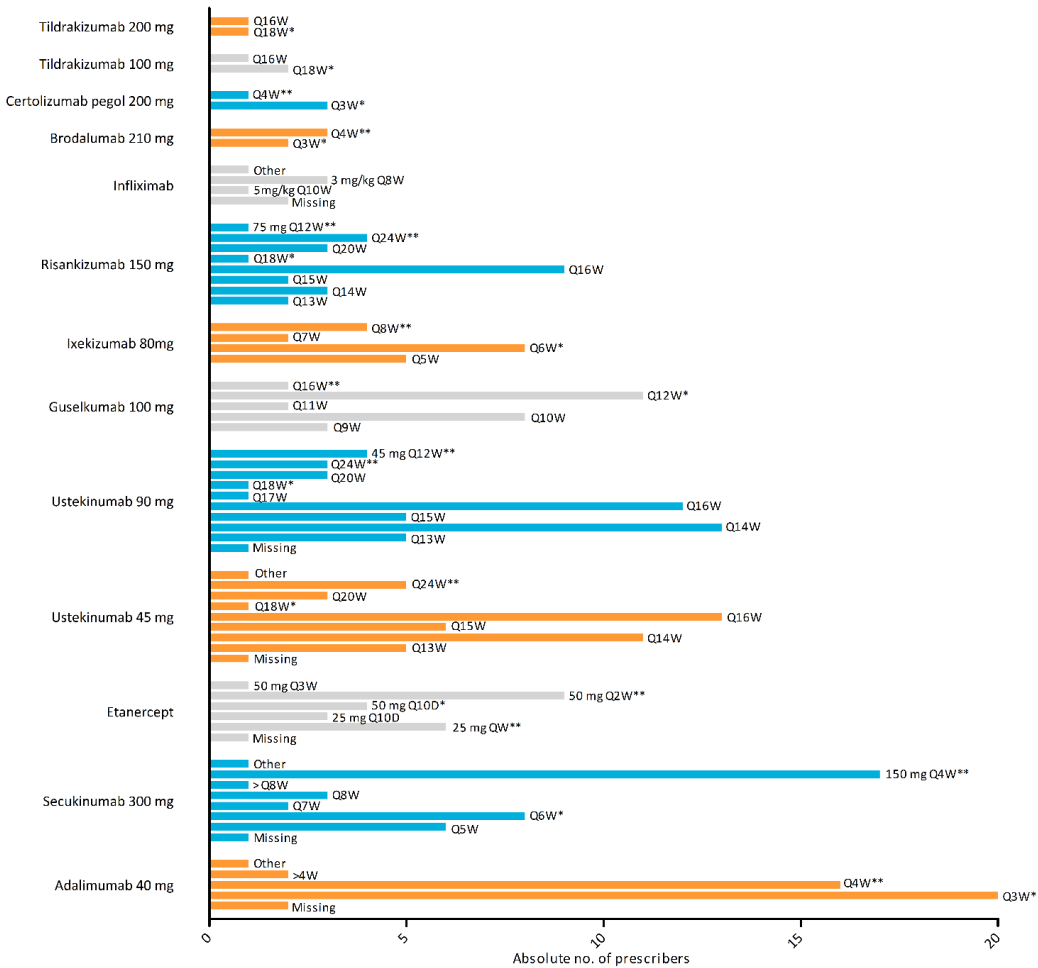


Figure 2. Dose reduction (DR) regimen per biologic.
Results are presented as absolute number of prescribers for each biologic. Respondents were asked to indicate how they applied DR per biologic they prescribed. Multiple answers were possible. Abbreviations: QW, every week; Q10D, every 10 days; mg, milligram; kg, kilogram. *33% reduction of the original dose, **50% reduction of the original dose.

Evaluation of patient eligibility, patient willingness and success rate of dose reduction (n=37 ‘DR dermatologists’)

Table 2 provides a detailed overview of the estimations given by DR dermatologists on the percentage of patients in which they considered DR, patients’ willingness for DR, and success rates of DR. The majority (n=29, 78.3%) estimated that their patients were frequently (‘often’ (n=17, 45.9%) or ‘always’ (n=12, 32.4%)) willing to start DR. There was a large variability in the evaluation of DR success, ranging from estimated success rates of <20% (n=3, 13.5%) to rates of >80% (n=4, 10.8%).

Table 2. Estimations by 'DR dermatologists' of patients on dose reduction (n=37)

Question	n (%)
In how many percent of your patients do you consider dose reduction? ^a	
<5%	12 (32.4%)
5-25%	16 (32.4%)
25-50%	7 (18.9%)
50-75%	1 (2.7%)
>75%	0
How often do your patients agree to start dose reduction?	
Rarely	1 (2.7%)
Sometimes	7 (18.9%)
Often	17 (45.9%)
Always	12 (32.4%)
In what percentage of your patients that underwent dose reduction, the dose reduction strategy was successful? ^b	
<20%	5 (13.5%)
20-40%	6 (16.2%)
40-60%	11 (29.7%)
60-80%	7 (18.9%)
>80%	4 (10.8%)
I don't know	3 (8.1%)

Data are presented as n (%) of total respondents applying dose reduction (i.e., 'DR dermatologists').

Missings: a = 1, b = 1.

Reasons for re-increasing the dose (n=37 'DR dermatologists')

In addition, 'DR dermatologists' were inquired about their criteria to stop DR, and/or re-increase the biologic dose. Twenty-six (70.3%) respondents based this decision on disease activity parameters, n=9 (24.3%) on a combination of disease activity and patients' request, n=1 (2.7%) decided to re-increase the dose solely on patients' request, and n=1 (2.7%) based this decision on 'nothing particular'. Among 'DR dermatologists' that used disease activity scores (n=26/37, 70.3%), n=14 out of 26 (53.8%) would re-increase the dose in case of PASI or BSA ≥ 3 . The maximum BSA at which a respondent would re-initiate treatment was BSA >10 (n=1/26, 3.8%). One respondent (n=1/26, 3.8%) would re-increase the dose if total remission was lost (BSA >0 or PGA >0). Another respondent (n=1/26, 3.8%) determined drug levels before re-increasing doses. Besides using disease activity measures, n=13 respondents (35.1%) made a general estimation of disease activity, and would re-

increase the dose in case of 'moderate disease activity'. Detailed responses to the question on re-treatment criteria are provided in **Table S3**.

Motivations and barriers for application of DR (n=37 'DR dermatologists')

Cost savings were one of the main reasons to apply DR (n=32 out of n=37 'DR dermatologists', 86.5%). Fixed answer options 'safety/less side effects' and 'at patients' request' were selected by n=16 (43.2%) and n=15 (40.5%) respondents, respectively (multiple answers possible). Two 'DR dermatologists' (5.4%) commented that patients should not be treated with more drugs than necessary. Twenty one (56.8%) 'DR dermatologists' would like to apply DR more often. Regarding reasons not to apply DR as much as they would like, n=6 respondents felt that they were hampered by limited experience with DR, and n=5 felt uncomfortable applying DR with biologics of the newer generations (IL-17/IL-23 inhibitors). Not having enough time (n=3) or staff for support (n=1), thinking the patient would not be interested (n=1), and fearing financial consequences (n=1) were other reasons not to apply DR more frequently. In addition, the risk of reduced effectiveness (n=1) and lack of guidelines/scientific evidence (n=3) were added as comments by respondents. To the question 'Did you apply dose reduction more often during the COVID-19 pandemic?', n=9 'DR dermatologists' (24.3%) responded that they applied DR more often.

Barriers against DR (n=16 'Non-DR dermatologists')

Fifteen out of the 16 'Non-DR dermatologists' (94%) did not apply DR due to the lack of scientific evidence on safety and efficacy of DR. However, n=10 (62.5%) 'Non-DR dermatologists' indicated that they would consider DR if scientific evidence was available, and n=6 (37.5%) would 'maybe' consider DR in that case. Apart from the lack of scientific evidence, frequently reported reasons not to apply DR were potential risk of psoriasis exacerbation (n=9, 56.3%), fear of antibody formation (n=7, 43.8%), loss of effectiveness (n=7, 43.8%), and having the opinion that the costs of biologics should be decreased instead of physicians applying DR (n=7, 43.8%) (multiple answers possible).

Dermatologists' attitudes towards DR (n=53, all respondents)

Thirty-five respondents (66.0%) reported a positive attitude towards DR of biologics for psoriasis. Five respondents (9.4%) had a negative attitude towards DR, of which n=4 actually applied DR themselves. Thirteen respondents (24.5%) described their attitude towards DR as neutral. Respondents were asked if they felt the necessity for a guideline on DR of biologics. In total, n=33 (62.3%) indicated that they felt the necessity for a guideline on biologic DR, of which n=32 indicated that scientific

background information should be covered in such a guideline. Nine respondents (17.0%) selected the answer option 'other'; of which n=6 stated that more clinical trials on DR should be conducted prior to the development of a guideline. Ten respondents (18.9%) did not feel the necessity for a guideline.

Discussion

Results of this survey among dermatologist councilors of the International Psoriasis Council showed that DR is applied in the treatment of psoriasis patients. Of 53 respondents, the majority (70%) applied DR, most frequently for the biologics adalimumab, etanercept, ustekinumab and secukinumab. Main reasons for application of DR were cost savings, safety, and patients' request. Barriers against DR in dermatologists that already applied DR were limited experience with DR, limited experience with the newer biologics in general, not having enough time or support, risk of reduced effectiveness, and lack of guidelines or scientific evidence. Among dermatologists who did not apply DR, barriers were the lack of scientific evidence, potential risk of flares, fear for antibody formation, loss of efficacy, and the opinion that costs should be decreased by the pharmaceutical companies.

The used approaches differed among respondents. Globally, a more conservative approach was used in biologics with long injection intervals, leading to smaller DR steps, and, therefore, relatively less reduction of the original dose, as opposed to biologics with shorter injection intervals. The criteria for starting DR also varied among respondents. Most respondents required the patient to have stable low disease activity for at least 1 year or 6 months, but the definition of low disease activity varied among respondents. Almost half of the respondents (45.9%) would only consider DR if patients were free from psoriasis, whereas 6 respondents would still consider DR in case of PASI or BSA ≥ 3 . This might be due to international differences in defined treatment goals and used outcomes.¹³⁻¹⁶ In defining criteria to initiate DR, or criteria for re-treatment in case of loss of response, various disease activity measures were used (PASI, BSA, PGA). Furthermore, some respondents would initiate DR based on a general estimation of the disease severity, making it difficult to draw general conclusions. Creating more uniform criteria to start and discontinue DR would facilitate further development of DR strategies.

Among barriers against DR were lack of guidelines and scientific evidence, and fear of disease flare. Currently, the option of biologic DR is only mentioned in a few guidelines.^{17,18} However, several studies have reported on the effects of DR in biologic therapies for psoriasis. Regarding the first generation biologics, several observational studies showed that DR of adalimumab, etanercept and ustekinumab is possible

and safe in patients with low disease activity without losing disease control.^{2,4-8,19,20} In addition, a randomized controlled trial showed non-inferiority regarding quality of life but not regarding disease activity, although DR of adalimumab, etanercept, and ustekinumab was possible in 53% of patients, without safety concerns.⁹ The development of anti-drug antibodies of ustekinumab did not differ between patients using a reduced dose versus the normal dose.² We recently conducted a scoping review on biologic DR in psoriasis, where we reported that for the newer IL-17 and IL-23 inhibitors, literature on DR was scarce.¹⁰ Furthermore, a uniform DR strategy has not been described yet. However, most studies described a minimal treatment duration or stable low disease activity of 6–12 months, which is in line with the results of our survey. In most studies in the review, the biologic dose was gradually reduced in fixed steps, leading to 33% and 50% reduction of the original dose. In the present survey, DR steps differed between biologics and did not exceed 50% reduction for most biologics (**Figure 2**). Regaining treatment response after relapse due to DR was achieved in most patients after re-treatment,⁷⁻⁹ although the number of studies on this topic were limited.¹⁰

A strength of this study is the inclusion of dermatologists worldwide. To our knowledge this study is a first evaluation of attitudes in an international group of experts, specifically regarding biologic DR in psoriasis. Similar to the results of this survey, a national survey among Dutch dermatologists showed that DR was already applied in daily practice and also DR strategies differed.¹² Motivations for applying DR were comparable. However, barriers to applying DR in Dutch dermatologists were the belief that patients would not want to reduce their doses, forgetting to discuss the option of DR, or insufficient time for application of DR. Among respondents who did not apply DR at all, reasons were low experience with prescription of biologics in general or not knowing how to reduce the dose. Together with local differences in organization of healthcare, availability of resources, and internationally different treatment goals, these differences in experiences emphasize the need for local, tailored strategies and availability of consensus documents or guidelines. As a result of the COVID-19 pandemic, some dermatologists stated that they applied DR more often. However, the effects of biologic therapies on susceptibility of COVID-19 and COVID-19 outcomes have not been fully elucidated, as well as the question if biologics should be interrupted.^{21,22} These questions add to reasons for further development of biologic DR strategies.

The main limitation of this study is the small sample size. For further validation of our results and for identifying global differences, replication in larger cohorts is needed. In addition, more structured methods that allow for consensus would be of value as well in future studies. By sending the survey through the International Psoriasis Council, there is a potential selection bias towards dermatologists with an interest in biological treatment, limiting the generalizability of our results.

In conclusion, the results of this worldwide survey among dermatologists show that 70% of responding psoriasis experts apply DR of biologics for psoriasis in clinical practice. However, respondents reported a large variety in used strategies regarding initiation and execution of DR. Dose reduction was applied less often in the more recently introduced biologics. Main motivations for applying DR were cost savings and improving safety. Among barriers against DR were the paucity of evidence or guidelines, and uncertainty on DR effect and risk of disease flares. Although growing evidence shows DR feasibility, future studies are needed for the development of local, tailored DR strategies and (inter)national guidelines.

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CHAPTER 2.3

Patients' perspectives towards biologic dose reduction in psoriasis: a qualitative study

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Abstract

Dose reduction of biologics for psoriasis could contribute to more efficient use of these expensive medicines. Evidence on opinions of patients with psoriasis regarding dose reduction is sparse. The objective of this study was therefore to explore patients' perspectives towards dose reduction of biologics for psoriasis. A qualitative study was conducted, comprising semi-structured interviews with 15 patients with psoriasis with different characteristics and treatment experiences. Interviews were analyzed by inductive thematic analysis. Perceived benefits of biologic dose reduction according to patients were minimizing medication use, lowering risks of adverse effects and lowering societal healthcare costs. Patients reported to have experienced a large impact of their psoriasis, and expressed concerns about loss of disease control due to dose reduction. Fast access to flare treatment and adequate monitoring of disease activity were among reported preconditions. According to patients, they should have confidence in dose reduction effects and should be willing to change their effective treatment. Moreover, addressing information needs and involvement in decision-making were deemed important among patients. In conclusion, addressing patients' concerns, fulfilling information needs, providing the possibility of resuming standard dose, and involving patients in decision-making are important according to patients with psoriasis when considering biologic dose reduction.

Introduction

Biologics have allowed patients with psoriasis to achieve adequate disease control, or even complete clearance.¹ The possibility of achieving good treatment responses now poses the question how these patients should be treated over the long term. Sustainable use of the expensive biologics is important as healthcare costs are increasing and access to biologics is unequal on a global scale. Dose reduction (DR) of biologics by means of injection interval prolongation for patients with stable low disease activity enables more efficient use of biologics with decreasing healthcare costs.²⁻⁴

DR is already performed in daily practice but not on a standard basis.^{5,6} Striving for standardization is however important: it leads to consistent and safe practice, and better uptake in routine care. For adoption of DR into practice, insight in factors which hamper or facilitate implementation is needed. Barriers to implementation of DR may arise at the patients' level.^{7,8} We previously showed that 'fear for psoriasis flares' was the most important reason among patients with psoriasis for unwillingness to start DR in a daily practice evaluation study on DR of adalimumab, etanercept or ustekinumab.⁹ In rheumatology, several qualitative studies reported that fear of relapse was a main concern among patients with inflammatory arthritis when considering biologic DR.¹⁰ Nevertheless, patients were willing to try DR after receiving information on DR, and if increasing the dose was possible when deemed necessary.¹¹ Currently, in-depth explorations of opinions of patients with psoriasis towards DR are lacking.

The aim of this study was to explore perspectives of patients with psoriasis regarding biologic DR. Results will inform healthcare providers on what is important for patients within the context of DR and could provide a solid basis for shared decision-making.

Materials and methods

Study design

A cross-sectional qualitative study was performed consisting of semi-structured interviews. A qualitative design was considered most suitable for broadly exploring patients' perspectives.¹² Reporting of this study followed the Standards for Reporting Qualitative Research.¹³

Participants

Adult patients with psoriasis treated with biologics at the department of Dermatology, Radboudumc, Nijmegen, the Netherlands, were recruited from the prospective BioCAPTURE cohort.¹⁴ Purposive sampling was used to obtain a variety

of patients regarding age, sex, type of biologic, treatment duration, treatment history, and experience with DR, to get insight into a broad range of experiences. Participants were not necessarily candidates for DR yet. Ethical approval was waived by the medical ethical committee Arnhem-Nijmegen (2021-12967). All participants provided written informed consent.

Data collection

A semi-structured interview guide was developed by the research team (LS, LV, JR, EJ), and addressed experiences with biologic treatment and DR, opinions and beliefs regarding DR, willingness to try DR, perceived opinions of people in patients' environment, preconditions for biologic DR, and information needs. Patient representatives from the national patients' association (IE, FO) reviewed the interview guide.

Interviews were conducted between September 2021 and March 2022 by one researcher (LS). This researcher/physician (LS) had no long-term treatment-relationship with participants, but conducted consultations with some participants in the past 6 months. Recruitment of patients ended when data saturation was reached (no new subthemes emerged from the last three interviews). Interviews were held by telephone, were audio-recorded and transcribed verbatim. No formal member check was performed, but a summary was presented to the participant at the end of the interview to check for accuracy. Patient and treatment characteristics were collected from BioCAPTURE.

Data analysis

Transcribed interviews were analysed by inductive thematic analysis using ATLAS.ti software. Thematic analysis comprises a flexible approach for identifying themes, without trying to fit data into any predetermined category.¹⁵ Repeated transcript reading was conducted to maximize data familiarity. Analytical rigor was sought using multiple coders (investigator triangulation):¹³ two researchers (LS, LV) coded the first three transcripts independently (open coding), resulting in a list of initial codes. Based on initial codes, next transcripts were systematically coded (axial coding) by one researcher (LS), and reviewed by another researcher (LV). Differences were discussed until consensus was reached. Newly identified themes were added to the codebook, using an inductive approach. Analysis was concurrent with data collection, to explore emerging themes further on in later interviews. When necessary, the interview guide was adapted. Constant comparison was applied throughout the whole process of data analysis, by comparison of emerging themes with new data.¹³ Results and saturation were discussed during the process. Analysis resulted in (sub)themes that play a role for patients with psoriasis regarding biologic

DR. Corresponding illustrative quotes were selected from the interviews, and were translated into English by a professional translation service. Results were revised based on discussion with key researches (LS, LV, JR, and EJ). Patient representatives (IE, FO, and AP) reviewed results to check whether results were formulated in a way compatible to the patient perspective.

Patient characteristics were summarized using SPSS Statistics version 25 (IBM Corp., Armonk, NY).

Results

Patient characteristics are summarized in **Table 1**. Among participants, differences in current biologic treatment, number of previous biologics used and experience with DR were present. Saturation was achieved after 15 completed interviews. Mean duration of interviews was 28 minutes. After analyzing the first three interviews, minor changes were made to the interview guide including addition of questions regarding psoriatic arthritis (PsA), and preferences for timing and channeling of information.

In total, seven main themes were identified: disease control, attitudes towards medication and DR, healthcare access and organizational aspects, cost reduction, information needs, social aspects, and decision-making. Corresponding subthemes are described below. An overview of (sub)themes and illustrative quotes is presented in **Table 2**. Summarized clinical implications based on (sub)themes arising from the interviews are graphically presented in **Figure 1**.

Disease control

Impact of psoriatic disease

Disease control was brought up as an important issue. Patients reported to have experienced a large physical and/or psychosocial impact of their psoriasis, which also involved feelings of shame. Having psoriatic disease also had an impact on work and daily functioning. Causing itch, pain and scaling, psoriasis had a large impact on patients' wellbeing. In case of concomitant PsA, joint symptoms had a major impact on patients' lives as well. In contrast, patients mentioned that being free of psoriatic disease provided a feeling of freedom. As such, patients did not want to go back to the days when they had severe psoriasis. Participants expressed that healthcare providers should pay attention to the (past) impact of the disease within the context of DR.

Table 1. Baseline patient characteristics

Characteristic	Total n=15
Sex (female)	6 (40)
Age (years) ^a	43 (28-75)
Disease duration until present (years) ^a	18 (7-47)
Psoriatic arthritis (yes)	5 (33.3)
Previous biological treatment	
Yes	9 (60)
No	6 (40)
Number of previous biologics used ^a	1 (0-6)
Current biologic	
Adalimumab	4 (26.7)
Etanercept	2 (13.3)
Ustekinumab	3 (20.0)
Secukinumab	1 (6.7)
Ixekizumab	2 (13.3)
Brodalumab	1 (6.7)
Risankizumab	2 (13.3)
Treatment duration of current biologic (years) ^a	4 (0.5-14)
Experience with biologic DR ^b	
Yes, successful	4 (26.7)
Yes, unsuccessful	4 (26.7)
No	7 (46.7)

Data are presented as n (%) unless otherwise indicated. ^aMedian (range). ^bSuccessful dose reduction was defined as use of a lower dose and maintenance of low disease activity (PASI ≤5). Abbreviations: DR, dose reduction.

Effort to reach low disease activity

Patients valued the option of the highly effective biologics. Participants reported to have used different treatment modalities over time, before qualifying for biologics. The effort to reach a state of low disease activity was therefore an identified barrier to DR. Initiation of DR after a long period of biologic treatment was reported as a factor to overcome this possible barrier, as this could gain patients' trust in DR effects and might prevent loss of effectiveness according to patients.

Fear of disease flares

Related to the past experiences of having severe psoriasis, fear of disease worsening was identified as an important theme among participants. It was reported that the risk of disease flares could result in unwillingness to start DR. Patients experienced with DR noted that concerns about disease flares may disappear after perceived maintained treatment effectiveness despite reducing the dose.

Treatment goals

Adequate disease control can be important for patients when starting or continuing DR. However, definitions of adequate disease control and the ideal duration of having good treatment effects before starting DR can differ between patients. The amount of psoriasis lesions and location of lesions could contribute to perceived disease activity. Treatment goals can change over time, depending on patients' life course and previous (un)successful treatment experiences. Hence, it was suggested that patients' goals should be addressed by healthcare providers. Although the accepted level of disease activity might differ between patients, participants mentioned that DR should preferably be initiated after adequate disease control is reached and maintained for a prolonged period.

Attitudes towards medication and DR***Attitude towards possible adverse effects***

Having experienced side effects or concerns regarding unknown risks of biologics may act as facilitators for DR. While some participants expressed these concerns, others did not fear the risk of side effects at all. Conversely, not experiencing side effects may act as a barrier for DR, as patients could see no reason why they would change their treatment.

Willingness to change effective treatment

Willingness to change effective treatment can play a role when considering DR. Participants expressed that (un)willingness to try DR depends on received information. Moreover, maintaining good treatment effects was deemed important for patients while reducing the dose, and confidence in effectiveness is needed before treatment alterations, according to patients. It was reported that the decision to start with DR could be based on a balance between willingness to try versus risking a flare. For patients experienced with DR, negative or positive experiences with DR could contribute to the willingness of reducing the dose again.

Use of concomitant topical treatment

Different views regarding the use of topical treatment were expressed. Some patients preferred to use topicals first before resuming the standard dose in case of increased psoriasis activity following DR. However, patients could also have experienced ineffectiveness of topicals or have negative feelings towards the use of topicals. As such, not having to use topicals again before resuming the standard dose was also mentioned as prerequisite before considering DR.

Confidence in DR

Participants expressed that there should be a level of confidence in the DR process. Confidence in DR effects and in reaching adequate treatment responses again after increasing the dose in case of psoriasis worsening were reported facilitators for DR.

Practical use of the biologic

As biologics are usually self-injected, administering less injections was a perceived benefit of DR, specifically for patients who disliked self-injecting. Likewise, less pharmacy visits or less pharmacy delivery moments were expressed as possible advantages of DR. However, for other patients, self-injections were perceived to be convenient and thus less injections will not provide much benefits.

Minimizing medication use

Minimizing medication use was an important reported motivation for DR. Participants expressed that medication in general is not good for one's body and there could be unknown long-term risks. Besides, patients did not want to be dependent of medication. However, biologics are needed for disease control, but the lesser the use, the better.

Healthcare access and organizational aspects

Access to treatment in case of disease flares

The possibility to re-increase the dose in case of psoriasis worsening following DR was a very important condition for patients. Fast access to dose alterations or alternative treatments was deemed essential. In addition, information about alternative treatment options in case of ineffectiveness of resumption of the standard dose should be available at DR start.

Access to the outpatient clinic

Patients appreciated the option to contact the outpatient clinic by telephone or digitally in case of questions or increased psoriasis activity, as this could be trust-gaining. After starting DR, a certain level of support should be available, for example through a digital app or a dedicated healthcare provider. This facilitates prompt access to care and generates feelings of being supported.

Importance of monitoring

Different opinions related to the frequency and importance of monitoring in the context of DR were expressed. Some patients wanted to have frequent outpatient visits after starting DR, while others did not. It was reported that live visits including skin-checks and blood monitoring could give feelings of being looked after. When

starting DR, monitoring disease activity was mentioned as an important factor. More generally, laboratory checks were valued due to possible risks of biologics.

Barriers at the healthcare providers' level

According to patients, possible barriers could lie at the healthcare providers' level as well. It was indicated that the treating healthcare provider should be aware of DR as treatment option. For them, continuing the standard dose might be the easiest way to go. Additionally, participants suggested that involvement of different healthcare providers might limit application of DR, as the treating clinician should know the patients history to make an estimation of eligibility for DR.

Cost reduction

Contribution to lowering costs of the national healthcare budget

Lowering costs was mentioned as an advantage of DR, as biologics are expensive. However, for individual patients there was no direct financial advantage, as they pay a fixed amount for their healthcare insurance in the Netherlands which covers their treatment costs. Still, it was reported that patients could contribute to lowering societal healthcare costs too. By contrast, patients mentioned that this would not be the case anymore when less expensive alternatives would become available (e.g., biosimilars).

Availability of biologics to more patients

Besides contributing to lowering societal healthcare costs, patients expressed the hope that biologics might become available for more patients due to decreased costs resulting from DR.

Information needs

Content of information about DR

Participants emphasized the need for information on DR, including the rationale and evidence, expected effectiveness and potential risks of DR. Study results or previous experiences could help to gain realistic expectations. Furthermore, it was reported that information on treatment options in case of loss of disease control during DR should be provided. Some patients reported that they wanted as much information as possible. However, it was also mentioned that it could differ between patients how much information is needed or preferred to agree to DR.

Preferences for timing and channel of information

Participants suggested that information should be presented by the treating healthcare provider during a face-to-face consultation as this promotes direct communication. As such, the healthcare provider can accurately estimate DR eligibility. Written information could add to orally presented information, could help patients to think about DR, and could provide more time for consideration. It was reported that the option of DR could be presented at the start of biologic treatment or alternatively when patients have sustained low disease activity and would be thus eligible for DR.

Social aspects

What others in patients' environment think of DR

Patients were asked about factors that may influence their decision to start DR. Consequently, they reported that discussing the option of DR with relatives or other close contacts is important, as the impact of having psoriasis also affects them. Other people can have other opinions or questions which might aid in the decision-making process. On the other hand, it was mentioned that patients would want to take the decision to start with DR themselves, as it concerns their own body and treatment.

Healthcare provider-patient relationship

Participants mentioned that healthcare providers should follow previously made agreements, for example regarding the option to resume the standard or previous dose after DR failure. Likewise, it was deemed important that healthcare providers listen, take patients seriously, and take time, as this is trust-gaining.

Decision-making

Expertise of the treating healthcare provider

A certain level of expertise of the involved healthcare provider with DR could give confidence according to patients. Moreover, some patients rely on advice of their physician. According to patients, physicians' experience with DR would imply that DR eligibility will be adequately estimated.

Personalized approach

As described before, impact of psoriasis and treatment history can differ between patients. Therefore, it was noted that a personalized approach is important when considering DR. Some patients are willing to try DR and others are not, and this should be respected. Moreover, it was reported that both patients' physical and mental health need to be addressed.

Decision-making process

Participants emphasized the need for clear agreements on DR processes. After receiving information, time should be offered to think about DR. Patients mentioned that the healthcare provider should initiate the conversation on biologic DR, but patients should be involved in the actual decision-making. Giving patients a choice is trust-gaining. Participants also reported that in case of psoriasis worsening, the next step should be discussed with the patient and decisions should be made with the patient as well.

Discussion

This qualitative study explored perspectives of patients with psoriasis towards biologic DR. Inductive thematic analysis of interviews with 15 patients with psoriasis uncovered seven main themes and 23 subthemes that play a role for patients when considering DR. Among concerns of patients was the risk of disease flares due to DR. Fast access to flare treatment and adequate monitoring of disease activity were among reported preconditions. By contrast, motivations for DR could be minimization of medication use, less injections, and a lower risk of adverse effects. Patients valued a good relationship with, and expertise of, their treating healthcare provider. Moreover, addressing information needs together with patient involvement in decision-making were deemed important.

To our best knowledge, this is the first study providing a broad exploration of perspectives of patients with psoriasis on biologic DR. In the context of DR, patients reported fear of disease worsening. This might be related to the reported (past) impact of the disease on patients' lives, which has been described before.¹⁶⁻¹⁹ A previous interview study among patients with psoriasis indicated having less impact of psoriasis as an important treatment goal, and the fear that treatment would not be effective (anymore) was reported as well.²⁰ In line with our results, fear of biologic discontinuation and the struggle to receive biologics were among reported issues by psoriasis patients before.^{17, 20} These issues should be addressed by healthcare professionals to reduce patients' uncertainties.¹⁷ A recent review showed that symptom control, treatment safety, confidence in care, communication with healthcare professionals and costs were among frequently reported patient-relevant outcomes in psoriasis.²¹ These findings correspond with our data and indicate that addressing concerns and needs of patients is of great importance when adjusting treatment.

Table 2. Identified (sub)themes with illustrative quotes of patient perspectives towards biologic dose reduction in psoriasis

Theme	Subtheme	Quotes
Disease control	Impact of psoriatic disease	'If the patches get worse, it will once again affect how I feel and the things I struggle with. All my old symptoms will return, and I will constantly itch in annoying places. It will show up in my face, and I won't be able to style my hair the way I like, because I will be covered in it. And it will hurt when I have sex.' [P6]
	Effort to reach low disease activity	'Look, you know where you've come from and that this isn't something you want to go back to, and I think that most people have had quite a long journey getting here. Before you get to the biologicals, you've usually tried two or three other things. Probably, none of them helped or not enough, and then the biological is this great solution, so clearly, you're not willing to lose it again.' [P15]
	Fear of disease flare	'It's not that I'm completely negative about it, only that if it gets worse, if the skin condition makes it difficult to move... Now, I'm not afraid to take a shower with the other guys. If more patches appear, it will be harder to move, so I'll no longer be able to play football one hour a week, or cycle with my child, and that certainly won't make my life easier.' [P12]
	Treatment goals	'I find it very important that my skin is healthy, and this is ultimately why I do it. If it stays the way it is for a year or so, without getting better or worse, I wouldn't mind trying to reduce the dose. But if I'm not fully satisfied, then I wouldn't agree to a lower dose. In fact, I'd probably be worried about whether the full dose is effective enough.' [P8]
Attitudes towards medication and DR	Attitude towards possible adverse effects	'On the other hand, it works really well and I'm not experiencing any side-effects, so I don't necessarily feel the need to reduce the dose.' [P6]
	Willingness to change effective treatment	'We have finally found something that works well for me, so I'd rather not mess with it. When something works, don't change it; that's how I feel about it intuitively.' [P8] 'Well, I would like to take the gamble. Because clearly, this can only be a win-win situation. It may be that your body responds well to the change, that you can handle a lower dose, which is great. If you don't try it, you'll never know. And if you find that you have to increase the dose again, at least you will have given it a try.' [P5]
	Use of concomitant topical treatment	'I've said it very clearly: I don't want to apply anymore of those ointments. All that ointments; I hardly had any skin left. And it's disgusting, fatty stuff. It made everything dirty: my clothes, my sofa, my bed, etc. I couldn't even hug my own children. So I'm completely done with those ointments; I don't want to have anything more to do with them.' [P9] 'I'm now supplementing with ointments, so I hope to see the effects better in a few weeks. If not, then I won't wait, but I'll switch right back to injections every 14 days.' [P5]

Table 2. Continued

Theme	Subtheme	Quotes
Attitudes towards medication and DR	Confidence in DR	'It's not as if you're suddenly completely covered in it, but it does take hold quite fast. Once it flares up, things can go fast. But I also noticed with the medication, that it starts working pretty quickly, so I expect it to take effect quickly too, which is why I'm not scared at all.' [P3] 'If the injection interval is extended now, I don't know what will happen. But as long as I don't return to the old level, and I remain at the level I'm at now, where I can go about my life, and sit down with my child on the floor, play with Lego, etc., that's worth more to me than trying to extend the period.' [P12]
	Practical use of the biologic	'I don't actually care that much how often it is. You just put it on your calendar, and make sure you've got enough medication in stock.' [P5] 'It's a question of ease, I think. The lower the dose, the less work for me. Now I've got one medicine that needs to be administered every twelve weeks, which isn't much at all. But I've also had medicines in the past that had to be administered every two weeks. Well, it would be great if I could reduce that to once every four weeks.' [P8]
	Minimizing medication use	'It's about the health aspect, right? These are biologicals, it's not just a simple medicine they're administering. I do try to think of my health; everyone does. I know it's a tough medicine; I'm fully aware of it. The less of it I need, the better for my body, as long as my skin stays in good shape, that is.' [P5]
	Access to treatment in case of disease flares	'If you try it once and find it doesn't work, or the symptoms get worse fast, and you can simply return to your previous dose, if that's something that is easy to arrange, then I wouldn't necessarily be against it.' [P6] 'At the start of the dose reduction track, there should already be a back-up plan ready. (...) Once that can be implemented immediately, without first having to wait one, two, three, or four months, while the symptoms are getting worse. Because this is a cumulative process; it starts with a small patch, and before you know it, your whole leg is covered in it.' [P12]
Healthcare access and organizational aspects	Access to the outpatient clinic	'The only thing that matters is that it should be possible to get an appointment if the symptoms return, or if I have questions or concerns, that I can call them. It should be possible at any time to plan in an interim appointment.' [P9] 'Maybe the monitoring could be done in the form of an app. (...) For example staying in touch via an app in the early phase of reducing the dose. That way, you don't necessarily need to see a doctor immediately; you can wait until the doctor has time. It would make things much easier, and I think it would work quite well.' [P3]

Table 2. Continued

Theme	Subtheme	Quotes
Healthcare access and organizational aspects	Importance of monitoring	'If we have more frequent check-ups and someone checks up on me on a regular basis, and this doesn't necessarily have to be a physical check-up, it could be contact by telephone, for example every six weeks. I think that, as a patient, I am quite capable of noticing whether things are improving or not. Because in this case, we're talking about a skin disease, and it's quite easy to see whether your skin is doing well or not. But maybe there could also be some blood tests, that kind of thing. If those kinds of tests are run more frequently at first, that would give me the feeling that the situation is being monitored adequately.' [P8]
	Barriers at the healthcare providers' level	'I understand that they don't go through my entire file in depth, and I don't see the same dermatologist every time. So within the short time that this person is treating me, they have to go through my whole file, and then it's easiest to say: It's going well, great, let's keep going!' [P1]
Cost reduction	Contribution to lowering costs of the national healthcare budget	'I know that this medicine is also very expensive, so why would I want to keep going no matter what. Especially if I can keep my condition stable with less. Maybe this means that other people can also get better help, and this might in turn keep the costs of health insurance lower for longer.' [P3]
	Availability of biologics to more patients	'I think that lowering the dose means that you can inject two people for the price of one. So I think in this way you can help more people, if you make biologicals more easily accessible. I think it would help a lot more people.' [P9]
Information needs	Content of information about DR	'What I'm mostly curious about is what previous research has to say about it. Because if this is offered to me as a patient, I'm assuming it has been tried before, at least to some extent. And that there are known results. That would help me to know better where I stand, and what I should also take into account.' [P8]
	Preferences for timing and channel of information	'I would like to get it from a doctor. Someone who has done research on it, or at least knows a lot about it.' [P14] 'When I'm sitting in one of your treatment rooms, and you sit opposite me, I'm able to process the information quickly, and figure out what it means for me. But that's not the case for everyone, which is why having a bit more time might be useful. And maybe also providing some kind of information, so I can read through it again at home. This is always useful, as much information as possible. It also depends a bit on what the risks are. Look, if nine people out of ten benefit from it, or have no negative effects from the lower dose, then I'd say, go ahead. And in that case, I don't really need much more information than that.' [P8]

Table 2. Continued

Theme	Subtheme	Quotes
Social aspects	What others in patients' environment think of DR	'My wife, of course. I'd certainly like to discuss it with her. Clearly, she also knows what it was like when I was suffering from it, and how ashamed I was. Plus, she might have questions about the future, and maybe she can see something that I haven't considered at all.' [P7] 'As far as I'm concerned, this is my decision. It's my life, my body, my decision. I may tell people about it, but as I said, only for information purposes.' [P9]
	Healthcare provider-patient relationship	'Maybe that last bit, about being heard. If I have the feeling that the effect is diminishing, and my symptoms are returning, I want to be taken seriously, and not end up in a discussion with the doctor about what I find acceptable versus what they find acceptable.' [P6]
	Expertise of the treating healthcare provider	'Just to be able to talk about it to the doctor, because this is all new to me, and you people have some experience with it. I don't have any experience with it, and I don't know anyone who does, you see. Which is why it's important to have a doctor who can say: listen, this is normal, and this isn't.' [P2] 'I'm open to it, and I trust the doctors I'm talking to. I also feel that my opinion matters, so I completely trust it, and if it doesn't work, I can always go back, of course.' [P5]
	Personalized approach	'When I first came in, this man asked me: How is it going? Fine. That first time, I rolled up my sleeves to show him my skin. But he said: No, I'm asking you how you are, not how your skin is. That really struck me: this is a human being, across from you. That's what I find important. Knowing that there is a human being in front of you, having an experience; not a number. Not: this is number six today, and I have to make sure they get off their medication. No, there is a human being there, and every human being is different. This is something I find very important.' [P13] 'I don't think I can recommend it to other people; I can only speak from my own experience. If people want to do it, that's fine, but I just want to tell them: keep an eye on it. By the way, I don't think any two cases of psoriasis are identical.' [P11]
Decision-making	Decision-making process	'I'm pretty motivated to lower the dose, but I do feel strongly that this is my decision. And that's what I find really important.' [P9] 'Well, I think it would be good if it started with a face-to-face talk, and then some information on paper, so you could read about it and think it through. That you would have time to think about it, instead of having to decide on the spot.' [P6]

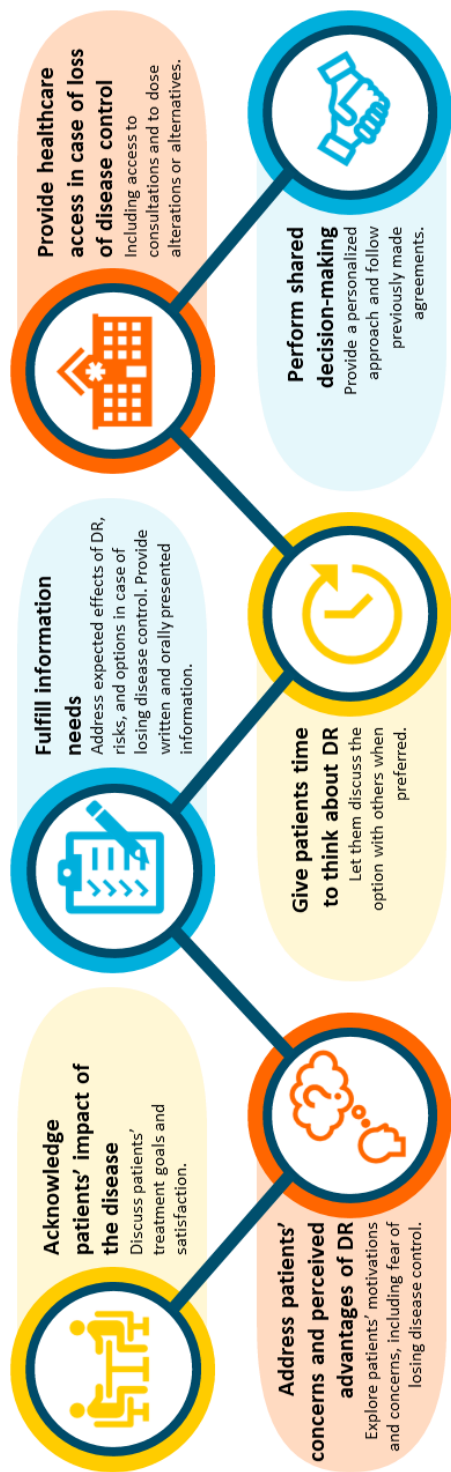


Figure 1. Summary of clinical implications based on identified (sub)themes arising from the interviews

We identified several factors influencing patients' willingness to try DR. Among patients' reported barriers was the fear for delayed access to consultations or to the previous dose in case of psoriasis worsening. Some participants reported the importance of monitoring disease activity during consultations, but actual preferences for frequency of monitoring were not provided. Preferences might depend on past experiences with received care and its quantity. Moreover, we believe that DR should be aimed at patients with low disease activity, with the goal to strive for the lowest effective dose. When educating patients and providing healthcare access in case of diminishing treatment effects, patients' wish for sufficient monitoring could be accommodated.

Previous studies among patients with inflammatory arthritis have found similar patient-reported factors towards biologic DR.^{10, 11, 22-24} Of note, DR strategies for inflammatory arthritis have been incorporated in guidelines and patients might consequently be used to the concept of DR as part of standard care.²⁵ It has also been suggested in rheumatological literature that by informing patients about possible future DR at treatment start, awareness and confidence could be created.^{11, 22, 23} For psoriasis, guidance of patients towards DR could as such be improved with incorporation of DR strategies into clinical practice and treatment guidelines.

This study has several strengths. First, we included a variety of patients with different treatments and experiences with DR, which allowed us to explore relevant perspectives of patients with psoriasis. Second, using a qualitative approach, a comprehensive exploration of patient-relevant factors could be accomplished. Results could contribute to further implementation of DR strategies by incorporating the patient perspective.

Limitations can be found in the study design. Data interpretation could have been influenced by possible framing of questions during interviews, and there might have been other relevant factors of which patients were unaware or which were not mentioned due to social desirability. Due to the qualitative design, interpreting exact numbers and drawing conclusions on most important patient-related opinions was not possible. Reported experiences might be culturally dependent and different findings could be found in other settings. Therefore, replication of this study in other settings would be of added value.

Results of this study show that patients' impact of their disease and concerns related to DR should be acknowledged when further implementing DR. According

to patients, information on and access to flare treatment should be incorporated in DR strategies, as well as information on DR rationale, expected effects and potential risks. Development of clear patient information and incorporation of patient-relevant factors into clinical guidelines on DR could enhance shared decision-making. Standardization of DR strategies and uptake in regular care may gain trust with patients. However, addressing individual treatment goals and satisfaction, and give each patient a choice remains important.

In conclusion, perceived benefits of biologic DR according to patients with psoriasis were minimizing medication use, lowering risks of adverse effects, and lowering societal healthcare costs. However, patients could have concerns related to loss of disease control following DR. Patient interviews indicated that this barrier needs to be addressed by providing adequate information, involving patients in decision-making, offering patients time to think about DR, and providing fast access to healthcare in case of disease flares. By acknowledging these patient-relevant factors when considering DR, further implementation of biologic DR strategies into clinical practice can be facilitated.

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CHAPTER 3

Implementation of dose
reduction of the first generation
biologics for patients with
psoriasis in daily practice



CHAPTER 3.1

Evaluation of a one-step dose reduction strategy of adalimumab, etanercept and ustekinumab in patients with psoriasis in daily practice

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Abstract

Dose reduction of biologics for psoriasis could contribute to lower drug exposure. This study evaluated a one-step, tightly controlled, biologic dose reduction strategy in a prospective daily practice cohort. In patients with psoriasis with low disease activity using adalimumab, etanercept or ustekinumab for at least 6 months, the dosing interval was prolonged with 33%. Patients could return to their normal dosing interval in case of disease flare. Of 108 eligible patients, 80 started dose reduction and were analysed. In total, 36/80 patients (45.0%) discontinued dose reduction after 19 months (95% confidence interval 14.9-23.1 months). Of 67 patients with 1-year follow-up, 45 (67.2%) still used the lower dose after 1 year. No serious adverse events related to dose reduction occurred. Cumulative dose and costs decreased by 22.7% during 1 year. In conclusion, a one-step tightly controlled dose reduction strategy for adalimumab, etanercept and ustekinumab has considerable potential to safely decrease biologic dosages in patients with psoriasis in daily practice.

Introduction

Biologics are effective therapies for moderate to severe psoriasis. However, treatment with biologics is often based on general guidelines and standard dosing regimens. This may not always suit the individual patient. Dose reduction (DR) of biologics in psoriasis could contribute to more personalized treatment. High costs and long-term safety concerns associated with biologics make DR desirable for implementation in daily practice.

In a recent pragmatic randomized controlled trial (RCT) we investigated a tightly controlled DR strategy in patients with psoriasis with stable low disease activity: the CONDOR study.¹ Although non-inferiority regarding disease activity was not demonstrated, DR of adalimumab, etanercept, and ustekinumab was possible in 53% of patients, without safety concerns. Other studies also showed that DR of adalimumab, etanercept and ustekinumab is possible in patients with low disease activity²⁻⁵, but success rates differ based on success definition, DR strategy and study design.

For further implementation of such a strategy, it is essential to study the gains and investments needed in daily practice. Therefore, the aim of this study was to prospectively evaluate a one-step tightly controlled DR strategy in daily practice. This strategy, based on the CONDOR study, was incorporated in clinical practice. The strategy is guided by disease activity and patients' reported quality of life (QoL). Instead of 2 DR steps in CONDOR, we started conservatively with only one-step, leading to 67% of the original dose. The use of this adapted, one-step tightly controlled DR strategy in daily practice was evaluated regarding time investment, practicability, patients' experiences, success rate, patient and treatment characteristics, safety and cost reduction.

Materials and methods

Design and participants

This prospective, clinical evaluation was conducted at the department of dermatology of Radboudumc, an academic hospital in The Netherlands, between February 2018 and February 2020. The tightly controlled DR strategy of the CONDOR study was adapted and evaluated in clinical practice in our hospital after retrieving first trial results.¹ In CONDOR, eligible patients had Psoriasis Area and Severity Index (PASI) scores ≤ 5 at 2 subsequent visits in the past 6 months and Dermatology Life Quality Index (DLQI) scores ≤ 5 at inclusion. In our daily practice strategy, patients were asked to participate in case of low disease activity for at least 6 months according to the treating physician, with PASI and DLQI scores ≤ 5 at start of DR.

Participation on patients' request despite PASI or DLQI >5 or treatment <6 months was allowed after approval from their treating physicians. In accordance with the trial, adult patients with plaque psoriasis as primary indication for biologic use, should use adalimumab, etanercept or ustekinumab in the registered dose (40 mg every other week, 50 mg per week, 45 mg or 90 mg every 12 weeks, respectively) for at least 6 months before starting DR. In case of psoriatic arthritis (PsA), patients should have adequately controlled joint inflammation. The treating rheumatologist was consulted for approval of DR in case of doubt. The use of concomitant anti-psoriatic drugs was permitted.

Instead of 2 DR steps, DR was started conservatively with only one-step. The interval was prolonged, leading to 67% of the original dose. In case of a disease flare (i.e., PASI and/or DLQI score >5), patients were advised to return to the (previous) effective or authorized dose of their biologic. Patients could also return to the (previous) effective dose at their own request.

All patients at our outpatient clinic for biological treatment were screened by a dedicated nurse, to determine whether they were possible candidates for DR. In case of a negative first screening result, patients were screened again before every subsequent visit. Possible eligible patients were asked to participate by their treating physician (i.e., shared decision-making). Patients' motivations for participating in the strategy and for not participating were collected.

Outpatient visits took place every 3-6 months with monitoring of disease activity by PASI and DLQI, according to usual practice. Extra visits could be scheduled at patients' request. Patients were also asked to complete the Skindex-29 questionnaire, a dermatology-specific quality of life questionnaire.⁶⁻⁸ During follow-up, patients were asked about their experiences with the DR strategy, as well as their reasons for discontinuation of DR. Patients were stimulated to contact their physician in case of disease worsening. When patients were not able to visit the clinic, a telephone contact was made. Safety monitoring was carried out according to existing guidelines for clinical practice, and serious adverse events (SAEs) possibly related to DR were collected.

All data were anonymized and collected using a web-based data management system, CASTOR.⁹ All patients have been included in the prospective BioCAPTURE registry, as described elsewhere,¹⁰ and therefore provided written informed consent to use their clinical data for scientific purposes.

Outcomes

The aim of this study was to evaluate the use of the adapted DR strategy in daily practice. Therefore, the numbers of patients eligible for DR were analysed. Patients' opinions and experiences were assessed, including reasons for participating and for not participating, and reasons for stopping DR. Success of the DR strategy was measured by the proportion of patients using a lower biologic dose up to 1 year, and the proportion of patients who stopped DR including time until stop. Regarding safety, SAEs possibly related to DR were assessed. Furthermore, disease activity (PASI scores) and patient-reported quality of life (DLQI and Skindex-29 scores) during 1 year of DR were evaluated. Cumulative reduced biologic doses and costs were compared with the normal doses. Other indirect costs, such as other medical costs or visit costs were not included. Biologic costs were based on actual Dutch prices during the study.¹¹

Statistical Analysis

Data were extracted from the database and imported into SPSS Statistics 25 (IBM, Armonk, NY, USA) for analysis. Patients who stopped DR ≤ 1 month and patients who were included < 3 months before data lock were excluded from analyses. Follow-up ended when patients discontinued DR or at the moment of data lock, whichever came first. Depending on the type of variable and its distribution, descriptive statistics are presented as percentages with absolute numbers, means with 95% confidence intervals (95% CI) or medians and interquartile ranges (IQR). In order to analyse outcomes for different time-points, visit data were centered into the nearest 3-monthly time-points (i.e., visit months) with a window of ± 6 weeks.

Screening results of patients possibly eligible for DR were summarized, and the number needed to screen (NNS) of all patients from the biologic outpatient clinic to detect one patient who started DR was calculated. Baseline characteristics of participating patients were summarized, as well as patients' motivations for participation or refusing participation, patients' experiences regarding DR, proportion of patients on a lower dose, proportion of patients who stopped DR (for the total cohort and per biologic), and reasons for stopping DR. The time until stop of DR was presented graphically by a Kaplan-Meier curve and patients were censored when follow-up ended. Median survival time was calculated for the total group and per biologic. Based on PASI and DLQI scores at the moment of DR discontinuation, the total number of patients who stopped due to a disease flare (i.e., PASI and/or DLQI > 5) was calculated. Of patients with PASI > 5 , further PASI course for the next 6 months was checked in their patient records. The proportion of patients who discontinued DR despite low PASI and/or DLQI scores was also calculated. SAEs possibly related to DR (e.g., psoriasis exacerbation requiring hospitalization) were counted.

For subanalyses of outcomes after 1 year, a subcohort of patients with sufficient follow-up was defined, including patients who started the DR strategy ≥ 1 year ago. For this subcohort, the proportion of patients who were still on a lower dose after 1 year was calculated. PASI, DLQI and Skindex-29 were analysed in two ways. First, data of continuing patients only were analysed ('as-treated' analysis), and second, 'intention to treat' (ITT) analysis with imputation of missing values using last observation carried forward (LOCF) was performed on the total group. The LOCF method carries forward the last available outcome, which leads to more conservative estimations.¹² The dose used in the first year of the DR strategy was calculated for the subcohort of patients who started DR ≥ 1 year ago. In case patients discontinued DR, their used dose during the rest of the year was substituted. The mean reduction in the biologic dose compared with the normal dose per label, and corresponding cost reduction, were calculated.

Results

Participants

In total 498 patients visiting our outpatient clinic for biological treatment were screened between February 2018 and February 2020. The screening results are shown in **Figure 1**. In total, 390 out of 498 patients did not qualify for DR, for the reasons stated in Figure 1. This resulted in a group of 108 patients eligible for DR. After re-screening of 390 ineligible patients, 15 patients were included because they achieved stable disease activity, used normal doses again, reached 6 months treatment duration or because of other reasons. In total, 85 out of 498 (total clinic population) started with DR, resulting in a NNS for one patient on DR of 5.9. Five patients were excluded from analysis (see Figure 1). The total follow-up duration ranged from 49 to 670 days (mean 365 days). A subcohort of 67 patients who started the DR strategy ≥ 1 year ago was defined for subanalyses. Time investment of the dedicated nurse was approximately 1 hour per 16 patients. Baseline characteristics of the participating patients are shown in **Table 1**. Overall, baseline PASI and DLQI scores were low. However, 3 patients started DR at their own request with DLQI scores >5 . One patient insisted on starting DR despite PASI >5 , but had a limited affected body surface area (2.3%) and a DLQI score of 0 and was therefore allowed to start DR.

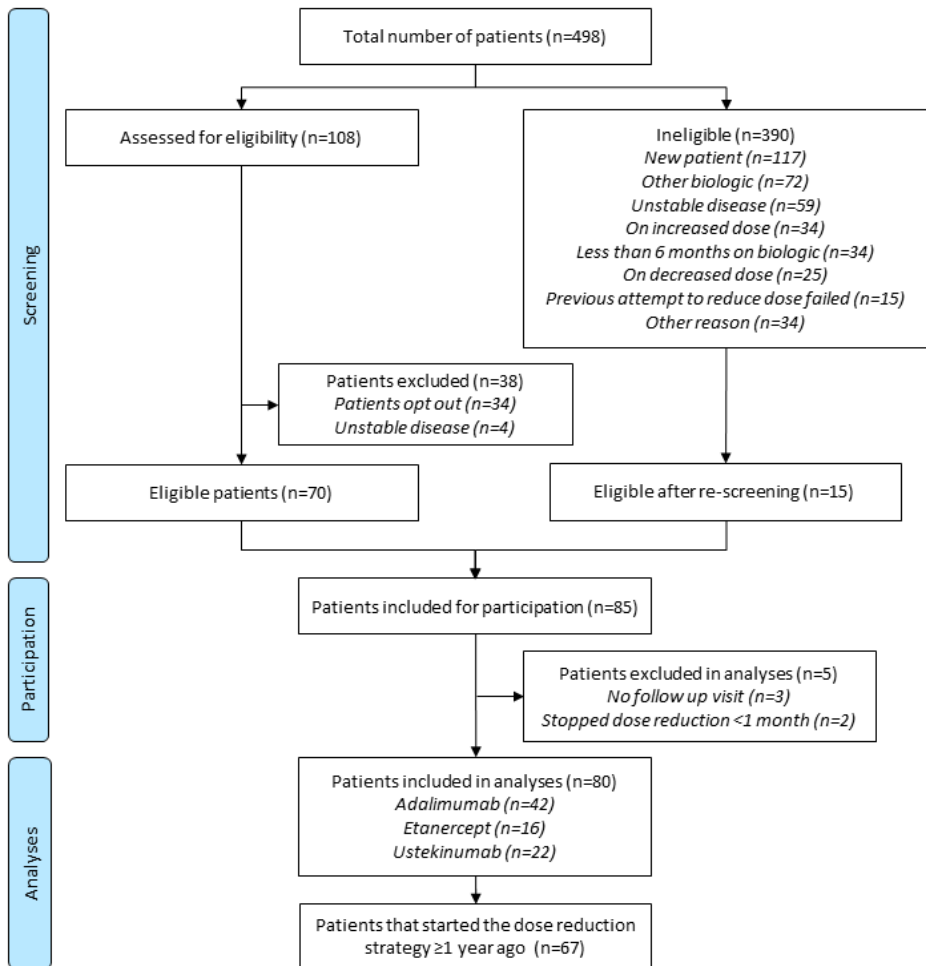


Figure 1. Screening results and eligible patients.

Patients with psoriasis who visited the outpatient clinic for biological treatment were screened between February 2018 and February 2020. Only patients with stable, low disease activity for at least 6 months and using adalimumab, etanercept or ustekinumab at the normal, registered dose could participate.

Table 1. Baseline characteristics of participating patients

Characteristics	Total (n=80)
Sex, male, n (%)	57 (71.3)
Age, years, median [IQR]	52 [43-64]
BMI, kg/m ² , median [IQR]	28.2 [21.4-31.7] ^a
Baseline PASI score, median [IQR]	1.6 [0-2.4] ^b
Baseline DLQI score, median [IQR]	0 [0-1] ^c
Baseline Skindex-29 score, median [IQR]	4.7 [0.9-13.8] ^d
Treatment, n (%)	
Adalimumab	42 (52.5)
Ustekinumab	22 (27.5)
Etanercept	16 (20)
Comorbidities, yes, n (%)	
Psoriatic arthritis	16 (20)
Rheumatoid arthritis	2 (2.5)
Spondylarthropathy	2 (2.5)
Hidradenitis suppurativa	1 (1.3)
Inflammatory bowel disease	0
Other	3 (3.8)
Comedication, n (%)	
Methotrexate/acitretin	5 (6.3)
Azathioprine/prednisolone	1 (1.3)

Abbreviations: BMI, body mass index; DLQI, Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; SD, standard deviation. Missing data (n): ^a12, ^b3, ^c2, ^d3.

Patients' opinions and experiences

Patients' reported motivations for participating are shown in **Table 2**. The most important reason for starting DR was 'minimizing medication use'. Of all patients who did not want to participate, the most frequently reported reason was 'fear of psoriasis flares'. During follow-up, a random sample of 55 participants were asked about their experiences. Of this sample, 36 patients (65.5%) were positive or satisfied regarding DR, 13 patients (23.6%) were slightly positive/moderately satisfied, and 6 patients did not respond. No participants were dissatisfied.

Dose reduction characteristics

Of all patients who started DR (n=80), regardless of their follow-up duration, 44 (55%) continued and 36 (45%) discontinued DR. DR was stopped by 19/42 (45.2%) adalimumab patients, 7/16 (43.8%) etanercept patients and 10/22 (45.6%) ustekinumab patients. The number of patients who discontinued DR per visit month is shown in **Table 3**. In total, 7/36 discontinuing patients had PASI and/or DLQI scores >5, whereas 22/36 patients discontinued DR despite low PASI and/or DLQI scores. Two patients stopped DR due to an increase of joint complaints, with one patient already having PsA. Rheumatological examination of the other patient did not reveal

PsA. During follow-up, a total of 8 patients showed temporarily a PASI >5, of which 4 patients continued DR at their own request and regained PASI <5 within 6 months. Of 4 patients with PASI >5 who discontinued DR, 3 patients regained PASI <5 within 6 months. One patient with baseline PASI >5 discontinued DR at 6 months (PASI >5). All patients with high baseline DLQIs (n=3) discontinued DR at month 3, with one patient having PASI >5. The median time until stop was 19 months (95% CI 14.9–23.1) as presented in a Kaplan-Meier curve (**Figure 2**). Reasons for stopping DR were reduced effectiveness experienced by the patient (n=18, 50%), reduced effectiveness experienced by both physician and patient (n=9, 25%), joint complaints (n=2, 5.6%), or another reason/missing (n=7, 19.4%). No serious adverse events (SAEs) related to DR were reported. There were no changes in concomitant immunosuppressant use.

From the subcohort of patients who started DR ≥ 1 year ago (n=67), 45 patients (67.2%) were still on a lower dose after 1 year. Twenty-seven out of 37 (72.9%) adalimumab patients, 8/14 etanercept patients (57.1%) and 10/16 (62.5%) ustekinumab patients were on a lower dose after 1 year.

Table 2. Reasons for participating (n=80)

Reason	n (%) ^a
Predefined answers	
To use a minimum amount of medication	47 (58.8)
Biologic use for a long time	18 (22.5)
To lower societal healthcare costs	12 (15)
Afraid of long-term effects	10 (12.5)
Experiencing side-effects	7 (8.8)
Open answers	
Stable low disease activity	9 (11.3)
According to suggestion treating physician	7 (8.8)
To contribute to research	3 (3.8)
Possible positive health effects	3 (3.8)
To see if skin remains clear	2 (2.5)
Why not	1 (1.3)
Patients request	1 (1.3)
Asked, but unknown	1 (1.3)

^a Data are presented as n (% of total participants). More answers were possible.

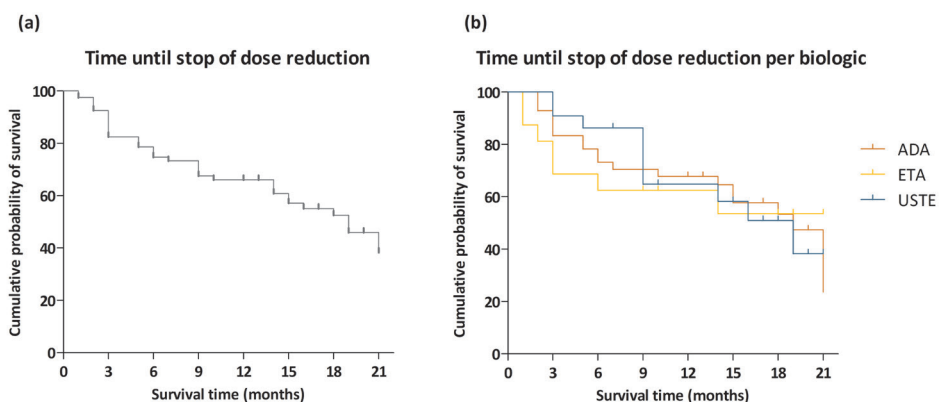
Table 3. Numbers of patients who discontinued dose reduction (DR) per visit month

	Time, months ^a							Total
	3	6	9	12	15	18	21	
Stop DR	14	6	6	1	4	2	3	36
PASI and/or DLQI >5	4	1	1	1	-	-	-	7 (19.4%) ^b
PASI and/or DLQI ≤5	8	4	3	-	2	2	3	22 (61.1%) ^b
Unknown PASI and/or DLQI	2	1	2	-	2	-	-	7 (19.4%) ^b

Abbreviations: PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index.

^a Data are presented as number of patients in the total cohort (n=80) who discontinued DR per visit month during follow-up.

^b Percentage of patients who discontinued DR.

**Figure 2. Kaplan-Meier survival curves for time until stop of dose reduction (DR).**

(a) Time until stop of DR for all biologics (n=80). Median time until stop was 19 months (95% CI 14.9-23.1 months). (b) Time until stop of DR split per biologic. Data include 42 patients on adalimumab (ADA) (n=19 stopped DR), 16 on etanercept (ETA) (n=7 stopped DR) and 22 on ustekinumab (USTE) (n=10 stopped DR). Median time until stop was 9 months (95% CI 4.7-23.3 months) for adalimumab, and 19 months (95% CI 12.0-26.0 months) for ustekinumab. For etanercept, the median time until stop of DR could not be calculated, as >50% was still active in the survival curve at end of analysis.

Disease activity and quality of life

PASI, DLQI and Skindex-29 during 1 year were analysed in two ways (as-treated and ITT with LOCF) as shown in **Figure 3**. Analyses were performed within the subcohort of patients who started DR ≥1 year ago (n=67). During 1 year of DR, PASI scores were low (median [IQR], 1.6 [0.2-2.5] at baseline, 1.7 [0.5-3.0] at month 6 and 1.9 [0.8-2.8] at month 12 in as-treated analyses) with a maximum range of 0-6.90. Median DLQI scores (as-treated) were 0 [0-1] at baseline, 0 [0-1.5] at month 6 and 0.5 [0-2] at month 12. For Skindex-29, median scores (as-treated) were 5.2 [0.9-16.4] at baseline, 5.2 [0.9-13.8] at month 6 and 6.9 [0.9-14.7] at month 12. Both median DLQI and Skindex scores correspond with minimal impact of psoriasis on patients' QoL.¹³⁻¹⁴ ITT analysis

with LOCF gave a more conservative estimate of PASI, DLQI and Skindex-29, with slightly higher scores after month 6 compared with the as-treated analysis.

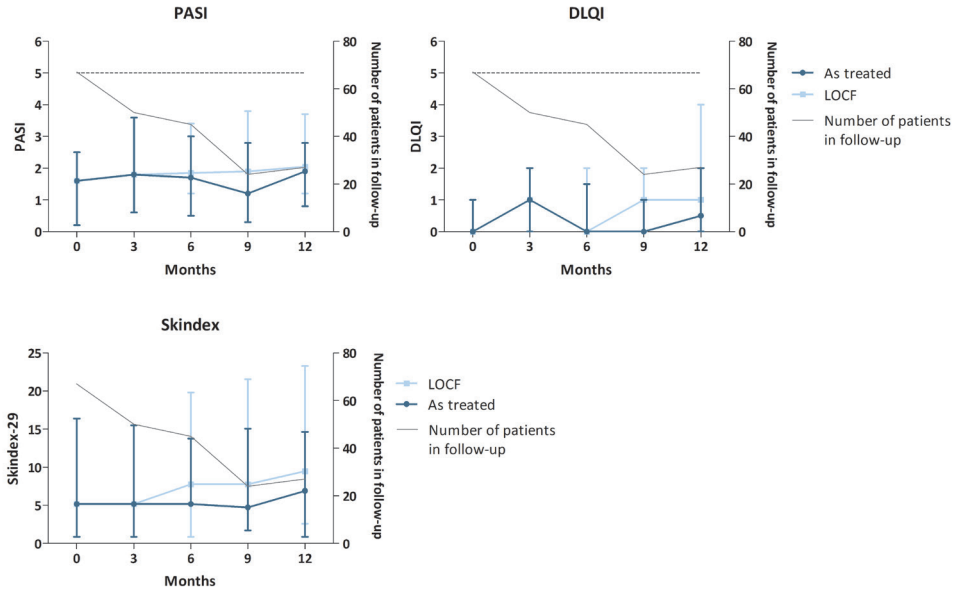


Figure 3. Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI) and Skindex-29 scores by analysis method.

Total patients n=67. Data are presented as medians with interquartile range[IQR]. Range of total possible scores: PASI 0-72, DLQI 0-30, Skindex-29 0-100. Number of missing observations per visit month for the as treated analyses (n): PASI 3 (month 0), 3 (month 3), 1 (month 6), 2 (month 9), 1 (month 12); DLQI 1 (month 0), 3 (month 3), 1 (month 6), 0 (month 9), 3 (month 12); Skindex-29 8 (month 0), 2 (month 3), 2 (month 6), 0 (month 9), 1 (month 12).

Biologic doses and costs

The cumulative dose during 1 year of the DR strategy was calculated for the subcohort of patients who started DR ≥ 1 year ago (n=67). In total, a 22.7% reduction of biologic dose and costs was achieved after 1 year compared with the per label dose, resulting in absolute cost savings of €159,228.16. Mean dose per patient per biologic, cost savings and the corresponding percentage reduction are shown in **Figure 4**.

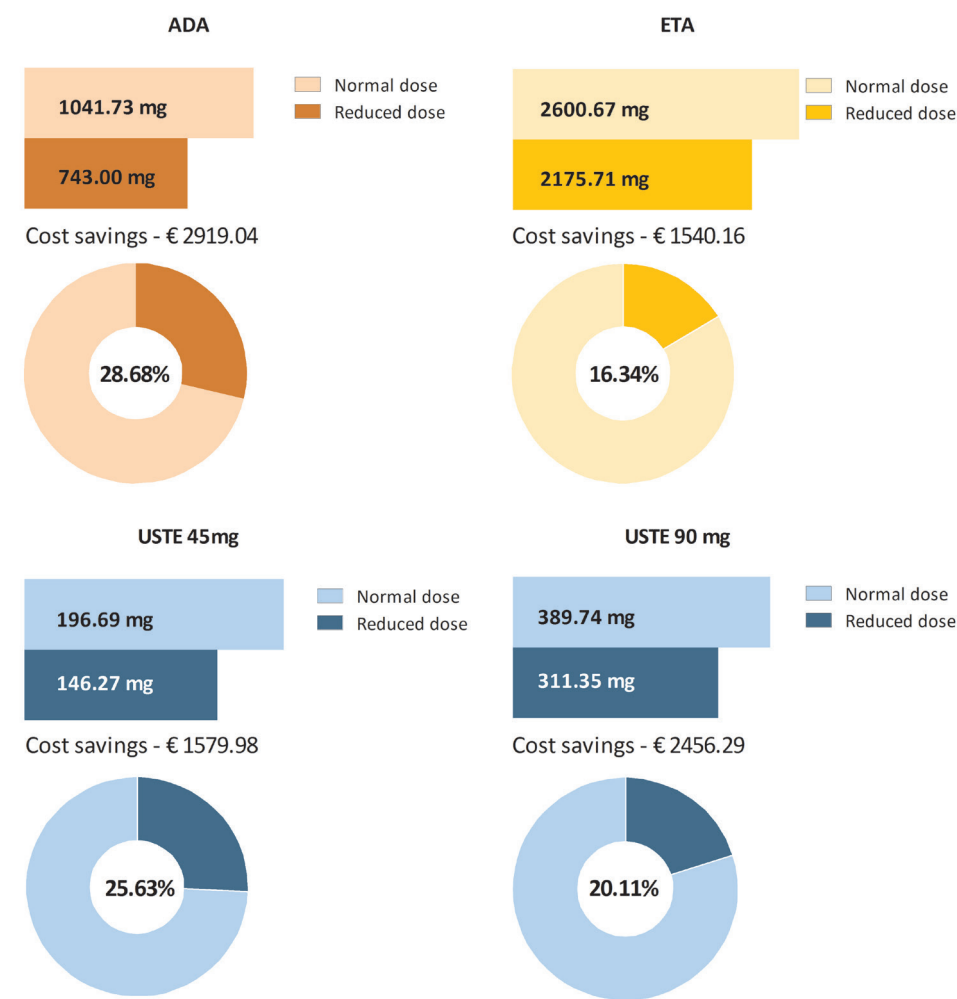


Figure 4. Mean doses per patient and percentage reduction in normal dose and costs after 1 year of dose reduction (DR) strategy.

Data are presented for the subcohort of patients who started DR ≥ 1 year ago (n=67). Cost savings are presented as mean per patient and were based on actual local prices per injection on April 1 2020: adalimumab (ADA) €390.87; etanercept (ETA) €181.92; ustekinumab (USTE) 45 mg €1410.13; ustekinumab 90 mg €2820.27.

Discussion

This prospective evaluation shows that a one-step tightly controlled DR strategy of adalimumab, etanercept and ustekinumab for patients with psoriasis is possible in daily practice. Of 108 patients with low disease activity, 85 started DR. The most important reason among patients for starting DR was 'minimizing medication use', whereas for not participating this was 'fear of psoriasis flares'. After 1 year, 67% of the patients were still on a lower dose. QoL and disease activity remained stable, and no SAEs related to DR occurred. Of patients with temporary PASI >5, disease remission was regained in the vast majority of patients. Consequently, direct medication costs were reduced substantially by 22.7%.

The DR strategy described here was based on a RCT on tightly controlled DR of adalimumab, etanercept and ustekinumab in patients with psoriasis (CONDOR).¹ In the current study, this strategy was adapted in order to make it more applicable for daily use. Inclusion criteria were less strict, the approach was more patient driven and the current study used only one step of DR (33% decrease of the normal dose) instead of two steps (50% decrease of the normal dose). The reason for this adaptation was that, in our early experience with the CONDOR study, the majority of patients successfully achieved this first step of DR. Furthermore, one step is more practical. It might be easier to convince to decrease their biologic dose by only 33%. In this clinical evaluation, a similar proportion of patients used a lower biologic dose after 1 year compared with the trial: 67% vs. 68% in the trial. The mean cumulative dose used in 1 year was less reduced than in CONDOR, which can be explained by the adapted strategy. With the final results of CONDOR we now know that 34% of patients achieved the second step of DR to 50% of the original dose.¹ Therefore, if one-step DR is successful, a further decrease should be discussed with the patient.

In line with these results, previous studies indicated that DR of biologics for psoriasis is possible. In these studies, patients could also reduce their dose after approximately 6 months and in case of low disease activity, but success rates ranged from 22-90% depending on the definition of success and study design.²⁻⁵ The current evaluation differs from previous studies, as it prospectively evaluated a modified, tightly controlled strategy from a recently conducted RCT.¹ We believe that tight control is needed in order to safely determine the lowest effective dose. Moreover, this study elucidates the investments needed to perform DR on a standard basis in clinical practice. A dedicated nurse was provided to support physicians and patients. This made it possible to collect data and it improved applicability of the strategy. The nurse screened all patients visiting our biologic outpatient clinic, with a time investment of 1 h per 16 patients. Of all 498 visiting patients, 85 eventually started

DR, resulting in a number needed to screen of 5.9 patients. Of 498 patients however, most patients were not eligible, as they did not use a biologic yet, had unstable disease, or used another biologic. Patients needed to be screened several times, as disease activity could become stable over time. This requires time investment. Installing a dedicated nurse or physician could contribute to the success of a new strategy, as coaching of patients is needed. Of the patients who stopped DR, 66% had a PASI and/or DLQI ≤ 5 , and reduced effectiveness experienced by the patient, while not experienced by the physician, contributed the most among reasons for stopping DR. It was possible for patients to stop DR on their request due to several reasons, such as fear of disease flare. On the other hand, one patient wanted to start DR with a PASI > 5 . Four patients continued DR despite PASI > 5 . Personalizing treatment goals and coaching of patients therefore seems important when considering DR.

Currently, the possibility of DR is mentioned in only a few published national guidelines.^{15,16} No clear protocols are available yet. A tightly controlled strategy, guided by disease activity and QoL, seems safe for daily use and allows evaluation of the success of the strategy. In the current strategy we used a PASI and/or DLQI score ≤ 5 as target for starting and continuing DR. It could be questioned whether this is the correct target, as in the field of psoriasis different treatment targets were defined in recent years. For example, the National Psoriasis Foundation defined their therapeutic goal as a body surface area of 1% or less,¹⁷ while a Spanish group recommended a PASI90 or Physicians' Global Assessment (PGA) ≤ 1 , with a DLQI ≤ 1 , and prolonged remission without loss of response and worsening of comorbidities.¹⁸ In Belgium, the target was multidimensional, including multiple criteria, such as disease activity, itch, DLQI, daily functioning and safety.¹⁹ Mahil et al.²⁰ recently stated that PASI ≤ 2 and PGA clear/almost clear are relevant for treat to target strategies. In our opinion however, not only disease activity but also QoL, should be taken into account, as it might differ among patients as to which PASI scores are acceptable.²¹ Therefore a low DLQI was a prerequisite, apart from PASI. Moreover, PASI is difficult to assess at lower score levels.²² Some patients with higher PASIs may still have limited disease activity and DLQI may be informative in this context.

A limitation of this evaluation is the study length in the context of long-term gains and risks of DR. However, in the current evaluation no safety issues related to DR occurred. Furthermore, 7/8 patients with PASI > 5 during the analysis period regained PASI < 5 within 6 months. Only 2 patients discontinued DR due to an increase in joint complaints, with one patient having PsA. The outcomes of DR regarding other inflammatory comorbidities were not assessed, although, according to clinical practice, DR was reconsidered in case of worsening of such comorbidities. Studying

the effect of DR on comorbidities specifically is for future research. In line with the current results, previous studies did not report safety issues related to DR, despite follow-up might not have been long enough for assessing all adverse outcomes.²³ The long-term extension results of our previous RCT showed a temporary, small increase in PASI scores, which decreased again after 18 months.²⁴ No patients who failed on DR needed to switch treatment within 24 months of follow-up, as treatment responses were regained by re-installing the normal dose. Impact on QoL remained low and there were no safety signals, including symptoms related to anti-drug antibody formation.²⁴ Another study found no difference in development of anti-drug antibodies of ustekinumab between patients on a reduced dose vs. the normal dose.⁴ It should be emphasized that, by striving for tight control, timely dose adjustments can lead to re-achievement of adequate treatment responses, hence limiting long-term safety risks. Still, more long-term data regarding DR is needed in order to provide insight into longer term risks and benefits.

A further limitation of the current study is that it did not analyse the use of topical steroids or other health-related costs. Consequently, indirect costs related to DR could not be calculated. In our previous RCT, more patients in the DR group used topical steroids compared with the usual care group, and healthcare usage was higher.^{1,25} However, the DR strategy resulted in substantial cost savings, with a minimal reduction in quality-adjusted life years.

In our opinion, this clinical evaluation shows that a pragmatic, one-step DR strategy of adalimumab, etanercept and ustekinumab for psoriasis is possible in daily practice. Seventy-eight percent of eligible patients started with DR. Two-thirds of patients who started DR at least 1 year ago were still on a lower dose after 1 year, without safety concerns. Although it requires some time investment, the study showed that even a one-step DR strategy has considerable potential to lower cumulative biologic doses with lowering of healthcare costs, without deterioration of psoriasis. More daily practice studies with longer follow-up of patients could contribute to accumulation of evidence regarding biologic DR.

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CHAPTER 3.2

Regaining adequate treatment responses in patients with psoriasis who discontinued dose reduction of adalimumab, etanercept or ustekinumab

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DEAR EDITOR, Previous studies showed that dose reduction (DR) of adalimumab, etanercept and ustekinumab is successful in a substantial number of patients with psoriasis with low disease activity and results in cost savings.¹⁻³ However, the question of whether adequate treatment responses can be regained when patients discontinue DR and resume the standard maintenance dose can be a concern for patients and clinicians. Therefore, the aim of the current study was to evaluate the effectiveness of re-treatment with the standard maintenance dose in patients who discontinued DR of adalimumab, etanercept or ustekinumab.

We performed an observational cohort study at the Radboud University Medical Center (Nijmegen, the Netherlands), consisting of a follow-up analysis of patients included in two previous DR studies (randomized controlled trial and daily practice cohort).^{2,4} In both studies, DR was guided by disease activity (Psoriasis Area and Severity Index, PASI) and impact on quality of life (Dermatology Life Quality Index, DLQI). Patients resumed the standard dose in case of PASI and/or DLQI >5, or at the patients' own request despite low PASI or DLQI. In the trial, DR schedules consisted of two steps by means of interval prolongation: first to 67% of the standard dose, and in the case of 3 months with DLQI and PASI ≤5, further to 50%.² Within the daily practice evaluation, only the first DR step to 67% was performed.⁴ Those results are described elsewhere.^{2,4}

The current analysis focused on patients from these studies who resumed the standard maintenance dose after DR of adalimumab, etanercept or ustekinumab. Inherent to the used strategy, patients resumed the standard dose in case of PASI and/or DLQI >5 or at the patients' request. Included patients were prospectively followed within the BioCAPTURE registry for 2 years after DR discontinuation.⁵ BioCAPTURE was approved by the local ethical committee (Arnhem-Nijmegen) in compliance with the Declaration of Helsinki 2008 and local regulations. All patients gave written informed consent.

Outcomes were disease activity scores (PASI) at the start of DR (baseline), at the moment of DR discontinuation, and at 6 and 12 months after DR discontinuation. For PASI scores at month 6 and 12, a range of ± 90 days was chosen in order to evaluate short- and long-term effects. Proportions of patients with PASI ≤5 and PASI ≤3, and absolute PASI differences between the different timepoints were calculated. Descriptive statistics were used to summarize outcomes. The time needed to reach PASI ≤5 was analysed by Kaplan-Meier survival analysis. Patients were censored when follow-up ended. In the case of loss to follow-up or treatment interruptions of >90 days, available data until the end of follow-up were used (as-treated analysis). Missing data were not imputed. Analysis was performed using SPSS Statistics 25 (IBM, Armonk, NY, USA).

In total, 119 patients from previous DR studies were included, of whom 58 patients (49%) continued DR and 61 (51%) discontinued DR and resumed the standard maintenance dose. The latter group was followed for 2 years after stopping DR. Two patients were lost to follow-up. Patient characteristics and PASI scores after DR discontinuation are presented in **Table 1**. At baseline (DR start), PASI scores were low [median 2.4, interquartile range (IQR) 1.5–3.0]. At the moment of DR discontinuation, PASI scores had increased to a median 4.1 (IQR 2.4–6.2). Six months after stopping DR and resuming the standard dose, PASI scores had decreased (median 2.7, IQR 2.0–4.0) and the absolute difference from the baseline PASI was small (median difference 0.6, IQR -0.5–1.8). At month 12 after DR discontinuation, most patients had achieved a comparable PASI to that before the start of DR: median difference 0 (IQR -0.8–0.7) and 0.3 (IQR -1.0–2.0) for patients who resumed the standard dose at their own request (n=19) vs. according to protocol (n=40). Of 17 patients with PASI >5 at the time of stopping DR, 15 (88%) reached PASI ≤5 again after a median time of 4 months (95% confidence interval 2.3–5.7).

Strengths of our study are the detailed follow-up of patients from prospective studies specifically designed to investigate DR effects. Limitations are the modest sample size and the lack of a control group. Inherent to the design of the previous studies, the included biologics were studied as one group and no subanalyses were performed on each biologic. In two smaller, retrospective studies on DR of adalimumab and etanercept, regaining adequate responses after resumption of the standard dose was also reported.^{6,7} In previous withdrawal studies, regaining adequate treatment responses after re-treatment was also reported.⁸ Future studies are needed to provide results on DR of the newer biologics (e.g., interleukin-17 and interleukin-23 inhibitors).

In conclusion, the results of this prospective evaluation of patients with psoriasis who resumed the standard maintenance dose after DR of adalimumab, etanercept or ustekinumab showed that most patients reached low disease activity again. Therefore, by following a controlled DR strategy, timely dose adjustments lead to restoration of adequate treatment responses, hence limiting long-term safety risks. These findings are reassuring for patients and clinicians who initiate DR of adalimumab, etanercept or ustekinumab.

Acknowledgments

We would like to thank Mascha Eilander, Department of Dermatology, Radboud University Medical Center, for her contributions to our dose reduction studies.

Table 1. Characteristics and disease activity measures of patients who discontinued biologic dose reduction

Characteristics	Total (n=59)
Demographic characteristics at baseline (start DR)	
Sex (male)	39 (66)
Age (years), median [IQR]	52.0 [43-60]
BMI (kg*m ⁻²), median [IQR]	28.3 [24-33] ^a
Treatment	
Adalimumab	23 (39)
Ustekinumab	20 (33)
Etanercept	16 (27)
Psoriatic arthritis (yes)	17 (28)
Concomitant methotrexate/acitretin	1 (2)
Disease activity measures	
PASI score at start DR, median [IQR]	2.4 [1.5-3.0]
PASI ≤5	59 (100)
PASI >5	0
PASI ≤3	47 (80)
PASI >3	12 (20)
PASI at stop DR, median [IQR]	4.1 [2.4 – 6.2] ^b
PASI ≤5	37 (69)
PASI >5	17 (31)
PASI ≤3	17 (32)
PASI >3	37 (68)
Delta PASI start DR – stop DR, median [IQR]	1.6 [0.4 – 3.5]
PASI 6 months after stop DR, median [IQR]	2.7 [2.0 – 4.0] ^c
PASI ≤5	43 (88)
PASI >5	6 (12)
PASI ≤3	30 (61)
PASI >3	19 (39)
Delta PASI start DR – 6 months after stop DR, median [IQR]	0.6 [-0.5 – 1.8]
PASI 12 months after stop DR, median [IQR]	2.4 [1.0 – 3.9] ^d
PASI ≤5	41 (84)
PASI >5	8 (16)
PASI ≤3	29 (59)
PASI >3	20 (41)
Delta PASI start DR – 12 months after stop DR, median [IQR]	0.0 [-0.8 – 1.5]

Data are presented as n (%) unless otherwise indicated. Abbreviations: BMI, body mass index; DR, dose reduction; IQR, interquartile range; PASI, Psoriasis Area and Severity Index.

Missing data (n): ^a2, ^b5, ^c11, ^d1.

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CHAPTER 3.3

Steps towards implementation of protocolized dose reduction of adalimumab, etanercept and ustekinumab for psoriasis in daily practice

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Abstract

Background

Dose reduction (DR) of adalimumab, etanercept and ustekinumab has proven to be (cost-)effective in psoriasis patients with low disease activity. Further implementation is needed to establish application of DR for eligible patients.

Objectives

To evaluate the implementation of protocolized biologic DR in daily practice.

Methods

A pilot implementation study was performed in 3 hospitals during 6months. By combining education and protocol development, involved healthcare providers (HCPs) were directed toward the adoption of protocolized DR. DR of adalimumab, etanercept, and ustekinumab was achieved by stepwise injection interval prolongation. Implementation outcomes (fidelity, feasibility) were assessed. Factors for optimizing implementation were explored in interviews with HCPs. Uptake was measured in patients by chart review.

Results

The implementation strategy was executed as planned. Implementation fidelity was less than 100% as not all provided tools were used across study sites. HCPs indicated the feasibility of implementing protocolized DR, although time investment was needed. Identified additional factors for successful implementation included support for patients, uptake of DR into guidelines, and supportive electronic health record systems. During the 6months intervention period, 52 patients were eligible for DR of whom 26 (50%) started DR. The proposed DR protocol was followed in 22/26 patients (85%) on DR.

Conclusion

Additional staff for support, extra time during consultations, education on DR for HCPs and patients, and effective tools such as a feasible protocol can lead to more patients on biologic DR.

Introduction

Dose reduction (DR) of the highly effective but expensive biologics for psoriasis could prevent overtreatment and result in more efficient use of these drugs. Previous studies showed that DR of the biologics adalimumab, etanercept, and ustekinumab is (cost-)effective in a substantial amount of psoriasis patients with low disease activity, without losing disease control.^{1,2} By following a disease-activity-guided DR protocol, the lowest effective dose can be achieved and timely actions can prevent the loss of adequate treatment responses.

Biologic DR is to some extent already performed in clinical practice. Practice is however heterogeneous, which may not always lead to safe and effective DR.³⁻⁵ Recommendations or guidelines are lacking. In order to standardize practice and establish the application of biologic DR for eligible patients, further implementation of protocolized DR into clinical practice is needed.

Factors that might influence the application of biologic DR in daily practice were previously explored by assessing the attitudes and behavior of dermatologists in national and international settings.^{3,4,6} Insight into factors influencing uptake of innovations into practice is important, as establishing the effectiveness of clinical innovations or incorporating innovations into guidelines does not guarantee uptake.^{7,8} Previously reported barriers to application of biologic DR among dermatologists were the belief that patients are not willing to reduce their dose, forgetting to discuss DR, lack of time, fearing reduced effectiveness, and lack of guidelines or scientific evidence.^{3,6} Our previous evaluation of a DR strategy of adalimumab, etanercept and ustekinumab in daily practice showed that performing such a strategy in daily practice was possible, but required some time investment.⁹ Based on these previously identified barriers, implementation of biologic DR could be improved by targeting healthcare providers' (HCPs) behavior with the provision of education and guidance.

Implementation research covers the field of research focusing on enhancing the uptake of research findings or innovations into routine practice.⁸ For better uptake of innovations, tailored implementation strategies can be developed which include methods or techniques used to enhance the adoption, implementation and/or sustainability of innovations into practice.^{10,11} For the development of such strategies, different frameworks or checklists exist of which constructs relevant to the specific context can be selected.¹²⁻¹⁶ These theoretical frameworks help to identify the most important barriers to change within a specific context, to develop a strategy with components targeting these barriers, and to select outcomes and guide data collection for appropriate evaluation of implementation processes.

In the present study, we conducted a pilot implementation study in a national setting. A multi-component implementation strategy was developed, which targeted several previously identified barriers to the application of DR among healthcare providers (HCPs) as described above. Components were based on a theoretical framework for effective implementation.¹³ Combining education, feedback, and development of local protocols, involved HCPs in 3 general hospitals were directed toward the adoption of protocolized DR of the biologics adalimumab, etanercept, and ustekinumab for patients with psoriasis. We aimed to evaluate the implementation process and explore possible factors for optimizing the implementation of biologic DR.

Materials and Methods

A pilot implementation study was performed in 3 general hospitals in the Netherlands during 6 months. Involved HCPs were directed toward adoption of protocolized DR of the biologics adalimumab, etanercept, and ustekinumab for psoriasis, using a multicomponent implementation strategy. DR was achieved by injection interval prolongation in two steps, leading to 67% and subsequently to 50% of the standard dose. Evaluation comprised two parts: 1) process evaluation focusing on fidelity and feasibility of the implementation strategy, and 2) effect evaluation comprising an explorative evaluation of the actual innovation uptake measured in patients (e.g., numbers of patients on biologic DR). Both quantitative and qualitative methods were utilized in order to provide broad insights into the implementation process. All used outcomes are described below.

This study was conducted according to the ICH GCP guidelines and the principles of the Declaration of Helsinki. The need for ethical approval was waived by the medical ethical committee Arnhem-Nijmegen (2021-8164). Local approval from the participating hospitals was requested. Written informed consent was obtained from all interview participants (part 1) and patients (part 2). Reporting follows the Standards for Reporting Implementation Studies (StaRI) statement,¹⁷ and the Standards for Reporting Qualitative Research (SRQR).¹⁸

Study setting and participants

Three hospitals were selected for participation. Eligible hospitals were general dermatology outpatient clinics with experience in treating psoriasis patients with biologics, without previous participation in clinical studies regarding protocolized DR. Participating hospitals were selected through the network of the Radboudumc and included Elizabeth-TweeSteden hospital Tilburg, Isala hospital Zwolle, and St. Antonius hospital Nieuwegein.

The implementation strategy was directed toward HCPs rather than directly at patients. Patient representatives from the national psoriasis patient association were however present within the overarching project team. This team also consisted of clinicians, researchers, and representatives from the Dutch dermatologists association, and was involved in steering different projects on biologic DR.

Dose reduction protocol

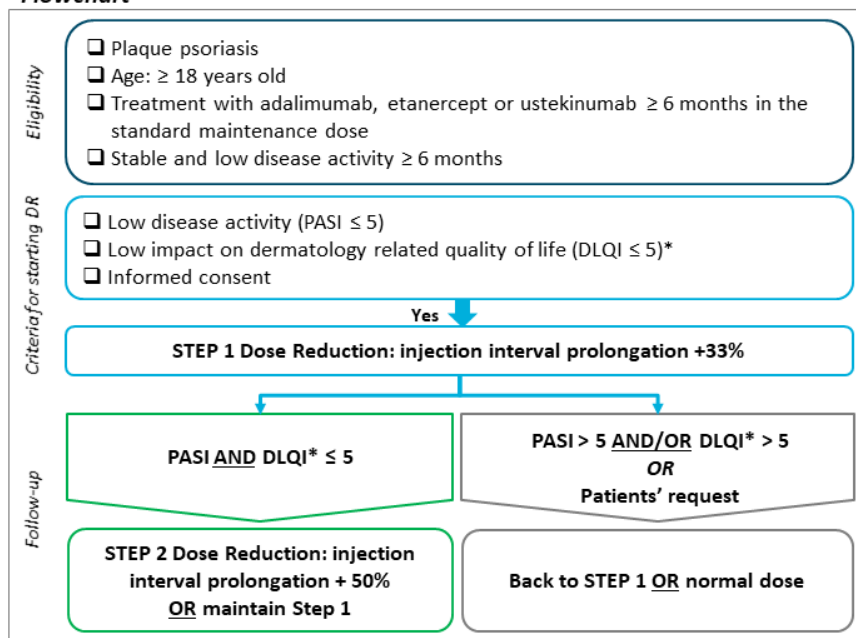
The studied innovation (e.g., protocolized biologic DR) focused on psoriasis patients with stable low disease activity for at least 6 months who were treated with adalimumab, etanercept, or ustekinumab in the standard dose for at least 6 months. The DR protocol was based on a previously conducted randomized trial.¹⁹ DR was achieved by injection interval prolongation to 67% and subsequently to 50% of the original dose when Psoriasis Area and Severity Index (PASI) (or description of disease activity) and preferably Dermatology Life Quality Index (DLQI) remained low (scores ≤ 5). DLQI was incorporated as a flexible criterion to improve the feasibility of the protocol. In case of scores >5 and/or at patients' request, the previous effective dose or normal dose was resumed. See **Figure 1** for the used DR protocol. Visit schedules were performed according to the usual practice in participating hospitals.

Implementation strategy

The used multicomponent implementation strategy combined education, feedback, and development of local protocols. This strategy was developed and provided by researchers (LvdS, JvdR, EdJ) with experience in performing protocolized biologic DR. The detailed content of the implementation strategy is presented in supplementary **Table S1**. Components of the strategy were based on the implementation framework of Flottorp et al.¹³ The strategy contained characteristics of an academic detailing approach, in which trained HCPs visit other HCPs to provide evidence-based information, tailored advice, and support according to the specific situation.²⁰ The strategy consisted of 5 meetings together with the development of local protocols and tools for the assistance of HCPs. Involved HCPs received a presentation with background information on biologic DR by the researcher, and local workflows were discussed. Tools included protocols, summary cards (**Figure 1**), patient information leaflets (**Figure S1**), and standardized texts for administrating DR procedures in patients' electronic health records. Tools were tailored to local situations. Feedback meetings were provided on group level split per participating hospital, and consisted of discussing local workflows, advice, and HCPs feedback on the implementation process. Outcomes of the effect evaluation (part 2) were provided at the final meeting. A summary of the planned strategy in each hospital is depicted in **Figure 2**.

PROTOCOL BIOLOGIC DOSE REDUCTION PSORIASIS
Adalimumab, etanercept, ustekinumab

Flowchart



Dose Reduction schedule per biologic

Biologic	Standard dose	STEP 1		STEP 2	
Adalimumab 40 mg	1x every 2 weeks	1x every 3 weeks		1x every 4 weeks	
Etanercept 50 mg	1x every week	1x every 10 days		1x every 2 weeks	
Ustekinumab 45 or 90 mg	1x every 12 weeks	1x every 15 weeks	1x every 18 weeks	1x every 21 weeks	1x every 24 weeks

*DLQI is not a prerequisite, but it is recommended to be performed apart from PASI.

Figure 1. Dose reduction protocol.

Abbreviations: PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index.

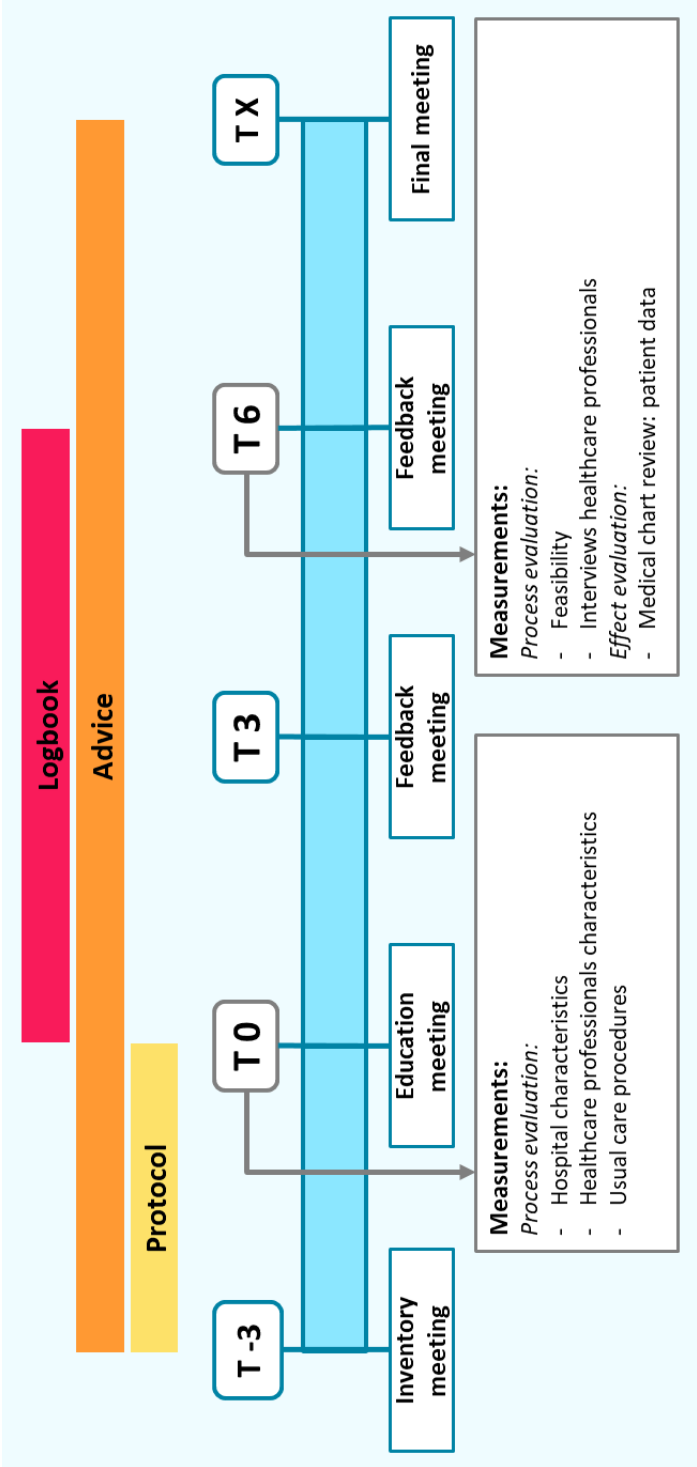


Figure 2. Summary and timeline of the implementation strategy.
Abbreviations: T, time in months.

Outcomes and data collection

Part 1. Process evaluation

Quantitative

Several outcomes were selected in order to evaluate the implementation process. These implementation outcomes were drawn from different implementation theories.^{11,16,21,22} First, sample characteristics (hospital characteristics, usual care procedures, and characteristics of involved HCPs) were assessed at baseline (T0, **Figure 2**). Second, implementation fidelity was measured. Implementation fidelity captures the degree to which an implementation strategy is delivered as prescribed.^{11,22} It was registered by using a logbook whether the strategy was executed according to schedule and what tools were developed and actually used. Third, the feasibility of the implementation process was evaluated. At the month 3 and 6 feedback meetings (T3, T6, **Figure 2**), the experiences of involved HCPs were asked by short questions covering feasibility and time investment. Data were pseudonymized and collected using a web-based data management system (www.castoredc.com).

Qualitative

Involved HCPs participated in semi-structured qualitative interviews (T6, **Figure 2**) in order to evaluate feasibility of the implementation process, and to explore possible factors for optimizing implementation of biologic DR. An interview topic guide was developed by the researchers (LvdS, JJ), and focused on general views toward the implementation strategy, acceptability, feasibility, and complexity of the intervention. Interviews were held by telephone by one researcher (LvdS). A sample size was not predefined, but all HCPs involved in the study were invited to participate.

Part 2. Effect evaluation

Actual uptake or adoption of the implemented innovation was measured in patients using data from medical charts. As this was a pilot study, we performed an explorative analysis of the percentage of patients starting biologic DR during the intervention period ('post-intervention'), as well as the percentage of patients eligible for DR but who did not initiate DR during the intervention period. It was assessed if the proposed DR protocol was followed and if outcome measures (PASI, DLQI) were used. Here, the main goal was to assess uptake of the implemented DR protocol and not to evaluate DR effectiveness or safety in patients. Data of patients on adalimumab, etanercept, and ustekinumab who provided written informed consent were collected in 2 participating hospitals (Elizabeth-TweeSteden hospital Tilburg and Isala hospital Zwolle) through retrospective medical chart review. One hospital was excluded from this analysis as local arrangements could not be made. Included patients were not

necessarily candidates for biologic DR, as all patients using adalimumab, etanercept, or ustekinumab were invited to participate. Collected patient characteristics included age, sex, body mass index (BMI), type of biologic, duration of psoriasis until the start of biologic, psoriasis subtype, comorbidities such as psoriatic arthritis (PsA), history of previous biologic use, concomitant systemic psoriasis treatment, baseline PASI and DLQI and previous DR. Baseline characteristics were collected from the last available visit before the start of the intervention period with a window of one year. During the intervention period, collected data included type of biologic, biologic dose, disease activity measures, and DR or biologic discontinuation with corresponding reasons upon availability. Here, data of the patients' most closely situated visit to the end of the 6 months intervention period was used. Data were pseudonymized and collected using a web-based data management system (www.castoredc.com).

Analysis

Part 1. Process evaluation

Quantitative data were summarized. Qualitative data from the interviews were analyzed using inductive thematic analysis,²³ with ATLAS.ti software. Interviews were audio-recorded, transcribed verbatim, checked for accuracy against the audio recordings and pseudonymized. Two researchers (LvdS, JJ) analyzed the first three transcripts independently (open coding). All other transcripts were coded by one researcher (JJ) and reviewed by another researcher (LvdS). Differences were discussed until consensus was reached. Based on the initial codes, the next transcripts were systematically coded (axial coding). Newly identified themes were added to the code list, using an inductive approach without trying to fit data into any predetermined category. Analysis resulted in a list of themes influencing the implementation of biologic DR. Corresponding quotes were selected from the interviews, and were translated into English. Final results were presented to participants in order to check for accuracy.

Part 2. Effect evaluation

Quantitative data were analyzed using descriptive statistics in SPSS Statistics 25 (IBM, Armonk, NY, USA). Baseline patient and treatment characteristics were summarized. Depending on the type of variable and its distribution, descriptive statistics are presented as percentages with absolute numbers, means with 95% confidence intervals (CI) or medians, and interquartile ranges (IQR). Proportions of patients on lowered dosages, and proportions of patients eligible for DR during the intervention period according to the proposed protocol (plaque psoriasis, sustained low disease activity ≥ 6 months, use of the standard maintenance dose ≥ 6 months, low impact of psoriasis on patients' dermatology-related quality of life, no failed previous DR attempt)

were calculated. Reasons for DR ineligibility were summarized. It was assessed if the proposed DR protocol was followed based on used dosing schedules and whether criteria were met. Additionally, it was counted if PASI and DLQI were measured.

Results

The study took place in 3 regional outpatient dermatology departments. Inventory meetings were held in April 2021 (hospitals 1 and 3) and May 2021 (hospital 2). The intervention period of 6 months (e.g., actual implementation of the DR protocol) started after education meetings in June 2021 (hospital 2) and July 2021 (hospitals 1 and 3).

Part 1. Process evaluation

Sample characteristics

Table 1 shows the characteristics of participating hospitals. Before the intervention period, PASI and DLQI were performed in 2 out of 3 participating centers, of which one center had automated PASI and DLQI calculations available in the electronic health record. DR was already performed, but not on a standard(ized) basis. No local protocols were available. Two hospitals reported initiating DR when patients had sustained low disease activity for at least 6 months.

Table 1. Baseline characteristics of participating hospitals and usual care procedures

	Hospital 1	Hospital 2	Hospital 3
Hospital type	Non-academic	Non-academic	Non-academic
PASI performed	Yes	No	Yes
PASI calculation available in electronic health record	Yes	No	No
DLQI performed	Yes	No	Yes
DLQI calculation available in electronic health record	Yes	No	No
DR performed	Yes	Yes	Yes
Time per outpatient visit (dermatologist), minutes	10	10	10
Time per outpatient visit (nurse/nurse practitioner), minutes	20	15	30
Mean number of outpatient visits for psoriasis patients on biologic treatment per year	3	2	3
Total number of patients per biologic			
Adalimumab	29	152	75
Etanercept	6	11	12
Ustekinumab	179	37	78

Abbreviations: PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; DR, Dose Reduction.

Implementation fidelity

All components of the implementation strategy (**Figure 2**) were delivered to participating sites. Education meetings (T0) were provided on site for hospital 1 and 3, and online for hospital 2. A total number of 5 meetings were proposed (**Figure 2**), but short additional online meetings were scheduled for each center to discuss the local workflow, resulting in 6 meetings per site. The research team provided additional support by e-mail. HCPs primarily involved in psoriasis care and responsible for the execution of the study participated in all meetings and in individual interviews. Other HCPs from participating centers were updated in regular team meetings by colleagues involved in the project. After the first feedback meeting (T3), hospital 1 reported to have used all provided tools, hospital 2 only used the protocol, patient information leaflet, and administration text, and hospital 3 used the summary card and patient information leaflet. As not all provided tools were used, fidelity was less than 100%.

Feasibility of the implementation process

At feedback meetings (T3, T6), HCPs indicated feasibility of implementation of the DR protocol, but extra time for patient education and adjusting prescriptions was sometimes needed. Moreover, adjustment of proposed protocols to the local situation and dissemination at the local workplace required some time investment for involved HCPs. In hospital 2, performing PASI and DLQI was not always possible due to a lack of time and lack of options to calculate scores within the used electronic health record system. It was however described in words whether patients had low disease activity in the individual health record. For hospital 1, DR was mainly applied to patients on ustekinumab, as those patients visited the hospital more frequently on a clustered outpatient clinic compared to patients on adalimumab or etanercept.

Interviews with involved healthcare providers

Ten HCPs (**Table 2**) participated in individual interviews between January and April 2022 (T6). The (sub)themes developed in the qualitative analysis with corresponding illustrative quotes are presented in **Table 3**. Main themes were divided into barriers and facilitators to the implementation of biologic DR.

Table 2. Summarized characteristics of involved healthcare providers

Characteristic	Total n=10
Sex (female)	8
Age (years), median (range)	58.5
Profession	
Dermatologist	3
Nurse practitioner	3
Nurse	2
Medical assistant	2
Professional experience (years)	
5-10	2
10-15	1
15-20	2
>20	5
Experience with biologic treatment (years)	
0-5	2
5-10	1
10-15	2
15-20	5
Experience with biologic DR (yes)	7

Data are presented as N unless otherwise indicated. Abbreviations: DR, dose reduction.

Participating HCPs reported a lack of routine and experience with DR and a lack of knowledge on DR as barriers to implementation of biologic DR. Education, awareness and familiarity could act as enhancers. Participating HCPs valued the developed tools, as these tools provide support for the clinician and the patient, make DR feasible and ensure that DR is applied more frequently. Repeated education and participation in research projects about DR could facilitate further implementation of biological DR according to participants. They suggested that besides the provided information on DR, further and future access to knowledge remains important and could be achieved by means of scientific publications, conference presentations, and the uptake of biologic DR in treatment guidelines.

Among factors influencing implementation of biologic DR according to involved HCPs were also patient-related factors. Participants reported that disbeliefs about DR among patients, fear of disease flares, and positive experiences with biologics (e.g., no side effects and high effectiveness) could contribute to patients' unwillingness to try DR. Sufficient patient education and involvement of patients in decision-making were suggested as facilitators by participating HCPs. They also reported that the provided patient information leaflets were useful for patients. Moreover, it was suggested that informing patients about DR at start of biologic treatment might be helpful, as well as providing information in one consultation and initiating DR at the next consultation. During DR, offering healthcare access

and communication or tools about new dosing schedules seemed important for patients according to involved HCPs.

Complexity of the DR protocol and incompatibility with current practice were identified factors that could limit implementation. It was mentioned that performing PASI and DLQI is more difficult than globally estimating disease activity and DR eligibility, specifically when scores cannot easily be processed within electronic health records. Performing the scores requires some time-investment and change of practice when not performed on a regular basis yet. Besides the scores, extra time might be needed for patient education and for modifying prescriptions. Among facilitators to overcome these barriers was the availability of staff for support. In case dermatologists are lacking time for installation of DR, it was suggested that other staff members such as nurses could perform patient education and clinical measurements. Furthermore, it was brought up that IT solutions such as availability of an automated PASI and DLQI scoring system and an automated decision aid within the electronic health record for checking DR eligibility could be useful. Regarding proposed dosing schedules, some participants reported that the DR steps for ustekinumab were too large (e.g., from 12 weeks to 18 weeks and subsequently to 24 weeks) or steps were taken too soon, as it might be difficult to motivate patients toward these large steps. As such, intermediate steps were preferred by participants.

Part 2. Effect evaluation

Patient characteristics and outcomes split per participating hospital are presented in **Table S2**. For the effect evaluation, 109 patients from 2 participating hospitals provided informed consent for data collection from their medical records. As in 8 patients no follow-up visits were available, 101 patients were included for analysis. See **Figure 3** for a graphical overview.

At baseline (e.g., before the start of the intervention period), 49 of 101 included patients (48.5%) were ineligible for DR, due to the fact that they already used a lowered dose (n=27), or did not fulfill the criteria for DR (n=18), or failed a previous attempt for DR (n=4) (**Figure 3**). During the intervention period of 6 months, 52 of 101 included patients (51.5%) were eligible for DR. In total, n=26 (50% of eligible patients) started with DR during the intervention period. The other 26 eligible patients did not start DR. Available reasons for not starting DR were: patients being afraid of psoriasis flares (n=2), experiencing increased psoriasis or itch at end of injection interval (n=2), and not willing to start DR during the winter period (n=1).

The proposed DR protocol was followed in 22 out of 26 patients (84.6%) who started DR during the intervention period. Four patients used other ustekinumab dosing schedules and one patients also not reached stable low disease activity for 6 months yet but did start DR. In hindsight, 12 out of 27 patients (44.4%) who already used a lowered dose at baseline followed the protocol. After the intervention, considerably more outcome measures (PASI, DLQI) were performed than at baseline of the intervention (**Table S2**). However, scores were still not measured in all patients on DR. Of note, according to the protocol, DLQI was not a prerequisite but was recommended to be performed apart from PASI.

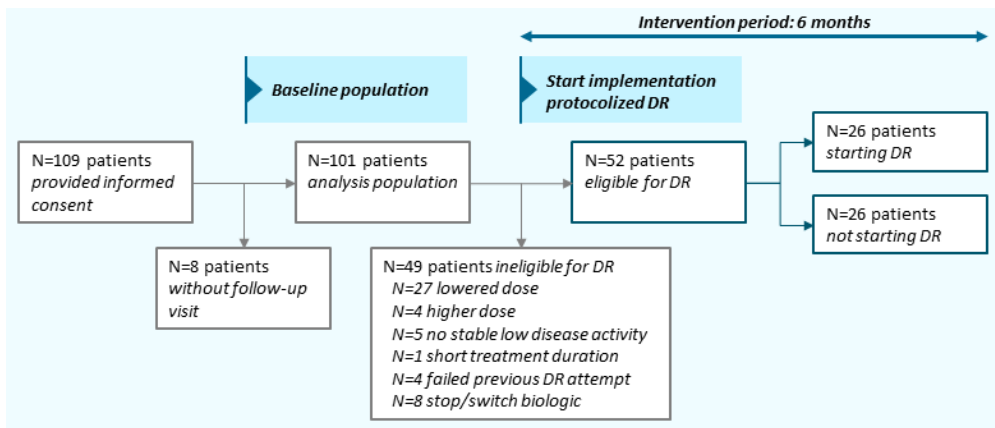


Figure 3. Flow chart of included patients, patients eligible for DR and patients starting DR during the intervention period.

Patient data were collected in 2 hospitals. Abbreviations: DR, dose reduction. DR eligibility was based on the following criteria: plaque psoriasis, sustained low disease activity ≥ 6 months, use of the standard maintenance dose ≥ 6 months, low impact of psoriasis on patients' dermatology-related quality of life, no failed previous DR attempt.

Table 3. Overview of (sub)themes and corresponding quotes resulting from the interviews

Theme	Subtheme	Quote
Healthcare providers' barriers	Lack of awareness and familiarity	'Everyone knows about the DR protocol, but from experience we have learned that it declines, specifically with the dermatologists. Therefore, I recall it from time to time, for example within staff meetings.' [HCP9]
	Lack of knowledge and disbeliefs about DR	'At first, I thought it to be a large step for those patients: how will I explain this to patients if I think to myself that it won't be possible? You will convey these feelings to your patients somehow.' [HCP4]
	Positive experiences with biologic treatment	'Effects are so good, and they have so little side effects of the medication, that's the largest advantage of biologics over for example methotrexate. And they are so happy with that.' [HCP2]
Patients unwillingness to try DR	Patients' disbeliefs about DR	'Look, there are patients who are saying: this might be a financial advantage for the hospital. Then I just think, well yes, it is an advantage for the hospital but it is also beneficial for yourself.' [HCP7]
	Fear of disease flares	'People who don't dare it at all; you can't convince them. They are so afraid to get back to the situation of having so much limitations in daily life. They just don't dare it.' [HCP2]
Practical issues	Incompatibility of the DR protocol with current practice	'Patients visit the doctor or the nurse practitioner at least once a year, but at the doctors' consultation, PASI or DLQI scores are not performed. It's just because all patients are scattered across different locations and different colleagues, DR is more difficult to apply.' [HCP1]
	Complexity of the DR protocol	'We then just check with the patient how they think it's going, what they think themselves, and if you see during the physical examination that the psoriasis is cleared, you can decide to start dose reduction.' [HCP3]
	Lack of time	'The consulting hours are very busy and you have different patients every 10 minutes. The challenge is to sit down and really take the time to explain these things.' [HCP6]
	Lack of available resources	'Your system must be in order to make sure you won't lose time when processing PASI and quality of life scores, that kind of things. That it just works efficiently, that's the most important thing because then it will be possible to integrate it into your consultations.' [HCP2]

Table 3. Continued

Theme	Subtheme	Quote
Healthcare providers' facilitators	Positive beliefs in the concept of DR	'Less injections are beneficial for patients. Furthermore, dose reduction will reduce costs, which is a good thing as consequently, we can keep prescribing biologics for patients who need them. [...] Yes, I can only see advantages of dose reduction.' [HCP5]
	Awareness and familiarity with DR	'If you will just keep informing each other and everyone will keep paying attention to dose reduction, then I think it will be possible. The whole team, all involved colleagues and dermatologists should stay involved.' [HCP8]
	Access to knowledge and education	'A clear explanation on beforehand is very important. It will make sure that you will be convinced about dose reduction yourself. This is important, as patients will feel it when you will not be convinced yourself. So I think that understanding dose reduction and being convinced about it yourself is very important.' [HCP4] 'Such a protocol as was proposed, maybe with reminders or mentioning it again in another staff meeting in order to get the information into everyone's heads again. Or through an article in our dermatologists' magazine, or at conferences. Yes, those should be the communication channels I think. Or maybe also a webinar.' [HCP6]
	Availability of tools and guidance	'Well, it helps when you are having clear guidance on how to apply dose reduction. And that it is nationally acknowledged, so that you are not doing it randomly.' [HCP8]
Facilitators	Available staff for support	'From experience, educating patients can best be delegated to nurse practitioners or nurses. You can shortly address dose reduction to patients and the nurse will do the refinements. It just takes too much time. Patients may have a lot of questions and before you know it 10 minutes will be gone, while you already are running out of time.' [HCP6]
	Availability of resources	'What helps is when your system works well, in a way that you can just work efficiently.' [HCP2]
	Patient involvement in the decision-making process	'In one consultation, we prepare patients towards dose reduction. As such, they will have the possibility to think about it and they will get used to it. Within the next visit, we will start with dose reduction. As such, patients can get used to the idea.' [HCP10]
Providing support for patients	Patient education	'We have leaflets on our desks and at the time of discussing dose reduction I present the leaflet to the patient. You can also point out the steps. It is just a really clear description and also measurable. Maybe it sounds stupid, but it's not a black-and-white copy but in real colors, that may also play a role. Speaking for myself, a colorless copy will provide less confidence than a clear leaflet in full color.' [HCP1]
	Patients' positive attitudes towards DR	'And eventually, everyone will feel the need to use less medications, that is some kind of a standard opinion in my experience. People want to take as little as possible.' [HCP2]

Abbreviations: DR, dose reduction; HCP, healthcare provider.

Discussion

This study aimed to investigate the implementation of protocolized DR of adalimumab, etanercept, and ustekinumab for patients with psoriasis in 3 general hospitals. Evaluation of the implementation process showed that a multicomponent implementation strategy including education for HCPs and provision of tools for assistance promoted uptake of protocolized DR. Different components of the implementation strategy were executed as planned and after the intervention, the proposed DR protocol was followed in the majority of patients that initiated DR.

Several additional factors for optimizing implementation of biologic DR were identified from interviews with involved HCPs. Among these factors was the need for staff for support, such as nurses who can provide patient education on DR. Another identified factor that could assist HCPs when performing DR was the availability of effective solutions within electronic health record systems such as decision aids or reminders together with the possibility for calculating scores (e.g., PASI and DLQI). This finding corresponds with previous rheumatological studies, which reported that issues with electronic health records could limit the uptake of dose optimization strategies, and providing treatment advice within electronic health records resulted in increased adherence to such a strategy.^{24,25} Besides these organizational factors, factors arising at the patients' level were deemed important as well according to involved HCPs. HCPs suggested that informing patients at the treatment start, performing shared-decision making, and providing support by offering healthcare access and tools for new dosing schedules could be of added value for further uptake of protocolized biologic DR. Addition of these organizational and patient-related factors to our developed implementation strategy could as such promote further implementation of biologic DR.

Our effect evaluation of uptake of the DR protocol in daily practice revealed that after the intervention, the proposed DR protocol was followed in most patients on DR. Our data suggest that the implementation strategy resulted in increased numbers of patients on protocolized DR per timespan. During the relatively short intervention period of 6 months, 26 patients (25.7% of the total population) started DR. Before the intervention period, 27 patients were on a lowered dose, but this time period covered a maximum of one year before the intervention period, resulting in a larger time-window in which DR could have been initiated. Although we were not able to calculate the numbers of patients initiating DR per time unit, this indicates that our intervention led to a sharp increase of patients starting DR within 6 months. Due to the fact that some active patients had not visited the outpatient clinic during the intervention period, the total number of patients that could reduce their dose could

have been higher with a longer follow-up. Among eligible patients were however patients unwilling to start DR. We also have previously demonstrated that a number of patients with psoriasis might not be willing to initiate DR due to fear of disease flares.⁹ This emphasizes that patient education is an important target for effective implementation, as information on the actual (low) risk of DR failure and the high probability of regaining low disease activity afterward is relevant for patients to balance the risks and benefits of DR.^{1,26,27}

As stated above, the proposed DR protocol was followed by HCPs in the majority (85%) of patients on DR. However, practice was heterogeneous across participating hospitals and clinical scores were not always performed. For ustekinumab, alternative dosing schedules were used sometimes, mostly consisting of subsequent injection interval prolongations of two weeks. HCPs indicated several barriers to the performance of the scores, including a lack of time and options to process scores within used electronic health record systems. The latter may explain why clinical scores were less frequently measured in hospital 2, where no automated calculations were available within the electronic health record system. Time constraints have previously been identified as a barrier for performing biologic DR in daily psoriasis care.^{3,6,9} However, in the light of potential cost savings resulting from DR, the question arises if HCPs should be given extra time in order to apply DR. Another possible solution would be the reported availability of staff for support of dermatologists or efficient IT solutions. It can however also be debated if more flexible approaches to the use of DR eligibility criteria should be allowed. However, use of clear criteria could enable timely actions to prevent disease flares.²⁶ Involved HCPs also reported that initiating DR based on outcome measures (e.g., PASI, DLQI) is more objective and transparent for both patients and clinicians, and scores make it possible to compare assessments between consultations. A possible solution here would be the use of less time-consuming outcome measures such as Physician Global Assessments (PGA) of disease severity.

A strength of our study is the combined evaluation of the implementation process itself and the actual uptake of protocolized biologic DR in clinical practice. Data were collected using both quantitative and qualitative methods, which broadened our findings. Combining both methods can provide unique insights in multifaceted phenomena such as implementation processes. In our study, qualitative analysis of interviews with involved HCPs enabled an in-depth evaluation of the implementation process and provided insight into relevant factors outside the targeted components of our implementation strategy. For future research, it could be considered to use focus groups instead of individual interviews in order to explore interactions between

participants and elaborate on solutions for identified barriers.²⁸ We developed a multicomponent implementation strategy that targeted several possible barriers for change. Such multicomponent strategies are more effective than simple approaches for the implementation of innovations in healthcare.^{14,15} Our used implementation components and identified additional factors influencing effective implementation of protocolized DR could help inform future efforts to implement DR on a larger scale.

This study also has its limitations. First, the implementation strategy was tested in a specific, national setting. This could influence generalizability to other healthcare systems as results of implementation processes are dependent of organizational and contextual aspects.¹³ Second, our intervention period was relatively short. This might have limited the actual uptake of the DR protocol and resulted in a possible underestimation. As some patients had no follow-up visit available, DR could not yet have been initiated in these patients. Third, due to the uncontrolled design, we were not able to conclude which part of our strategy was most effective nor to define a causal relationship between the intervention and results as theoretically, other factors in the intervention period could have influenced results. Additionally, not all provided tools were used across participating hospitals. Last, we were only able to analyze patient data of patients who provided informed consent, resulting in a response rate of approximately 30%. Hence, analyses were explorative and no precise estimations of differences between before- and after measures could be made.

In conclusion, results of our pilot study demonstrated feasibility of a strategy to implement protocolized biologic DR for patients with psoriasis in daily dermatological practice. Provision of protocols, patient information leaflets, and education for HCPs were important tools for implementation of DR, and led to an increase of patients that underwent protocolized DR of the biologics adalimumab, etanercept or ustekinumab. Important factors for further dissemination of protocolized biologic DR into practice may include the availability of additional staff for support of physicians and patients, extra time during consultations, uptake of DR into treatment guidelines, and effective tools such as feasible protocols and IT solutions. An integrated approach combining these relevant factors in the context of the targeted healthcare setting together with the involvement of relevant stakeholders could lead to increased numbers of patients on protocolized biologic DR. Eventually, this will lead to decreased long-term drug exposure for our patients and substantial cost savings.^{2,9}

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patients' association (Psoriasispatiënten Nederland) and with the Dutch Association for Dermatology and Venereology in the overarching project team involved in different projects on implementation of biological dose reduction in the Netherlands.

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Supplement

Dose reduction of biologics in adult patients with moderate to severe psoriasis

You are treated with one of the following biologics for your psoriasis: adalimumab, etanercept, or ustekinumab.

What are biologics?
Biologics are medicines that have been designed to treat psoriasis. They work by specifically targeting proteins in the body which are involved in inflammation. By blocking these proteins, biologics can improve symptoms of psoriasis. Biologics may decrease the body's ability to fight infections. Among the most frequently reported side effect are mild infections such as cold and flu symptoms.

Dose reduction of biologics
The goal of dose reduction of biologics is to strive for the lowest but still effective dose. Previous research has shown that the dose can be reduced in a part of the patients with psoriasis, while the treatment effect remains good. With dose reduction, the risk of side effects will be reduced. The societal healthcare costs will also decrease with the application of dose reduction.

If your psoriasis is clear or almost clear for at least 6 months when using the standard dose, we will try to reduce the dose. The dose will be reduced by extending the time between the injections, in two steps. By reducing the dose carefully in two steps, you will eventually receive the lowest, effective dose. The biologic will not be stopped, because we know that psoriasis will then eventually return.

What if my psoriasis worsens?
If your psoriasis worsens when using a lowered dose or in case you do not feel comfortable with using the lowered dose, the dose can be increased or the standard dose can be resumed in consultation with your treating healthcare professional.

Dose reduction of biologics in adult patients with moderate to severe psoriasis

You are treated for at least 6 months with a biologic and the treatment effect is good.



Biologic



6 months



Good effect



Your treating healthcare provider will discuss dose reduction of your biologic with you.



STEP 1 dose reduction



At the next appointment, your treatment effect will be evaluated. The next step will be discussed with you.

Still a good effect?
The dose can be further reduced.
Or you remain at STEP 1.



Less treatment effect?
You may return to your previous dose.





STEP 2 dose reduction

Figure S1. Patient information leaflet

English translation of the used patient information leaflet. Of note, this leaflet is a generic example and does therefore not include dosing schedules per biologic. Within the implementation pilot, different versions per biologic were provided with inclusion of dosing schedules per biologic.

Table S1. Implementation strategy: components and theoretically based barriers that are targeted

Components	Barriers that are targeted ¹
Inventory First meeting to make an inventory of the situation in the hospital and make a planning for the total project.	• Feasibility: local situation is specific for each hospital, tailoring is needed. • Source of the recommendation: do the organisation(s) and people who made the recommendation have credibility with the targeted healthcare providers? • Effort: what amount of effort is required to change or adhere?
Education Distribution of relevant documents/ articles, presentation with overview of the literature about tightly controlled biologic dose reduction in psoriasis patients.	• Lack of knowledge: tailored information or education that helps the targeted healthcare providers to fit the recommended behaviour into their current practice is needed. • Lack of awareness and familiarity. • Compatibility of recommended protocol with current practices. • Lack of patients motivation: provide the targeted healthcare providers with aids or strategies to motivate patients.
Protocols Development of, and agreement on, relevant local treatment protocols.	• Lack of assistance for clinicians: healthcare providers have no protocols to help them adhere to the recommendations. • Feasibility: ensuring that clinical intervention is practical for optimal adherence.
Feedback Feedback meetings including provision of advice, discussing local workflows, and involved healthcare providers' feedback on the implementation process after 3 and 6 months.	• Lack of insight into own practice, incl. visibility of benefits of the new strategy.

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Table S2. Patient and treatment characteristics split per participating hospital

	Hospital 2 (n=55)	Hospital 3 (n=54)	Total (n=109)
Baseline characteristics			
Sex (female)	21 (38.2)	23 (42.6)	44 (40.4)
Age (years), median (IQR)	57 (46 – 68)	58 (49 – 65)	58 (47.5 – 66)
BMI (kg/m ²), median (IQR)	27 (24.5 – 29.4) ^a	29 (26.1 – 34.9) ^b	27.6 (25.1 – 30.5) ^c
Disease duration (years)	16 (13 – 26) ^d	27 (16.3 – 40.7) ^e	20 (14 – 33) ^f
Psoriasis subtype (current)			
Plaque psoriasis	53 (96.4)	46 (85.2)	99 (90.8)
Plaque psoriasis and other subtype	2 (3.6)	4 (7.4)	6 (5.5)
Other subtype ^g	0	4 (7.4)	4 (3.7)
Comorbidities			
Psoriatic arthritis	14 (26.4) ^h	11 (20.4)	25 (22.9) ⁱ
Other spondyloarthropathy	0	1 (1.9)	1 (0.9)
Hidradenitis suppurativa	0	0	0
Inflammatory bowel disease	2 (3.6)	0	2 (1.8)
History of previous biologic use (yes)	19 (34.5)	23 (42.6)	42 (38.5)
Current treatment			
Adalimumab	44 (80)	21 (38.9)	65 (59.6)
Etanercept	3 (5.5)	5 (9.3)	8 (7.3)
Ustekinumab	8 (14.5)	28 (51.9)	36 (33)
Treatment duration (years), median (IQR)	3.1 (1 – 8.3)	5.6 (2.5 – 8.7)	4 (1.4 – 8.3)
Previous DR			
Yes, successful	11 (20)	18 (33.3)	29 (26.6)
Yes, unsuccessful	5 (9.1)	17 (31.5)	22 (20.2)
No, not discussed	28 (69.1)	19 (35.2)	57 (52.3)
No, patient was not willing	1 (1.8)	0	1 (0.9)
Comedication			
Methotrexate	0	1 (1.9)	1 (0.9)
Acitretin	0	1 (1.9)	1 (0.9)
Prednisolone	0	1 (1.9)	1 (0.9)
None	0	51 (94.4)	106 (97.2)
Patients on lowered dose at baseline	8 (14.5)	19 (35.2)	27 (24.8)
Adalimumab ^j	8 (18.2)	6 (28.6)	14 (21.5)
Etanercept ^j	0	1 (20)	1 (12.5)
Ustekinumab ^j	0	12 (42.9)	12 (33.3)
Outcome measures used (patients on lowered dose)			
DLQI	0	14 (73.7)	14 (41.9)
PASI	0	8 (42.1)	8 (29.6)

Table S2. Continued.

	Hospital 2 (n=55)	Hospital 3 (n=54)	Total (n=109)
Effect evaluation outcomes (intervention period)			
Patients starting DR	14 (25.4)	12 (22.2)	26 (23.9)
Adalimumab ⁱ	12 (27.3)	6 (28.6)	18 (27.7)
Etanercept ⁱ	1 (33.3)	0	1 (12.5)
Ustekinumab ⁱ	1 (12.5)	6 (21.4)	7 (19.4)
DR protocol followed (patients on DR) ^k	14 (100)	8 (66.7)	22 (84.6) ^l
Outcome measures used (patients on DR)			
DLQI	11 (78.6)	10 (83.3)	21 (80.8)
PASI	6 (42.9)	6 (50)	12 (46.2)

Data are presented as N (%) unless otherwise indicated. Abbreviations: BMI, body mass index; DR, Dose Reduction; DLQI, Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index. Missing data (N): ^a22, ^b46, ^c68, ^d12, ^e18, ^f30, ^g2, ^h2. ^gReported psoriasis subtypes included inverse psoriasis, nail psoriasis, palmoplantar psoriasis, and palmoplantar pustulosis. ^hProportions were calculated based on numbers of patients per biologic. ^kDR protocol was followed when proposed dosing schedules were used and when criteria were met. ^lN=4 patients used other DR dosing schedules and N=1 also not reached stable low disease activity for 6 months yet but did start DR. In case PASI scores were not performed it had to be reported that psoriasis was (almost) clear in order to follow the proposed protocol.



CHAPTER 3.4

National consensus on biologic dose reduction in psoriasis: a modified eDelphi procedure

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Abstract

Background

Dose reduction of biologics for psoriasis is applied in daily practice, although guidelines are lacking. Striving for clear criteria is important, as it leads to a consistent application of dose reduction.

Objective

To achieve consensus on criteria for biologic dose reduction in psoriasis patients with stable and low disease activity.

Methods

An online Delphi procedure (eDelphi) was conducted. Dutch dermatologists were invited to participate in a maximum of 3 voting rounds. Proposed statements were selected based on literature review and included criteria for the application of dose reduction and dosing schedules. Biologic dose reduction was defined as 'application of injection interval prolongation'. Proposed statements were rated using a 9-point Likert scale; consensus was reached when $\geq 70\%$ of all voters rated 'agree' (7–9) and $< 15\%$ rated 'disagree' (1–3).

Results

A total of 27 dermatologists participated and reached a consensus on 15 recommendations over 2 voting rounds. Agreed statements included criteria for dose reduction eligibility, criteria for dose reduction (dis)continuation, and dosing schedules for adalimumab, etanercept, and ustekinumab. Based on the eDelphi outcomes, an algorithm fit for implementation in current practice was developed.

Conclusions

Recommendations of this national consensus process can guide clinicians, and consequently their patients, toward consistent application of biologic dose reduction.

Introduction

Biologics are effective but expensive drugs for patients with moderate-to-severe psoriasis.¹ As psoriasis is a chronic disease with a large impact on a patient's quality of life, lifelong treatment is mostly needed for long-term disease control. Treatment with a fixed dose may however not be necessary for patients with good treatment responses, as some patients may be overtreated.² Dose reduction (DR) of biologics for psoriasis patients with low disease activity is a possible solution for more efficient use. Overtreatment might be prevented and healthcare costs can be reduced when striving for the lowest effective dose.^{3,4} Guidance is however needed, as DR could theoretically lead to loss of disease control.

Dose reduction by injection interval prolongation of adalimumab, etanercept, and ustekinumab is possible in patients with low disease activity without losing disease control, but success rates differ based on success definition, DR strategy, and study design.^{3,5-7} In a previously conducted randomized trial, no differences in persistent disease flares were observed between patients on DR vs. patients on the standard maintenance dose of adalimumab, etanercept, or ustekinumab.⁸ Most studies described a minimal treatment duration and/or stable low disease activity of 6–12 months prior to DR, and the biologic dose was mostly reduced gradually in fixed steps leading to 67% and 50% of the original dose. Regaining adequate treatment responses after the resumption of the standard dose in case of relapse due to DR was described in several studies.^{7,9-11} For the relatively newer biologics (e.g., IL-17 and IL-23 inhibitors), data are sparse.¹²⁻¹⁵

At present, DR is performed in daily practice but clear criteria have not been elaborated in clinical guidelines.^{6,7,16-18} A recently performed national survey among 114 dermatologists in the Netherlands showed that biologic DR was already practiced by the majority of respondents, most frequently for the biologics adalimumab, ustekinumab, and etanercept.¹⁹ There was a variation in the used criteria for starting and stopping DR. In total, 78% of all respondents felt the necessity of a guideline on biologic DR, with scientific evidence and practical advice. Internationally, a survey among 53 dermatologists revealed that 66% performed DR, mainly for the biologics adalimumab, etanercept, ustekinumab, and secukinumab.²⁰ Again, the criteria for the application of DR differed between respondents. Among the barriers to the application of DR was the lack of guidelines or scientific evidence.

For further uptake of biologic DR into clinical practice, it is important to strive for clear criteria that guide healthcare professionals, and consequently their patients, toward safe application of DR. As criteria for applying DR and the actual manner of reducing

dosages varied between studies and among dermatologists, agreement upon criteria for practicing DR should be achieved among involved healthcare professionals, supported by the existing evidence. Therefore, the aim of the current study was to achieve consensus among Dutch dermatologists on criteria for biologic DR in psoriasis patients and propose an algorithm fit for implementation in current practice.

Materials and methods

An online Delphi procedure (further referred to as ‘eDelphi’) was conducted. The Delphi approach comprises sequential questionnaires answered by experts. Gradually, consensus evolves as the range of answers decreases and the group converges toward a consensus opinion over the course of several rounds.^{21,22} See **Figure 1** for a graphical overview of the study design. This study was conducted according to the ICH GCP guidelines, and the principles of the Declaration of Helsinki. Data collection was performed in accordance with the Dutch Act on Implementation of General Data Protection. The need for ethical approval was waived by the Medical Ethical Committee Arnhem-Nijmegen (2021-12627). Consent to participate was assumed through self-registration and round completion. Consent to be acknowledged in this publication was specifically sought. Reporting followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) 2.0 guidelines.²³

Preparation phase and eDelphi survey development

A Steering Committee (SC) (L.S., E.B., A.E., S.M., S.W., J.R., E.J.) was installed in order to provide guidance and feedback on the eDelphi process. Members were experts with a background in psoriasis-related research and/or clinical practice leadership and representatives of the Dutch Association for Dermatology and Venereology. The SC advised on the development and refinement of the eDelphi statements, determined consensus criteria, and deliberated on proposals for revision of statements. Dermatologist members of the SC (E.B., S.M., E.J.) were allowed to vote during the eDelphi rounds. Patient representatives (I.E., A.P.) were delegated by the Dutch National Psoriasis Patient Association and were asked to review the consensus outcomes in order to incorporate the patient perspective.

A literature review was conducted in order to identify possible relevant outcomes for the application of DR in daily practice. We used the results of a previously conducted scoping review on DR of biologics in adult patients with psoriasis.⁵ The search strategy of this review was updated until June 2021. Selection criteria for inclusion of studies and format of data extraction complied with the used methods from the scoping review.⁵ After obtaining results from the literature review, the eDelphi statements were drafted. Additionally, results from a previously conducted

survey among Dutch dermatologists regarding used criteria for the application of DR in clinical practice were incorporated in the eDelphi statements.¹⁹ Dose reduction was defined as ‘the application of injection interval prolongation’ and was aimed at psoriasis patients with stable and low disease activity. Dose reduction by means of decreasing the absolute dosage in milligrams was excluded due to limited available evidence on this strategy.⁵ Within the eDelphi statements, criteria for starting DR, DR (dis)continuation, and DR schedules per biologic were proposed. Here, it was aimed to define criteria for selecting patients with stable low disease activity. Moreover, criteria for guidance of patients on DR were proposed in order to allow timely action to prevent loss of disease control. Based on previous literature and current practice, included disease activity measures used for DR eligibility criteria were the Psoriasis Area and Severity Index (PASI), Physicians Global Assessment (PGA), and impact on the patient’s quality of life measured with Dermatology Life Quality Index (DLQI). Proposed thresholds for these outcome measures were based on prevailing national treatment targets,¹⁷ and on a previously conducted multicentre, randomized controlled trial in the Netherlands, as this was the only available randomized controlled trial designed for DR evaluation.¹¹ Upper limits of proposed thresholds included PASI 5, PGA 0-2, and DLQI 5, and were chosen in order to provide some room for the application of DR in daily practice, as the accepted or reachable level of disease activity might differ between patients. Note that the proposed thresholds were not treatment targets in this context, but were defined as critical thresholds to advise DR discontinuation. Proposed dosing intervals were also based on the previous trial.¹¹ When developing the statements, it was aimed to only include the biologics adalimumab, etanercept, and ustekinumab, as for these biologics most evidence regarding DR was available.^{5,11} Infliximab was excluded as DR might lead to an increased risk of infusion reactions.²⁴ Statements were written in Dutch.

In order to optimize response rates and practicability, it was aimed to include a maximum number of 20–25 statements. Each statement should be rated on a 9-point Likert scale, with 1–3 labeled ‘not important/disagree’, 4–6 labeled ‘important but not critical/neither agree nor disagree’ and 7–9 labeled ‘critical/ agree’. With each statement, a blank text box for comments was provided and participants were asked to suggest additional items. The questionnaire was accompanied by background information on the Delphi process and on how candidate items have been selected. Consensus on any statement required $\geq 70\%$ of all voters to rate the outcome with a score of 7–9 (agree) and $< 15\%$ to rate the outcome with a score of 1-3 (disagree).²⁵⁻²⁷

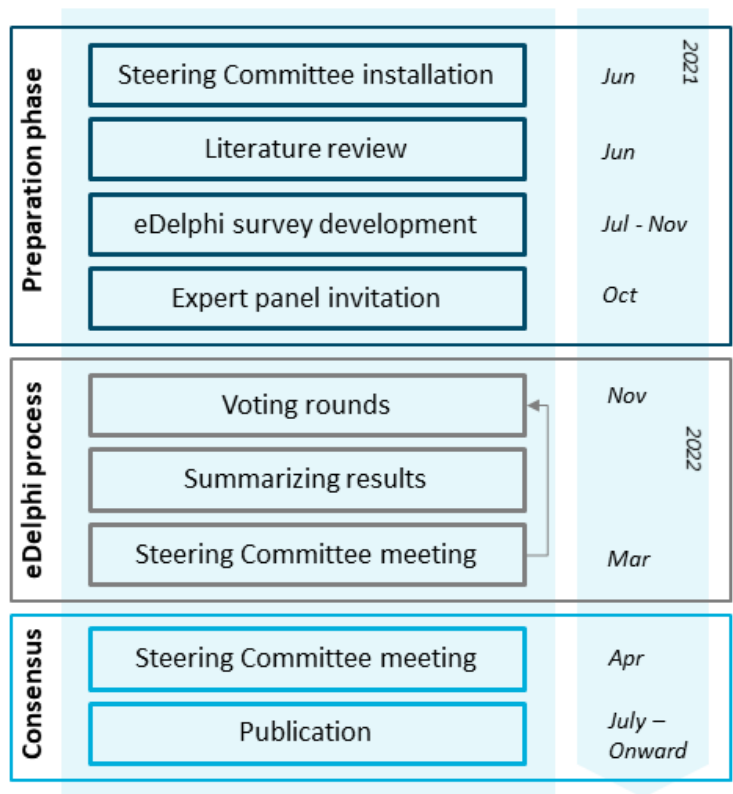


Figure 1. Flow chart study design.

Participants and recruitment

Dermatologists experienced in treating psoriasis patients with biologics were recruited through the Dutch Association for Dermatology and Venereology by an invitation e-mail. Within the invitation e-mail, it was noted that experience with biologic treatment was mandatory in order to participate. Respondents to the invitation were invited for the first eDelphi round. The sample size was not pre-defined.

eDelphi process

The questionnaire was distributed by the Dutch Association for Dermatology and Venereology using a password-protected web-based survey system: Survio (www.survio.com). The survey was pilot tested before going live.

A maximum of 3 rounds of online Delphi voting were planned. The total number of rounds depended on whether consensus was achieved or not. In case no consensus was reached after 3 rounds, a consensus meeting would be held with all participants

in order to resolve the remaining disagreements. Participants were asked to rate each item within the questionnaire. All questions were mandatory to answer. To reduce the risk of attrition bias, the importance of completing all eDelphi rounds was highlighted to all participants at each round. Participants were asked to complete each round within 4 weeks. Reminder e-mails were sent weekly to increase the response rate. Round 1 included participant characteristics (age, gender, position, type of practice/hospital, years of experience with treatment of psoriasis patients with biologics).

After each voting round, answers were analyzed in order to determine whether consensus on statements was reached based on the pre-stated consensus criteria. Results were discussed with the SC. It was decided which 'non-consensus' statements and/or participants' other suggestions should continue to the next round and when necessary, statements were re-defined by the SC based on participants' comments. Consensus could not be overturned by the SC.

In each subsequent round, participants were asked to re-score non-consensus items. Feedback and results of the previous round were provided. Participants who did not participate in, or did not complete the previous round were not invited to the subsequent round. The total number of participants who completed the survey was recorded as the number of participants for each round. After the eDelphi exercise, the results were shared with all participants.

Analysis

Collected data was pseudonymized by the use of unique numerical identifiers. Results were password protected. Data were imported into Microsoft Excel for analysis. Descriptive analysis was used to summarize responses and determine if consensus thresholds were reached. Statements were translated into English for the final report.

Results

In October 2021, 850 dermatologists were invited to participate in the eDelphi process. A total number of 44 dermatologists experienced with biologic treatment for psoriasis registered for participation, of which 27 eventually participated in the first eDelphi round. In total, 2 voting rounds took place. In round 2, all 27 dermatologists of round 1 participated. The demographics of participants are presented in **Table 1**. Years of experience in prescribing biologics exceeded the number of years of working experience as a dermatologist, as respondents could have had experience with prescribing biologics during their residency.

Table 1. Demographic characteristics of participants in the eDelphi survey

Characteristic	n=27
Sex (female)	19 (70.4)
Age (years), median (range)	43 (32-65)
Working experience as a dermatologist (years), median (range)	9 (0.5-30)
Experience in prescribing biologics (years), median (range)	11 (3-28)
Hospital type ^a	
Academic hospital	9 (33.3)
General hospital	18 (66.7)
Independent treatment center	3 (11.1)

Data are presented as n (%) unless otherwise indicated. ^a Multiple answers were possible.

In round 1, conducted from 22 November 2021 until 14 January 2022, 15 statements were presented to the participants. See **Appendix S1** for the survey. In total, three reminders were sent. After round 1, agreement was achieved on 10 items regarding DR eligibility, (dis)continuation, and dosing schedules for adalimumab and etanercept. See **Table 2** for the results.

Within the first round, agreed criteria for DR eligibility and (dis)continuation included the following thresholds for disease activity measures: PASI ≤ 5 , PGA 0–2, and DLQI ≤ 5 . Some participants commented however to prefer using lower PASI scores (≤ 2 –3) and/or PGA scores (0–1). It was agreed that outpatient visits should not be performed more frequently when applying DR, although participants commented that patients should be instructed to contact the clinic in case of disease flares. The proposed dosing schedules of two steps leading to 67% and 50% of the standard dose were agreed upon for adalimumab and etanercept. For ustekinumab, agreement was not achieved in the first round and participants suggested the use of intermediate DR steps. In addition, the option of reducing the dose of ustekinumab from 90 to 45 mg every 12 weeks was suggested. As the consensus was aimed at DR by means of interval prolongation, this option was not included.

After round 1, five non-consensus items were revised and proceeded to round 2. See **Table S1** for an overview of revised statements including the rationale. Revisions were made to the criteria on the minimal duration of low disease activity before starting DR, and minimal treatment duration before consideration of further DR. Moreover, DR steps for ustekinumab were adjusted: intermediate DR steps were added to the proposed schedule, resulting in four subsequent DR steps for this biologic. Based on participants' comments, the statement which indicated cautiousness for consideration of DR of the newer biologics was rephrased in a way that DR of the newer biologics could be considered in individual patients.

Round 2 was conducted from 7 March 2022 until 31 March 2022. Two reminders were sent. See **Appendix S2** for the survey. Of the 5 presented revised statements, agreement was achieved on all items. All final results are presented in **Table 2**. No new statements were proposed by participants. An algorithm based on the agreed criteria is presented in **Figure 2**.

Table 2. Results of the eDelphi consensus: criteria for biologic dose reduction in patients with psoriasis

	Statement	Disagree (%)	Neither agree nor disagree (%)	Agree (%)	Mean voting score
Eligibility	Patients should have a minimal treatment duration of 6 months before DR is started ^a	11.1	11.1	77.8	7.2
	Patients should preferably have a minimal duration of having low disease activity of 6 months before DR is started ^b	11.1	7.4	81.5	7.4
	The decision to start with DR should be based on disease activity and the impact of psoriasis on a patients' quality of life ^a	0	11.1	88.9	7.9
	In case of psoriatic arthritis, a rheumatologist should be consulted first before DR is started ^a	0	0	100	8.6
	When starting DR, the PASI score should be ≤ 5 and/or the de PGA should be 0-2, together with a DLQI ≤ 5 ^a	7.4	22.2	70.4	7.0
	Outpatient clinic visits should not be performed more frequently in case of DR ^a	3.7	14.8	81.5	7.8
	While awaiting more scientific evidence for dose reduction of the newer biologics (certolizumab pegol, IL-17 inhibitors, IL-23 inhibitors) no recommendations can be provided for dose reduction schedules of these biologics. However, DR can be considered in individual patients ^b	3.7	25.9	70.4	7.4
(Dis)continuation	DR can be continued in case of PASI ≤ 5 and/or PGA 0-2, together with DLQI ≤ 5 ^a	7.4	22.2	70.4	7.4
	In case of PASI > 5 and/or PGA > 2 and/or DLQI > 5 and/or at a patients' request, it should be considered to return to the standard dose or the previous effective dose ^a	3.7	11.1	85.2	7.7
	At patients' request or in case it is deemed necessary by the treating physician, it is always possible to return to the standard dose or the previous effective dose ^a	0	3.7	96.3	8.2

Table 2. Continued

	Statement	Disagree (%)	Neither agree nor disagree (%)	Agree (%)	Mean voting score
Dis/continuation	It can be considered to further reduce the dose: ^b After at least 3 months for biologics with a short injection interval according to the standard dose (standard interval <8 weeks). After at least 6 months for biologics with a longer injection interval according to the standard dose (standard interval ≥8 weeks).	3.7	25.9	70.4	7.4
	Dose reduction adalimumab: ^a Step 1: 40mg every 3 weeks Step 2: 40mg every 4 weeks	3.7	7.4	88.9	8.0
Dose reduction schedules	Dose reduction etanercept: ^a Step 1: 50mg every 10 days Step 2: 50mg every 14 days	3.7	18.5	77.8	7.2
	Dose reduction ustekinumab 45mg: ^b Step 1: 45mg every 15 weeks (optional) Step 2: 45mg every 18 weeks Step 3: 45mg every 21 weeks (optional) Step 4: 45mg every 24 weeks	0	11.1	88.9	7.8
	Dose reduction ustekinumab 90mg: ^b Step 1: 90mg every 15 weeks (optional) Step 2: 90mg every 18 weeks Step 3: 90mg every 21 weeks (optional) Step 4: 90mg every 24 weeks	0	14.8	85.2	7.6

Abbreviations: DR, dose reduction; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; DLQI, Dermatology Life Quality Index. ^aStatements for which consensus was reached after round 1. ^bStatements for which consensus was reached after round 2.

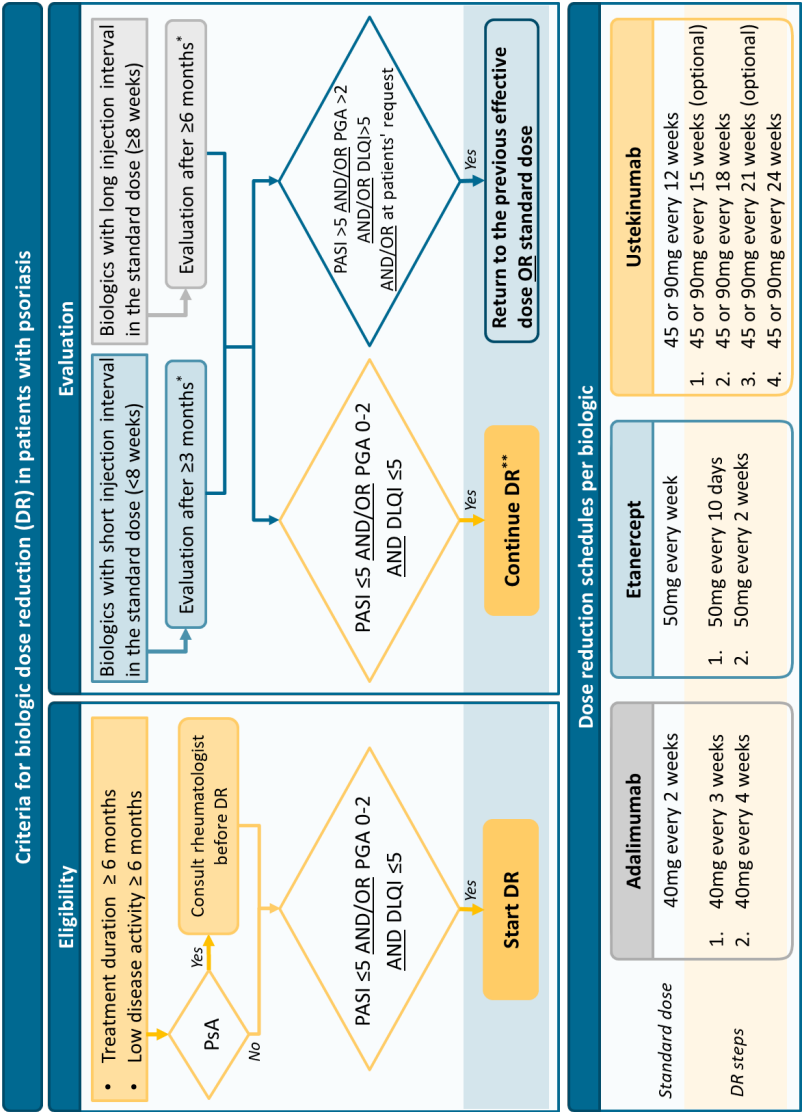


Figure 2. Algorithm for biologic dose reduction (DR) in patients with psoriasis based on the consensus
Abbreviations: DR, dose reduction; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PsA, psoriatic arthritis; DLQI, Dermatology Life Quality Index.

*DR can be discontinued at any time point in case of increased psoriasis or at patients' request.

**Continue DR: next step DR or continue lowered dose. For dosing schedules see lowest part of the algorithm

Discussion

By using an eDelphi consensus process involving Dutch dermatologists, consensus was reached within 2 eDelphi rounds on all 15 statements regarding criteria for the application of biologic DR by means of interval prolongation in patients with psoriasis. In addition, a clear algorithm was developed, ready for use in clinical practice.

Agreed criteria for eligibility and (dis)continuation of biologic DR included thresholds of outcome measures (PASI, PGA, DLQI). By using these criteria, timely action can prevent disease flares in case of loss of treatment response. Thresholds were based on a literature review and on prevailing national treatment targets.¹⁷ The PGA was added to the PASI in order to provide a more practical tool for clinicians in daily practice, as PASI measurements can be time-consuming. Of note, thresholds were defined with the aim to select patients with low disease activity and should not be considered treatment goals or targets. It can be debated if the proposed thresholds are low enough, as in the field of psoriasis more stringent targets were described in recent years.^{28,29} Some respondents indicated that they preferred to use lower thresholds, for example, PASI 2 or 3 instead of 5. From our experience, however, the acceptable level of disease activity can be different for each individual patient.⁸ In addition, the thresholds are upper limits and hence, the option to start DR with lower scores as well is provided. Moreover, combining PASI with DLQI scores will probably lead to patients with lower PASI scores initiating DR, as can be seen from the included patients in the CONDOR trial (median PASI at starting DR 1.8).¹¹ It should also be emphasized that the aim of the used thresholds is to select patients with stable and low disease activity and that DR should only be initiated within a shared-decision making approach.

Within the eDelphi process, DR schedules for the biologics adalimumab, etanercept, and ustekinumab were proposed, as most evidence regarding the DR of these biologics was available.^{5,11} Of note, very long-term data regarding the DR of these biologics still needs to follow and more insight into predictors for successful DR is warranted.⁵ The newer biologics (i.e., IL-17 and IL-23 inhibitors) were excluded due to limited scientific evidence on DR effects. To our best knowledge, few studies regarding the DR of the IL-17 inhibitors and IL-23 inhibitors were available.^{12,14,15,30,31} First, a statement was included describing cautiousness for DR of the newer biologics, but participants commented that DR for the newer biologics was already applied in daily practice. In the second round, the statement was revised in order to provide more room for application of DR for the newer biologics. However, the statement still indicated some caution because more evidence needs to follow, as the risk remains that future evidence could provide disappointing results. In case more evidence appears, it should be decided whether current criteria and dosing regimens can also be applied to the newer agents.

For ustekinumab, it was suggested to reduce the dose from 90 mg every 12 weeks to 45 mg every 12 weeks in case of adequate response. It was decided not to include a statement regarding this option, as there is limited literature available on this option, and the consensus was aimed at DR by means of interval prolongation. Moreover, this intervention would lead to a reduction of 50% of the original dose, which is a relatively large step. Future studies could consider exploring further options for DR including reducing dosages in milligrams per injection, and DR guided by drug levels based on evidence from therapeutic drug monitoring studies.³²

To our best knowledge, this is the first consensus on criteria for biologic DR in psoriasis. Another strength is that by design, the risk of bias was minimized as our anonymous eDelphi approach avoided possible dominance by any of the participants. Furthermore, implementation of the final results will be promoted due to collaboration with the Dutch Association for Dermatology and Venereology. The main limitation is the low number of respondents. Demographic characteristics showed however those participants represent both general and academic practice and were experienced in the treatment of psoriasis patients with biologics, as the median reported time of experience with prescription of biologics was 11 years. As results comply with the results of a previous survey among Dutch and international dermatologists,^{19,20} we believe that the agreed criteria can be incorporated into clinical practice. As stated above, another limitation is that no statements regarding DR of the newer biologics (e.g., IL-17 and IL-23 inhibitors) were formulated due to the scarcity of scientific evidence on DR of these agents. However, one statement on how to handle DR in these drugs was added. Furthermore, exclusion of patients in the voting process can be considered a limitation, although patients' representatives reviewed the consensus outcomes. Further elaboration on the patient perspective regarding biologic DR is however important for further implementation of DR strategies. This is an important issue for future work.

Another important next step could be to reach international consensus and enhance uptake of the proposed criteria for biologic DR in guidelines. Dermatologists worldwide indicated the lack of guidelines on biologic DR as main barrier to the application of DR.²⁰ However, ideal criteria might differ between countries due to differences in commonly used disease activity measures and differences in cultural and healthcare organizational aspects. Future research could therefore aim at defining international consensus on criteria for biologic DR, for which the current consensus might form a basis.

In conclusion, recommendations resulting from this national consensus process can guide clinicians, and consequently their patients, toward consistent application of biologic DR in daily clinical practice. Further implementation and uptake of biologic DR in (inter)national clinical guidelines is important for future perspective.

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Supplement

Appendix S1. eDelphi survey round 1

Instructions:

- Please rate each statement on a 9-point Likert scale, with 1 to 3 labelled 'not important/disagree', 4-6 labelled 'important but not critical/neither agree nor disagree' and 7-9 labelled 'critical/agree'.
- With each statement, a blank text box for additional comments is provided. In case of additional comments or suggestions, please note them in the blank text box below each statement.

Dose reduction eligibility

Explanatory notes: within this consensus, dose reduction (DR) of biologics is defined as 'application of injection interval prolongation'. As DR could in theory lead to disease exacerbations, criteria for starting and discontinuing DR are described in previous literature (e.g., 'tightly control'). In case of loss of adequate treatment responses, timely action based on these criteria can prevent disease flares. Within this consensus procedure we ask you to rate your level of agreement with the proposed criteria for application of biologic DR. The proposed thresholds for starting DR are based on previous literature and a survey among 114 Dutch dermatologists.^{1,2} Results of clinical trials with a withdrawal phase in which the biologic is discontinued showed that biologic discontinuation eventually leads to exacerbations. Therefore, the aim of DR is not to stop the biologic, but to strive for the lowest effective dose with maintenance of adequate treatment responses.

1. Patients should have a minimal treatment duration of 6 months before DR is started.

Explanatory notes: based on a review of the literature, most studies described a minimal treatment duration before DR was started. The duration varied between 3 months and ≥ 1 year. The majority of studies reported a minimal treatment duration of 6 months.¹ Based on the time needed to achieve adequate treatment responses for most biologics of 6 weeks to 6 months, a minimal treatment duration of 6 months seems an adequate threshold before starting DR, in case adequate responses have been reached during this period.

2. Patients should have a minimal duration of low disease activity of 6 months before DR is started.

Explanatory notes: DR seems possible in a substantial amount of psoriasis patients with low disease activity. As DR could in theory lead to disease exacerbations, criteria for starting and discontinuing DR are described in previous literature (e.g., 'tightly

control'). In case of loss of adequate treatment responses, timely action based on these criteria can prevent disease flares. These criteria can be based on thresholds of disease activity measures. The definition of low disease activity and the duration for reaching low disease activity as requirements for biologic DR varied between studies.¹ Most studies described a minimal treatment duration and/or reaching low disease activity of at least 6 to 12 months. Therefore, we propose a minimal duration of having low disease activity besides a minimal treatment duration before DR is started.

3. The decision to start with DR should be based on disease activity and the impact of psoriasis on a patients' quality of life.

Explanatory notes: in the only available randomized controlled trial designed for evaluation of DR of adalimumab, etanercept and ustekinumab, the DLQI was incorporated within the criteria for starting and (dis)continuing DR.³ With the inclusion of the DLQI, the patients perspective was ensured. In case of low disease activity measures but a large impact of the psoriasis on a patients' quality of life, DR could be discontinued.

4. In case of psoriatic arthritis, a rheumatologist should be consulted first before DR is started.

Explanatory notes: this statement applies to patients with concomitant psoriatic arthritis (PsA), when the biologic is also indicated for PsA. In patients with active PsA, it could be considered undesirable to reduce the biologic dose. Undertreatment of PsA could lead to irreversible joint damage.

5. Outpatient clinic visits should not be performed more frequently in case of DR.

Explanatory notes: in a previous survey among 114 Dutch dermatologists, outpatient clinic visits were not changed by dermatologists who applied DR.²

Criteria for start of DR and DR evaluation

Explanatory notes: As DR could in theory lead to disease exacerbations, criteria for starting and discontinuing DR are described in previous literature (e.g., 'tightly control'). In case of loss of adequate treatment responses, timely action based on these criteria can prevent disease flares. The proposed thresholds for starting DR are based on previous literature and a survey among 114 Dutch dermatologists.^{1,2} It is proposed that DR can be initiated when the PASI score is ≤ 5 together with a minimal impact of the disease on a patients quality of life, defined as a DLQI of ≤ 5 . A maximum PASI score of 5 provides some room for application of DR in daily practice, as the desired level of disease activity might differ between patients. Besides the PASI score, the physician global assessment (PGA) can be used. This is a practical instrument to estimate the disease activity based

on the physicians' assessment. With the PGA, an estimation of the psoriasis severity is made based on the following scores: 0 – no psoriasis, 1 – minimal, 2 – mild, 3 – moderate, 4 – moderate-to-severe, 5 – severe. A PGA 0-1 is comparable to a PASI ≤ 2 .⁴

6. When starting DR, the PASI score should be ≤ 5 and/or the de PGA should be 0-2, together with a DLQI ≤ 5 .
7. DR can be continued in case of PASI ≤ 5 and/or PGA 0-2, together with DLQI ≤ 5 .
8. In case of PASI > 5 and/or PGA > 2 and/or DLQI > 5 and/or at a patients' request, it should be considered to return to the standard dose or the previous effective dose.
9. After a minimal duration of 3 months, it can be considered to further reduce the dose.
Explanatory notes: the effect of biologic DR can be evaluated after a minimal duration of 3 months. It can be considered to further reduce the dose. Of note, a minimal duration is proposed, therefore the effect can also be evaluated after a longer period of time.
10. At patients' request or in case it is deemed necessary by the treating physician, it is always possible to return to the standard dose or the previous effective dose.

Dose reduction schedules per biologic

Explanatory notes: within this consensus, it is aimed to achieve consensus on fixed steps of dose reduction by means of interval prolongation per biologic. By aiming for fixed steps, DR will be standardized, leading to a more uniform approach in daily practice. The biologics adalimumab, etanercept and ustekinumab are included, as for these biologics most evidence for biologic DR is available.¹ The proposed dosing schedules are based on the available literature and consist of interval prolongation leading to 67% and 50% of the standard dose.

11. Dose reduction adalimumab:
Step 1: 40mg every 3 weeks
Step 2: 40mg every 4 weeks
The standard dose of adalimumab is 40mg every 2 weeks.
12. Dose reduction etanercept:
Step 1: 50mg every 10 days
Step 2: 50mg every 14 days
The standard dose of etanercept is 50mg every week.

13. Dose reduction ustekinumab 45mg (<100kg):

Step 1: 45mg every 18 weeks

Step 2: 45mg every 24 weeks

The standard dose of ustekinumab is 45mg every 12 weeks (body weight <100kg).

14. Dose reduction ustekinumab 90mg (≥100kg):

Step 1: 90mg every 18 weeks

Step 2: 90mg every 24 weeks

The standard dose of ustekinumab is 90mg every 12 weeks (body weight ≥100kg).

15. Currently, cautiousness is required when considering dose reduction of the newer biologics (certolizumab pegol, IL-17 inhibitors, IL-23 inhibitors) due to the limited amount of scientific evidence.

Explanatory notes: the biologics adalimumab, etanercept and ustekinumab are included in this consensus procedure, as for these biologics most evidence regarding DR is available. In case more evidence appears, it should be decided whether criteria and dosing regimens following this consensus can also be applied to the newer agents.

Table S1. Revisions made prior to eDelphi round 2

eDelphi round 1		eDelphi round 2	
Statement	Agreement (%)	Revised statement	Rationale for revision
Patients should have a minimal duration of low disease activity of 6 months before DR is started	60.3	Patients should preferably have a minimal duration of having low disease activity of 6 months before DR is started	Comments included longer or shorter durations (up to 12 months or 3-4 months) and requiring stable low disease activity independently from duration. Revision: the statement was rephrased in order to give more room for application in daily practice. The threshold was not changed as most studies reported a duration of stable low disease activity of 6-12 months. Within the proposed criteria, both statements for duration of low disease activity and treatment duration were incorporated in order to select patients eligible for DR.
After a minimal duration of 3 months, it can be considered to further reduce the dose	63.0	It can be considered to further reduce the dose: - After at least 3 months for biologics with a short injection interval according to the standard dose (interval <8 weeks) - After at least 6 months for biologics with a longer injection interval according to the standard dose (interval ≥8 weeks)	Comments included a shorter duration at patients request, a duration of 6 months, and that the decision would depend on the dosing schedule of the biologic. Revision: the statement was divided for biologics with a shorter vs. longer injection interval according to the standard dose, with a threshold of 8 weeks. For biologics with a longer interval according to the standard dose, reduced dosages could extend a period of 3 months. As such, decisions to further reduce the dose should be made after a longer period of time. A threshold of 8 weeks was chosen as this could possibly be applied for the newer biologics as well in the future. It was explained within the survey that a minimal duration was included, therefore treatment decisions could always be taken after a longer period.
			81.5
			70.4

Table S1. Continued

eDelphi round 1			eDelphi round 2	
Statement	Agreement (%)	Revised statement	Rationale for revision	Agreement (%)
Dose reduction ustekinumab 45mg: Step 1: 45mg every 18 weeks Step 2: 45mg every 24 weeks	59.3	Dose reduction ustekinumab 45mg: Step 1: 45mg every 15 weeks (optional) Step 2: 45mg every 18 weeks Step 3: 45mg every 21 weeks (optional) Step 4: 45mg every 24 weeks	Comments included preference of shorter steps in the DR schedules. Revision: two additional in-between DR steps were added to the first proposed steps of reduction to 67% and 50% of the standard dose. The initial steps were maintained as these correspond with the DR algorithm applied to all biologics. Added steps were optional, as based on the literature DR to 67% and 50% of the standard dose was possible.	88.9
Dose reduction ustekinumab 90mg: Step 1: 90mg every 18 weeks Step 2: 90mg every 24 weeks	51.9	Dose reduction ustekinumab 90mg: Step 1: 90mg every 15 weeks (optional) Step 2: 90mg every 18 weeks Step 3: 90mg every 21 weeks (optional) Step 4: 90mg every 24 weeks	Comments included preference of shorter steps in the DR schedules. Additionally, participants mentioned the option of lowering the biologic dose to 45mg every 12 weeks instead of interval prolongation. Revision: two additional in-between DR steps were added to the first proposed steps of reduction to 67% and 50% of the standard dose. See explanation above (ustekinumab 45mg). There was no statement included regarding DR by means of decreasing the absolute dosage in milligrams, as limited literature was available on this strategy.	85.2
Currently, cautiousness is required when considering dose reduction of the newer biologics (certolizumab pegol, IL-17 inhibitors, IL-23 inhibitors) due to the limited amount of scientific evidence	25.9	While awaiting more scientific evidence for dose reduction of the newer biologics (certolizumab pegol, IL-17 inhibitors, IL-23 inhibitors) no recommendations can be provided for dose reduction schedules of these biologics. However, DR can be considered in individual patients.	Comments included that DR was already applied in daily practice for the newer biologics as well, and several participants rated that they did not know or had no experience yet. Revision: the statement was rephrased in a way that DR could be considered in individual patients but still a level of cautiousness should be applied while awaiting more evidence regarding DR of the newer biologics. No recommendations were formulated regarding dosing schedules, due to the lack of scientific evidence. In case more evidence becomes available, it should be assessed whether criteria for DR and proposed DR schedules could be applied to the newer biologics as well.	70.4

Abbreviations: DR, dose reduction.

Appendix S2. eDelphi survey round 2

Instructions:

- *Please rate each statement on a 9-point Likert scale, with 1 to 3 labelled 'not important/disagree', 4-6 labelled 'important but not critical/neither agree nor disagree' and 7-9 labelled 'critical/agree'.*
- *Within the explanatory notes, the rationale for each statement is added.*
- *With each statement, a blank text box for additional comments is provided. In case of additional comments or suggestions, please note them in the blank text box below each statement.*

1. Patients should preferably have a minimal duration of having low disease activity of 6 months before DR is started.

Statement round 1: Patients should have a minimal duration of low disease activity of 6 months before DR is started.

Explanatory notes: the statement was rephrased in order to give more room for application in daily practice. A duration of 6 months is proposed, however a longer or shorter duration is possible in individual cases. Previous studies mostly described a minimal treatment duration and/or reaching low disease activity of at least 6 to 12 months as requirements for biologic DR.¹ Within the proposed criteria, both statements for duration of low disease activity and treatment duration were incorporated in order to select patients eligible for DR.

2. It can be considered to further reduce the dose:
 - After at least 3 months for biologics with a short injection interval according to the standard dose (standard interval <8 weeks).
 - After at least 6 months for biologics with a longer injection interval according to the standard dose (standard interval ≥8 weeks).

Statement round 1: After a minimal duration of 3 months, it can be considered to further reduce the dose.

Explanatory notes: this statement includes a minimal duration after which it can be considered to further reduce the dose. The statement was divided for biologics with a shorter vs. longer injection interval in the standard dose, with a threshold of 8 weeks. For biologics with a longer interval according to the standard dose (for example ustekinumab), reduced dosages could extend a period of 3 months. As such, decisions to

further reduce the dose should be made after a longer period of time. For biologics with a shorter interval according to the standard dose (for example adalimumab, etanercept), the effects of DR can be evaluated after 3 months. Of note, a minimal duration is proposed. As such, effects can also be evaluated after a longer period of time.

3. Dose reduction ustekinumab 45mg (<100kg):

- Step 1: 45mg every 15 weeks (optional)
- Step 2: 45mg every 18 weeks
- Step 3: 45mg every 21 weeks (optional)
- Step 4: 45mg every 24 weeks

Statement round 1: Dose reduction ustekinumab 45mg (<100kg):

- Step 1: 45mg every 18 weeks
- Step 2: 45mg every 24 weeks

Explanatory notes: two additional in-between DR steps (every 15 weeks, every 21 weeks) were added to the first proposed steps. The initial steps (every 18 weeks, every 24 weeks) were maintained as these correspond with the DR algorithm applied to all biologics (reduction to 67% and 50% of the standard dose). This provides a more uniform approach for all biologics. In addition, it is prevented that steps are too small, as an interval prolongation with 2 weeks on a total interval of 12 weeks is a relatively small difference. The added steps are optional, as based on the literature DR to 67% and 50% of the standard dose was possible.

4. Dose reduction ustekinumab 90mg (≥100kg):

- Step 1: 90mg every 15 weeks (optional)
- Step 2: 90mg every 18 weeks
- Step 3: 90mg every 21 weeks (optional)
- Step 4: 90mg every 24 weeks

Statement round 1: Dose reduction ustekinumab 90mg (≥100kg):

- Step 1: 90mg every 18 weeks
- Step 2: 90mg every 24 weeks

Explanatory notes: two additional in-between DR steps (every 15 weeks, every 21 weeks) were added to the first proposed steps. The initial steps (every 18 weeks, every 24 weeks) were maintained as these correspond with the DR algorithm applied to all biologics (reduction to 67% and 50% of the standard dose). This provides a more uniform approach for all biologics. In addition, it is prevented that steps are too small, as an

interval prolongation with 2 weeks on a total interval of 12 weeks is a relatively small difference. The added steps are optional, as based on the literature DR to 67% and 50% of the standard dose was possible.

There was no statement included regarding DR by means of decreasing the absolute dosage in milligrams (e.g., from 90mg every 12 weeks to 45mg every 12 weeks), as limited literature was available on this option.

5. While awaiting more scientific evidence for dose reduction of the newer biologics (certolizumab pegol, IL-17 inhibitors, IL-23 inhibitors) no recommendations can be provided for dose reduction schedules of these biologics. However, DR can be considered in individual patients.

Statement round 1: Currently, cautiousness is required when considering dose reduction of the newer biologics (certolizumab pegol, IL-17 inhibitors, IL-23 inhibitors) due to the limited amount of scientific evidence.

Explanatory notes: DR of the newer biologics is already performed in daily practice.² The statement was rephrased in a way that DR could be considered in individual patients. However, there is limited scientific evidence available regarding DR of the newer biologics. Some studies regarding DR of IL-17 inhibitors were available, but not for IL-23 inhibitors.⁵⁻⁸ Described DR schedules differed between studies. Due to the limited scientific evidence, no recommendations were formulated regarding dosing schedules. As the risk remains that future evidence could provide less positive results, a level of cautiousness should be applied when considering DR of the newer biologics. In case more evidence becomes available, it should be assessed whether criteria for DR and proposed DR schedules could be applied to the newer biologics as well.

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CHAPTER 4

Dose reduction of the new
generation biologics
(IL-17 and IL-23 inhibitors)
in psoriasis



CHAPTER 4.1

Dose reduction of the new generation biologics (IL-17 and IL-23 inhibitors) in psoriasis: study protocol for an international, pragmatic, multicenter, randomized, controlled, non-inferiority study - the BeNeBio study

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Abstract

Background

Psoriasis is a chronic immune-mediated inflammatory skin disease for which biologics are effective treatments. Dose reduction (DR) of the first generation biologics seems a promising way for more efficient use of expensive biologics. A substantial part of patients on tumor necrosis factor (TNF)-alfa inhibitors and ustekinumab could successfully lower their dose, after following a tightly controlled DR strategy. The objective of this study is to assess whether controlled DR of interleukin (IL)-17 and IL-23 inhibitors in psoriasis patients with low disease activity is non-inferior (NI) to usual care (UC).

Methods

This is an international, prospective, multicenter, pragmatic, randomized, non-inferiority trial. A total of 244 patients with stable low disease activity (Psoriasis Area and Severity Index (PASI) ≤ 5) for at least 6 months and using secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, or tildrakizumab in the standard dose, together with stable low disease activity, defined as a PASI ≤ 5 and Dermatology Life Quality Index (DLQI) ≤ 5 at the moment of inclusion, will be randomized 2:1 to DR or UC. In the DR group, dosing intervals will be prolonged stepwise to achieve 66% and 50% of the original dose. Disease activity is monitored every 3 months by PASI and DLQI. In case of disease flare (i.e., PASI and/or DLQI increase), treatment is adjusted to the previous effective dose. The primary outcome is the incidence proportion of persistent flares (PASI > 5 for ≥ 3 months), which will be compared between arms. Secondary outcomes include proportion of patients with successful DR, (course of) PASI and DLQI, serious adverse events (SAEs), health-related quality of life, costs, and pharmacokinetic profile. Outcomes of DR will be compared to UC.

Discussion

With this study, we aim to assess whether DR of IL-17 and IL-23 inhibiting biologics can be achieved for psoriasis patients with low disease activity, without losing disease control. Reducing the dose may lead to more efficient use of biologics.

Trial registration

ClinicalTrials.gov NCT04340076. Registered on April 9 2020.

Introduction

Background

Psoriasis is a chronic, immune-mediated skin disease, which is associated with important comorbidities such as cardiovascular disease and psoriatic arthritis. Disease-related quality of life impairment is large in patients with moderate-to-severe psoriasis.¹ Biologics are effective treatments which have enlarged treatment options for psoriasis patients in the past decades. Biologics block specific cytokines (tumor necrosis factor-alpha (TNF- α), interleukin (IL)-12, IL-23, or IL-17) in the psoriasis pathogenesis pathway. The very long-term safety profile is yet to be established. Besides their effectiveness, biologics are expensive and impose a high burden on national healthcare expenditures.² Effective and efficient use of biologics is therefore warranted, including the optimal dose for the individual patient.

A new generation of biologics entered the market in recent years: IL-17 inhibitors (IL-17i) (secukinumab, ixekizumab, and brodalumab) and IL-23 inhibitors (IL-23i) (guselkumab, risankizumab, and tildrakizumab). Trial data are promising, with higher effectiveness rates than in first generation biologics like TNF- α inhibitors or ustekinumab.³⁻⁵ These biologics are registered in a fixed dose, although not every patient might need this standard dose. Previous research aiming to identify therapeutic windows of biologics showed for example that for adalimumab, one third of patients with good responses had drug levels outside the therapeutic window and were likely to be 'overtreated'.⁶ Hence, dose reduction (DR) seems a promising method to more efficiently and safely prescribe biologics. In the field of rheumatology, DR of TNF- α inhibitors is comparable to continuation of the standard dose in patients with low disease activity.⁷ For psoriasis, we recently conducted a randomized non-inferiority trial on DR of adalimumab, etanercept and ustekinumab in patients with stable low disease activity, which showed that in 53% of the patients, the dose was successfully lowered after 12 months.⁸ Here, DR was achieved by extending the dosing interval of the biologics. Non-inferiority of DR based on Psoriasis Area and Severity Index (PASI) scores was not demonstrated, yet there was no difference regarding persistent disease flares, defined by disease activity and quality of life measures (PASI and/or Dermatology Life Quality Index (DLQI) scores >5) during 3 months or longer. Furthermore, the DR strategy resulted in substantial cost savings.⁹ Other studies indicated that DR of biologics in psoriasis patients might lead to lower cumulative drug exposure without losing clinical efficacy.¹⁰⁻¹³ Direct translation of results from previous DR studies towards the newer biologics cannot be made, due to possible differences between drug classes. To our knowledge, literature regarding DR of IL-17i is sparse, and there are no studies yet that report on DR of IL-23i in psoriasis.^{14,15}

With the first generation biologics (TNF- α inhibitors), it was shown that discontinuing biologic treatment resulted in quick exacerbations of psoriasis.¹⁶ For IL-17i and IL-23i, withdrawal is also associated with a risk of disease flare, although after retreatment with the original dose a substantial number of patients rapidly regained response.¹⁷⁻²² Consequently, DR is preferred above treatment withdrawal. To prevent risk of disease flare with DR, we here propose a tightly controlled disease activity-guided strategy.

We designed a multicenter, pragmatic, randomized, controlled non-inferiority study with the aim to identify the number of psoriasis patients that maintain clinical effectiveness and quality of life with a reduced dose of IL-23 and IL-17 inhibiting biologics. We anticipate at least non-inferiority of DR compared to usual care (UC) on the basis of the incidence of persistent disease flares.

Objectives

The aim of this study is to investigate whether disease activity-guided DR of IL-17 and IL-23 inhibiting biologics for psoriasis patients is non-inferior with regard to persistent disease flares compared to therapy with the standard dose. This translates into the following primary and secondary objectives.

Primary objective

The primary objective is to assess if tightly controlled DR of IL-17i and IL-23i in psoriasis patients with low disease activity is non-inferior to UC with regard to the incidence proportion of persistent disease flares (PASI >5 for ≥ 3 months) after 18 months.

Secondary objectives

- To assess the proportion of patients with successful DR after 12 and 18 months, defined as using a lower dose than the standard dose and PASI ≤ 5 .
- To assess differences in course of disease activity (PASI) and dermatology-related quality of life (DLQI) in patients with DR versus UC in 18 months.
- To assess and compare absolute PASI and DLQI scores at month 12 and month 18 in patients with DR versus UC.
- To assess the incidence of short disease flares (PASI >5 at one time point) after 18 months in patients with DR versus UC.
- To assess the time until the first persistent flare (PASI >5 for ≥ 3 months).
- To identify predictors for successful DR.
- To count and compare the number of serious adverse events (SAE) and adverse events of special interest (AEoSI) in patients with DR versus UC. AEoSI include, but are not limited to, infections, malignancies, and joint complaints or new-onset psoriatic arthritis.

- To assess the pharmacokinetic profile of reduced biologics versus the standard dose.
- To assess if DR is cost-effective compared to UC.
- To assess the proportion of patients with initiation of other anti-psoriatic treatments during the study (intensive topical therapies, methotrexate, acitretin) in patients with DR versus UC.

Methods

Trial design

This is a multicenter, pragmatic, randomized, controlled non-inferiority trial. This trial will be conducted in 17 medical centers in Belgium and the Netherlands. A comparison will be made between an intervention group (DR) and a control group receiving UC (normal dose). In total, 244 patients will be randomized (2:1). In the intervention arm, the dose of the biologic will be reduced by means of prolongation of the intervals between two doses. We aim to determine whether administration of a reduced dose of the biologic is non-inferior compared to the normal, standard dose. Consequently, a randomized controlled non-inferiority design was chosen. Study setting This study will be carried out in 18 departments of dermatology in Belgium and the Netherlands. Nine centers in the Netherlands will participate: five academic centers (Radboud University Medical Center Nijmegen, Erasmus Medical Center Rotterdam, Maastricht University Medical Center, University Medical Center Utrecht, University Medical Center Groningen) and five nonacademic centers (Bravis hospital Bergen op Zoom, Catharina hospital Eindhoven, Gelre hospital Apeldoorn, Ziekenhuisgroep Twente Almelo/Hengelo, and Slingeland hospital Doetinchem). In Belgium, the participating centers include five academic centers (Ghent University Hospital, Cliniques Universitaires Saint-Luc Brussels, Centre Hospitalier Universitaire (CHU) de Liège, Erasme Hospital Brussels, University Hospital Leuven) and three non-academic centers or private practices (AZ Maria Middelaars Ghent, AZ Sint-Lucas Ghent, and Dermatologie Maldegem).

Ethical approval for this study was obtained from the Medical Ethical Committee (Arnhem-Nijmegen) for the Dutch sites and from the competent authorities (FAMH P) and the Ethics Committee of University Hospital Ghent and University Ghent after consulting the Ethics Committees of each participating site in Belgium. Written informed consent will be obtained from each participant.

Eligibility

Adult patients with plaque psoriasis who are treated with IL-17i or IL-23i in the standard, registered dose for at least 6 months, and who have stable low disease activity, are

eligible. Low disease activity is defined as PASI ≤ 5 in the previous 6 months and at the moment of inclusion, together with a DLQI ≤ 5 at inclusion. In case no PASI scores are available, it should be clear from the patient record that the psoriasis was 'clear' or 'almost clear' in the past 6 months. A PASI ≤ 5 is chosen based on experts' opinion and our previous DR study.⁸ The DLQI score was added in order to adjust to the impact of psoriasis on the patients' quality of life.²³ A DLQI ≤ 5 indicates mild influence on quality of life.²⁴ In order to establish whether good disease control is present, a combination of PASI as a clinical outcome measure and DLQI as a patient reported outcome measure will be assessed every 3 months during the study (tight control). Patients who are eligible for inclusion in this study must meet the following criteria:

Inclusion criteria:

- Plaque psoriasis (primary indication for biologic).
- Treatment for at least 6 months with IL-23i or IL-17i in the standard dose (dose advised by the label).
- PASI ≤ 5 in the previous 6 months. If no PASI scores are available in the previous 6 months, it should be clear from the patient record that the psoriasis was clear or almost clear.
- PASI ≤ 5 at inclusion.
- DLQI ≤ 5 at inclusion.

Exclusion criteria:

- Another indication than plaque psoriasis as the main indication for biologic use (e.g., psoriatic arthritis).
- Concomitant use of systemic immunosuppressants other than methotrexate or acitretin.
- Severe comorbidities with short life-expectancy.
- Presumed inability to follow the study protocol.

Recruitment

All patients who are eligible for this study will be asked by their treating physician. They will receive oral and written information from the local investigator. The investigator will obtain written informed consent and the patient will be randomized. The dosing schedule will be explained depending on which biologic the patient uses. Patients can leave the study any time for any reason without consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. When subjects are withdrawn from the study, they will not be replaced.

Randomization, blinding, and treatment allocation

The investigator will enroll participants. After including the participant and obtaining written informed consent, the investigator will enter participants in a web-based randomization program (Castor). Participants will be allocated to each group (DR or UC) by this web-based randomization program (Castor) that generates block randomization (variable block size of 6, 9, 12) with a random (2:1) allocation sequence and stratified by biologic. After randomization, the randomization group is visible for the investigator and the investigator will inform the participant. Patients will be randomized 2:1 to DR or continuation of the normal dose (UC). The ratio of 2:1 is chosen to be able to include more determinants in an analysis for successful DR. Due to the pragmatic character of this trial, and due to the nature of the intervention (injections), patients and investigators will not be blinded. Patients in the DR group will receive secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, or tildrakizumab, and doses will be lowered according to the schedule as described below (**Table 1**).

Patients in the control group will receive the normal, standard dose of secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, or tildrakizumab without interval prolongation.

Table 1. Dose reduction (DR) steps per biologic

Biologic	Normal dose	First step DR	Second step DR
Secukinumab	300 mg/4 weeks	300 mg/6 weeks	300 mg/8 weeks
Ixekizumab	80 mg/4 weeks	80 mg/6 weeks	80 mg/8 weeks
Brodalumab	210 mg/2 weeks	210 mg/3 weeks	210 mg/4 weeks
Guselkumab	100 mg/8 weeks	100 mg/12 weeks	100 mg/16 weeks
Risankizumab	150 mg/12 weeks	150 mg/18 weeks	150 mg/24 weeks
Tildrakizumab	100 or 200 mg/12 weeks	100 or 200 mg/18 weeks	100 or 200 mg/24 weeks

Abbreviations: DR, dose reduction; mg, milligram.

Study groups

Control group

Patients in the control group will continue treatment with the normal, standard dose based on the prevailing national guidelines. Treatment decisions are made at the discretion of the treating physician following these guidelines. Control visits are planned every 3 months and patients are explained to contact their physician when they experience increased disease activity. The PASI and DLQI are performed during 3-monthly outpatient clinic visits. Topical therapies and concomitant use of

methotrexate or acitretin are allowed. In case of a disease flare, treatment will be adjusted. Topical and/or systemic therapy will be optimized and when required the dose of the biologic will be increased or the biologic will be switched to another agent. In case of treatment alternations, the patient will remain in the study for follow-up.

Dose reduction group

The doses of secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, or tildrakizumab will be lowered by interval prolongation in two steps to 66% and 50% of the original dose, respectively (**Table 1**). The intervals of drug administration will be prolonged depending on the PASI and DLQI score (**Figure 1**). DR is allowed in case of low disease activity, defined as PASI ≤ 5 and DLQI ≤ 5 . First, the dose will be decreased to 66% of the normal dose of the biologic (by interval prolongation with a factor 1.5). After 3 months, if there remains low disease activity (PASI ≤ 5 and DLQI ≤ 5), the dose will be further reduced to 50% of the original dose (by doubling the original interval). When disease flare occurs (PASI > 5 and/or DLQI > 10), or when the patient is not willing to further use the lower dose, the patient will return to the previous effective dosing interval. In case of PASI ≤ 5 and DLQI > 5 but ≤ 10 , it will be discussed with the patient if the reduced dose remains acceptable and can be continued or not. If possible, the patient will stay on the lowest dose. Each step will be analyzed after 3 months, or when the patient visits earlier due to complaints. In case a patient returned to the previous effective dosing interval, the dose will not be reduced again at a later time point. Topical therapies and concomitant use of methotrexate or acitretin are allowed. When there is still no disease control after reintroduction of the normal dose, treatment will be adjusted. Topical and/or systemic therapy will be optimized and, when required, the dose of the biologic will be increased or patients will switch to another agent. In case of treatment alternations, the patient will remain in the study for follow-up.

Procedures and outcome measures

At baseline, patient and treatment characteristics will be collected, such as sex, age, treatment history, comorbidities, and disease duration. Patients will be followed for 18 months and regular visits will be planned at baseline, month 3, 6, 9, 12, 15, and 18. An overview of interventions and assessments by study time point is presented in **Table 2**. If a patient has a disease flare outside the regular visits, an additional study visit will be planned. Every 3-monthly visit, PASI and DLQI scores will be retrieved, and blood samples will be drawn for determining anti-drug antibody levels and modeling drug trough levels. Also, dosage schedules, adverse events, and concomitant topical and systemic medication use will be registered. Medication dispensing records will

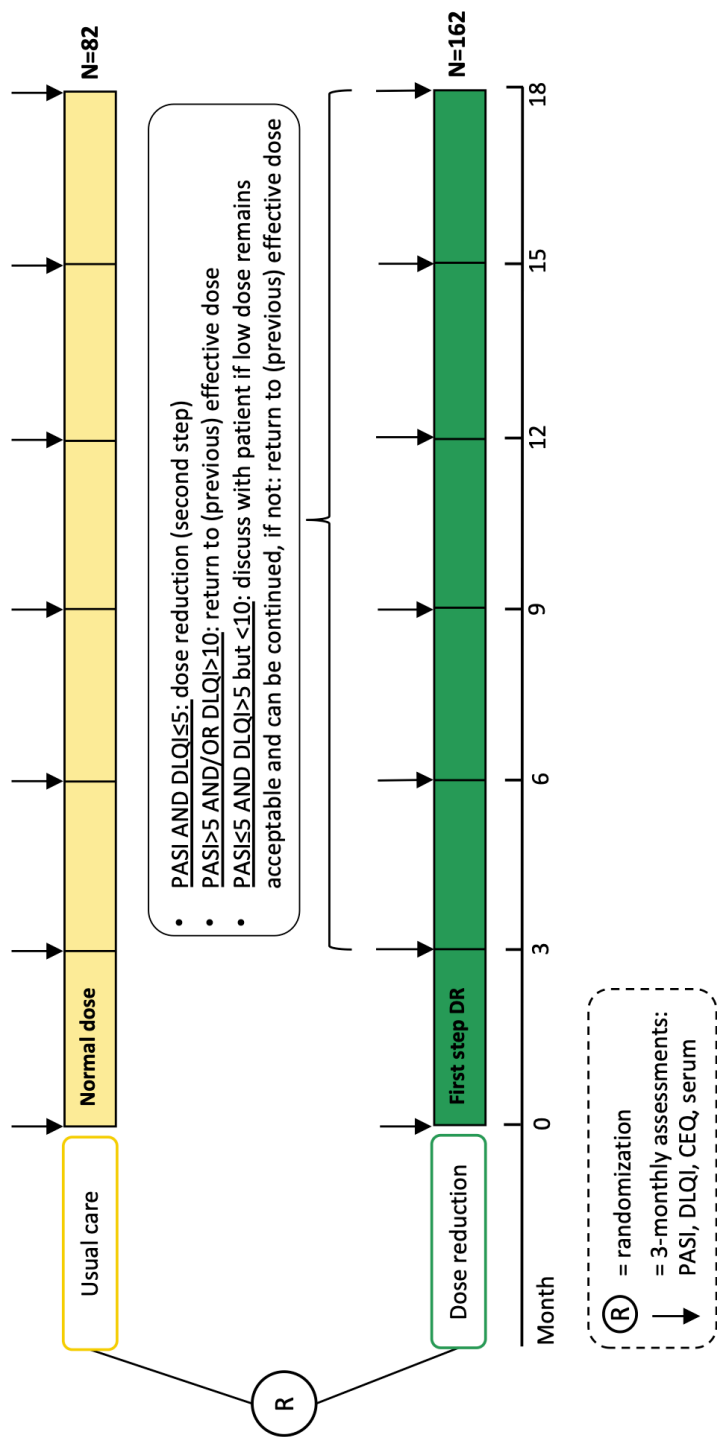


Figure 1. Participant timeline.

Patients (n=244) using secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, or tildrakizumab will be randomized to dose reduction or usual care. Control visits will be scheduled every 3 months for assessment of PASI, DLQI, cost-effectiveness questionnaires (EQ-5D-5L, SF-36, iMTA MCQ, and PCQ), drug levels, and anti-drug antibodies. Abbreviations: CEQ, Cost-Effectiveness Questionnaires; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index.

be collected for each participant from their pharmacies. Patients will be asked to fill in patient diaries with information on medication use. Questionnaires relevant for cost-effectiveness analysis will be completed in by the patients at these visits. These include the European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) questionnaire,²⁵ the Short Form (SF)-36 questionnaire,²⁶ and adapted versions of the 'institute for Medical Technology Assessment' (iMTA) Medical Consumption Questionnaire (MCQ) and Productivity Cost Questionnaire (PCQ).²⁷

Our primary outcome is non-inferiority of the incidence proportion of persistent flares (PASI >5 for ≥ 3 months) in the intervention group. If the 95% confidence interval from the difference in incidence of persistent flares in the intervention group versus control group exceeds the non-inferiority margin (15% difference in persistent flares) at 18 months of follow-up, it can be concluded that non-inferiority could not be demonstrated for DR.

Our secondary study outcomes are as follows:

- Whether participants will have successful DR after 12 and 18 months, defined as using a lower dose than the normal dose and PASI ≤ 5 .
- Psoriasis disease activity, measured with the Psoriasis Area and Severity Index (PASI) at each 3- monthly study visit. The PASI is a composite measure of erythema, scaling, induration, and extensiveness of the psoriasis plaques.²⁸ It results in a single score for psoriasis severity ranging from 0 to 72 with lower scores indicating lower disease activity.
- Dermatology-related quality of life as measured with the Dermatology Life Quality Index (DLQI) at each 3-monthly study visit. The DLQI is a practical questionnaire for routine clinical use and consists of 10 questions surveying the impact of skin disease on health-related quality of life. A total sum score ranging from 0 to 30 is derived from all questions, with lower scores indicating limited impact on disease-related quality of life.²³
- Whether participants will have short disease flares throughout the study period (18 months), defined as a PASI >5 at one time point.
- Whether other anti-psoriatic medication will be initiated in participants during the study period (18 months). Investigators will report start of other medications at every study visit.
- Whether participants will have serious adverse events (SAE) and adverse events of special interest (AEoSI) during the study period. AEoSI include, but are not limited to, infections, malignancies, and joint complaints or new-onset psoriatic arthritis. All adverse events reported spontaneously by the participant or observed by the investigator will be recorded in the CRF during the study period (18 months).

- Drug trough levels of each included drug will be measured in blood serum samples which will be collected from participants at each 3-monthly time point. Serum samples will be analyzed through an enzyme-linked immunosorbent assay (ELISA) for serum drug and anti-drug antibody levels.
- Anti-drug antibody levels of each included drug will be measured in blood serum samples which will be collected from participants at each 3-monthly time point. Serum samples will be analyzed through an enzyme-linked immunosorbent assay (ELISA) for serum drug and anti-drug antibody levels.
- Utilities will be derived from EQ-5D-5L questionnaires, which will be measured at each 3-monthly time point. The EQ-5D-5L questionnaire consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), and each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. In addition, patients are asked to complete a visual analog scale to rate their health status at a scale of 0–100.²⁵ Utility scores will be used to calculate quality-adjusted life years (QALYs) which are used to determine cost-effectiveness of DR.
- Health status of participants will be assessed by using the Short Form 36 (SF-36) version 2 questionnaire at every 3-monthly time point. The SF-36 consists of 36 questions regarding 8 domains of health, including physical functioning, physical role, pain, general health, vitality, social function, emotional role, and mental health.^{26,29} Scores from all domains will be summarized with differing weightings to calculate mental component scores (MCS) and physical component scores (PCS). Utilities will be derived as well from the SF-36 for sensitivity analyses, calculated based on the 12 specific SF-36 questionnaire answers included in the SF6D system.
- Volumes of care, as measured with the iMTA Medical Consumption Questionnaire (MCQ) at each 3-monthly time point. The iMTA MCQ measures all relevant health care related costs like out-patient visits at any medical specialist, hospitalizations, and imaging procedures.²⁷ Scores will be used to calculate direct medicals costs and non-medical costs.
- Loss of productivity and presenteeism of participants, as measured with the iMTA Productivity Cost Questionnaire (PCQ) at each 3-monthly time point. The iMTA PCQ measures patient-reported absences from paid or unpaid labor.³⁰ Scores will be used to calculate direct medicals costs and non-medical costs.

Definition of disease flare

We defined a psoriasis flare as a PASI score >5. A short disease flare was defined as a flare at one time point, and a persistent flare as a PASI >5 for at least 3 months. Successful DR was defined as use of a lower biologic dose and a PASI ≤5. A PASI cutoff

of 5 was chosen in absence of a validated definition for psoriasis flare. This cutoff was based on our previous DR trial,³¹ where PASI 5 was chosen based on expert opinion and on previous data that showed that patients who remain on a biologic reach average PASI scores ≤ 5 .³² Although disease flare is based on disease activity only, quality of life measured by DLQI is incorporated in the tightly controlled DR strategy. In patients where PASI 5 reflects active disease, patients can always return to their previous effective dose or the normal dose when they experience larger impact of their psoriasis on their quality of life. Incidence of persistent flares was chosen as primary outcome to assess non-inferiority. Brief, temporary flares that improve after treatment adjustments or reintroduction of higher doses, and without large impact on overall disease control, might occur more frequent in a DR arm and are inherent to such a strategy. However, to not harm the patient, such effects should not last too long. For this reason, persistent flares are chosen as the primary outcome. PASI is used instead of Psoriasis Global Assessment (PGA) as PASI is a common used tool in Europe daily practice and in clinical trials. Assessment of PASI is standardized, whereas for PGA different scales and subtypes are used.³³ PASI has been reported to be a reliable instrument to evaluate treatment success when measured at baseline and during treatment.³⁴

Table 2. Schedule of enrolment, interventions, and assessments by study time point

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT	M0	M0	M3	M6	M9	M12	M15	M18
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Dose reduction								
Usual care								
ASSESSMENTS:								
Demographics	X							
Dosage schedules	X		X	X	X	X	X	X

Table 2. Continued

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT	M0	M0	M3	M6	M9	M12	M15	M18
Comedication	X		X	X	X	X	X	X
PASI	X		X	X	X	X	X	X
DLQI	X		X	X	X	X	X	X
EQ-5D-5L	X		X	X	X	X	X	X
SF-36	X		X	X	X	X	X	X
iMTA MCQ	X		X	X	X	X	X	X
iMTA PCQ	X		X	X	X	X	X	X
Adverse events			X	X	X	X	X	X
Serum	X		X	X	X	X	X	X

Abbreviations: M, months; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Level questionnaire; SF-36, Short Form-36 questionnaire; iMTA MCQ, institute for Medical Technology Assessment Medical Consumption Questionnaire; PCQ, Productivity Cost Questionnaire.

Power and sample size analyses

The primary outcome is non-inferiority of persistent flares (PASI >5 for ≥ 3 months) in the intervention group with a non-inferiority margin of 15%. If the upper limit of the 95% confidence interval of the difference in persistent flares between the intervention group versus control group exceeds 15% at 18 months of follow-up, it must be concluded that non-inferiority could not be demonstrated for DR.³⁶ A margin of 15% was chosen based on clinical grounds, and on previous DR studies.^{8,37} Inherent to the intervention, there could be a small increase in disease flares (i.e., loss of disease control) as drug dosages are lowered. However, it is expected, based on other studies,^{8,35} that most flares will be easy to control in the end without residual damage for patients, for example by reintroduction of a higher dose or switch to another biologic. It is therefore expected that persistent flares will not occur very frequently, as has also been shown in the CONDOR trial.⁸ In addition, in the UC arm, there will be disease flares as well, as PASI scores might fluctuate over time and some patients might experience loss of effectiveness of their biologic.³⁸ The chosen non-inferiority margin of 15% is to some extent arbitrary, but refers to a clinically acceptable difference in persistent flares. Of note, the point estimate should be much lower than the margin of 15%, because the margin refers to the upper limit of

the 95% confidence interval of the difference in persistent flares which should not exceed 15%. Therefore, we found a margin of 15% (hence a point estimate $\ll 15\%$) for the difference in persistent flares acceptable, especially because we know that effectiveness could often be regained in patients with persistent flares in studies on other biologics.^{8,35} With an expected chance of being able to reduce biologic dosages in $>50\%$ of patients,⁸ the benefit-harm ratio seems well balanced by accepting this anticipated increase of persistent flares in patients undergoing DR compared to UC. With this margin, one-sided testing ($\alpha=0.025$; $1-\beta=0.8$) and a randomization ratio of 2:1 DR versus UC, we calculated that 222 patients need to be included to reject the null-hypothesis of inferiority. Taking a drop-out rate of 10% into account, 244 patients need to be included, with 162 in the DR arm and 82 in the UC arm.

Data collection and management

All data will be collected and entered in Castor, an electronic data management system, which is setup for clinical trials.³⁹ Data will be coded and kept based on the rules for good clinical practice (GCP) by GCP-certified personnel.⁴⁰ Handling of personal data will comply with the General Data Protection Regulation.⁴¹ All blood samples will be coded before sending to Ghent University Hospital for storage and to University Hospitals Leuven where the samples will be analyzed.

Statistical analyses

All analysis will be done according to a per protocol analysis, as this is the preferred and most conservative analysis for non-inferiority studies.⁴² Of note, all patients that follow the DR protocol (**Figure 1**) will remain in the group they were allocated to, including DR patients that returned to their normal dose according to the protocol. Patients on a lower dose who should return to a higher dose according to the protocol are not included in per protocol analysis after the moment of protocol deviation. They will however complete the study procedures, and occurred protocol deviations will be summarized and reported. Subjects lost to follow-up will be included in analyses until their lost to follow-up date only. Information about patients lost to follow-up will be described. Intention-to-treat (ITT) analysis will be performed as well on all outcomes for sensitivity reasons, and as they are needed for the cost-effectiveness analysis. Data of patients who deviated from the protocol will be included in ITT analysis. For the ITT analyses, last observation carried forward (LOCF) will be used for imputation of missing data. The last available data from patients who are lost to follow-up will be imputed. Extent and nature of missing data will be described. Patient and treatment characteristics will be summarized as means or medians and percentages, depending on the type of measurement.

The primary outcome incidence proportion of persistent flares will be calculated for both groups. Number of patients with a persistent flare will be presented as proportions with corresponding confidence intervals. Confidence intervals of proportions will be calculated by Fishers exact tests (Clopper-Pearson), and the proportions will be compared using Fisher exact tests (open source calculator OpenEpi, V3.01).⁴³ If the difference in incidence proportion of persistent flares in the intervention group versus the UC group exceeds the non-inferiority margin (15% difference in persistent flares) at 18 months of follow-up, it will be concluded that non-inferiority could not be demonstrated for DR. Time until the first persistent flare in both groups will be graphically presented by Kaplan-Meier survival estimation.

The proportion of patients with successful DR will be expressed using descriptive statistics. PASI and DLQI course throughout the study will be compared between the intervention and control groups using mixed methods analysis. All disease-activity scores (PASI) will also be directly compared at each time point (every 3 months) between the two groups using an unpaired t test or a non-parametric alternative. PASI and DLQI at 12 and 18 months will be analyzed with ANCOVA in which the baseline values will be included as a covariate to gain efficiency. A multivariable regression analysis will be carried out in order to identify predictors for successful DR at month 12 and month 18. Possible candidate predictors will include baseline patient and treatment characteristics and baseline trough drug concentrations. Based on group size, we will test the four most promising variables. Proportions, rate ratios, and relative rate ratios, with corresponding confidence intervals, of SAEs and AEOsI will be described and differences between groups will be tested using classical statistical methods (Fisher exact test). SAEs and AEOsI related to DR will also be counted and expressed as proportions and rate ratios. A subanalysis for all outcomes will be made for the different drug classes and on individual drug level if appropriate (depending on numbers included per class).

Cost-effectiveness analysis

Cost-effectiveness of DR will be calculated based on health-status (SF-36), utilities measured with EQ-5D-5L, volumes of care (iMTA Medical Consumption Questionnaire), and loss of productivity and presenteeism (iMTA Productivity Cost Questionnaire). Utilities will be estimated by weighing the scored answers on the EQ-5D-5L with the local tariffs and using the trapezium rule quality-adjusted life years (QALYs) will be calculated. A sensitivity analyses will be conducted by calculating QALYs based on utilities from the SF6D system, derived from answers on the 12 specific SF-36 questionnaire answers. Cost prices for each volume of consumption will be determined based on standard local cost prices. Productivity losses will be valued by means of

the friction cost method. Volumes of care will be multiplied with the cost prices for each volume of care to calculate costs. Because we anticipate non-inferiority of the DR strategy, cost-savings will be analyzed. Direct medical cost as well as total costs (medical and non-medical costs) will be compared between the intervention and control group. A possible small but acceptable loss of effect can be incorporated in the analyses by determining a decremental cost-effectiveness ratio by dividing the difference in costs by the difference in QALYs between the groups. The decremental cost-effectiveness ratio expresses with how much money a loss of 1 QALY is compensated. If this amount is high, decision-makers are willing to accept a loss of effect. Uncertainty in the decremental cost-effectiveness ratio will be non-parametrically determined using bootstrap techniques (1000 replications). Results from this analysis will be presented in a scatter plot and willingness to pay (or accept) curve. Furthermore, the net monetary benefit per patient will be calculated for different levels of willingness to pay in dollars per QALY, using the formula: willingness to pay*effect (difference in QALY)—costs. This results in the net amount of money saved, when the possible loss of QALY is corrected for, using different willingness to pay levels per QALY.

Pharmacokinetic analyses

Pharmacokinetic analyses will be performed for each biologic to determine anti-drug antibody levels and drug trough levels. Modeling of drug and anti-drug antibody levels will be done based on Bayesian statistics with NONMEM to gain insight in the clearance of the biologics during DR and to identify factors that influence pharmacokinetics. A maximum of variables (age, gender, disease severity, disease duration, dosing scheme (day of injection), etc.) will be introduced in the model where possible. The validity of the model will be assessed through goodness of fit with the aim to model the area under curve estimation.

Oversight and monitoring

The study will be overseen by the trial steering committee. The trial steering committee consists of the research committee, funders, statistician, and patient representatives. The research committee consists of the principal and coordinating investigators of the sponsor (Radboud University Medical Center) and national coordinating center (Ghent University Hospital) and an independent expert. The responsible ethical committees and competent authorities require annual reports. No other audits will be performed, unless requested by the study sponsor, funding source, or the responsible competent authorities.

Data of all centers will be monitored following guidelines of the Radboud University Medical Center for the Dutch sites and the guidelines of Ghent University Hospital

for the Belgian sites. A data safety monitoring board will not be installed as this study is judged as a negligible risk trial.

All adverse events will be recorded in the source document (patient medical record) and electronic data management system after randomization. Safety reviews will be performed annually by the trial steering committee. Interim safety reviews will be performed when this is deemed necessary. The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor and national coordinating center have a full insurance that covers the costs of potential harms.

All major protocol modifications will be approved by the responsible ethical committees, and participants will be reconsented as necessary. Changes will be added to the ClinicalTrials.gov protocol. Upon trial finalization, findings will be submitted for publication to an open-access peer-reviewed journal. Results will be presented at relevant national and international conferences, as well as in relevant patient associations. All publications will be in accordance with international recognized scientific and ethical standards concerning publications and authorship, including the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors. There is no intended use of professional writers.

Discussion

DR of biologics in patients with low disease activity seems a promising way to provide personalized treatment, improve safety, and reduce healthcare costs. Until now, DR has mainly been described for TNF- α inhibitors and ustekinumab.¹⁰⁻¹³ The possibility of DR is only mentioned in a few guidelines.^{44,45} To our knowledge, the current study is the first randomized, controlled trial designed to investigate disease activity-guided DR of IL-17i and IL-23i for psoriasis patients with low disease activity in a multicentric and pragmatic setting.

This study was partially based on our previous tightly controlled DR study on adalimumab, etanercept, and ustekinumab.⁸ We chose a different primary outcome, i.e., incidence of persistent flares, instead of difference in disease activity. Disease activity should certainly be incorporated in the primary outcome, as it is the domain that should be non-inferior. Because of the tightly controlled strategy however, disease activity could possibly not differ between the two groups at study end. Therefore, disease activity should be analyzed over time, but time-integrated disease activity measures are more difficult to interpret and less informative for daily practice than percentage of patients

with a flare. Incidence of flares is therefore chosen as primary outcome in the majority of DR studies.³⁷ Persistent flares are clinically more important than short disease flares due to larger impact on overall disease control. For this reason, persistent flares are chosen as the primary outcome. In addition, inclusion criteria are less strict in the current study compared with the previous study, as patients can also be included in case no PASI scores were available in the past 6 months. We believe that this might improve external validity and practicability, as PASI is not measured in every clinic. We extended the follow-up duration compared to the previous study to 18 months instead of 12 months, because biologics with relatively long dosing intervals (risankizumab and tildrakizumab) were included. As the DR schedules of these biologics might extend the 3-monthly visits in time, there should be more time to assess the DR effect. A longer follow-up duration allows longer term safety analysis as well.

The strength of this study is that it will be performed in two different countries, and in various academic and non-academic centers, to improve external validity. Moreover, the real-world practice setting, flexibility of treatment schedule, and outcomes relevant to patients lead to a highly pragmatic trial of which outcomes have a high generalizability.⁴⁶ A possible limitation is the open-label design of this study, as reporting bias might occur for patient reported outcomes such as adverse events. However, as said, the aim of this pragmatic study is to provide high external validity, which would be lowered by blinding.

The focus of this study is on the strategy of DR in general. Hence, the study is powered for the total group and not per biologic. In addition, subanalyses per drug class and per biologic will be performed when appropriate.

More knowledge on DR of biologics might contribute to more efficient and effective use of biologics. The COVID19 situation has emphasized the need for more research regarding personalized dosing and the possibility of lower dosages of immunomodulatory biologic.⁴⁷ In this prospective, multicenter, randomized controlled non-inferiority trial, the possibility of DR of the newer generation biologics (IL-17i and IL-23i) will be investigated. If DR is non-inferior to UC with standard dosages, we can provide patients with more personalized treatment. This may lead to lower cumulative doses of therapy, a lower risk of side-effects, and reduction of healthcare costs.

Trial status

Recruitment started at the 20 August 2020. Last visit is planned for July 2023. Current protocol version 1.5, date 29 July 2021.

Research Involving Human Subjects), as well as all ethical bodies of each participating site, approved the study. In Belgium, the study was approved by the competent authorities (FAMHP) and the Ethics Committee of Ghent University Hospital and University Ghent after consulting the Ethics Committees of each participating Belgian site. The trial protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. Written informed consent will be obtained from each participant. Participants should give their permission for reuse of their data and biological specimens within the written informed consent form.

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CHAPTER 5

Perspectives on biological
treatment for psoriasis, focusing
on personalized treatment



CHAPTER 5.1

Female patients are less satisfied with biological treatment for psoriasis and experience more side-effects than male patients: results from the prospective BioCAPTURE registry

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Abstract

Background

Female sex has been reported as a predictor for treatment discontinuation with biological therapies for psoriasis, although reasons remain unclear. It can be hypothesized that lower satisfaction with biological treatment in women might add to the lower drug survival rates.

Objectives

To identify possible differences in satisfaction with biological treatment between female and male patients using the Treatment Satisfaction Questionnaire for Medication (TSQM).

Methods

Data of psoriasis patients treated with biologics were obtained from the prospective, multicentre, daily-practice BioCAPTURE registry. Longitudinal TSQM data were analysed by linear mixed models. Relevant patient characteristics were incorporated as possible confounding factors. Post hoc analysis of adverse events was performed in order to investigate differences between sexes.

Results

We included 315 patients with 396 corresponding treatment episodes (137 adalimumab, 90 etanercept, 137 ustekinumab, 24 secukinumab and 8 infliximab). Almost forty per cent of the patients were female. Women had significantly lower baseline PASI scores ($P=0.01$). Longitudinal analyses demonstrated lower TSQM scores for 'side-effects' ($P=0.05$) and 'global satisfaction' ($P=0.01$) in female patients compared with male patients over 1 year of treatment. Women reported more relevant adverse events in the context of biologic treatment compared to men (rate ratio 1.79; $P<0.001$), with more fungal (rate ratio 2.20; $P=0.001$) and herpes simplex infections (rate ratio 3.25; $P=0.005$).

Conclusions

This study provides a prospective, longitudinal analysis of treatment satisfaction with biologics in female and male patients with psoriasis. Women were slightly less satisfied with treatment regarding side-effects and global satisfaction. Differences in treatment satisfaction and side-effects might add to the fact that women discontinue biological treatments more often.

Introduction

Biological agents have enlarged the treatment options for patients with psoriasis, and still new biologics are developed.^{1,2} Many daily-practice registries are nowadays available in order to evaluate and optimize treatment with biologics.³⁻⁷ These studies have assessed drug survival of individual biologics, or they searched for clinical characteristics that predict the discontinuation with biological treatment. Data from several studies suggest that female sex is a predictor for treatment discontinuation with biologics.⁴⁻¹⁰ Although Zweegers et al.⁸ reported female sex as a predictor for treatment discontinuation due to side-effects, other reasons remain unclear. We hypothesized that female patients have lower drug survival rates compared with male patients as a result of lower satisfaction with biological treatment.

Treatment satisfaction is important in patients with psoriasis, as it corresponds with adherence, patients' preferences and health-related quality of life.^{11,12} Therefore, 'satisfaction with medication' is an important patient-reported outcomes (PROs) in the field of psoriasis used in the evaluation of treatments.¹³ For this purpose, the Treatment Satisfaction Questionnaire for Medication (TSQM) can provide insight into different domains of treatment satisfaction: effectiveness, convenience, global satisfaction and side-effects.¹⁴ In general, treatment satisfaction with biologics is high,^{3,15-19} although we previously demonstrated that there still remains room for improvement in treatment satisfaction.³

In recent years, several publications have provided information on gender differences in health care.^{20,21} It has been observed that sex differences exist in the presentation of symptoms, communication and treatment outcomes.^{21,22} Although there is no difference in the male-to-female prevalence ratio for patients with psoriasis,²³ there is some evidence for gender differences in psoriasis with regard to response to biological treatment.^{24,25}

In order to identify possible differences in satisfaction with biological treatment between female and male patients using the TSQM, this study provides a prospective, longitudinal analysis of treatment satisfaction in female and male patients with psoriasis treated with biologics in daily practice care. This approach may further elucidate reasons for worse drug survival with biologics in women compared to men with psoriasis.

Materials and Method

The BioCAPTURE database

Data were extracted from the prospective, multicentre, long-term Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE registry). Since 2005, daily practice data from patients with psoriasis treated with biologics have been imported into this registry. The registry contains data from two academic and 14 nonacademic centres in the Netherlands. Currently used biologics in the BioCAPTURE registry are adalimumab, etanercept, ustekinumab, infliximab, secukinumab, ixekizumab, guselkumab, brodalumab and the small molecule apremilast. BioCAPTURE was approved by our medical ethics committee. Although not mandatory for this non-interventional study according to the Dutch Law, informed consent was obtained from every patient in this registry. Patients included in the registry received treatment according to the Dutch guidelines.²⁶

Treatment satisfaction questionnaire for medication (TSQM)

From 2010, all patients included in the BioCAPTURE registry starting a biologic for the first time or switching to another biologic were asked to fill out a TSQM (version II). Patients received questionnaires at baseline and at every 3 months, or until the moment of discontinuation. From 12 months, patients were asked to fill out questionnaires every year. The TSQM (version II) is a generic, multilingual validated questionnaire developed for different patients and medications, and is therefore applicable to our patient group. The TSQM covers four domains: effectiveness, convenience, global satisfaction and side-effects. The score for every domain ranges from 0 (extremely dissatisfied) to 100 (extremely satisfied).¹⁴ Baseline measures provide information about the last treatment used before the initiation of the biologic, as the questionnaire refers to the timeframe 2–3 weeks prior to completion of the questionnaire.

Data collection and extraction

Scores retrieved from TSQM questionnaires were entered into the BioCAPTURE database. Patient characteristics and TSQM scores were extracted from the BioCAPTURE database for all patients from 2010 until August 2018. We included TSQM scores over 1 year of treatment or until the moment of discontinuation whichever came first. Baseline characteristics extracted from the database were sex, age at start with biological therapy, type of biologic, duration of psoriasis until start with biological therapy, body mass index (BMI), baseline PASI score, experience with prior biologics, presence of psoriatic arthritis and hospital type (academic or non-academic).

All treatment episodes with biologics in the BioCAPTURE registry with completed longitudinal TSQM questionnaires were included in this study: adalimumab, etanercept, ustekinumab, infliximab and secukinumab. One treatment episode accounted for the time the patient was actively treated with a biologic; interruptions with a maximum of 90 days were accepted within a treatment episode. When patients had received different biologics over time, all treatment episodes with completed TSQM questionnaires were included. TSQM questionnaires of treatment episodes with brodalumab, guselkumab and ixekizumab were not available yet. Treatment episodes with the small molecule apremilast and treatment episodes without completed TSQM questionnaires at all time frames were excluded from analyses.

Statistical analysis

Cross-sectional Data were extracted from the BioCAPTURE database and imported into SPSS version 25 (IBM, Armonk, NY, USA) for further analysis. A P-value <0.05 was considered significant in all analyses.

Descriptive statistics [means $\pm$ SD or medians (range)] were used to summarize continuous patient and treatment characteristics of the first available treatment episode. For categorical variables, numbers and percentages were used. Baseline continuous variables were compared between male and female patients using an independent t-test in case of a parametric distribution, or a Mann–Whitney U-test in case of a non-parametric distribution. Differences in categorical variables between male and female patients were analysed by Pearson's chi-square tests for independence.

Longitudinal Treatment Satisfaction Questionnaire for Medication scores per domain ('effectiveness', 'side-effects', 'convenience' and 'global satisfaction') over time were studied using linear mixed models (LMMs). LMMs were chosen in order to account for the unbalanced data with a different number of treatment episodes per patient. LMMs are able to accommodate all available data with flexible assumptions regarding missing data.²⁷

The TSQM subdomain scores were defined as dependent variables, and time (in months) from baseline visit, sex and TSQM subdomain baseline score were key independent variables. Possible confounding factors based on clinical relevance were incorporated in the models: age, duration of psoriasis, baseline PASI score, BMI, presence of psoriatic arthritis, type of biologic and experience with prior biologics.

Confounders that altered the unadjusted exposure–outcome effect by $\geq 10\%$ or confounders that contributed statistically significant were kept in the model.

Consequently, every TSQM subdomain model contains different confounders. Variance components were used as covariance type (default setting of SPSS). Statistics were based on all cases with valid data for all variables in the model. Corresponding estimated marginal means (EMMs) over time and for each moment of time from baseline visit were calculated for male and female patients.

Post hoc analysis of adverse events

Post hoc analysis of adverse events was performed in order to further explain differences in satisfaction with side-effects between female and male patients. Adverse events were defined as any undesirable medical event that occurred during biological treatment. In general, physicians inquired actively for adverse events at every BioCAPTURE visit. In case of serious adverse events (SAEs), additional information was requested from the treating physicians in most cases. We analysed SAEs and defined clinical relevant adverse events of special interest (AEoSI) in the context of biologic use, see **Table 2**. Other mild adverse events were excluded. AEoSI, which were also covered by criteria for SAEs, were included in both groups. Incidence rates were calculated, based on the number of events per 100 actively treated patient-years. The incidence rates were compared between men and women using Mid-P exact tests (open source calculator OpenEpi, V.3).²⁸ Sensitivity analyses were performed in order to correct for gender-related adverse events, such as gynaecological events in female patients.

Results

Patient and treatment characteristics

In total, 315 patients were included in this study, with a total of 396 treatment episodes. Corresponding total patient-years 'on drug' were 417 years for female patients, and 677 years for male patients. Seventy-eight patients without completed TSQM questionnaires at all timeframes were excluded. Baseline patient characteristics of the first treatment episode and number of used agents in all treatment episodes are presented in **Table 1**. More than half of the patients were male (59.7%, n=188). In both groups, patients had median BMIs in the range of overweight (median BMI 28.09 and 28.07, for male and female patients, respectively). The median baseline PASI score was significantly higher in male patients (11.4 vs. 10.1 in female patients; $P=0.01$).

Female patients report lower 'side-effects' and 'global satisfaction' scores

Longitudinal analysis for the 'effectiveness' domain showed no difference in 'effectiveness' scores between male and female patients over time [male, EMM 68.40 (95% CI: 62.28–74.50); female, EMM 62.31 (95% CI: 56.22–68.40); $P=0.06$]. Results

were corrected for possible confounders at baseline, including presence of psoriatic arthritis and type of biological agent.

For the 'side-effects' domain, the LMM demonstrated an overall lower score over time in female patients compared with male patients [female, EMM 87.99 (95% CI: 84.55–91.44); male, EMM 92.86 (95% CI: 89.26–96.45); $P=0.05$]. Results were corrected for possible confounders at baseline, including presence of psoriatic arthritis, age, duration of psoriasis and baseline PASI score.

The LMM of the TSQM 'convenience' domain demonstrated no differences over time between male and female patients [male, EMM 79.20 (95% CI: 75.00–83.41); female, EMM 78.65 (95% CI: 74.52–82.78); $P=0.82$]. Results were corrected for type of biologic, presence of psoriatic arthritis, age, duration of psoriasis, BMI, prior experience with biologics and baseline PASI score.

Female patients had an overall lower 'global satisfaction' score over time compared with male patients [female, EMM 71.57 (95% CI: 66.25–76.89); male, EMM 78.69 (95% CI: 73.26–84.13); $P=0.01$]. Results for the 'global satisfaction' model were corrected for type of biologic, presence of psoriatic arthritis and BMI.

Estimated marginal means calculated by the LMMs for the different timeframes for male and female patients are presented in **Figure 1**. **Tables S1–S4** provide detailed information about the models used.

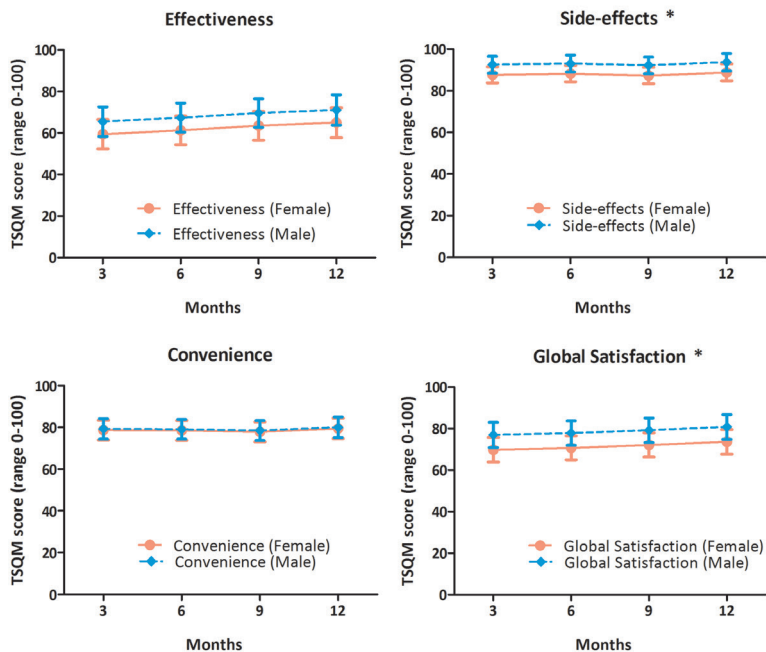
Table 1. Patient and treatment characteristics of the first treatment episode of male and female patients (n=315)

	Total (n=315)	Male (n=188, 59.7%)	Female (n=127, 40.3%)	p-value ^a
Age (years), mean $\pm$ SD	48.85 $\pm$ 13.10	48.71 $\pm$ 12.58	49.06 $\pm$ 13.88	0.82 ^b
Duration of psoriasis until start of biologic (years), median (IQR)	19.49 (14.93) ^c	19.49 (13.67) ^d	19.80 (19.07) ^e	0.63 ^f
BMI (kg*m ⁻²), median (IQR)	28.07 (7.48) ^g	28.09 (5.79) ^h	28.07 (10.07) ⁱ	0.61 ^f
Baseline PASI score, median (IQR)	11.20 (8.5) ^j	11.4 (8.7) ^k	10.1 (9.0) ^l	0.01 ^f
Psoriatic arthritis (yes)	76 (24.1) ⁿ	36 (19.1) ^o	40 (31.5) ^p	0.07 ^m
Treatment ^q	396 (100)	229 (100)	167 (100)	-
Adalimumab	137 (34.6)	76 (33.2)	61 (36.5)	-
Etanercept	90 (22.7)	54 (23.6)	36 (21.6)	-
Infliximab	8 (2.0)	4 (1.7)	4 (2.4)	-
Secukinumab	24 (6.1)	13 (5.7)	11 (6.6)	-
Ustekinumab	137 (34.6)	82 (35.8)	55 (32.9)	0.91 ^m

Table 1. Continued

	Total (n=315)	Male (n=188, 59.7%)	Female (n=127, 40.3%)	p-value^a
Hospital type				
Academic	213 (67.6)	123 (65.4)	90 (70.9)	-
Non academic	102 (32.4)	65 (34.6)	37 (29.1)	0.33 ^m
Experience with prior biologics				
Experienced (non-naïve)	140 (44.4)	84 (44.7)	56 (44.1)	-
Inexperienced (naïve)	175 (55.6)	104 (55.3)	71 (55.9)	1.00 ^m

Data are presented as n (%) unless otherwise indicated. Abbreviations: BMI, body mass index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index. ^a based on the difference between male and female patients. ^b independent t-test, ^c Mann-Whitney U-test, ^m Pearson's X²-test. Missing data: ^c12, ^d9, ^e3, ^g37, ^h27, ⁱ10, ^j53, ^k34, ^l19, ⁿ65, ^o48, ^p17. ^q Total number of treatment episodes for all used biologics.



Each figure shows estimated marginal means with 95% CI (whiskers) as calculated by the LMMs. Asterisks (*) represent a significant difference ($p<0.05$) between male and female patients for the specific TSQM domain over time.

Figure 1. Treatment Satisfaction Questionnaire for Medication (TSQM) measures for female and male patients over one year of treatment with biologics.

Each figure shows Estimated Marginal Means (EMMs) for the specific TSQM domain with 95% confidence intervals (whiskers) as results of the Linear Mixed Models. Asterisk represent a significant difference ($p<0.05$) between male and female patients for the specific TSQM domain over time.

Abbreviations: TSQM, Treatment Satisfaction Questionnaire for Medication.

Adverse events

Serious adverse events and AEoSI were incorporated in these analyses. Total numbers and corresponding incidence rates per 100 patient-years (PY) of SAEs and AEoSI are presented in **Table 2**. The total number of SAEs in women was 41, compared to 48 SAEs in men. No significant difference was found between men and women (rate ratio 1.30; $P = 0.13$). Regarding AEoSI, the total number was significantly higher in women, with 120 AEoSI in women vs. 109 in men (rate ratio 1.79; $P < 0.001$). Regarding subcategories, there were significantly more fungal infections reported among female patients ($n=38$ vs. $n=28$; rate ratio 2.20; $P=0.001$). Female patients also reported more mucosal fungal infections compared with male patients (rate ratio 12.99; $P < 0.001$) and more herpes simplex infections compared with male patients (rate ratio 3.25; $P=0.005$). Adjustment for gender-related AEoSI revealed no differences in significance (rate ratio 1.68; $P=0.01$; data not presented).

After stratifying per type of biologic, incidence rates for SAEs did not differ between male and female patients for all biologics. With regard to AEoSI, female patients had higher incidence rates compared with male patients for etanercept (rate ratio 2.29; $P=0.002$) and infliximab (rate ratio 9.89; $P=0.001$). No differences in pattern of adverse events were found between all biologics for female and male patients.

Discussion

This prospective, multicentre, longitudinal study showed that female patients reported significantly lower treatment satisfaction, measured by TSQM, regarding the domains 'side-effects' and 'global satisfaction' compared with male patients. In general, treatment satisfaction with biologics was high in both groups. Post hoc analyses on side-effects revealed that female patients had more fungal infections and herpes simplex infections. The number of reported SAEs did not differ between men and women. Unique in our study is the confounder corrected, longitudinal analysis of treatment satisfaction in male and female patients treated with biologics for psoriasis in daily practice care. As such, our study exceeds previous cross-sectional and longitudinal studies on treatment satisfaction with shorter follow-up duration.¹⁵

The purpose of this study was to find possible explanations for the lower drug survival with biologics in female patients, which has been reported before by several large studies.^{4–10,29} However, reasons for the lower drug survival in women remain scarce. We assessed treatment satisfaction because this is an important PRO related to adherence and patients' preferences.^{11,12,30} Therefore, lower treatment satisfaction in women might partly explain the lower drug survival in women.

In our cohort, female patients scored significantly lower on the 'global satisfaction' domain and were also less satisfied regarding 'side-effects' than men, although differences were small. Our post hoc analyses showed more AEoSI in female patients, with significantly more fungal infections and more herpes simplex infections in females. Adjustment for gender-related adverse events revealed no differences in significance. After sensitivity analyses with correction for recurrent episodes of infections, a trend of more mucosal fungal infections was seen in women (data not presented). These differences could explain the difference in satisfaction rates and might partly explain the lower drug survival rates in women. Despite possible reporting bias due to patient-reported adverse events, we can assume that the burden of patient-reported adverse events is higher than the burden of unreported adverse events. In general medicine, women tend to have more adverse drug reactions.^{20,31} Therefore, we suppose that differences regarding reported adverse events between men and women with psoriasis need attention. This could be conducive to the development of more personalized medicine.³²

Besides differences in side-effects between sexes, other differences in disease perception have been described and could explain the lower satisfaction among female patients. Lesuis et al.³³ demonstrated a higher symptomatic disease burden compared to male patients. Another study reported that women with psoriasis perceived a greater impact of their psoriasis on mental health and quality of life.³⁴ Whereas these results indicate worse subjective disease perception in female patients, it has been documented that men have more severe disease.^{24,25} This is also found in our study: baseline analyses (start of medication) showed that almost sixty per cent of the patients were male, and men had higher baseline PASI scores compared with women.

Our study is the first to provide a longitudinal analysis of treatment satisfaction with adalimumab, etanercept, infliximab, secukinumab and ustekinumab over 1 year of treatment, in order to investigate differences between male and female patients. Furthermore, we performed correction for possible confounders, and we investigated differences in adverse events between male and female patients. As such, our findings go beyond previously reported cross-sectional findings and longitudinal studies with shorter follow-up duration.¹⁵ For example, a previous BioCAPTURE study assessed treatment satisfaction with all biologics as one group in 106 patients for a period of 6 months.³ The present study contains data until 2018, from 315 male and female patients with 396 corresponding treatment episodes, with newer biologics for a period of 12 months. The latter is important, as satisfaction scores could change over time and patients are mostly on biologics for many years. Moreover, our gender-focused approach could contribute to more personalized medicine.

A limitation of this study is the possibility of responder bias as a result of questionnaire research and regarding side-effects. Furthermore, we had to deal with missing data due to non-responders to questionnaires and incomplete follow-up. We used LMMs, which are able to accommodate all available data with flexible assumptions regarding missing data.²⁷ Therefore, imputation of missing data was not useful, as estimated outcomes from our models would be similar. Still bias can occur as a result of incomplete prediction by the model due to missing data. When we analysed TSQM scores from the first vs. subsequent treatment episodes separately, we found no large differences in TSQM scores (data not presented). Furthermore, the LMMs accounted for the fact that some patients had more than one treatment episode. Correction for possible influence of the different types of biologics used was performed in the mixed models, although some of the groups were small.

In conclusion, this prospective, multicentre, longitudinal study shows that female patients are less satisfied with biological treatment for psoriasis over 1 year of treatment regarding TSQM 'side-effects' and 'global satisfaction' domains. Female patients reported more AEOs, with more fungal infections and herpes simplex infections. From a clinical perspective, this study shows that treatment with biologics for psoriasis is not the same for men and women. Our results might give an explanation for the earlier discontinuation with biological treatment of female patients. Further clarifying the background of gender differences in psoriasis patients treated with biologics is valuable to increase awareness and provide more personalized care according to the patients' needs. This might improve satisfaction and will consequently lead to better adherence, improved health outcomes, and reduced costs of treatment with biologics.³⁵

Acknowledgements

We thank all patients who completed questionnaires for the BioCAPTURE registry.

Table 2. Incidence rates per 100 patient years of serious adverse events (SAEs) and adverse events of special interest (AEoSI)

	Female			Male			Total		Rate ratio ^a	p-value ^b
	Number of AEs	Incidence per 100 PY	Number of AEs	Number of AEs	Incidence per 100 PY	Number of AEs	Incidence per 100 PY	Number of AEs		
SAEs (total)	41	9.8 (7.2-13.2)	48	7.1 (4.3-9.3)	89	8.1 (6.6-9.9)	1.39	0.13		
Life-threatening events	9	2.2 (1.1-3.9)	13	1.9 (1.1-3.2)	22	2.0 (1.3-3.0)	1.13	0.78		
Death	2	0.5 (0.1-1.6)	1	1.5 (0.1-7.3)	3	0.3 (0.7-7.5)	0.32	0.38		
(Prolonged) hospitalization	24	5.8 (3.8-8.4)	29	4.3 (2.9-6.1)	53	4.8 (3.7-6.3)	1.35	0.29		
Persistent or significant disability or incapacity	6	1.4 (0.6-3.0)	5	0.7 (0.3-1.6)	11	1.0 (0.5-1.7)	1.95	0.28		
Congenital anomaly or birth defects	0	-	0	-	0	-	-	-		
AEoSI (total)	120	28.8 (24.0-34.3)	109	16.1 (13.3-19.3)	229	20.9 (18.3-23.7)	1.79	<0.001		
Malignancies ^c	1	0.2 (0.01-1.2)	4	0.7 (0.2-1.4)	5	0.5 (0.2-1.0)	0.41	0.46		
Melanoma	1	0.2 (0.01-1.2)	4	0.7 (0.2-1.4)	5	0.5 (0.2-1.0)	0.41	0.46		
Nmsc	9	2.2 (1.1-4.0)	14	2.1 (1.2-3.4)	23	2.1 (1.4-3.1)	1.04	0.91		
Hematological cancers	1	0.2 (0.01-1.2)	0	-	1	0.1 (0.01-0.5)	-	-		
MACE	7	1.7 (0.7-3.3)	6	0.9 (0.4-1.8)	13	1.2 (0.7-2.0)	1.89	0.26		
Hematological events	1	0.2 (0.01-1.2)	0	-	1	0.1 (0.01-0.5)	-	-		
Neurological events	1	0.2 (0.01-1.2)	2	0.3 (0.1-1.0)	3	0.3 (0.1-0.7)	0.80	0.91		
Autoimmune diseases	4	1.0 (0.3-0.2)	1	0.2 (0.01-0.7)	5	0.5 (0.2-1.0)	6.50	0.08		
Severe infections leading to clinical admission	11	2.6 (1.4-4.6)	12	1.8 (1.0-3.0)	23	2.1 (1.4-3.1)	1.49	0.35		
TB, HIV, hepatitis	3	0.7 (1.8-2.0)	0	-	3	0.3 (0.1-0.7)	-	-		
Herpes infections										

Table 2. Continued

	Female		Male		Total		Rate ratio ^a	p-value ^b
	Number of AEs	Incidence per 100 PY	Number of AEs	Incidence per 100 PY	Number of AEs	Incidence per 100 PY		
Total	17	4.1 (2.5-6.4)	15	2.2 (1.3-3.6)	32	2.9 (2.0-4.1)	1.84	0.09
Herpes simplex	16	2.8 (2.3-6.1)	8	1.2 (0.6-2.2)	24	2.2 (1.4-3.2)	3.25	0.005
Herpes zoster	1	0.2 (0.01-1.2)	7	1.0 (0.5-1.1)	8	0.7 (0.3-1.4)	0.23	0.15
Fungal infections	38	9.1 (6.5-12.4)	28	4.1 (2.8-5.9)	66	6.0 (4.7-7.6)	2.20	0.001
Skin	22	5.3 (3.4-7.9)	26	3.8 (2.6-5.6)	48	4.4 (3.3-5.8)	1.37	0.28
Mucosa	16	3.8 (2.3-6.1)	2	0.3 (0.1-1.0)	18	1.6 (1.0-2.5)	12.99	<0.001
Adverse drug reactions and injection site reactions	17	4.1 (2.5-6.4)	16	2.4 (1.4-3.8)	33	3.0 (2.1-4.2)	1.73	0.12
Exacerbation of psoriasis	1	0.2 (0.01-1.2)	1	0.2 (0.01-0.7)	2	0.2 (0.03-0.6)	1.62	0.76
Liver fibrosis or steatosis	3	0.7 (1.8-2.0)	2	0.3 (0.1-1.0)	5	0.5 (0.2-1.0)	2.40	0.36
Depression	3	0.7 (1.8-2.0)	2	0.3 (0.1-1.0)	5	0.5 (0.2-1.0)	2.40	0.36
Diabetes mellitus	2	0.5 (0.1-1.6)	2	0.3 (0.1-1.0)	4	0.4 (0.1-0.9)	1.60	0.65

Number of adverse events are cumulative. Incidence rates per 100 patient years are n (95% confidence interval). Abbreviations: AE, adverse events; PY, patient years; NmSc, non melanoma skin cancer; MACE, major adverse cardiovascular event; TB, tuberculosis; HIV, human immunodeficiency virus.

^a Rate ratio based on female vs. male incidence rates per 100 patient years.

^b Mid-P exact test.

^c Excluding melanoma, NmSc, hematological cancers.

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Supplement

Table S1. Linear Mixed Model used to estimate TSQM subdomain 'Effectiveness' scores during one year follow up in male (n=188) and female (n=127) psoriasis patients treated with biologics, with a total of 396 treatment episodes

Variable	Estimate	Confidence Interval		p-value ^b
		lower limit	upper limit	
Intercept	56.574736	37.681539	75.467933	0.000
Sex				0.056
Female	-6.079310	-12.468738	2.684045	
Male	0 ^a	-	-	
Time from baseline visit (months)				0.270
3	-5.583075	-11.611985	0.445834	0.069
6	-3.718498	-9.675283	2.238287	0.220
9	-1.502726	-7.484442	4.478990	0.622
12	0 ^a	-	-	
Type of biologic				0.125
Adalimumab	12.054731	-5.195719	29.305182	0.170
Etanercept	7.673358	-9.840113	25.186829	0.389
Ustekinumab	11.245058	-5.917555	28.407672	0.198
Secukinumab	23.800312	3.415483	44.185141	0.022
Infliximab	0 ^a	-	-	
Presence of psoriatic arthritis				0.749
No	-1.083592	-7.756624	5.589441	
Yes	0 ^a	-	-	
Baseline 'Effectiveness' score	0.090775	-0.028088	0.209639	0.134

Abbreviations: TSQM, Treatment Satisfaction Questionnaire for Medication.

^a This parameter is set to zero because it is redundant.

^b P-values associated with type 3 tests of fixed effects.

Table S2. Linear Mixed Model used to estimate TSQM subdomain ‘Side effects’ scores during one year follow up in male (n=188) and female (n=127) psoriasis patients treated with biologics, with a total of 396 treatment episodes

Variable	Estimate	Confidence Interval		p-value ^b
		lower limit	upper limit	
Intercept	84.979259	72.030374	97.928144	0.000
Sex				0.047
Female	-4.862464	-9.657722	-0.067205	
Male	0 ^a	-	-	
Time from baseline visit (months)				0.814
3	-1.164955	-4.400261	2.070351	0.713
6	-0.626723	-3.853684	2.600237	0.630
9	-1.491320	-4.718840	1.736199	0.864
12	0 ^a	-	-	
Presence of psoriatic arthritis				0.689
No	-1.081897	-6.411700	4.247906	
Yes	0 ^a	-	-	
Baseline ‘Side Effects’ score	0.192050	0.105727	0.278373	0.000
Age (years)	-0.358227	-0.561115	-0.155340	0.001
Duration of psoriasis (years)	0.390678	0.185438	0.595918	0.000
Baseline PASI score	0.177580	-0.097200	0.452359	0.205

Abbreviations: TSQM, Treatment Satisfaction Questionnaire for Medication; PASI, Psoriasis Area and Severity Index.

^a This parameter is set to zero because it is redundant.

^b P-values associated with type 3 tests of fixed effects.

Table S3. Linear Mixed Model used to estimate TSQM subdomain 'Convenience' scores during one year follow up male (n=188) and female (n=127) psoriasis patients treated with biologics, with a total of 396 treatment episodes

Variable	Estimate	Confidence Interval		p-value ^b
		lower limit	upper limit	
Intercept	87.315022	66.116797	108.513247	0.000
Sex				0.817
Female	-0.553756	-5.270420	4.162908	
Male	0 ^a	-	-	
Time from baseline visit (months)				0.891
3	-0.775120	-4.771905	3.221666	0.703
6	-0.953353	-4.905800	2.999094	0.635
9	-1.588365	-5.578880	2.402149	0.434
12	0 ^a	-	-	
Type of biologic				0.035
Adalimumab	-13.668196	-24.601082	-2.735310	0.015
Etanercept	-12.999106	-24.463270	-1.534943	0.026
Ustekinumab	-8.558974	-19.335503	2.217555	0.119
Secukinumab	0 ^a	-	-	
Experience with prior biologics				0.255
Inexperienced (naïve)	2.701842	-1.970967	7.374650	
Experienced (non-naïve)	0 ^a	-	-	
Presence of psoriatic arthritis				0.726
No	0.943244	-4.376735	6.263223	
Yes	0 ^a	-	-	
Baseline 'Convenience' score	0.149877	0.030248	0.269506	0.014
Age (years)	-0.104230	-0.308290	0.099829	0.314
Duration of psoriasis	0.181522	-0.024385	0.387429	0.083
BMI	-0.295996	-0.728692	0.136701	0.178
Baseline PASI score	-0.097394	-0.423517	0.228729	0.557

Abbreviations: TSQM, Treatment Satisfaction Questionnaire for Medication; BMI, body mass index; PASI, Psoriasis Area and Severity Index.

^a This parameter is set to zero because it is redundant.

^b P-values associated with type 3 tests of fixed effects.

Table S4. Linear Mixed Model used to estimate TSQM subdomain ‘Global Satisfaction’ scores during one year follow up in male (n=188) and female (n=127) psoriasis patients treated with biologics, with a total of 396 treatment episodes

Variable	Estimate	Confidence Interval		p-value ^b
		lower limit	upper limit	
Intercept	84.401832	59.929612	108.874052	0.000
Sex				0.013
Female	-7.125133	-12.734091	-1.516176	
Male	0 ^a	-	-	
Time from baseline visit (months)				0.295
3	-3.835551	-8.052995	0.381893	0.075
6	-2.965285	-7.049413	1.118843	0.154
9	-1.568087	-5.716986	2.580813	0.458
12	0 ^a	-	-	
Type of biologic				0.001
Adalimumab	12.879123	-1.195679	26.953924	0.073
Etanercept	12.386024	-2.039380	26.811429	0.092
Ustekinumab	15.721841	1.858572	29.585110	0.026
Secukinumab	33.120088	17.262309	48.977866	0.000
Infliximab	0 ^a	-	-	
Presence of psoriatic arthritis				0.180
No	-4.310394	-10.639432	2.018645	
Yes	0 ^a	-	-	
Baseline ‘Global Satisfaction’ score	0.157906	0.049083	0.266729	0.005
BMI	-0.863576	-1.383930	-0.343221	0.001

Abbreviations: TSQM, Treatment Satisfaction Questionnaire for Medication; BMI, body mass index.

^a This parameter is set to zero because it is redundant.

^b P-values associated with type 3 tests of fixed effects.



CHAPTER 5.2

Risk of respiratory tract infections and serious infections in psoriasis patients treated with biologics: Results from the BioCAPTURE registry

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Abstract

Background

Limited real-world studies are available comparing infection risk between biologics for psoriasis.

Objectives

The primary aim was to determine the differential effect of currently available biologics on the risk of respiratory tract infections (RTI) among psoriasis patients in a real-world setting. Secondary aims were to explore the differential risk of all types of serious infections (SI) between biologics and to provide an early overview of SARS-CoV-2 infections during the pre-vaccine era.

Methods

Crude incidence rates of RTI and SI were calculated per 100 patient-years (PY) per biologic using prospective BioCAPTURE data. Negative Binomial Regression modeling was used to explore the risk of RTI. Frailty Cox proportional hazards modeling was used to estimate hazard ratios for the risk of the first SI. Confounders adjusted for both models were selected by a directed acyclic graph. A post hoc exploratory analysis of SARS-CoV-2 infection incidence rates during 2020 was performed.

Results

We included 714 patients with 1325 treatment episodes (3607.7PY between 2005 and 2020), in which 2224 RTI and 63 SI occurred. Among RTI, 1.3% were serious. The crude incidence rates were 61.7 (95% confidence interval [CI]: 59.1–64.3) per 100PY for RTI, and 1.8 (95% CI: 1.4–2.2) per 100PY for SI. Confounder adjusted analyses showed no differential risk of RTI between adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and guselkumab. For SI, no differential risk was found between biologics either. Extended single-center data showed 3.8 (95% CI: 2.2–6.1) SARS-CoV-2 infections per 100PY in 2020.

Conclusions

Confounder adjusted analyses showed no differential risks of RTI or SI between included biologics (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and guselkumab) in a prospective psoriasis patients cohort. In general, absolute numbers of all types of SI were low.

Introduction

Psoriasis is a chronic inflammatory skin disease for which biologics have enlarged treatment options.¹ To date, four classes of biologic therapies are available: tumor necrosis factor- α (TNF- α) inhibitors, interleukin-12/23 (IL-12/23) inhibitors, IL-17 inhibitors and IL-23 inhibitors. Inherent to their mechanism of action, biologics might increase infections risk. TNF- α plays a role in immune defense against intracellular infections, including viral infections.² IL-12 regulates T-cell mediated immunity by production of interferon- γ .³ IL-17 and IL-23 are involved in the regulation of T-helper 17 cells, providing cellular immunity.⁴ In addition, IL-17 is involved in the defense against fungal infections.⁵ Both IL-17 and IL-23 seem important in mucosal immunity, with antagonizing resulting in a potentially increased risk of respiratory tract infections (RTI).⁶

Evidence regarding infection risk and types or course of infections among biologic users is necessary, as it may guide treatment choice and treatment decisions in case of infections (e.g., continuing or interrupting treatment). Predicting infection risk seems also important from patients' perspectives.⁷ The COVID-19 pandemic resulted in attention to the risk of RTI in psoriasis patients on biological therapies, as the risk of RTI might relate to susceptibility to SARS-CoV-2 infections. RTI are the most frequently reported adverse events (AEs) among biologic users in trials and registries.^{8–14} Meta-estimates showed an increased risk of RTI in IL-17 inhibitors compared with placebo, but not for TNF- α or IL-23 inhibitors.^{15–17} However, trial data could lack generalizability due to short follow-up and selective patient populations.^{18–20} To our knowledge, daily practice studies focusing on the risk of RTI specifically are sparse.

Regarding the risk of serious infections (SI), several observational studies have assessed the risk of SI among biologic users, but different comparators and methods were used, resulting in conflicting results. For instance, increased risks of SI were reported,^{21–23} while other studies did not observe higher risks for biologics compared with conventional systemic treatments.^{24–29} Limited real-world studies comparing SI risk between biologics, including newer generation biologics, are available.^{27,30,31}

In conclusion, more comparative real-world data regarding infection risk in psoriasis patients treated with biologics is warranted to guide tailored treatment choices. COVID-19 highlighted the need for more data regarding RTI in this population. Therefore, the primary aim of this study was to determine the differential effect of currently available biologics on the risk of RTI among psoriasis patients in a real-world setting. Secondary aims were to explore the differential risk of all SI between

biologics and to provide an early overview of SARS-CoV-2 infections including outcomes in our cohort during the pre-vaccine era.

Materials and Methods

Participants and data collection

This study was based on data from the prospective Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE).³² BioCAPTURE was approved by the local ethical committee (Arnhem-Nijmegen) in compliance with the Declaration of Helsinki 2008, and local regulations. All patients gave written informed consent. Treatment choices were made by the treating clinicians, without an imposed national preference policy.

Patient and treatment characteristics were extracted from BioCAPTURE. Baseline characteristics included sex, age at the start of biologic, type of biologic, duration of psoriasis until the start of biologic, body mass index (BMI), baseline Psoriasis Area and Severity Index (PASI) score, history of biologic use, concomitant systemic treatment (e.g., methotrexate), lifestyle factors and medical history. Specific information regarding AEs was collected prospectively and included severity, follow-up, hospitalization and outcomes. AEs were identified by the site investigator and reviewed by two authors (LvdS and JvdR). RTIs included upper RTI, flulike symptoms, pneumonia, sinusitis, general airway infections, bronchitis, influenza, pharyngitis and laryngitis.¹⁵ We defined SI as infections associated with (1) death, (2) lifethreatening condition, (3) persistent/significant disability or incapacity, (4) cause or prolongation of hospitalization and/or (5) another medically important condition including the use of intravenous antimicrobial therapy. Serious RTI contributed to both groups. Infections that occurred before the start of exposure to the biologic, or after exposure ended, were not included.

For each biologic in the registry, the total number of treatment episodes (TE) was extracted. One TE accounted for the time of active treatment with a biologic; interruptions with a maximum of 90 days were accepted. Each patient could contribute to more than one TE, that is, in the case of using different biologics over time. The index date (initiation of follow-up) for the cohort was the start date of biologic therapy. Follow-up started at the index date until: (1) death, (2) withdrawal from the registry, (3) last data cut, (4) 90 days after discontinuation of treatment or (5) switching of treatment (whichever came first). The corresponding number of exposed patient years (PY) on the drug was calculated. Biologics with <50PY of follow-up were excluded from the analysis.

Covariates

We identified a sufficient set of confounders using directed acyclic graphs (DAG). DAGs are a graphical approach for identifying confounding variables when estimating causal effects, based on theoretical assumptions about relationships between variables.^{33,34} See **Figure 1** for the DAG and **Appendix S1** for additional information. Based on the DAG, the minimal adjustment set consisted of the variables age, BMI, disease severity (PASI), history of previous biologic use, inflammatory arthritis, pulmonary disease, history of (latent) tuberculosis and history of infections (**Figure 1**). History of infections was defined as ≥ 1 infection requiring prescription medication within 3 years of the index date. We did not include immunodeficiency syndromes, as no cases were present. A sufficient set of confounders resulting from the DAG was included in all multivariable analyses. Missing data were imputed in a multiple imputation model of 10 cycles.

Statistical analyses

Patients' characteristics were summarized. Depending on the distribution, data were presented as absolute numbers with percentages, means with standard deviations (SD), or medians with interquartile ranges (IQR). Crude incidence rates with 95% confidence intervals (CI) of RTI and SI were calculated per 100PY for each biologic. SI were summarized to describe the type of infection and relevant characteristics. Mixed negative binomial regression (NBR) modeling with maximum-likelihood estimations (LaPlace) was used to estimate adjusted incidence rate ratios (aIRR) for the risk of RTI corrected for confounders. This model was chosen as RTI was expected to occur relatively frequently during follow-up. NBR is used for modeling over-dispersed count variables (i.e., the variance is greater than the mean).³⁵ All reported RTIs were counted and included in the model. The log function of treatment duration in years was used as offset time variable. Based on the model, estimated means (EM) of expected numbers of RTI per biologic over 1 year were calculated.

Frailty Cox proportional hazards regression modeling with a time scale of PY was used to estimate hazard ratios (HR) for the risk of first SI. A frailty Cox model is an extension of the proportional hazard model and was chosen to correct for clustering of multiple TEs within patients. Biologic dose changes over time were not included, as Cox regression models are not able to include time-varying factors. However, we checked whether high-normal-low dosages were used at the time of SI. Each biologic was consecutively entered into the model as the reference to calculate HR for explorative, pairwise comparisons. The proportionality assumption was tested in the final model. Both models were based on the imputed data set. Hence, results were based on pooled estimates.

Data were analyzed using SPSS Statistics 25 (IBM, Armonk, NY, USA), and SAS 9.4 (SAS Institute Inc.).

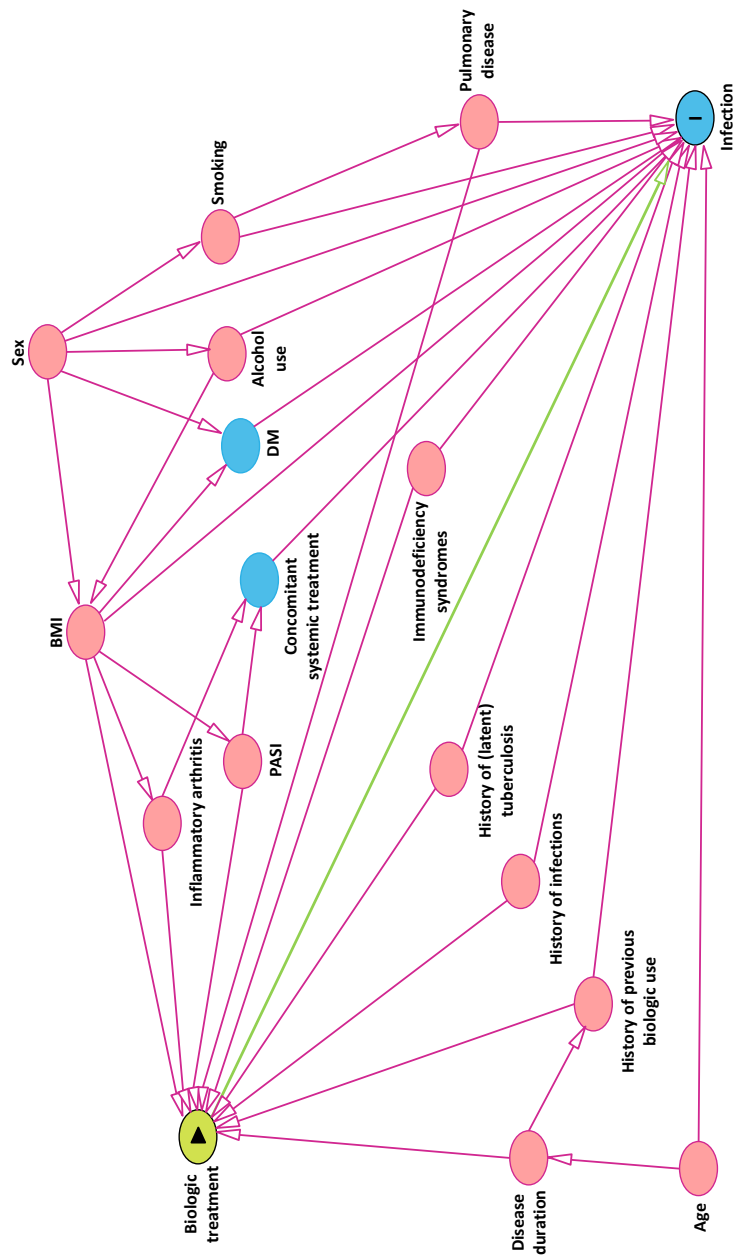


Figure 1. Directed acyclic graph (DAG) for biologic exposure and the association with infections.

Based on the DAG, the minimal adjustment set of variables to include in the multivariable models are: age, BMI, PASI, history of previous biologic use, concomitant inflammatory arthritis, pulmonary disease, history of (latent) tuberculosis, history of infections and immunodeficiency syndromes.

Abbreviations: BMI, body mass index; PASI, Psoriasis Area and Severity Index.

Post hoc exploratory analysis of SARS-CoV-2 infections

Exploratory analysis of SARS-CoV-2 infections was performed to provide an up-to-date overview of incidence rates in 2020. Reported infections from one center (Radboudumc) in BioCAPTURE during 2020 were included, as data from other participating centers were not yet available in the BioCAPTURE database. Incidence rates were calculated based on the number of events per 100PY for TEs that had been active in 2020. As during the timeframe of data collection no COVID-19 vaccines were available in the Netherlands, vaccination status was not incorporated in our analysis.

Results

In total, 714 patients with 1325 TEs between 2005 and 2020 were included, resulting in 3607.7PY of follow-up at the time of analysis. Certolizumab pegol, brodalumab and risankizumab had <50PY of follow-up and were therefore excluded from analyses. Baseline demographic and disease characteristics of patients per TE are summarized in **Table 1**. For the number of missings per characteristic, see supplementary **Table S1**. Adalimumab had the highest number of TEs (n=404), whereas etanercept had the longest follow-up duration (1142.5PY). The newer generation biologics (IL-17 and IL-23 inhibitors) had more patients with a history of biologic use (**Table 1**). Infliximab and ixekizumab users had most frequently psoriatic arthritis (PsA) (n=23 [62.2%] and n=26 [41.9%], respectively).

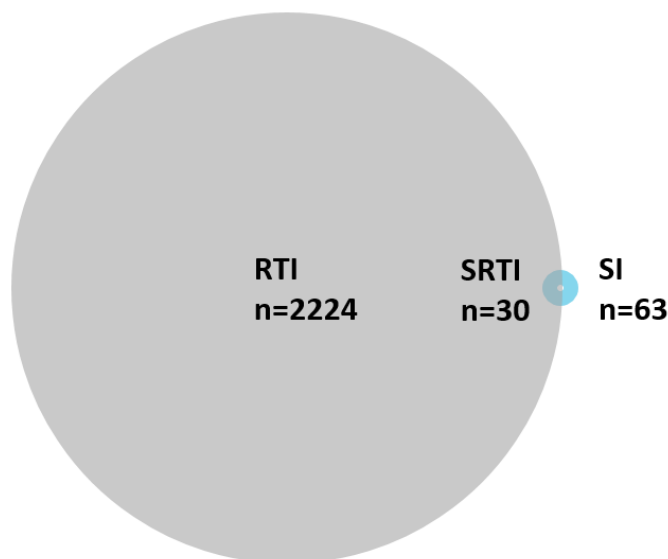


Figure 2. Representation of respiratory tract infections, serious respiratory tract infections, and serious infections within the total cohort.

Table 1. Baseline patient demographics and disease characteristics split per biologic per treatment episode (TE)

	Adalimumab (404 TE, 1113.6 PY)	Etanercept (330 TE, 1142.5 PY)	Infliximab (37 TE, 74.8 PY)	Ustekinumab (347 TE, 999.6 PY)	Secukinumab (94 TE, 139.6 PY)	Ixekizumab (62 TE, 82.8 PY)	Guselkumab (51 TE, 54.8 PY)
Demographics							
Age (years) ^a	49.3 ± 13.6	47.7 ± 13.0	48.2 ± 13.0	48.9 ± 13.6	51.4 ± 12.3	49.8 ± 11.8	49.9 ± 13.8
Sex (male)	246 (60.9%)	194 (58.8%)	16 (43.2%)	192 (55.3%)	46 (48.9%)	32 (51.6%)	27 (52.9%)
BMI (kg/m ²) ^b	28.2 [25.2-31.9]	27.8 [24.6-31.5]	29.8 [27.3-34.0]	28.4 [25.3-32.9]	27.4 [24.9-31.2]	30.9 [25.8-34.3]	29.8 [27.5-36.0]
Disease characteristics							
Disease duration (years) ^b	19.3 [12.2-31.2]	21.1 [14.1-31.1]	19.7 [13.8-23.7]	18.9 [12.2-27.6]	22.5 [16.2-31.6]	21.6 [13.3-29.7]	20.6 [14.8-28.0]
Baseline PASI score ^b	10.1 [6.4-14.6]	12.0 [8.9-17.4]	13.4 [8.1-20.0]	11.1 [6.7-17.0]	10.0 [5.9-14.3]	7.4 [5.2-11.2]	8.3 [4.8-15.0]
History of previous biologic use (yes)	219 (54.2%)	156 (46.3%)	36 (97.3%)	233 (67.1%)	90 (95.7%)	59 (95.2%)	46 (90.2%)
Concomitant systemic treatment at baseline ^c	85 (21%)	68 (20.6%)	15 (40.5%)	59 (17%)	10 (10.6%)	5 (8.1%)	4 (7.8%)
No. cycles with concomitant systemic treatment	118 (29.2%)	95 (28.8%)	16 (43.2%)	64 (18.4%)	16 (17%)	9 (14.5%)	5 (9.8%)
Lifestyle factors							
Alcohol use (yes)	273 (67.6%)	222 (67.3%)	17 (45.9%)	221 (63.7%)	51 (54.3%)	35 (58.1%)	28 (54.9%)
Smoking							
Never smoked	102 (25.2%)	78 (23.6%)	6 (16.2%)	89 (25.6%)	24 (25.5%)	20 (32.3%)	11 (21.6%)
Current smoking	121 (30.0%)	118 (35.8%)	16 (43.2%)	115 (33.1%)	31 (33.0%)	14 (22.6%)	10 (19.6%)
Stopped smoking	155 (38.4%)	125 (37.9%)	11 (29.7%)	113 (32.6%)	31 (33.0%)	25 (40.3%)	23 (45.1%)
Medical history							
PsA	113 (28%)	90 (27.3%)	23 (62.2%)	92 (26.5%)	30 (31.9%)	26 (41.9%)	12 (23.5%)
Other inflammatory arthritis	6 (1.5%)	5 (1.5%)	3 (8.1%)	8 (2.3%)	3 (3.2%)	2 (3.2%)	1 (2%)
Cardiovascular disease ^d	50 (12.4%)	46 (13.9%)	5 (13.5%)	37 (10.7%)	14 (14.9%)	10 (16.1%)	6 (11.8%)

Table 1. Continued

Medical history	Adalimumab (404 TE, 1 113.6 PY)	Etanercept (330 TE, 1 142.5 PY)	Infliximab (37 TE, 74.8 PY)	Ustekinumab (347 TE, 999.6 PY)	Secukinumab (94 TE, 139.6 PY)	Ixekizumab (62 TE, 82.8 PY)	Guselkumab (51 TE, 54.8 PY)
Pulmonary disease ^e	63 (15.6%)	33 (10%)	7 (18.9%)	55 (15.9%)	19 (20.2%)	7 (11.3%)	8 (15.7%)
Hepatic disease	44 (10.9%)	29 (8.8%)	5 (13.5%)	41 (11.8%)	11 (11.7%)	15 (24.2%)	11 (21.6%)
Chronic renal disease	7 (1.7%)	12 (3.5%)	1 (2.7%)	14 (4.0%)	2 (2.1%)	2 (3.2%)	1 (2.0%)
Malignancy ^f	14 (3.5%)	18 (5.5%)	1 (2.7%)	11 (3.2%)	2 (2.1%)	0	1 (2.0%)
Nmsc ^g	19 (4.7%)	13 (3.9%)	3 (8.1%)	13 (3.7%)	7 (7.4%)	2 (3.2%)	1 (2.0%)
Diabetes mellitus	54 (13.4%)	49 (14.8%)	14 (37.8%)	43 (12.4%)	16 (17.0%)	13 (21.0%)	9 (17.6%)
Inflammatory bowel disease	12 (3.0%)	5 (1.5%)	2 (5.4%)	11 (3.2%)	1 (1.1%)	1 (1.6%)	3 (5.9%)
Significant infections ^g	17 (4.2%)	14 (4.2%)	0	9 (2.6%)	3 (3.2%)	2 (3.2%)	4 (7.8%)
Past TB (incl. LTBI)	20 (5.0%)	18 (5.5%)	5 (13.5%)	22 (6.3%)	2 (2.1%)	5 (8.1%)	1 (2.0%)
Hepatitis B or C	8 (2.0%)	11 (3.3%)	0	14 (4.0%)	1 (1.1%)	3 (4.8%)	1 (2.0%)
Immunodeficiency syndromes	0	0	0	0	0	0	0
Psychiatric illness (anxiety, depression)	36 (8.9%)	34 (10.3%)	5 (13.5%)	31 (8.9%)	8 (8.5%)	6 (9.7%)	3 (5.9%)

Data are n (%) unless otherwise indicated. Abbreviations: TE, treatment episode; PY, patient years; SD, standard deviation; IQR, interquartile range; BMI, body mass index; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; Nmsc, non-melanoma skin cancer; TB, tuberculosis; LTBI, latent tuberculosis infection. Missings: see supplementary table S1.

^a Mean $\pm$ SD

^b Median [IQR]

^c Concomitant systemic treatment include acitretin, ciclosporin, fumaric acid esters, and methotrexate.

^d Cardiovascular disease include MACEs (incident myocardial infarction, stroke), heart failure, coronary artery disease, coronary or peripheral revascularization, atrial fibrillation, transient ischemic attack, valvular disease, pericarditis (non-infectious).

^e Pulmonary disease include asthma, COPD, OSAS.

^f Nmsc and malignancies were counted once in case of recurrent disease or more than one episode per patient.

^g Significant infections were defined as infections requiring treatment within 3 years before registry enrollment.

Crude incidence rates and nature of infections

In the total cohort, cumulative numbers of 2224 RTI and 63 SI were reported (**Table 2**). Thirty infections were serious RTI and contributed to both groups (**Figure 2**). Accordingly, 1.3% of all RTIs were serious.

RTI

For RTI, the total cumulative crude incidence rate was 61.7 per 100PY, with the highest rates for infliximab (72.2, 95% CI: 54.8–93.5), etanercept (67.4, 95% CI: 62.8–72.3) and ixekizumab (62.8, 95% CI: 47.4–81.7) and lowest rates for secukinumab (48.7, 95% CI: 38.1–61.4) (**Table 2**). Of all RTI, 6 (0.3%) were highly suspected or proven SARS-CoV-2 infections. The most frequently reported RTIs were ‘upper RTI’ or ‘flu-like symptoms’ (**Table S2**).

SI

The cumulative crude incidence rate for SI was 1.8 per 100PY. Stratified by biologic, rates of SI were highest for ixekizumab (6.0, 95% CI: 2.2–13.4) and infliximab (4.0, 95% CI: 1.0–10.9) and lowest for secukinumab (0.7, 95% CI: 0.1–3.5).

Table 2. Crude incidence rates of respiratory tract infections (RTI) and serious infections (SI)

Treatment	TE (n)	PY (n)	RTI (n)	Incidence per 100PY	SI (n)	Incidence per 100PY
Adalimumab	404	1113.6	669	60.1 (55.7-64.8)	19	1.7 (1.1-2.6)
Etanercept	330	1142.5	770	67.4 (62.8-72.3)	21	1.8 (1.2-2.8)
Infliximab	37	74.8	54	72.2 (54.8-93.5)	3	4.0 (1.0-10.9)
TNF-α inhibitors	771	2330.9	1493	64.1 (60.9-67.4)	43	1.6 (1.4-2.5)
Ustekinumab	347	999.6	582	58.2 (53.6-63.1)	13	1.3 (0.7-2.2)
IL-12/23 inhibitor	347	999.6	582	58.2 (53.6-63.1)	13	1.3 (0.7-2.2)
Secukinumab	94	139.6	68	48.7 (38.1-61.4)	1	0.7 (0.1-3.5)
Ixekizumab	62	82.8	52	62.8 (47.4-81.7)	5	6.0 (2.2-13.4)
IL-17 inhibitors	156	222.4	120	53.9 (44.9-64.3)	6	2.7 (1.1-5.6)
Guselkumab	51	54.8	29	52.9 (36.1-75.0)	1	1.8 (0.1-9.0)
IL-23 inhibitor	51	54.8	29	52.9 (36.1-75.0)	1	1.8 (0.1-9.0)
Total	1325	3607.7	2224	61.7 (59.1-64.3)	63	1.8 (1.4-2.2)

Incidence rates per 100 patient years are n (95% CI). Abbreviations: TE, treatment episodes; PY, patient years (e.g., number of days exposed / 365.25); RTI, respiratory tract infections; SI, serious infections.

The most commonly reported SI were lower RTI or lung infections ($n = 27$, 42.9%), followed by skin and soft tissue infections ($n = 13$, 20.6%) (**Table S3**). Of all SI, 2 (3.2%) were highly suspected SARS-CoV-2 infections. In total 3 SI (4.8%) resulted in death. Regarding biologic doses at the time of SI, 13 patients (20.6%) used a higher

dose than the standard dose, and 2 patients (3.2%) used a lower dose. Other patients used the standard dose. See **Table S4** for detailed patient characteristics per SI.

Adjusted rates of RTI

A multivariable negative binomial regression model showed no statistically significant association between each biologic and RTI risk ($p > 0.05$). See **Table S5** for detailed model information. Stratified by biologic, we observed trends of higher RTI rates for the TNF- α inhibitors compared to the other biologics, whereas for secukinumab and guselkumab trends towards lower rates were observed (**Figure 3**). Estimated means (EM) of the expected number of RTI occurring in 1 year are shown in **Figure 4**. Estimated numbers of RTI per year were highest for etanercept (EM 0.97, 95% CI: 0.78–1.21) and lowest for secukinumab (EM 0.70, 95% CI: 0.50–0.99), but differences were not statistically significant.

Adjusted analysis for the risk of first SI

A frailty Cox proportional hazards regression model showed no difference in risk of first SI ($n=56$) between biologics ($p > 0.05$) (**Figure 3**). For detailed model information see **Table S6**. The proportionality assumption was met for each imputed data set (data not shown).

Crude incidence rates of SARS-CoV-2 infections

Cohort characteristics of patients included in the extended analysis of SARS-CoV-2 infections are shown in **Table S7**. Of 482 TEs among 358 patients, 22 SARS-CoV-2 infections were reported ($n=15$ [68.2%] proven, and $n=7$ [31.8%] highly suspected infections). One patient was admitted to the hospital. No complications occurred. Two-thirds of the patients recovered, and 31.8% recovered with sequelae. The total cumulative crude incidence rate was 5.6 (95% CI: 3.6–8.3) per 100PY. For proven infections only, this was 3.8 (95% CI: 2.2–6.1) (**Table 3**).

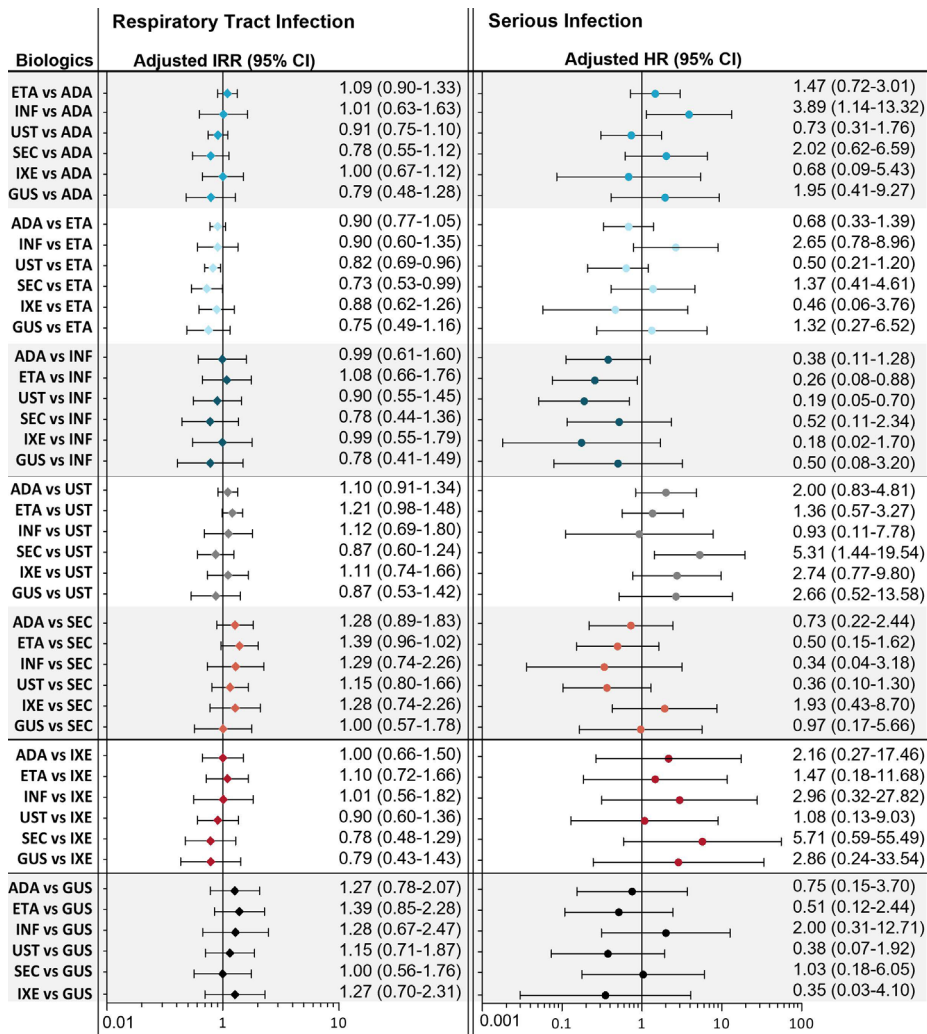


Figure 3. Forest plots for adjusted Incidence Rate Ratios for risk of Respiratory Tract Infections and Hazard Ratios for the risk of first Serious Infection stratified by biologic.

Discussion

The results of this prospective cohort study on RTI in psoriasis patients using biologics, showed no differences in risk of RTI between adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and guselkumab. Among 2224 RTI, only 1.3% were serious. Generally, crude incidence rates of all SI were less than 2 per 100PY, and in an explorative comparison, no differential risk was found between biologics either.

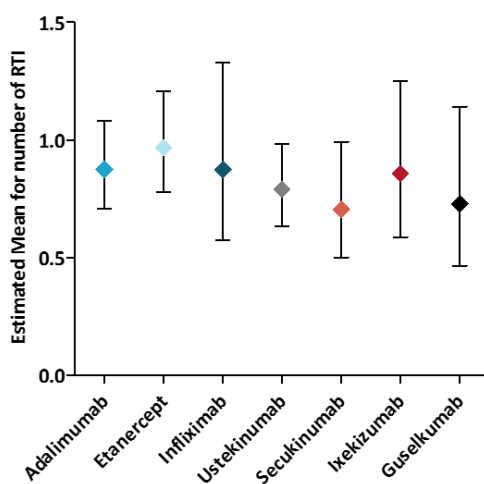


Figure 4. Estimated Means for number of expected RTI in one year per biologic based on the negative binomial regression model.

Table 3. Crude incidence rates of SARS-CoV-2 infections during 2020

Treatment	TE (n) ^a	PY (n)	SARS-Cov-2 infections (all) (n)	Incidence per 100PY	SARS-Cov-2 infections (proven) (n)	Incidence per 100PY
Adalimumab	151	120.7	5	4.1 (1.5-9.2)	2	1.7 (0.3-5.5)
Certolizumab pegol	9	4.8	1	21.1 (1.1-103.6)	0	-
Etanercept	57	46.3	5	10.8 (3.9-23.9)	2	4.3 (0.7-14.3)
Infliximab	7	5.6	0	-	0	-
TNF-α inhibitors	224	177.4	11	6.2 (3.3-10.8)	4	2.3 (0.7-5.4)
Ustekinumab	144	128.4	7	5.45 (2.4-10.8)	7	5.5 (2.4-10.8)
IL-12/23 inhibitor	144	128.4	7	5.45 (2.4-10.8)	7	5.5 (2.4-10.8)
Secukinumab	33	25.3	2	7.90 (1.3-26.1)	2	7.9 (1.3-26.1)
Ixekizumab	37	30.7	1	3.26 (0.2-16.1)	1	3.3 (0.2-16.1)
Brodalumab	8	6.5	1	15.3 (0.8-75.5)	1	15.3 (0.8-75.5)
IL-17 inhibitors	78	62.5	4	6.4 (2.0-15.4)	4	6.4 (2.0-15.4)
Guselkumab	25	19.5	0	-	0	-
Risankizumab	11	6.7	0	-	0	-
IL-23 inhibitors	36	26.2	0	-	0	-
Total	482	394.5	22	5.6 (3.6-8.3)	15	3.8 (2.2-6.1)

Incidence rates per 100 patient years are n (95% CI). Abbreviations: TE, treatment episodes; PY, patient years (e.g., number of days exposed / 365.25).

^aBased on extended single-centre data until December 2020.

Despite RTI being among the most frequently reported AEs in biologic users, there is limited real-world data focusing on RTI specifically. Our adjusted, comparative analysis showed no association between type of biologic and RTI risk. Nevertheless, trends toward higher adjusted rates for TNF- α inhibitors, and trends towards lower adjusted rates for secukinumab and guselkumab were observed. In contrast, a Swedish cohort study showed a slightly increased adjusted risk of RTI for secukinumab compared to ustekinumab.²⁸ In clinical trials, most data showed no major increases in the risk of RTI for biologics compared to placebo,^{36–39} except for one meta-analysis which showed an increased risk for IL-17 inhibitors.¹⁵ Nevertheless, meta-analyses are not able to account for selective patient populations in trials. Additionally, head-to-head comparisons are more informative as clinicians are nowadays often able to choose between biologics. Therefore, our analysis of detailed real-world data could add to previous studies regarding infection risk and biological treatment.

In our study, higher crude rates and trends towards higher adjusted risks of RTI and SI for infliximab were observed. Higher infection risk in infliximab users compared with other biologics has been reported before.^{22,23,29} In our cohort, characteristics of infliximab patients differed from the other groups. For instance, infliximab patients were more likely to have PsA. It could therefore be debated whether infliximab should have been excluded from analyses. However, our models corrected for treatment effects and confounders.

As stated, our adjusted analysis did not reveal associations between the included biologics (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and guselkumab) and risk of SI. Of note, this comparison is based on a low event rate and could therefore have been underpowered. Most previously conducted observational studies did not observe an increased risk of SI among biologics users as well, but biologics were compared with nonbiologic systemic treatments and included mostly the 'older' generation biologics.^{24–29} Regarding the 'newer' biologics, few studies are available. Li et al. found no difference in SI risk across TNF- α , IL-17, or IL-12/23 inhibitors in biologic-experienced patients, although in biologic-naïve patients a lower risk for ustekinumab versus TNF- α and IL-17 inhibitors was observed.²⁷ Jin et al. reported lower risks of hospitalized SI for ustekinumab as well when compared with TNF- α , IL-17 inhibitors, and apremilast.³⁰ A French cohort showed lower risks for ustekinumab users versus etanercept, whereas the risk of SI was higher for infliximab and adalimumab. For IL-17 inhibitors, guselkumab and apremilast, risks were not increased.³¹ However, comparisons between other biologics were not made.

Although some trends were seen, the results of our study might indicate that the risk of RTI or SI should not be a discriminating factor when choosing between biologics. However, integrating our data with other real-world data by means of meta-analysis would be of added value. As different methods are used across studies for estimating infection risk among biologic users, comparison of studies could be challenging. Focusing on harmonizing methods of analyzing and reporting observational data is therefore necessary. Within such analyses, correction for confounders seems highly important, as actual treatment decisions could be based on risk factors for AEs, including infections.

Our analysis of RTI might not directly answer the question of whether biologic users are more prone to SARS-CoV-2 infections. However, rates of SARS-CoV-2 infections in our cohort were comparable to the total Dutch population during 2020 (3.8 [95% CI: 2.2–6.1] per 100PY in our cohort vs. 4.7 [95% CI: 4.7–4.8] for the Dutch population).⁴⁰ A few patients were admitted to the hospital and no complications occurred, which is in line with previous studies.^{41–46} However, our data only stretches the first period of the pandemic in a single-center setting, and risk-mitigating behaviour could contribute to the low rates observed and lower risk of adverse COVID-19 outcomes.⁴⁷ This should be further investigated. Likewise, the impact of the COVID-19 pandemic on infection risk in general and the possible influence of shielding behavior is an important issue for future research.

The main strength of this study is the comparative, confounder-adjusted analysis of currently used biologics in a real-world setting. In addition, we focused on RTI, which might be of special interest in the COVID-19 era. Unique in our approach is the use of statistical models which accounted for the clustering of several TEs per patient. Furthermore, we selected confounders through a DAG, which is a relatively new method within the field of dermatological research. DAGs consider the role of each variable in relation to the exposure and the outcome of interest. Based on graphical theories, a minimally sufficient set of variables can be selected,³⁴ resulting in more precise estimates as over-adjustment is prevented. In contrast, the use of statistical criteria for covariate selection could introduce selection bias and residual confounding if nonconfounders are included or potential confounders are excluded.⁴⁸ Therefore, we believe that the selection of covariates by using a DAG improved our analyses.

The main limitation of our study is the smaller group size for the newer biologics, which may have resulted in inadequate power to detect differences. In addition, risankizumab, tildrakizumab and brodalumab were not included due to insufficient

follow-up data. For SI, the low absolute numbers can lead to a type II error. However, this low SI rate in a large group with long follow-up poses the question if possible small differences only detected in extremely large groups, would be clinically relevant. Another limitation is that due to the observational study design, information biases might be present. Underreporting and misclassification of infections might occur, but this is unlikely to differ between biologics. Furthermore, information regarding influenza or pneumococcal vaccination status was not included in BioCAPTURE. Influenza vaccination is however frequently advised to patients on biologics in the Netherlands, but pneumococcal vaccines are not advised on a standard basis. Although vaccination status is unlikely to differ between biologics, it might have influenced rates of reported RTI.

In conclusion, we observed no differences in confounder adjusted risks of RTI between adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and guselkumab in a prospective daily practice cohort of psoriasis patients. Although RTI were frequently reported, only a fraction of RTIs were serious. Generally, among 1325 TE of TNF- α , IL-12/23, IL-17 and IL-23 inhibiting biologics, crude rates of SI were low (<2 per 100PY). Rates of SARS-CoV-2 infections in our cohort thus far did not seem to signal increased COVID-19 susceptibility, although the impact of shielding behavior was not incorporated. Replication of these findings in other real-world cohorts is important. In connection with the still growing arsenal of biologics for psoriasis, such data could add to treatment decisions within a personalized approach.

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Supplement

Appendix S1. Directed Acyclic Graphs (DAGs) – extended methods

DAGs are non-parametric graphical representations of assumed causal relations of measurements and variables in a specific context.^{1,2} DAGs are acyclic, e.g., they contain no feedback loops as variables cannot cause itself. See **Figure 1** for the DAG specified for the current study. Within the graph, variables are connected by unidirectional arrows, depicting the hypothesized relationship between them. Arrows flowing in the same direction represent a causal path (pink lines). The total causal effect of an exposure on an outcome, is the effect transmitted through all causal paths connecting the exposure to the outcome. In our DAG, the total effect (e.g., biologic treatment on occurrence of infections, green line) resembles the direct effect as there are no indirect effects of influence. A variable is a confounder of the exposure-outcome effect if it is a common cause of both the exposure and the outcome. Descendant variables within the DAG which lie between a confounder and the exposure or outcome are called proxy confounders (for example 'Smoking' and 'Alcohol use'). The confounding effect is transmitted through these variables. Proxy confounders which are directly caused by the exposure and in turn cause the outcome (e.g., they also lie directly between the exposure and the outcome), are called mediators. Such variables were not identified in our DAG (**Figure 1**). Variables which cause the outcome but are not caused by nor cause the exposure are called competing exposure variables or predictors of the outcome (blue variables). Adjustment for competing exposure variables does not affect bias, but might improve precision at cost of the degrees of freedom of linear regression models.¹ As we mainly focused on the relationship between biologic treatment and infections, other possible predicting factors for infections such as personal hygiene, other comedication, and other lifestyle factors were not included.

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Table S1. Missing data per variable

Variable	Adalimumab (404 TE)	Etanercept (330 TE)	Infliximab (37 TE)	Ustekinumab (347 TE)	Secukinumab (94 TE)	Ixekizumab (62 TE)	Guselkumab (51 TE)	Total ^a
Age	2	0	0	1	1	1	0	5 (0.4%)
Sex	7	0	0	12	3	2	2	26 (1.7%)
Disease duration	23	3	0	20	7	2	5	60 (4.5%)
BMI	43	33	6	54	24	13	19	171 (12.9%)
Alcohol	27	9	4	29	9	4	8	90 (6.8%)
Smoking	26	9	4	30	8	3	7	87 (6.6%)
PASI	58	28	6	60	17	10	4	110 (8.3%)

^aData are n (%) of total number of treatment episodes (n=1325). Abbreviations: BMI, body mass index; PASI, psoriasis area and severity index; TE, treatment episode.

Table S2. Types of respiratory tract infections per biologic

	Airway infection - general	Bronchial infection	Influenza	Laryngitis	Lung infection (pneumonia)	Pharyngitis	Sinusitis	Upper RTI/flu-like symptoms	Total
Adalimumab	18	11	4	0	49	24	18	545	669
Etanercept	19	20	2	1	22	35	19	652	770
Infliximab	2	1	0	0	1	3	6	41	55
TNF-α inhibitors	39	32	6	1	72	62	43	1238	1493
Ustekinumab	12	1	0	0	34	11	13	510	581
IL-12/23 inhibitor	12	1	0	0	34	11	13	510	581
Secukinumab	1	2	0	0	2	1	0	63	69
Ixekizumab	3	0	0	0	4	2	0	43	52
IL-17 inhibitors	4	2	0	0	6	3	0	106	121
Guselkumab	1	0	0	0	4	0	0	24	29
IL-23 inhibitor	1	0	0	0	4	0	0	24	29
Total^a	56 (2.5%)	35 (1.6%)	6 (0.3%)	1 (0.04%)	116 (5.2%)	76 (3.4%)	56 (2.5%)	1878 (84.4%)	2224

^aData are n (%) of total number of respiratory tract infections (RTI).

Table S3. Types of serious infection per biologic

	Abdominal and gastro-intestinal infections	Bone and joint infections	Lower respiratory tract and lung infections	Other	Post-operative infections	Sepsis	Skin and soft tissue infections	Upper respiratory tract infections	Urinary tract infections	Total
Adalimumab	4	0	7	1	0	1	4	0	2	19
Etanercept	1	2	7	1	1	1	5	2	1	21
Infliximab	0	0	1	0	0	0	2	0	0	3
TNF-α inhibitors	5	2	15	2	1	2	11	2	3	43
Ustekinumab	1	0	10	0	1	0	0	1	0	13
IL-12/23 inhibitor	1	0	10	0	1	0	0	1	0	13
Secukinumab	0	0	0	0	0	1	0	0	0	1
Ixekizumab	0	1	1	0	0	0	2	0	1	5
IL-17 inhibitors	0	1	1	0	0	1	2	0	1	6
Guselkumab	0	0	1	0	0	0	0	0	0	1
IL-23 inhibitor	0	0	1	0	0	0	0	0	0	1
Total^a	6 (9.5%)	3 (4.8%)	27 (42.9%)	2 (3.2%)	2 (3.2%)	3 (4.8%)	13 (20.6%)	3 (4.8%)	4 (6.3%)	63

^aData are n (%) of total number of serious infections.

Table S4. Serious infections with corresponding patient and disease characteristics

Infection characteristics			Treatment characteristics		Lifestyle factors		Medical history					
Serious infection type	Narrative description	Time until SI (days)	Treatment	Concomitant systemic treatment at time of SI	Alcohol use	Smoking status	Inflammatory arthritis	DM	Pulmonary disease	Past TB (incl. LTBI)	Significant infections	
1	Abdominal and gastrointestinal infections		Appendicitis	222	ADA 40mg EOW	-	Yes	Current smoking	No	Yes	No	No
2	Abdominal and gastrointestinal infections		Appendicitis	1668	ETA 50mg OW	-	Yes	Stopped smoking	Yes	No	No	No
3	Abdominal and gastrointestinal infections		Viral enterocolitis	456	ADA 40mg EOW	-	Yes	Never smoked	No	Yes	Yes	No
4	Abdominal and gastrointestinal infections		Gastroenteritis	72	UST 45mg every 12 weeks	-	Yes	Current smoking	No	Yes	No	No
5	Abdominal and gastrointestinal infections		Gastroenteritis	2431	ADA 40mg every 4 weeks	-	No	Stopped smoking	Yes	No	No	No
6	Abdominal and gastrointestinal infections		Gastroenteritis	1078	ADA 40mg EOW	-	No	-	No	Yes	No	No
7	Bone and joint infections		Osteomyelitis	287	IXE 80mg every 4 weeks	-	Yes	Never smoked	Yes	No	No	No
8	Bone and joint infections		Septic arthritis	3685	ETA 75mg OW	-	No	Never smoked	Yes	No	No	No

Table S4. Continued

Infection characteristics			Treatment characteristics		Lifestyle factors		Medical history				
Serious infection type	Narrative description	Time until SI (days)	Treatment	Concomitant systemic treatment at time of SI	Alcohol use	Smoking status	Inflammatory arthritis	DM	Pulmonary disease	Past TB (incl. LTBI)	Significant infections
9	Influenza infections										
10	Lower respiratory tract and lung infections										
11	Lower respiratory tract and lung infections										
12	Lower respiratory tract and lung infections										
13	Lower respiratory tract and lung infections										
14	Lower respiratory tract and lung infections										
15	Lower respiratory tract and lung infections										
16	Lower respiratory tract and lung infections										

Table S4. Continued

Infection characteristics			Treatment characteristics		Lifestyle factors		Medical history				
Serious infection type	Narrative description	Time until SI (days)	Treatment	Concomitant systemic treatment at time of SI	Alcohol use	Smoking status	Inflammatory arthritis	DM	Pulmonary disease	Past TB (incl. LTBI)	Significant infections
17	Lower respiratory tract and lung infections	78	INF 5mg/kg every 8 weeks	MTX 25mg OW	Yes	Current smoking	Yes	No	No	No	No
18	Lower respiratory tract and lung infections	1216	ETA	-	Yes	Current smoking	No	No	No	No	No
19	Lower respiratory tract and lung infections	66	ETA 50mg OW	-	Yes	Stopped smoking	No	No	Yes	No	No
20	Lower respiratory tract and lung infections	1952	ETA 100mg OW	-	Yes	Stopped smoking	Yes	Yes	No	No	No
21	Lower respiratory tract and lung infections	1625	ETA 75mg OW	-	Yes	Stopped smoking	Yes	Yes	Yes	No	No
22	Lower respiratory tract and lung infections	55	ADA 40mg EOW	-	Yes	Stopped smoking	No	No	Yes	No	Yes
23	Lower respiratory tract and lung infections	499	ADA 40mg EOW	-	Yes	Stopped smoking	No	No	Yes	No	Yes
24	Lower respiratory tract and lung infections	1383	UST 45mg every 12 weeks	-	No	Stopped smoking	No	No	No	No	No

Table S4. Continued

Infection characteristics			Treatment characteristics		Lifestyle factors		Medical history				
Serious infection type	Narrative description	Time until SI (days)	Treatment	Concomitant systemic treatment at time of SI	Alcohol use	Smoking status	Inflammatory arthritis	DM	Pulmonary disease	Past TB (incl. LTBI)	Significant infections
25	Lower respiratory tract and lung infections	1453	ADA 40mg every 2 weeks	-	Yes	Stopped smoking	Yes	No	Yes	No	Yes
26	Lower respiratory tract and lung infections	159	UST 45mg every 12 weeks	MTX 15mg OW	Yes	Stopped smoking	Yes	No	No	No	No
27	Lower respiratory tract and lung infections	694	UST 90mg every 8 weeks	-	Yes	Stopped smoking	No	No	Yes	No	No
28	Lower respiratory tract and lung infections	318	UST 45mg every 12 weeks	-	Yes	Stopped smoking	Yes	Yes	Yes	No	No
29	Lower respiratory tract and lung infections	215	GUS 100mg every 8 weeks	-	Yes	Stopped smoking	No	No	Yes	No	Yes
30	Lower respiratory tract and lung infections	119	ETA 100mg OW	-	Yes	Never smoked	No	No	No	No	No
31	Lower respiratory tract and lung infections	161	UST 90mg every 12 weeks	MTX 20mg OW	Yes	Never smoked	Yes	No	No	No	No
32	Lower respiratory tract and lung infections	587	UST 90mg every 12 weeks	MTX 5mg OW	No	Never smoked	Yes	Yes	Yes	No	No

Table S4. Continued

Infection characteristics			Treatment characteristics		Lifestyle factors		Medical history				
Serious infection type	Narrative description	Time until SI (days)	Treatment	Concomitant systemic treatment at time of SI	Alcohol use	Smoking status	Inflammatory arthritis	DM	Pulmonary disease	Past TB (incl. LTBI)	Significant infections
33	Lower respiratory tract and lung infections	805	UST 90mg every 12 weeks	-	No	Never smoked	Yes	Yes	Yes	No	No
34	Lower respiratory tract and lung infections	1471	UST 90mg every 12 weeks	-	No	Never smoked	Yes	Yes	Yes	No	No
35	Lower respiratory tract and lung infections	1078	ADA 40mg every 2 weeks	-	No	-	No	Yes	No	No	No
36	Lower respiratory tract and lung infections	281	ADA 40mg every 2 weeks	-	No	Never smoked	No	No	No	No	No
37	Other	3445	ETA 50mg OW	-	Yes	Current smoking	No	No	No	No	No
38	Other	319	ADA 40mg EOW	-	Yes	Current smoking	No	No	No	No	No
39	Postoperative infection	408	ETA 75mg OW	-	No	Current smoking	No	No	No	No	No
40	Postoperative infection	59	UST 45mg every 12 weeks	-	Yes	Never smoked	No	Yes	No	No	No
41	Sepsis	564	ETA 50mg OW	-	Yes	Current smoking	No	No	No	No	Yes

Table S4. Continued

Infection characteristics			Treatment characteristics		Lifestyle factors		Medical history				
Serious infection type	Narrative description	Time until SI (days)	Treatment	Concomitant systemic treatment at time of SI	Alcohol use	Smoking status	Inflammatory arthritis	DM	Pulmonary disease	Past TB (incl. LTBI)	Significant infections
42 Sepsis	Urosepsis	166	ADA 40mg EOW	-	Yes	Current smoking	No	No	No	No	No
43 Sepsis	Urosepsis	35	SEC	-	-	-	Yes	Yes	No	No	No
44 Skin and soft tissue infections	Abscess	303	ETA 50mg OW	MTX 5mg OW	Yes	Stopped smoking	No	Yes	No	No	No
45 Skin and soft tissue infections	Varicella zoster	17	INF 5mg/kg every 8 weeks	-	Yes	Current smoking	Yes	No	No	No	No
46 Skin and soft tissue infections	Thumb infection	1682	ETA 50mg OW	-	Yes	Current smoking	No	Yes	No	No	No
47 Skin and soft tissue infections	Erysipelas	61	IXE 80mg EOW	-	Yes	Current smoking	No	No	No	No	No
48 Skin and soft tissue infections	Erysipelas	195	IXE 80mg EOW	-	Yes	Current smoking	No	No	No	No	No
49 Skin and soft tissue infections	Cellulitis	24	ADA 40mg EOW	-	No	Stopped smoking	No	Yes	No	No	No
50 Skin and soft tissue infections	Erysipelas	39	ADA 40mg EOW	-	No	Stopped smoking	No	Yes	Yes	No	No
51 Skin and soft tissue infections	Wound infection	1533	ADA 40mg EOW	-	Yes	Stopped smoking	Yes	No	Yes	No	Yes
52 Skin and soft tissue infections	Erysipelas	1277	ETA 50mg OW	-	Yes	Never smoked	Yes	Yes	No	No	No

Table S4. Continued

Infection characteristics			Treatment characteristics		Lifestyle factors		Medical history				
Serious infection type	Narrative description	Time until SI (days)	Treatment	Concomitant systemic treatment at time of SI	Alcohol use	Smoking status	Inflammatory arthritis	DM	Pulmonary disease	Past TB (incl. LTBI)	Significant infections
53	Skin and soft tissue infections	Erysipelas	445	ADA 40mg EOW	-	Yes	Never smoked	No	Yes	No	No
54	Skin and soft tissue infections	Cellulitis	207	INF 5mg/kg every 8 weeks	-	Yes	Never smoked	Yes	Yes	No	No
55	Skin and soft tissue infections	Erysipelas	1173	ETA 50mg OW	-	Yes	Never smoked	Yes	No	No	No
56	Skin and soft tissue infections	Erysipelas	1279	ETA 50mg OW	-	Yes	Never smoked	Yes	No	No	No
57	Upper respiratory tract infections	Airway infection	482	ETA	-	No	Current smoking	Yes	No	No	Yes
58	Upper respiratory tract infections	Sinusitis with fever	2798	ETA 100mg OW	-	No	Current smoking	No	No	No	No
59	Upper respiratory tract infections	Upper respiratory tract infection	1266	UST 45mg every 12 weeks	-	Yes	Current smoking	No	No	Yes	No
60	Urinary tract infections	Pyelonephritis, prostatitis	2024	ETA 50mg OW	MTX 20mg OW	Yes	Stopped smoking	Yes	Yes	No	No
61	Urinary tract infections	Urinary tract infection	3354	ADA 40mg EOW	-	No	Never smoked	No	No	No	No
62	Urinary tract infections	Urinary tract infection	1590	ADA 40mg every 3 weeks	MTX 10mg OW	-	Current smoking	No	No	Yes	Yes
63	Urinary tract infections	Urinary tract infection	560	IXE 80mg every 4 weeks	-	Yes	Stopped smoking	No	No	Yes	No

Abbreviations: SI, serious infection; DM, diabetes mellitus; TB, tuberculosis; LTBI, latent tuberculosis infection; ADA, adalimumab; ETA, etanercept; UST, ustekinumab; INF, infliximab; SEC, secukinumab; IXE, ixekizumab; GUS, guselkumab; mg, milligram; EOW, every other week; OD, once daily; OW, once weekly.

Table S5. Output of the negative binomial regression model used to estimate incidence rate ratios for risk of respiratory tract infections

Variable	Estimate	Standard Error	95% Confidence Interval		P-value ^a
Biologic					0.18-0.22
Adalimumab	-0.102	0.078	-0.256	0.052	-
Infliximab	-0.103	0.204	-0.503	0.297	-
Ustekinumab	-0.204	0.082	-0.365	-0.043	-
Secukinumab	-0.318	0.158	-0.627	-0.009	-
Ixekizumab	-0.123	0.179	-0.474	0.229	-
Guselkumab	-0.285	0.230	-0.716	0.145	-
Etanercept ^b	-	-	-	-	-
Age at start with biologic	-0.011	0.003	-0.016	-0.006	-
Body Mass Index	0.010	0.006	-0.002	0.022	-
PASI	-0.001	0.004	-0.010	0.008	-
History of biologic use (yes)	0.055	0.067	-0.076	0.185	-
Inflammatory arthritis (yes)	0.179	0.072	0.037	0.320	-
Pulmonary disease (yes)	0.218	0.098	0.026	0.410	-
History of (latent) tuberculosis (yes)	0.188	0.136	-0.078	0.455	-
History of significant infection (yes)	0.305	0.153	0.004	0.606	-

The final model was based on the imputed dataset. Adjusted incidence rates are calculated exponents of the model estimates, and are presented in Figure 2. For adjusted incidence rate ratios stratified by biologic (Figure 2), each biologic was consecutively entered into the model as the reference.

^a P-values associated with type 3 tests of fixed effects. A range of values is presented as a result of each imputed model.

^b Reference.

Table S6. Output of the Frailty Cox regression model used to estimate hazard ratios for risk of serious infections

Variable	Estimate	Standard Error	95% Confidence Interval		P-value ^a
Biologic					0.14-0.20
Adalimumab	-0.385	0.366	-1.102	0.332	-
Infliximab	0.974	0.621	-0.245	2.192	-
Ustekinumab	-0.694	0.447	-1.571	0.182	-
Secukinumab	0.317	0.617	-0.893	1.527	-
Ixekizumab	-0.768	1.067	-2.860	1.323	-
Guselkumab	0.284	0.812	-1.308	1.875	-
Etanercept ^b	-	-	-	-	-
Age at start with biologic	0.027	0.012	0.004	0.051	-
Body Mass Index	0.068	0.024	0.020	0.115	-
PASI	-0.024	0.022	-0.067	0.019	-
History of biologic use (yes)	0.003	0.315	-0.614	0.620	-
Inflammatory arthritis (yes)	0.183	0.302	-0.409	0.774	-
Pulmonary disease (yes)	0.691	0.352	0.002	1.381	-
History of (latent) tuberculosis (yes)	-0.121	0.624	-1.344	1.101	-
History of significant infection (yes)	0.827	0.458	-0.071	1.725	-

The final model was based on the imputed dataset. Adjusted Hazard Ratios are calculated exponents of the model estimates and are presented in Figure 2. For Hazard Ratios stratified by biologic (Figure 2), each biologic was consecutively entered into the model as the reference. Abbreviations: PASI, Psoriasis Area and Severity Index.

^a P-values associated with type 3 tests of fixed effects. A range of values is presented as a result of each imputed model.

^b Reference.

Table S7. Baseline patient and disease characteristics per treatment episode (TE) (n=482) of the 2020 cohort including SARS-CoV-2 infections characteristics

Demographics	
Age (years), mean $\pm$ SD	49.6 $\pm$ 13.1
Sex (male)	301 (62.4%)
BMI (kg/m ²), median [IQR] ^a	27.5 [24.7-32.0]
Disease duration (years), median [IQR]	21.04 [14.1-31.9]
Baseline PASI score, median [IQR] ^b	9 [5.5-14.0]
History of biologic use (yes)	325 (67.4%)
Alcohol use (yes) ^c	351 (72.8%)
Smoking ^d	
Never smoked	132 (27.4%)
Current smoking	154 (32%)
Stopped smoking	194 (40.2%)
Treatment	
Adalimumab	151 (31.3%)
Certolizumab pegol	9 (1.9%)
Etanercept	57 (11.8%)
Infliximab	7 (1.5%)
Ustekinumab	144 (29.9%)
Secukinumab	33 (6.8%)
Ixekizumab	37 (7.7%)
Brodalumab	8 (1.7%)
Guselkumab	25 (5.2%)
Risankizumab	11 (2.3%)
Medical history	
PsA (yes) ^e	134 (27.8%)
Other inflammatory arthritis	16 (3.3%)
Cardiovascular disease ^f	56 (11.6%)
Pulmonary disease ^g	62 (12.9%)
Hepatic disease	56 (11.6%)
Chronic renal disease	15 (3.1%)
Malignancy ^h	13 (2.7%)
Nmsc ^d	24 (5.0%)
Diabetes mellitus	49 (10.2%)
Inflammatory bowel disease	8 (1.7%)
Significant infections ⁱ	20 (4.1%)

Table S7. Continued

Medical history	
Past TB (incl. LTBI)	29 (6%)
Hepatitis B or C	15 (3.1%)
Immunodeficiency syndromes	0
Psychiatric illness (anxiety, depression)	41 (8.5%)
SARS-CoV-2 infection characteristics	
Positive SARS-CoV-2 test	15 (68.2%)
Highly suspected SARS-CoV-2 infection	7 (31.2%)
Course of disease	
Severe	1 (4.5%)
Moderate-to-severe	12 (54.5%)
Mild	9 (40.9%)
Temporary stop biologic (yes)	12 (54.4%)
Worsening psoriasis (yes)	11 (45.5%)
Complications (no)	22 (100%)
Recovered (yes)	15 (68.2%)
Recovered with sequelae	7 (31.8%)

Data are n (%) unless otherwise indicated. Abbreviations: TE, treatment episode; SD, standard deviation; IQR, interquartile range; BMI, body mass index; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; Nmssc, non-melanoma skin cancer; TB, tuberculosis; LTBI, latent tuberculosis infection.

Missings: ^a99, ^b90, ^c4, ^d2, ^e9.

^fCardiovascular disease include MACEs (incident myocardial infarction, stroke), heart failure, coronary artery disease, coronary or peripheral revascularization, atrial fibrillation, transient ischemic attack, valvular disease, pericarditis (non-infectious).

^gPulmonary disease include asthma, COPD, OSAS.

^hNmssc and malignancies were counted once in case of recurrent disease or more than one episode per patient.

ⁱSignificant infections were defined as infections requiring treatment within 3 years before registry enrollment.



CHAPTER 5.3

Effectiveness and safety of systemic therapy for psoriasis in older adults: a systematic review

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Abstract

Importance

Treating older adults with psoriasis can be challenging owing to comorbidities, concomitant medication use, and consequent safety risks. Although many studies focus on the effectiveness and safety of systemic antipsoriatic therapies in the general population, their effectiveness in older adults with psoriasis has not been systematically assessed.

Objective

To evaluate the effectiveness and safety of systemic antipsoriatic therapies in patients 65 years or older.

Evidence review

A systematic literature search was conducted in Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) on November 11, 2019. No date limit was used. Randomized clinical trials, cohort studies, large case series, and meta-analyses assessing efficacy (or effectiveness) and/or safety of systemic antipsoriatic therapies in patients 65 years or older were included.

Findings

The initial search yielded 11 096 results, of which 31 unique articles with 39 561 patients were included in analysis. Overall, limited data were available per systemic agent, and overall quality of the included studies on conventional systemic therapies was low. At the end of the induction phase (12-16 weeks after start of treatment), a reduction of 75% in Psoriasis Area and Severity Index was achieved in 49% of 74 methotrexate sodium users 65 years or older, 46% to 52.6% of 178 older cyclosporin users, 27% to 47.8% of 108 older acitretin users, 15.6% to 64% of 256 etanercept users 65 years or older, 66.7% to 93% of 43 infliximab users 65 years or older, 60.7% to 65% of 100 adalimumab users 65 years or older, 56.5% of 46 ustekinumab users 65 years or older, and 86.4% of 67 secukinumab users 65 years or older. Effectiveness of acitretin, etanercept, adalimumab, and secukinumab appeared not to be associated with age; studies regarding other systemic antipsoriatic therapies did not provide age group comparisons. Older age was significantly associated with renal function deterioration in cyclosporin users and with lymphopenia in fumaric acid esters users (hazard ratio, 2.42; 95% CI 1.65-3.55; $P < 0.001$). Infections were the most frequently reported adverse event in patients 65 years or older using biologics, but no significant association with age was found.

Conclusions and relevance

On the basis of limited available evidence, age alone should not be a limiting factor in psoriasis management. Awareness of comorbidities and concomitant medication use is very important, as well as appropriate dosing and frequent laboratory and clinical monitoring. More real-world evidence and (sub)analyses of prospective cohort studies on the effectiveness and safety of systemic therapies in older adults are critical to optimize personalized, effective, and safe antipsoriatic management in this growing patient group.

Introduction

Psoriasis is an immune-mediated inflammatory disease associated with significant morbidity. Owing to the chronic course of psoriasis and aging of the world population, older patients with psoriasis constitute a large and growing population.^{1,2} Psoriasis management in older adults can be challenging, with the aim of achieving an optimal benefit-to-risk ratio while considering comorbidities, comedication, organ impairment, and functional deterioration.³

Although many studies have been conducted on the efficacy and safety of systemic antipsoriatic therapies, older adults are frequently excluded from clinical trials.⁴ Therefore, many dermatologists seem to maintain a cautious approach when treating this population, possibly leading to undertreatment.⁵ The aim of this systematic review was to systematically evaluate available evidence concerning efficacy or effectiveness and safety of systemic antipsoriatic therapies in patients 65 years or older.

Methods

Search strategy

This systematic review was conducted and reported according to the Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.^{6,7} On November 11, 2019, a systematic literature search was conducted in Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL). With the support of a medical librarian, all relevant synonyms of the terms psoriasis and older adults were combined with all currently available conventional and modern systemic antipsoriatic therapies (**eTable 1**). No date limit was used. Reference lists of included articles were screened for additional relevant studies.

Study selection

Eligibility assessment, data extraction, quality assessment, and risk of bias assessment were performed independently by 2 reviewers (M.E.C.vW. and L.S.vdS. or M.vdLI.A.). In case of discrepancies, a third reviewer (J.M.P.A.vdR. or S.F.K.L.) was consulted. Randomized clinical trials (RCTs), cohort studies, large case series (≥ 10 patients), and meta-analyses assessing efficacy, effectiveness, and/or safety in patients with psoriasis 65 years or older were included. To provide a complete overview, additional studies could be included in case both reviewers agreed on the relevance of the article, for example, in case a different age cutoff value was used, or for studies in which a relatively old population was included. Studies in languages other than English, Spanish, German, French, and Dutch were excluded, as well as case reports, small case series (< 10 patients), conference

abstracts, oral communications, and expert opinions. At least 2 attempts were made to contact authors of the original articles if their full text could not be accessed or to request additional information.

Outcome measures

The primary outcome measure was the efficacy or effectiveness (for readability, hereinafter both are denoted as effectiveness), evaluated by the percentage of older adults achieving a reduction of 75% in the Psoriasis Area and Severity Index (PASI75) at weeks 12 to 16. Secondary outcome measures were PASI50, PASI90, and PASI100 at weeks 12 to 16 and long-term effectiveness, as well as treatment-related safety and tolerability profiles.

Data Extraction and Quality Assessment

Data were extracted using a predesigned form. Percentages were calculated by the reviewers wherever possible, if not stated in the articles. Study quality was graded according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies⁸ and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for RCTs.⁹ Risk of bias was assessed using the Newcastle-Ottawa Scale for cohort and case-control studies¹⁰ and the Cochrane Risk of Bias Tool for RCTs.⁶ $P < 0.05$ indicated significance.

Results

Study Characteristics

The literature search yielded a combined total of 8632 unique articles, of which 17 reported on effectiveness and safety of systemic antipsoriatic therapies in a cumulative 5352 treatment episodes in patients 65 years or older (**Figure 1**).^{11,18-33} Fourteen additional articles did not describe (sub)analyses of patients 65 years or older but were considered relevant by both reviewers and subsequently included (**Table 1 and eTables 2-8**).^{12-17,34-41} A total of 39 561 patients were included in the analysis. Baseline comorbidities were mentioned in 18 (58%) of the included articles,^{11,16-18,21-29,31,33,34,36,37} and 4 (22%) of these^{17,22,33,37} included comorbidities as independent variables or predictors in analyses. Twelve studies (39%)^{12,13,18,24,26,34,35,37-41} showed a high risk of selection bias, and overall quality of the studies on modern systemic therapies was higher than that of studies on conventional therapies (**Table 2 and eTables 2-10**). No studies were available assessing the effectiveness and/or safety of ixekizumab, brodalumab, guselkumab, certolizumab pegol, tildrakizumab, and risankizumab in patients 65 years or older. A comparison of efficacy measures between treatment modalities in patients 65 years or older is presented in **Figure 2** and **Figure 3**.

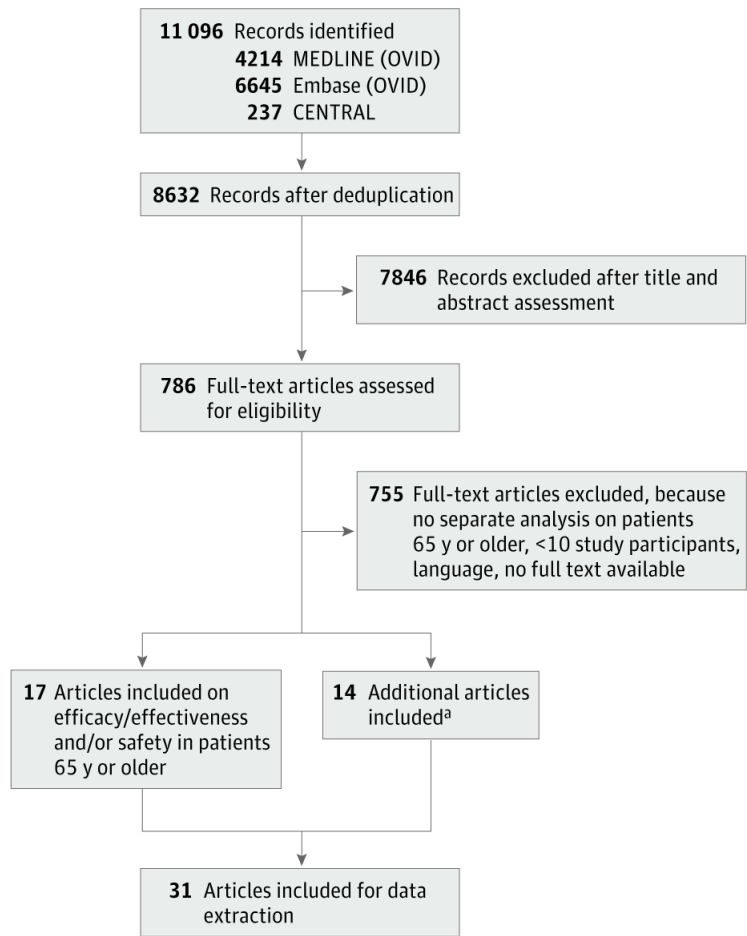


Figure 1. Flow Diagram of the Literature Search

^aAdditional studies were included when both reviewers agreed on the relevance of the article, for instance in case of a relatively old population or in case a different age cutoff was maintained.

Methotrexate sodium

Three articles¹¹⁻¹³ assessed methotrexate effectiveness in older adults, and 4 studies^{11,26,28,31} assessed methotrexate safety and tolerability in patients 65 years or older. At week 12, 49% of 74 patients 65 years or older achieved PASI75 (**Table 2**).¹¹ Two studies^{11,12} concluded that the mean effective dose of methotrexate was significantly lower for patients older than 70 years compared with younger patients. No data were available regarding long-term effectiveness. The most frequently reported adverse events in older methotrexate users were nausea (24%-80%) and elevated liver enzyme levels (18.2%-56%).^{13,34,35,38,39,41} Two studies^{26,41} reported on the association of methotrexate safety and age; no significant associations were found (**eTable 2**).

Cyclosporine

Three studies^{11,14,15} assessed cyclosporine effectiveness in a cumulative number of 178 older adults, and 3 studies^{11,31,32} assessed cyclosporine safety and tolerability in patients 65 years or older. At week 12, 46% to 52.6% of the included patients reached PASI75. No data were available regarding long-term effectiveness. The most frequently reported adverse events were hypertension and renal insufficiency,^{11,32} the latter being significantly more prevalent in patients 65 years or older (4 of 12 patients [33%]) compared with patients younger than 65 years (10 of 110 patients [9%]; $P=0.03$).³² Other frequently reported adverse events in older cyclosporine users were hypercholesterolemia, hypertriglyceridemia, and infections (**eTable 2**).^{32,40} Cyclosporine use in patients 65 years or older was associated with a significantly higher overall rate of adverse events (1.4 per patient-year) compared with methotrexate (0.12 per patient-year; $P < 0.001$).¹¹

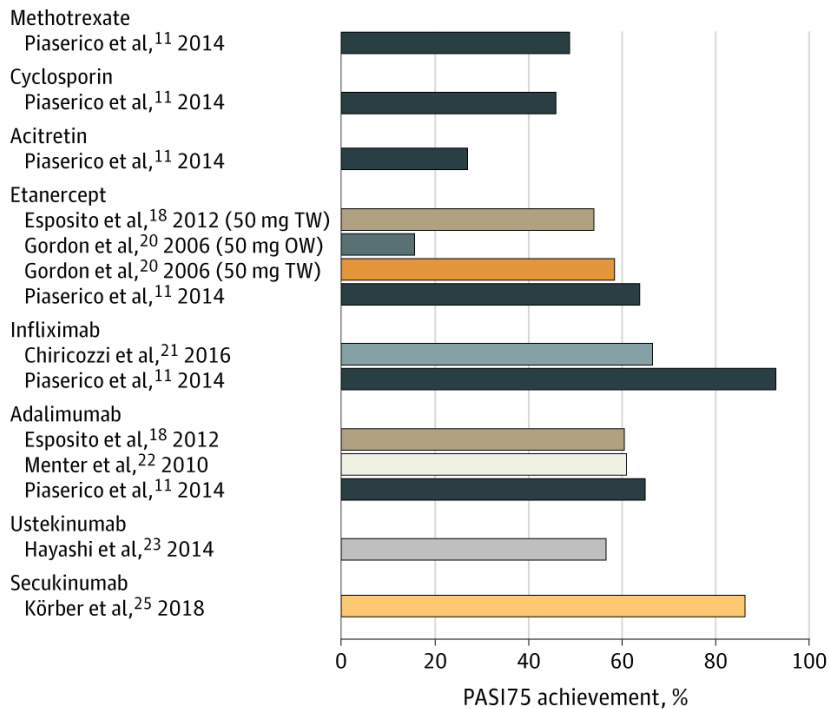


Figure 2. Efficacy or Effectiveness in Patients 65 Years or Older at Induction Phase (Weeks 12-16)

Each bar indicates the percentage of patients 65 years or older achieving a 75% reduction in Psoriasis Area and Severity Index (PASI75) per antipsoriatic agent. Studies describing patient groups with different age cutoffs were not included in this Figure. Data were too heterogeneous to perform appropriate meta-analyses. No data on effectiveness at the induction phase were available for fumaric acid esters, apremilast, ixekizumab, brodalumab, guselkumab, certolizumab pegol, tildrakizumab, and risankizumab. OW indicates once weekly; TW, twice weekly.

Table 1. Studies included for data extraction on the efficacy or effectiveness of systemic antipsoriatic therapies in older adults (≥65 years old)^a

Author, year	Study design, methodological approach ^b	Treatment	Age cut-off, y	Mean age (SD) [range]	Mean baseline PASI (SD) [range]	n≥65y ^c	n<65y
Piaserico et al, ¹¹ 2014	Retrospective, NRI	Methotrexate, 11.7mg OW (mean)	65	71.3 (5) [65-NR] ^d	12.7 (5.8) [4-32]	74	-
Fairris et al, ¹² 1989	NR ^e	Methotrexate, mean dose, NR (minimum 2.5mg/week)	50	NR (NR) [50-93]	NR	23 (>50y)	-
Kaur et al, ¹³ 1995	Retrospective, NR ^e	Methotrexate, 25-30mg OW	50	55.4 (NR) [51-65]	NR	14 (>50y)	-
Piaserico et al, ¹¹ 2014	Retrospective, NRI	Cyclosporin, 3.5mg/kg (mean)	65	71.3 (5) [65-NR] ^d	17 (5.9) [6-32]	36	-
Timonen et al, ¹⁴ 1990	Integrated analysis of 5 dose-finding studies, ITT, LOCF	Cyclosporin, 1.25-5.00mg/kg/day	40	42 (NR) [18-75] ^d	25 (NR) [NR] ^d	120 (>40y)	129 (≤40y)
Abe et al, ¹⁵ 2007	Prospective, as treated	Cyclosporin, 2.5mg/kg/day	-	59.7 (7.75) [NR]	NR (NR) [12-18]	19 ^d	-
Piaserico et al, ¹¹ 2014	Retrospective, NRI	Acitretin, 0.38mg/kg (mean)	65	71.3 (5) [65-NR] ^d	14.8 (6.9) [2-32]	62	-
Borghini et al, ¹⁶ 2015	Retrospective, as treated	Acitretin, 22.5mg/day (mean)	-	61.4 (15.3) [28-90]	20.3 (7.8) [10-41.4]	46 ^d	-
Dickel et al, ¹⁷ 2019 ^g	Retrospective, as treated	Dimethyl fumaric acid, 345.8mg (167.0) (monotherapy), 416.8mg (196.2) (combination therapy)	55	47.8 (14.6) [9-90] ^d	22.3 (8.1) [2.4-43.2] ^d	88 (>55y)	221 (≤55y)
Esposito et al, ¹⁸ 2012	Retrospective, ITT, LOCF ^e	Etanercept, 50mg TW (wk 0 to wk 12), 25mg TW/50mg OW (after wk 12)	65	70.0 (NR) [65-82]	11.3 (NR) [0.4-68.3]	15 (wk 0-NR) 46 (wk 0-156)	-
Giunta et al, ¹⁹ 2014	Retrospective, LOCF	Etanercept, dose NR	65	50.7 (NR) [18-83] ^d	11.50 (NR) [NR]	56	244
Gordon et al, ²⁰ 2006	Integrated analysis, 3 RCTs, LOCF	Etanercept, 50mg OW/TW	65	45.4 (12.2) [NR] ^d	18.8 (8.4) [NR] ^d	25 placebo 32 50mg OW 24 50mg TW	389 placebo 383 50mg OW 334 50mg TW
Piaserico et al, ¹¹ 2014	Retrospective, NRI	Etanercept, dose NR	65	71.3 (5) [65-NR] ^d	14.9 (6.4) [3-35]	83	-

Table 1. Continued

Author, year	Study design, methodological approach ^b	Treatment	Age cut-off, y	Mean age (SD) [range]	Mean baseline PASI (SD) [range]	n≥65y ^c	n<65y
Chiriccozzi et al, ²¹ 2016	Retrospective, as treated	Infliximab, dose NR, at 0, 2, 6 and every 8 wk	65	72 (5.2) [65-85]	15.6 (10.2) [NR]	27	-
Piaseur et al, ¹¹ 2014	Retrospective, NRI	Infliximab, dose NR	65	71.3 (5) [65-NR] ^d	14.8 (5.7) [4-20]	16	-
Esposito et al, ¹⁸ 2012	Retrospective, ITT, LOCF ^e	Adalimumab, 80mg ID and 40mg EOW	65	69.3 (NR) [65-75]	10.4 (NR) [0.4-23.8]	11 (wk 0-NR) 17 (wk 0-156)	-
Menter et al, ²² 2010	PHA: 1 RCT, ITT, NRI	Adalimumab, 80mg ID and 40mg EOW	65	NR	NR	30 placebo 54 adalimumab	368 placebo 760 adalimumab
Piaseur et al, ¹¹ 2014	Retrospective, NRI	Adalimumab, dose NR	65	71.3 (5) [65-NR] ^d	14.3 (4.1) [9-20]	18	-
Hayashi et al, ²³ 2014	Retrospective, analysis NR	Ustekinumab, 45mg at wk 0 and 4 and every 12 wk for ≥1y ^f	65	73.1 (7.4) [65-88]	12.9 (7.9) [3.0-30.2]	24	-
Megna et al, ²⁴ 2016	Retrospective, analysis NR ^e	Ustekinumab, 45mg (<100kg) and 90mg (>100kg) at wk 0 and 4 and every 12 wk for ≥2y	65	70.3 (4.6) [65-79]	13.7 (5.1) [5.4-28.2]	22	-
Körber et al, ²⁵ 2018	PHA: 3 RCTs, ITT, NRI	Secukinumab, 300mg OW for wk 0-4 and every 4 wk for wk 8-48	65	≥65y: 69.3 (NR) [NR] <65y: 42.9 (NR) [18-64]	≥65y: 20.2 (7.5) [NR] <65y: 22.9 (9.4) [NR]	67	842

Abbreviations: EOW, every other week; ID, initiation dose; ITT, intention-to-treat analysis; LOCF, last observation carried forward; NR, not reported; NRI, nonresponder imputation; OW, once weekly; PASI, Psoriasis Area and Severity Index; PHA, post hoc analysis; RCT, randomized clinical trial; TW, twice weekly.

^a Results are listed per antipsoriatic agent; therefore articles containing results on multiple treatment modalities are mentioned more than once.

^b In case type of analysis was unclear, methods regarding missing patients were specified.

^c In case the number of patients 65 years or older was unclear (e.g., in case a different age cut-off was used, or in case of a population with a relatively overall high mean age), the total number of patients was given.

^d Total study population, including placebo or other treatment/age groups.

^e Results should be interpreted with caution; a high risk of selection bias was present in this study.

^f Four patients (16.7%) received 90mg owing to insufficient effectiveness. The corresponding author of the original article was contacted and verified the dosing regimen as presented herein.

^g The corresponding author of the original article was contacted and additional information as presented here was shared.

Retinoids

Two studies^{11,16} assessed acitretin effectiveness in a cumulative number of 108 older adults, and 4 studies^{11,16,28,31} assessed acitretin safety and tolerability in older adults. None of the studies described a combination of acitretin and UV phototherapy in older adults. At weeks 12 to 16, 27% to 47.8% of the included patients achieved PASI75,^{11,16} and no significant association between age and treatment failure or response rate was seen.¹⁶ The effectiveness of acitretin (PASI75 achieved by 27%) was significantly lower compared with the effectiveness of other systemic therapies (49% [$P=0.01$] for methotrexate, 64% [$P<0.001$] for etanercept, 65% [$P<0.01$] for adalimumab, and 93% [$P<0.05$] for infliximab).¹¹ No data were available regarding long-term effectiveness. The most common adverse effects were alopecia, xerophthalmia, cheilitis, and fatigue (**eTable 2**). One study¹⁶ reported on the association between acitretin safety and age; no correlation was found between the incidence of adverse effects and age ($P=0.62$, not otherwise specified).

Fumaric Acid Esters

No studies were identified examining effectiveness of fumaric acid esters in patients 65 years or older. However, 1 study¹⁷ reported similar PASI75 responses in 88 patients older than 55 years compared with 221 patients 55 years or younger (51 [58.0%] vs. 111 [50.2%]; $P=0.22$). In this study, PASI75 was achieved at different time points, which limits comparison with other studies. Older age was significantly associated with the development of T-cell lymphopenia (hazard ratio, 2.42; 95% CI 1.65-3.55; $P<0.001$) during treatment with fumaric acid esters (**eTable 2**).

Etanercept

Four studies^{11,18-20} assessed etanercept effectiveness in a cumulative number of 256 patients 65 years or older, and 6 studies^{11,18,28-31} assessed safety and tolerability in etanercept users 65 years or older. PASI75 was attained by 15.6% to 64% of patients 65 years or older at week 12^{11,18,20} and by 83.6% to 86.9% after 1 to 3 years (**Figure 3**).¹⁸ Response rates varied between etanercept doses (**Table 2**). Two studies^{19,20} comparing patients 65 years or older with patients younger than 65 years found no difference in effectiveness between age groups. As is shown in **eTable 3**, the most frequently reported adverse events were mild infections (e.g., flulike symptoms).^{11,18,29} No significant difference was seen in incidence of serious infections in etanercept users 65 years or older compared with methotrexate users 65 years or older.²⁸ One article³⁶ with participants with a high overall mean age reported an increased risk for malignant neoplasms for tumor necrosis factor inhibitors, although a separate analysis including only etanercept did not reach significance (odds ratio [OR], 1.37; 95% CI 0.94-2.01; $P=0.10$). One study³⁰ reported on the association between

etanercept safety and age; serious adverse events were more frequently seen in patients 65 years or older compared with patients younger than 65 years, although according to the authors none of these were associated with etanercept use (not further specified).

Infliximab

Two retrospective studies^{11,21} assessed infliximab effectiveness with a cumulative inclusion of 43 patients 65 years or older, and 5 studies^{11,21,28,29,33} assessed safety and tolerability in infliximab users 65 years or older. PASI75 response at week 12 ranged from 66.7% to 93%,^{11,21} including 6 patients using combination therapy with methotrexate, 7.5 to 15.0 mg/wk.²¹ No data were available regarding long-term effectiveness. As is shown in **eTable 4**, the most frequently reported adverse events were mild infections.^{21,29,33} Two studies described a trend of an increased infection rate with rising age, although the differences found were not statistically significant (11 of 117 [9.4%] patients aged ≥ 65 years vs. 28 of 647 [4.3%] patients aged < 65 years; $P=0.06$)³³ or not reported (4 of 6 [66.7%] patients aged ≥ 76 years vs. 2 of 22 [9.1%] patients aged ≤ 75 years; P value not reported).²⁹ Comorbidities were associated with an increased incidence of infections, especially respiratory disease.³³ Fiorentino et al.³⁶ reported an increased risk for malignant neoplasms in older patients using tumor necrosis factor inhibitors, although a separate analysis including only infliximab did not reach significance (OR, 1.01; 95% CI 0.59-1.74; $P=0.96$).

Adalimumab

Three studies^{11,18,22} assessed adalimumab effectiveness in a cumulative number of 100 patients 65 years or older, and 5 studies^{11,18,27,28,31} assessed safety in adalimumab users 65 years or older. At weeks 12 to 16, PASI75 was achieved in 60.7% to 65% of patients 65 years or older^{11,18,22} and in the longer term (1-3 years) in 67.9% to 71.4%.¹⁸ No statistically significant association was seen between PASI75 response and age.²² One study²⁷ reported on the association between adalimumab safety and age; a similar frequency of adverse events was seen in patients older than 65 years (2 of 16 [12.5%]) compared with patients 65 years or younger (13 of 101 [12.9%]; P value not reported), most commonly infections (**eTable 5**). No statistically significant difference was seen in incidence of infections in adalimumab users 65 years or older compared with methotrexate users 65 years or older.²⁸ An increased risk for malignant neoplasms in older patients using tumor necrosis factor inhibitors was reported by Fiorentino et al.,³⁶ although a separate analysis including only adalimumab did not reach significance (OR, 1.37; 95% CI 0.93-2.02; $P>0.99$).

Ustekinumab

Two retrospective studies^{23,24} assessed ustekinumab effectiveness in a cumulative 46 patients 65 years or older, and 3 articles^{23,24,28} assessed safety and tolerability in ustekinumab users 65 years or older. At week 16, PASI75 was achieved in 56.5% of patients 65 years or older,²³ and in the long term (52-100 weeks) by 60.0% to 90.9%.^{23,24} As is shown in **eTable 6**, no significant difference was seen in incidence of infections in ustekinumab users 65 years or older compared with methotrexate users 65 years or older.²⁸ Moreover, a large prospective cohort study reported that no increased risk for malignant neoplasms was seen in older ustekinumab users compared with older patients not using ustekinumab.³⁶ None of the studies compared outcomes with those of patients younger than 65 years.

Secukinumab

One study assessed secukinumab effectiveness and safety in 67 patients 65 years or older.²⁵ PASI75 was achieved by 86.4% of patients 65 years or older at week 16 compared with 89.0% of patients younger than 65 years (P value not reported). Long-term effectiveness (52 weeks) was achieved by 81.8% of patients 65 years or older and 79.4% of patients younger than 65 years (P value not reported). As is shown in **eTable 7**, the most frequently reported adverse events were infections, which were seen in 36 of 67 patients (53.7%) 65 years or older vs. 527 of 839 (62.8%) younger than 65 years ($P \geq 0.05$, not otherwise specified).²⁵ Cardiac disorders were seen in 8 of 67 patients (11.9%) 65 years or old vs. 24 of 839 (2.9%) younger than 65 years (P value not reported), although patients 65 years or older also had significantly more pre-existent cardiovascular comorbidities at baseline (e.g., hypertension in 71.8% of patients aged ≥ 65 years vs. 20.8% of patients aged < 65 years [$P < 0.001$]; myocardial infarction in 7.7% of patients aged ≥ 65 years vs. 1.9% of patients aged < 65 years [$P = 0.02$]); coronary artery disease in 10.3% of patients aged ≥ 65 years vs. 1.7% of patients aged < 65 years [$P < 0.001$]). Treatment-related serious adverse events were seen in 4.5% of patients 65 years or older and in 1.8% of patients younger than 65 years (P values not reported, not otherwise specified).²⁵

Apremilast

No studies were identified studying the effectiveness of apremilast in patients 65 years or older. Dommasch et al.²⁸ found no significant increase in risk of serious infections in apremilast users 65 years or older compared with methotrexate users 65 years or older (propensity score-adjusted hazard ratio, 0.51; 95% CI 0.05-5.60; $P = 0.58$). No other studies were identified assessing apremilast safety and tolerability in older adults (**eTable 8**).

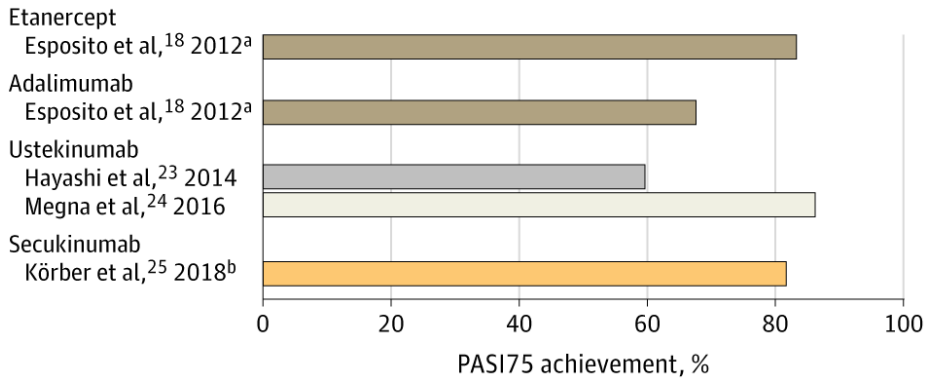


Figure 3. Long-term (Week 52) Efficacy or Effectiveness in Patients 65 Years or Older.

Each bar indicates the percentage of patients 65 years or older achieving 75% reduction in Psoriasis Area and Severity Index (PASI75) per antipsoriatic agent. Data were too heterogeneous to perform appropriate meta-analyses. No data on long-term effectiveness were available for cyclosporin, methotrexate, retinoids, fumaric acid esters, apremilast, infliximab, ixekizumab, brodalumab, guselkumab, certolizumab pegol, tildrakizumab, and risankizumab.

^aThe study used intention-to-treat analysis with the last observation carried forward. Results should be interpreted with caution; a high risk of selection bias was present in this study.

^bThe study used intention-to-treat analysis with nonresponder imputation.

Table 2. Study Outcomes, Quality, and Risk of Bias^a

Study characteristics		Outcomes <52wk		Patients aged <65y	Outcomes ≥52wk	Patients aged <65y	Overall quality ^b /risk of bias ^c
Source	Treatment	Patients aged ≥65y	Patients aged <65y	Patients aged ≥65y	Patients aged <65y	Patients aged ≥65y	Overall quality ^b /risk of bias ^c
Piaseirico et al, ¹¹ 2014	Methotrexate	Wk 12: PASI75, NR (49%)	-	-	-	-	B/5
Fairris et al, ¹² 1989	Methotrexate	Wk 12: PASI75, NR ^d	-	-	-	-	C/2 ^e
Kaur et al, ¹³ 1995	Methotrexate	Wk 12: PASI75, NR; mean time to PASI75, 7.1 wk	-	-	-	-	C/4 ^e
Piaseirico et al, ¹¹ 2014	Cyclosporin	Wk 12: PASI75, NR (46%)	-	-	-	-	B/5
Timonen et al, ¹⁴ 1990	Cyclosporin	Wk 12: PASI75, 57 (47%); >40y)	PASI75: 51 (40%) (≤40y) ^f	-	-	-	B/4
Abe et al, ¹⁵ 2007	Cyclosporin	Wk 12: PASI75, 10 (52.6%) ^j	-	-	-	-	C/4
Piaseirico et al, ¹¹ 2014	Acitretin	Wk 12: PASI75, NR (27%)	-	-	-	-	B/5
Borghi et al, ¹⁶ 2015	Acitretin	Wk 10-16: PASI50, 40 (87%) Wk 10-16: PASI75, 22 (47.8%) After wk 16: PASI75, 31 (67.4%) ^g	-	-	-	-	A/6
Dickel et al, ¹⁷ 2019 ^b	Dimethyl fumaric acid	PASI75: 51 (58.0%), > 55y, different time points	PASI75: 111 (50.2%), ≤55y, different time points ^f	-	-	-	B/5
Esposito et al, ¹⁸ 2012	Etanercept	Wk 12: PASI50, NR (82.0%) Wk 12: PASI75, NR (54.1%) Wk 24: PASI50, NR (90.2%) Wk 24: PASI75, NR (78.7%)	-	Wk 52: PASI50, NR (90.2%) Wk 52: PASI75, NR (83.6%) Wk 104: PASI50, NR (91.8%) Wk 104: PASI75, NR (86.9%) Wk 156: PASI50, NR (91.8%) Wk 156: PASI75, NR (83.6%)	-	-	B/4 ^e

Table 2. Continued

Study characteristics		Outcomes <52wk		Outcomes ≥52wk		Overall quality ^b /risk of bias ^c
Source	Treatment	Patients aged ≥65y	Patients aged <65y	Patients aged ≥65y	Patients aged <65y	
Giunta et al, ¹⁹ 2014	Etanercept	Wk 12: PASI50, NR (83.9%) Wk 24: PASI75, NR (64.3%)	Wk 12: PASI50, NR (91.4%) ^f Wk 24: PASI75, NR (71.3%) ^f	-	-	B/5
Gordon et al, ²⁰ 2006	Etanercept	Wk 12: PASI75, 0 (placebo) Wk 12: PASI75: 5 (15.6%) (OW) Wk 12: PASI75: 14 (58.3%) (TW)	Wk 12: PASI75, 13 (3.3%) (placebo) Wk 12: PASI75, 134 (35.0%) (OW) ^j Wk 12: PASI75, 163 (48.8%) (TW) ^j	-	-	B/4
Piaseirico et al, ¹¹ 2014	Etanercept	Wk 12: PASI75, NR (64%)	-	-	-	B/5
Chiricozzi et al, ²¹ 2016	Infliximab	Wk 12: PASI50, 21 (77.8%) Wk 12: PASI75, 18 (66.7%) Wk 12: PASI90, 13 (48.1%)	-	-	-	B/5
Piaseirico et al, ¹¹ 2014	Infliximab	Wk 12: PASI75, NR (93%)	-	-	-	B/5
Espósito et al, ¹⁸ 2012	Adalimumab	Wk 12: PASI50, NR (85.7%) Wk 12: PASI75, NR (60.7%) Wk 24: PASI50, NR (82.1%) Wk 24: PASI75, NR (71.4%)	-	Wk 52: PASI50, NR (78.6%) Wk 52: PASI75, NR (67.9%) Wk 24: PASI50, NR (82.1%) Wk 104: PASI50, NR (82.1%) Wk 24: PASI75, NR (71.4%) Wk 104: PASI75, NR (71.4%) Wk 156: PASI50, NR (82.1%) Wk 156: PASI75, NR (71.4%)	-	B/4 ^e

Table 2. Continued

Study characteristics		Outcomes <52wk		Outcomes ≥52wk		Overall quality ^b /risk of bias ^c
Source	Treatment	Patients aged ≥65y	Patients aged <65y	Patients aged ≥65y	Patients aged <65y	
Menter et al, ²² 2010	Adalimumab	Wk 16: PASI75, NR (3%) (placebo) Wk 16: PASI75, NR (61%) (adalimumab)	Wk 16: PASI75, NR (7%) (40-64 y) and 6% (<40y) (placebo) Wk 16: PASI75, NR (70%) (40-64y) (adalimumab) ^f Wk 16: PASI75, NR (74%) (<40y) (adalimumab)	-	-	B/5
Piaserico et al, ¹¹ 2014	Adalimumab	Wk 12: PASI75, NR (65%)	-	-	-	B/5
Hayashi et al, ²³ 2014	Ustekinumab	Wk 16: PASI50, NR (87.0%) Wk 16: PASI75, NR (56.5%) Wk 28: PASI50, NR (81.8%) Wk 28: PASI75, NR (59.1%)	-	Wk 52: PASI50, NR (95.0%) Wk 52: PASI75, NR (60.0%)	-	B/5
Megna et al, ²⁴ 2016	Ustekinumab	Wk 28: PASI50, NR (86.4%) Wk 28: PASI75, NR (63.6%) Wk 28: PASI90, NR (13.6%) Wk 28: PASI100, NR (4.5%)	-	Wk 52: PASI50, NR (90.9%) Wk 28: PASI75, NR (63.6%) Wk 52: PASI75, NR (86.4%) Wk 28: PASI90, NR (13.6%) Wk 28: PASI90, NR (54.5%) Wk 28: PASI100, NR (4.5%) Wk 52: PASI100, NR (36.4%) Wk 76: PASI50, NR (95.4%) Wk 76: PASI75, NR (90.9%) Wk 76: PASI90, NR (77.3%) Wk 76: PASI100, NR (54.5%) Wk 100: PASI50, NR (100%) Wk 100: PASI75, NR (90.9%) Wk 100: PASI90, NR (86.4%) Wk 100: PASI100, NR (54.5%)	-	B/4 ^e

Table 2. Continued

Study characteristics		Outcomes <52wk		Outcomes ≥52wk		Overall quality ^b /risk of bias ^c
Source	Treatment	Patients aged ≥65y	Patients aged <65y	Patients aged ≥65y	Patients aged <65y	
Körber et al, ²⁵ 2018	Secukinumab	Wk 16: PASI75, NR (86.4%) Wk 16: PASI90, NR (72.7%) Wk 16: PASI100, NR (40.9%)	Wk 16: PASI75, NR (89.0%) Wk 16: PASI90, NR (74.3%) Wk 16: PASI100, NR (40.9%)	Wk 52: PASI75, NR (81.8%)	Wk 52: PASI75, NR (79.4%) ⁱ	B/5

Abbreviations: NR, not reported; PASI, Psoriasis Area and Severity Index; PASI50, 50% reduction in PASI; PASI75, 75%reduction in PASI; PASI90, 90% reduction in PASI; PASI100, 100% reduction in PASI.

^a Results are listed per antipsoriatic agent; therefore, articles containing results on multiple treatment modalities are mentioned more than once.

^b Study quality was graded according to the Strengthening the Reporting of Observational Studies criteria for observational studies and the Consolidated Standards of Reporting Trials statement for randomized trials.^{8,9} A indicates more than 80% of criteria fulfilled; B, 50% to 80% of criteria fulfilled; and C, less than 50% of criteria fulfilled.

^c Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{10,6} More detail is provided in eTables 9 and 10 in the Supplement.

^d A significant correlation was seen between the minimum therapeutic dose and increasing age ($r=-0.74$; $P<.001$). For patients older than 70 years, amethotrexate dose lower than 10mg/wk was effective in 6 of 10 (60%), and in 4 patients older than 80 years (total NR) a dose of 2.5mg/wk was adequate (i.e., disease did not relapse, patients were satisfied with disease control).

^e Results should be interpreted with caution; a high risk of selection bias was present in this study.

^f Indicates no significant difference between age groups.

^g No difference was seen between age of those who achieved PASI75 (mean [SD] age, 60.8 [15.9] y) and nonresponders (mean [SD] age, 62.7 [14.5] y; $P=0.96$).

^h The corresponding author of the original article was contacted and additional information as presented here was shared.

ⁱ Statistical comparison not reported.

^j Total study population, including other age groups.

Discussion

Disease management in older adults (aged ≥ 65 years) with psoriasis can be challenging owing to patient-related factors and the lack of scientific guidance owing to disproportional exclusion of older adults in clinical trials.^{4,42} This systematic review was conducted to provide an overview of the literature on effectiveness and safety of systemic antipsoriatic therapies in older adults.

At the end of the induction phase (weeks 12-16), PASI75 was achieved in 15.6% to 64% of etanercept users 65 years or older,^{11,18,20} 66.7% to 93% of infliximab users 65 years or older,^{11,21} 60.7% to 65% of adalimumab users 65 years or older,^{11,18,22} 56.5% of ustekinumab users 65 years or older,²³ and 86.4% of secukinumab users 65 years or older.²⁵ Conventional therapies were studied less frequently; PASI75 after the induction phase was achieved by 49% of methotrexate users 65 years or older,¹¹ 46% to 52.6% of older cyclosporine users,^{11,14,15} and 27% to 47.8% of older acitretin users.^{11,16} The included studies were heterogeneous regarding the age cutoff, treatment regimens, and methodological approaches. Moreover, overall quality of the studies on conventional therapies was low. Interestingly, 2 studies^{11,12} reported that the mean effective methotrexate dose was lower in patients older than 70 years compared with patients 70 years or younger, possibly owing to impaired renal function associated with aging.⁴²⁻⁴⁴ No data were available regarding drug level monitoring in older patients with psoriasis, although this could be an interesting consideration for further research. Long-term effectiveness was not studied in older adults using conventional systemic treatment, whereas 4 studies^{18,23-25} reported on long-term (week 52) effectiveness of etanercept (PASI75 in 83.6%), adalimumab (PASI75 in 67.9%), ustekinumab (PASI75 in 60.0%- 86.4%), and secukinumab (PASI75 in 81.8%). Overall, effectiveness in patients 65 years or older appears to be in line with effectiveness in patients younger than 65 years,^{16,19,20,22,25,45-49} although several studies were subject to selection bias leading to overestimation of the outcomes. No data on effectiveness in patients 65 years or older were available for fumaric acid esters, apremilast, ixekizumab, brodalumab, guselkumab, certolizumab pegol, tildrakizumab, and risankizumab.

For conventional systemic treatment, the most important adverse events in patients 65 years or older included liver dysfunction in methotrexate users,^{26,34,35,38,39} hypertension and renal function deterioration in cyclosporine users,^{11,32,40} and lymphopenia in fumaric acid ester users.¹⁷ Literature is inconsistent on methotrexate related hepatotoxicity and the association with age. Whereas some studies have identified age as a risk factor for hepatotoxicity,^{50,51} more recent studies found no such association.^{26,52,53} Cyclosporine should be prescribed in patients 65 years or

older with absolute caution, because it appears to be associated with the highest adverse events rate of all antipsoriatic systemic therapies,¹¹ and an association of adverse events with increasing age was identified.^{32,37} However, most adverse events associated with conventional systemic therapies were reversible after dose adjustment or discontinuation or were successfully treated (e.g., hypertension, laboratory changes).^{16,32,39,40}

Infections were the most frequently reported adverse events in patients 65 years or older using biologics. In this systematic review, no evidence was found of differences in infection risk by age category.^{25,28,33} Other previous studies are inconsistent regarding the association between age and infection risk; Kalb et al.⁵⁴ found a higher risk of serious infections with increasing age in 11 466 patients with psoriasis (mean [SD] age, 48.5 [13.8] years), in contrast to a meta-analysis⁵⁵ with a cumulative number of 17 739 patients (mean [SD] age, 49.1 [14.6] years). In rheumatoid arthritis and inflammatory bowel disease, an increased infection risk was seen in patients 65 years or older using biologics.⁵⁶ However, multiple studies have suggested that adverse events in patients with psoriasis might differ from those seen in patients with other immune-mediated inflammatory diseases owing to differences in the underlying immunologic changes.⁵⁶⁻⁵⁸ Moreover, combination therapy with other immunomodulators is maintained far more frequently (15%-79%) than in dermatological daily practice.⁵⁶ In line with previous research, no increased risk of malignant neoplasms (excluding nonmelanoma skin cancer) was seen in methotrexate and ustekinumab users (mean [SD] age, 59.9 [10.9] years).^{36,59} Although tumor necrosis factor inhibitors (etanercept, adalimumab, and infliximab) were associated with a higher risk for malignant neoplasms after at least 12 months, analysis per agent did not show significant associations, possibly owing to a lack of statistical power.³⁶ No data were available for patients 65 years or older specifically. Therefore, results of real-world studies are needed to identify rare long-term adverse events of antipsoriatic therapies and the association with older age (≥ 65 years).

Some studies have reported a higher incidence of serious adverse events in patients 65 years or older, irrespective of whether or not an association with antipsoriatic treatment was suspected.⁶⁰ However, the definition of serious adverse events in RCTs entails hospitalization and emergency department visits, regardless of association with the treatment. Patients 65 years or older frequently have more comorbidities and a higher a priori chance of hospitalization than younger patients. It is therefore questionable whether the results on serious adverse events in these studies, frequently lacking a control group with patients of the same age, can be attributed to antipsoriatic treatment. Considering the risk-to-benefit ratio remains

important in every individual patient. Because coronavirus disease 2019 (COVID-19) is at present a global threat to older adults, many dermatologists might hesitate to prescribe or continue immunomodulatory therapies. Clinical guidelines advise not to cease systemic antipsoriatic therapies unless COVID-19 symptoms arise.⁶¹ The scarce available data do not imply a more severe course of the disease in patients using antipsoriatic therapies, some of which possibly even ameliorate the organ damage associated with severe COVID-19.⁶²⁻⁶⁶ However, much is still unknown, and further research, specifically in older adults, is needed to clarify recommendations.

The results of this systematic review on psoriasis management in older adults indicate that age should not be a limiting factor in its own right. Obviously, awareness of comorbidities and concomitant medication use is very important when selecting antipsoriatic treatment. However, disproportional age-based reluctance to optimally treat older patients with psoriasis could be a pitfall.

Limitations

Thirteen of the included studies^{12-15,19,20,30,32,35,38-41} did not report baseline comorbidities, which limits interpretation of the results in the heterogeneous population older adults comprise. Moreover, data were too scarce and heterogeneous to perform appropriate metaanalyses, which limits generalizability of the results. Outcomes varied among studies owing to dosing differences, inclusion of biologic-naïve patients or those previously exposed to biologics, concomitant medication, and differences in sample sizes, study design, and methodological approach. Head-to-head comparisons between systemic agents with age-matched control participants and comparisons with younger patient groups are needed to provide more guidance in treating older psoriasis patients.

Conclusions

Age alone should not be a limiting factor in psoriasis management. The available studies have demonstrated that response to several systemic therapies is not influenced by age. Results on safety are scarce but appear to be limited to a higher chance of laboratory abnormalities and (mild) infections. Appropriate monitoring of physical and laboratory changes is essential in this patient group, as well as dose adjustments when indicated. More data on efficacy, effectiveness, and safety of systemic therapies in patients 65 years or older, from RCTs and real-world studies, are critical to optimize personalized, effective, and safe psoriasis management in this growing patient group.

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Supplement

eTable 1. Search Strategy

	Search d.d. 11-11-2019	Results Medline
#1	psoriasis/ OR psorias*.tw,kf	46 865
#2	*Drug Therapy/ OR adalimumab/ OR certolizumab pegol/ OR Cyclosporine/ OR Dimethyl Fumarate/ OR etanercept/ OR infliximab/ OR Methotrexate/ OR dt.fs. OR retinoids/ or acitretin/ or etretinate/ OR ustekinumab/ OR (Acitretin OR adalimumab OR AIN?457 OR am#evita OR Amethopterin OR apremilast OR avakine OR benepali OR brodalumab OR CC?10004 OR certolizumab OR Ciclosporin* OR cimzia OR cnto?1275 OR cosentyx OR CyA-NOF OR Cyclosporin* OR D2E7 OR Dimethylfumarate OR e#brel OR erelzi OR etanercept OR ethylhydrogenfumarate OR Etratin* OR Etrinoate OR FAG 201 OR flixabi OR Fumaderm OR Fumarate OR Fumaric OR guselkumab OR humira OR ilumetri OR immunosuppressive OR inflectra OR infliximab OR Isoacitretin OR Isoetretin OR ixekizumab OR kyntheum OR Liarozole OR LY?2439821 OR Methotrexate OR Mexate OR Neoral OR Neotigason OR otezla OR Psorinovo OR Rambazole OR remicade OR remxima OR Retinoids OR revellex OR risankizumab OR Sandimmun OR secukinumab OR siliq OR Skyrizi OR Soriatane OR stelara OR Systemic calcineurin inhibitor* OR SYSTEMIC MONOTHERAPIES OR SYSTEMIC MONOTHERAPY OR Systemic pharmacolog* OR SYSTEMIC THERAPIES OR SYSTEMIC THERAPY OR Talarozole OR taltz OR Tigason OR Tigazon OR tildrakizumab OR TN#R?Fc OR TNF-FC OR TNR?001 OR tremfya OR trudexa OR ustekinumab OR (anti-IL* adj2 agent*) OR (anti-IL* adj2 drug*) OR (anti-IL* adj2 therap*) OR (anti-IL* adj2 treatment*) OR (anti-interleukin* adj2 agent*) OR (anti-interleukin* adj2 drug*) OR (anti-interleukin* adj2 therap*) OR (anti-interleukin* adj2 treatment*) OR (anti-TNF* adj2 agent*) OR (anti-TNF* adj2 drug*) OR (anti-TNF* adj2 therap*) OR (anti-TNF* adj2 treatment*) OR (anti-tumo?r adj2 necrosis adj2 factor* adj2 agent*) OR (anti-tumo?r adj2 necrosis adj2 factor* adj2 drug*) OR (anti-tumo?r adj2 necrosis adj2 factor* adj2 therap*) OR (anti-tumo?r adj2 necrosis adj2 factor* adj2 treatment*) OR (IL* adj2 blocker*) OR (IL* adj2 blocking adj2 agent*) OR (IL* adj2 inhibitor*) OR (interleukin* adj2 blocker*) OR (interleukin* adj2 blocking adj2 agent*) OR (interleukin* adj2 inhibitor*) OR (MAb adj2 cA2) OR (monoclonal adj2 antibody adj2 cA2) OR (TN# adj2 receptor adj2 fusion adj2 protein) OR (TNF* adj2 blocker*) OR (TNF* adj2 blocking agent*) OR (TNF* adj2 inhibitor*) OR (tumo?r adj2 necrosis adj2 factor* adj2 blocker*) OR (tumo?r adj2 necrosis adj2 factor* adj2 blocking adj2 agent*) OR (tumo?r adj2 necrosis adj2 factor* adj2 inhibitor*).tw,kf	2 326 241
#3	exp aged/ OR exp geriatrics/ OR exp nursing homes/ OR Geriatric assessment/ OR Exp aging/ OR ((old adj2 adult*) OR (old adj2 age*) OR (old adj2 females) OR (old adj2 males) OR (old adj2 men) OR (old adj2 patient*) OR (old adj2 population) OR (old adj2 subject*) OR (old adj2 women) OR (older adj2 adult*) OR (older adj2 age*) OR (older adj2 females) OR (older adj2 males) OR (older adj2 patient*) OR (older adj2 population) OR (older adj2 subject*) OR (older adj2 women) OR (oldest?old) OR (senior* adj2 patient*) OR (senior* adj2 population) OR (very adj2 old) OR Ageing OR aging OR centarian* OR centenarian* OR community-dwelling OR elder* OR eldest OR frail* OR geriatri* OR nonagenarian* OR oct#genarian* OR old people OR older OR oldest OR Psychogeriatrics OR septuagenarian* OR sexagenarian OR supercentenarian*).tw,kf	3 613 081
#4	#1 AND #2 AND #3	4 214

The search strategy for Medline was shown, a similar search was developed for the other databases.

eTable 2. Summary of Included Studies on Safety of Conventional Systemic Treatment in Older Adults

Study characteristics			Results		
Author, year Study design	Treatment	Age cut-off, y	Study Participants	Malignancies	
Almeyda et al, ³⁴ 1972 Retrospective combined with prospective cohort study	Methotrexate daily or weekly, oral or parenteral. Dose varying from 10-40mg/wk (mean NR).	-	Mean age 55y (SD NR, range 21-77) n=42 ^c (methotrexate) n=25 ^c (controls) No age group comparisons were made.	NR	
Bauer et al, ²⁶ 2017 Retrospective	Methotrexate, dose NR	>65	Range 19-85y ^e n=20 (>65y) n=87 (≤65y)	NR	
Birnie et al, ³⁵ 1985 Prospective	Methotrexate, 5-15mg/wk, IV	-	Mean age 55.5y±7.8 (range NR) n=14 ^c (methotrexate) n=29 ^c (controls) No age group comparisons were made.	NR	

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	NR	NR	Abnormal liver function tests were seen in 21/42 (50.0%) of treated patients compared with 8/25 (25.0%) of untreated patients (p-value NR). Abnormal liver biopsies were seen in 25/42 (59.5%) treated patients: 12/42 (28.6%) showed fibrosis, 3/42 (7.1%) showed cirrhosis, these patients were heavy drinkers^f. Abnormal liver biopsies were seen in 8/25 (44.0%) of untreated patients. No p-values were reported comparing the different treatment groups.	NR	C/4
	NR	NR	For women, age >65y was not significantly correlated with worsening of hepatic fibrosis scores with cumulative methotrexate dose when compared to patients ≤65y (not otherwise specified). For men >65y, NR.	maximum of 7y	B/3
	NR	NR	Elevated alkaline phosphatase levels were seen in 2/11 (18.2%) patients (p<0.025 compared to controls, not otherwise specified) and elevated gamma glutamyl transpeptidase activity in 1/11 (9.1%; p<0.05 compared to controls, not otherwise specified).	Mean/median FU NR (range 1-16y)	C/4

eTable 2. Continued

Study characteristics			Results		
Author, year Study design	Treatment	Age cut- off, y	Study Participants	Malignancies	
Dommasch et al, ²⁸ 2019 Retrospective	Methotrexate, dose NR	≥65	Mean age 53.7y±15.5 (IQR 42-61) n=1484 (65-74y) 707 (≥75y) 6279 (<65y)	NR	
Duhra et al, ⁴¹ 1993 Prospective	Methotrexate, mean dose 11.8mg±0.6/wk (range 2.5-30)	-	Mean age 61.3y±1.6 (range 34-94) n=78 ^c No age group comparisons were made.	NR	
Fiorentino et al, ³⁶ 2017 Prospective	Methotrexate, dose NR	-	Mean age 59.9y±10.9 (range NR) ^d n=192 ^c No age group comparisons were made.	No increased risk for malignancies was seen for all age patients after ≥12 months of mono- or combination therapy including methotrexate (OR, 0.98; 95% CI 0.63-1.54, p-value NR).	

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	No significant increased risk of serious infections was seen in patients aged ≥65y using ETA, IFX, ADA or UST compared to methotrexate users ≥65y (PS-adjusted HR presented in eTables 3-6). No comparisons between age groups were made.	NR	NR	Median 215d (IQR 146-399)	A/7
	NR	NR	Gastrointestinal symptoms were seen in 25/78 (32.1%) patients, nausea was reported by 80%, abdominal discomfort by 25% and vomiting in 12% (n NR). The weekly methotrexate dose was higher in the patients with AEs compared to patients without AEs. No significant difference in age was seen between the patients with AEs and the patients without AEs.	FU NR, mean treatment duration 4.75y ± 0.49 (range 3m-17y)	C/4
	NR	NR	NR	Median of 4.17y ^c (range NR, maximum 8.2y) Total patient-years: 48 870 ^c	A/6

eTable 2. Continued

Study characteristics			Results		
Author, year Study design	Treatment	Age cut-off, y	Study Participants	Malignancies	
Kaur et al, ¹³ 1995 Retrospective	Methotrexate, dose varying from 25-30mg OW	>50	Mean age 55.4y (SD NR, range 51-65) n=14 ^c No age group comparisons were made.	NR	
Napolitano et al, ³¹ 2016 Prospective	Methotrexate, dose NR	>65	Mean age >65y: 69.1y±7.7 ^d (n=29) ≤65y: 39.2±14.7 ^d (n=38)	NR for patients >65y.	
Nyfors et al, ³⁹ 1970 Study design NR	Methotrexate, dose varying from 7.5-25mg/wk	-	Mean age 60y (SD NR, range 18-83) n=50 ^c No age group comparisons were made.	NR	

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a / RoB ^b
	NR	NR	Nausea, vomiting and vertigo were reported by 5/14 (35.7%) patients. No other AEs of methotrexate were noticed.	Mean duration of methotrexate intake 34.5wk (SD NR, range 19-44), mean follow-up after methotrexate with-drawal: 5.1m (range 2-7).	C/4
	NR	NR	No adverse events were reported for methotrexate users >65y. No significant differences between age groups were seen regarding the incidence of adverse events in conventional antipsoriatic therapies as a group (including methotrexate, cyclosporin and acitretin, p-value not otherwise specified).	AEs as presented here were assessed at 6m.	B/5
	Folliculitis was seen in 2/50 (4%) patients.	NR	Nausea was seen in 12/50 (24%) patients, mouth ulcers in 6/50 (12%) patients, fatigue in 8/50 (16%) patients, hair loss in 2/50 (4%) patients, glutamic oxaloacetic transaminase-elevation in 28/50 (56%) patients, prothrombin decrease in 11/50 (22%) patients, thrombocytopenia in 4/50 (8%) patients, leucopenia in 2/50 (4%) patients, elevated serum creatinine levels in 2/50 (4%) patients, atypical cells in urine in 24/50 (48%) patients. All laboratory changes were reversible.	Mean/ median FU NR, minimum 1y	C/2

eTable 2. Continued

Study characteristics			Results		
Author, year Study design	Treatment	Age cut-off, y	Study Participants	Malignancies	
Nyfors, ³⁸ 1978 Study design NR	Methotrexate, dose varying up to 25mg/wk	-	Mean age 55y (SD NR, range 21-86) n=24 ^c No age group comparisons were made.	NR	
Piaserico et al, ¹¹ 2014 Retrospective	Methotrexate, mean dose 11.7mg OW (SD, range NR)	≥65	Mean age 71.3y±5 ^d (range 65-NR) n=74 No age group comparisons were made.	Ovarian carcinoma was seen in 1/74 (1.4%) patient (SAE).	
Abe et al, ¹⁵ 2007 Prospective	Cyclosporin, 2.5mg/kg/day	-	Mean age 59.7y±7.75 (range NR) n=19 ^c No age group comparisons were made.	NR	

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	Transient pulmonary infiltrate was seen 2/248 (0.08%) patients. One patient discontinued treatment due to pyelonephritis.	NR	Nausea was reported in 52% (n NR), oral blisters 23% (n NR), cirrhosis in 20/248 (8.1%) patients. No elevated serum creatinine levels were seen. Two patients temporarily discontinued treatment because of recurrence of duodenal ulcer, two patients due to thrombocytopenia and two due to alcohol abuse.	Mean 37m (range 2-105)	C/3
	The infection rate was 0.01/patient-year.	Myocardial infarction was seen in 1/74 (1.4%) patient (SAE).	The overall adverse event rate was 0.12/patient-year, type of AEs not otherwise specified.	76 patient-years	B/5
	NR	NR	No adverse events were seen.	12wk	C/4

eTable 2. Continued

Study characteristics			Results		
Author, year Study design	Treatment	Age cut-off, y	Study Participants	Malignancies	
Grossman et al, ³⁷ 1998 PHA: 2 RCTs, 1 prospective study	Cyclosporin, 2.5-5mg/kg	>50	Median age 37y (range 18-75) n=122 ^c	NR	
Napolitano et al, ³¹ 2016 Prospective	Cyclosporin, dose NR	>65	Mean age >65y: 69.1y±7.7 ^d (n=14) ≤65y: 39.2y±14.7 ^d (n=51)	NR	
Ohtsuki et al, ³² 2003 RCT	Cyclosporin, mean dose 3.24±0.27 mg/kg/day (continuous group) and 2.78±0.26 mg/kg/day (intermittent group)	≥65	Mean/median NR n=12 (≥65y) n=110 (<65y)	Gastric cancer and hepato-cellular carcinoma was seen in 2/122 (1.6%) patients, age group unknown.	

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	NR	NR	Patients >50y were more likely to discontinue treatment due to side effects than patients ≤50y (p=0.04, not otherwise specified). Moreover, pre-existent elevated serum creatinine level was correlated with treatment discontinuation due to side effects (HR NR, p=0.02) and diastolic pressure before treatment was correlated with an increased risk of hypertension during treatment (HR NR, p=0.001).	Mean/median FU NR (range 6-76m)	B/5
	Herpes zoster was seen in 1/14 (7.1%) patient >65y.	NR	No significant differences between age groups were seen regarding the incidence of adverse events in conventional antipsoriatic therapies as a group (including methotrexate, cyclosporin and acitretin, p-value not otherwise specified).	AEs as presented here were assessed at 6m.	B/5
	Infection (not specified) was seen in 4/12 (33%) patients ≥65y vs. 36/110 (38%) of <65y, p-value NR.	Hypertension was seen in 5/12 (42%) patients ≥65y vs. 26/110 (24%) in <65y, p-value NR.	An increased blood urea nitrogen level was seen in 6/12 (50%) patients ≥65y vs. 15/110 (14%) in <65y, p=0.008. Elevated serum creatinine levels were seen in 4/12 (33%) in patients ≥65y, vs. 10/110 (9%) in <65y, p=0.032. No patients ≥65y discontinued treatment due to adverse events, vs. 4/110 (3.6%) in <65y.	Mean 55.9±4.6m	C/1

eTable 2. Continued

Study characteristics			Results		
Author, year Study design	Treatment	Age cut-off, y	Study Participants	Malignancies	
Piaserico et al, ¹¹ 2014 Retrospective	Cyclosporin, mean dose 3.5mg/kg	≥65	Mean age 71.3y±5 ^d (range 65-NR) n=36 No age group comparisons were made.	NR	
Veller Fornasa et al, ⁴⁰ 2003 Retrospective	Cyclosporin, dose varying from 3-5mg/kg/day	-	Mean age 56.9y±13.6 (range NR) n=67 ^c No age group comparisons were made.	NR	
Borghi et al, ¹⁶ 2015 Retrospective	Acitretin, mean dose 22.5mg/ day (SD NR, range 5.2–48.9)	-	Mean age 61.4y±15.3 (range 28-90) n=46 No age group comparisons were made.	NR	

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	The infection rate was 0.0/patient-year.	The hypertension rate was 0.76/patient-year.	The overall adverse event rate was 1.4/patient-year. The renal insufficiency rate was 0.35/patient-year. The adverse event rate was significantly higher compared with methotrexate ($p<0.0001$).	14.4 patient-years	B/5
	Infections were seen in 1/67 (1.5%) patient, not otherwise specified.	Hypertension was seen in 8/67 (11.9%) patients, hyper-cholesterolemia in 15/67 (22.4%) patients, and hypertriglyceridemia in 10/67 (14.9%).	Elevated serum creatinine levels were seen in 7/67 (10.4%) patients, hyperuricemia in 6/67 (8.9%) patients, and nausea in 3/67 (4.5%) patients.	Mean/median FU NR, range 2-89m (majority of patients ≤ 12 m)	C/3
	NR	NR	AEs were seen in 18/46 (39.1%) patients, most were mild. AEs resolved spontaneously or after dose reduction in most patients, 4/46 (8.7%) patients discontinued due to depression, headache, myalgia and hair loss. After termination of treatment, AEs resolved. No correlation was seen between age and the incidence of AEs ($p=0.616$, not otherwise specified). Most frequently reported adverse events were alopecia in 6/46 (13.0%) patients, xerophthalmia in 5/46 (10.9%) patients, cheilitis in 5/46 (10.9%) patients, fatigue in 5/46 (10.9%) patients, gastrointestinal disorders in 4/46 (8.7%) patients, hyperlipidemia in 4/46 (8.7%) patients, reduced vision in 3/46 (6.5%) patients.	Mean duration of treatment 15.0m (SD, range 1-79)	A/6

eTable 2. Continued

Study characteristics			Results		
Author, year Study design	Treatment	Age cut- off, y	Study Participants	Malignancies	
Dommasch et al, ²⁸ 2019 Retrospective	Acitretin, dose NR	≥65	Mean age 52.3y±13.9 (IQR 43-61) n=324 (65-74y) 137 (≥75y) 2265 (<65y)	NR	
Napolitano et al, ³¹ 2016 Prospective	Acitretin, dose NR	>65	Mean age >65y: 69.1y±7.7 ^d (n=16) ≤65y: 39.2y±14.7 ^d (n=13)	NR	

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a / RoB ^b
	No significant difference was seen in acitretin users ≥65y compared to methotrexate users ≥65y (PS-adjusted HR, 2.00; 95%CI 0.64-6.18, p=0.23 for patients aged 65-74y, PS-adjusted HR, 0.60; 0.18-2.06, p=0.42 for patients ≥75y). No comparisons between age groups were made.	NR	NR	Median 188d (IQR 148-312)	A/7
	NR	NR	No adverse events were reported for acitretin. No significant differences between age groups were seen when the incidence of adverse events in conventional antipsoriatic therapies were analyzed as a group (including methotrexate, cyclosporin and acitretin, p-value NR).	AEs as presented here were assessed at 6m.	B/5

eTable 2. Continued

Study characteristics			Results		
Author, year Study design	Treatment	Age cut-off, y	Study Participants	Malignancies	
Piaserico et al, ¹¹ 2014 Retrospective	Acitretin, mean dose 0.38mg/kg	≥65	Mean age 71.3y±5 ^d (range 65-NR) n=62 No age group comparisons were made.	NR	
Dickel et al, ¹⁷ 2019 Retrospective subcohort	Dimethyl fumaric acid, mean dose 345.8±167.0mg (mono-therapy) and 416.8±196.2mg (combination therapy)	>55	Mean age 47.8y±14.6 ^c (range 9-90) n=371 ^c	NR	

Results are listed per antipsoriatic agent, therefore articles containing results on multiple treatment modalities are mentioned more than once.

Abbreviations: ADA, adalimumab; AE, adverse events; CI, confidence interval; d, days; ETA, etanercept; FU, follow-up; IFX, infliximab; IQR, interquartile range; HR, hazard ratio; IV, intravenously; m, months; NR, not reported; OR, odds ratio; OW, once weekly; PHA, post-hoc analysis; PS, propensity score; RCT, randomized controlled trial; RoB, risk of bias; SAE, serious adverse event; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies; UST, ustekinumab; wk, weeks; y, years.

^a Study quality was graded according to the STROBE criteria for observational studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials.^{8,9} A, >80% of criteria fulfilled; B, 50-80% of criteria fulfilled; C, <50% of criteria fulfilled.

^b Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{10,6} More detail is provided in in eTables 9 and 10.

^c Total number of patients; unknown number of patients ≥65y.

^d Reporting results for total number of patients; including other treatment groups.

^e The reported mean age in the original article appears not correct, authors could repeatedly not be reached to provide appropriate mean age.

^f Results need to be interpreted with caution; alcoholics and one patient with liver fibrosis were included in this study and were given methotrexate as well, since treatment in this patient group was initiated before the concern of hepatotoxicity arose.

					Quality
	Infections	Cardio-vascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	The infection rate was 0.0/patient-year.	NR	The overall adverse event rate was 0.32/patient-year, type of AEs not otherwise specified.	47.3 patient-years	B/5
	NR	NR	Age >55y was associated with T-cell lymphopenia (HR, 2.42; 95%CI 1.65-3.55, p<0.0001), with age <40y as a reference.	Mean 2.9y ± 2.7 (range 0.1-11.7)	B/5

eTable 3. Summary of Included Studies on Safety of Etanercept in Older Adults

Study characteristics		Results		
Author, year Study design	Treatment	Study Participants	Malignancies	
Dommasch et al, ²⁸ 2019 Retrospective	ETA, dose NR	Mean age 45.5y±13.0 (IQR 38-56) n=372 (65-74y) 94 (≥75y) 6636 (<65y)	NR	
Esposito et al, ¹⁸ 2012 Retrospective	T0-W12: ETA 50mg TW >wk12: ETA 25mg TW/ 50mg OW	Mean age 70.0y (SD NR, range 65-82) n=61 No age group comparisons regarding AEs were made.	Basal cell carcinoma was seen in 1/61 (1.6%) patient, gastric cancer in 1/61 (1.6%) patient (SAE, patient withdrew).	
Fiorentino et al, ³⁶ 2017 Prospective	ETA, dose NR	Mean age 59.9y±10.9 ^c (range NR) n=234 No age group comparisons were made.	No increased risk for malignancies was seen for all age patients after ≥12 months of ETA (OR, 1.37 [95%CI 0.94-2.01], p=0.101). A significant increased odds ratio for TNF-alpha inhibitors was seen when grouped (OR, 1.54, 95%CI 1.10-2.15, p=0.01).	
Migliore et al, ²⁹ 2009 Retrospective	ETA, 50mg OW	Mean age 71.4y ^c (SD NR, range 65-89) n=84 No age group comparisons were made.	Melanoma was seen in 1/84 (1.2%) patient.	

					Quality
	Infections	Cardiovascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	No significant increased risk of serious infections was seen in ETA users ≥65y compared to methotrexate users ≥65y (PS-adjusted HR, 0.40; 95%CI 0.12-1.32 for patients aged 65-74y, p=0.13, PS-adjusted HR, 1.66; 0.30-9.11, p=0.56 for patients ≥75y). No comparisons between age groups were made.	NR	NR	Median 287d (IQR 173-537)	A/7
	Mild upper respiratory infections were seen in 7/61 (11.5%) patients, a urinary tract infection was seen in 1/61 (1.6%) patient.	Tachycardia was seen in 1/61 (1.6%) patient (SAE, patient withdrew).	Injection site reactions were seen in 4/61 (6.6%) patients, weight gain ≥5kg was seen in 4/61 (6.6%) patients. No significant difference in AEs were seen between ADA users ≥65y and ETA users ≥65y.	Mean/median FU NR, 3y for at least 46/61 (75.4%) patients (15/61 [24.6%] patients withdrew from treatment, time frame NR).	B/4
	NR	NR	NR	Median 4.17y ^c (range NR, maximum 8.2y) Total patient-years: 48 870 ^c	A/6
	Infections were seen in 9/84 (10.7%) patients; mild infections in 8 patients (resolved without antibiotics), moderate infections in one patient (use of antibiotics needed, no hospitalization).	Myocardial infarction was seen in 1/84 (1.2%) patient.	Allergic reactions were seen in 5/84 (6.0%) patients; mild allergic reactions in three patients (urticaria, local rash) and moderate allergic reactions in two patients (asthma, angioedema).	Mean/median FU NR, mean treatment duration 25m±11.	B/4

eTable 3. Continued

Study characteristics		Results		
Author, year Study design	Treatment	Study Participants	Malignancies	
Militello et al, ³⁰ 2006 PHA: 2 RCTs ^d	ETA 25mg OW ETA 50mg OW ETA 50mg TW	Mean age NR (SD, range NR) n=77 (≥65y) n=1158 (<65y)	NR	
Napolitano et al, ³¹ 2016 Prospective	ETA, dose NR	Mean age >65y: 69.1y±7.7 ^c (n=25) ≤65y: 39.2y±14.7 ^c (n=57)	NR	
Piaserico et al, ¹¹ 2014 Retrospective	ETA, dose NR	Mean age 71.3y±5 ^c (range 65-NR) n=83 No age group comparisons were made.	NR	

Abbreviations: ADA, adalimumab; AEs, adverse events; CI, confidence interval; d, days; ETA, etanercept; FU, follow-up; IFX, infliximab; HR, hazard ratio; IQR, interquartile range; m, months; NR, not reported; OR, odds ratio; OW, once weekly; PHA, post-hoc analysis; PS, propensity score; RCT, randomized controlled trial; RoB, risk of bias; SAE, serious adverse event; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies; TNF, tumor necrosis factor; TW, twice weekly; UST, ustekinumab; wk, weeks; y, years.

^a Study quality was graded according to the STROBE criteria for observational studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials.^{8,9} A, >80% of criteria fulfilled; B, 50-80% of criteria fulfilled; C, <50% of criteria fulfilled.

^b Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{10,6} More detail is provided in eTables 9 and 10.

^c Including other treatment groups.

^d Efficacy outcomes of both RCTs were included in the results of Gordon et al²⁰ (Table 1). Only per-label results were included in this systematic review.

					Quality
	Infections	Cardiovascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	NR	NR	No difference was seen between age groups in injection site reactions. An increase in serious adverse events was seen in ≥65y (not associated with study treatment, not further specified).	12wk	B/5
	NR	NR for >65y.	No adverse events were reported for ETA users >65y. No significant differences between age groups were seen when the incidence of adverse events in biologics were analyzed as a group (including ETA, IFX, ADA, UST and golimumab, p-value NR).	AEs as presented here were assessed at 6m.	B/5
	The infection rate was 0.05/patient-year. A pneumonia requiring hospitalization was seen in 1/83 (1.2%) patient, and herpes zoster in 1/83 (1.2%) patient (SAE).	Pericarditis was seen in 1/83 (1.2%) patient, and atrial fibrillation in 1/83 (1.2%) patient.	The overall adverse event rate was 0.11/patient-year. Myasthenia gravis was seen in 1/83 (1.8%) patient (SAE).	147.6 patient-years	B/5

eTable 4. Summary of Included Studies on Safety of Infliximab in Older Adults

Study characteristics		Results		
Author, year Study design	Treatment	Study Participants	Malignancies	
Chiricozzi et al, ²¹ 2016 Retrospective	IFX, dose NR, at wk0, wk2, wk6 and every 8wk	Mean age 72y±5.2 (range 65-85) n=27 No age group comparisons were made.	Basal cell carcinoma was seen in 2/27 (7.4%) patients.	
Dommasch et al, ²⁸ 2019 Retrospective	IFX, dose NR	Mean age 50.2y±14.6 (IQR 40-59) n=49 (65-74y) 21 (≥75y) 338 (<65y)	NR	
Fiorentino et al, ³⁶ 2017 Prospective	IFX, dose NR	Mean age 59.9y±10.9 ^c (range NR) n=124 No age group comparisons were made.	No increased risk for malignancies was seen for all age patients after ≥12 months of mono- or combination therapy including IFX (OR, 1.01; 95%CI 0.59-1.74, p=0.958). A significant increased odds ratio for TNF-alpha inhibitors was seen when grouped (OR, 1.54, 95%CI 1.10-2.15, p=0.01).	
Migliore et al, ²⁹ 2009 Retrospective	IFX 3-5mg/kg every 6-8wk	Mean age 71.4y ^c (SD NR, range 65-89) n=28 No age group comparisons were made.	NR	

					Quality
	Infections	Cardiovascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	Flu-like symptoms were seen in 12/27 (44.4%) patients, candidiasis in 5/27 (18.5%) patients, cystitis in 2/27 (7.4%) patients, herpes zoster in 2/27 (7.4%) patients.	Hypertension was seen in 4/27 (14.8%) patients, hyperlipidemia in 1/27 (3.7%) patient.	Diarrhea was seen in 1/27 (3.7%) patient.	n=12: 208wk n=15: 12wk/NR	B/5
	No significant increased risk of serious infections was seen IFX users ≥65y compared to methotrexate users ≥65y (PS-adjusted HR, 3.57; 95%CI 0.29-43.94 for patients aged 65-74y, p=0.32, PS-adjusted HR for patients ≥75y could not be calculated due to low sample size). No comparisons between age groups were made.	NR	NR	Median 217d (IQR 119-377)	A/7
	NR	NR	NR	Median 4.17y ^c (range NR, maximum 8.2y) Total patient-years: 48 870 ^c	A/6
	Infections were seen in 6/28 (21.4%) patients; mild infections in five patients (resolved without antibiotics), moderate infections in one patient (use of antibiotics needed, no hospitalization).	NR	Allergic reactions were seen in 4/28 (14.3%) patients; mild allergic reactions in two patients (urticaria, local rash) and moderate allergic reactions in two patients (asthma, angioedema).	Mean/median FU NR, mean treatment duration 25m±11.	B/4

eTable 4. Continued

Study characteristics		Results		
Author, year Study design	Treatment	Study Participants	Malignancies	
Piaserico et al, ¹¹ 2014 Retrospective	IFX, dose NR	Mean age 71.3y±5 ^c (range 65-NR) n=16 No age group comparisons were made.	NR	
Torii et al, ³³ 2016 Prospective	IFX 5mg/kg at wk0, wk2, wk6, and every 8wk	Mean age 49.7y±13.2 (range 16-86) n=117 (≥65y) n=647 (<65y)	NR for >65y.	

Abbreviations: AEs, adverse events; CI, confidence interval; d, days; EOW, every other week; ETA, etanercept; FU, follow-up; IFX, infliximab; HR, hazard ratio; ID, initiation dose; IQR, interquartile range; m, months; NR, not reported; OR, odds ratio; PS, propensity score; RoB, risk of bias; SAE, serious adverse event; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies; TNF, tumor necrosis factor; wk, weeks; y, years.

^a Study quality was graded according to the STROBE criteria for observational studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials.^{8,9} A, >80% of criteria fulfilled; B, 50-80% of criteria fulfilled; C, <50% of criteria fulfilled.

^b Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{10,6} More detail is provided in eTables 9 and 10.

^c including other treatment groups.

					Quality
	Infections	Cardiovascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	The infection rate was 0.05/patient-year. A pneumonia requiring hospitalization was seen in 1/16 (6.25%) patient (SAE).	Myocardial infarction was seen in 1/16 (6.25%) patient, and thromboembolism in 1/16 (6.25%) patient (both SAEs).	The overall adverse event rate was 0.19/patient-year.	37.2 patient-years	B/5
	Infections were seen in 11/117 (9.4%) patients ≥ 65y vs. 28/647 (4.3%) patients < 65y, $p=0.060$. A significantly higher incidence of infections was seen in patients with comorbidities (6.65% vs. 3.35%, $p=0.047$), especially in patients with respiratory disease. Association between comorbidities and age was not described.	NR for >65y.	Overall adverse events were seen in 30/117 (25.64%) patients ≥ 65y vs. 142/647 (21.9%) patients < 65y, $p=0.158$.	AEs as presented here were assessed at 6m.	B/6

eTable 5. Summary of Included Studies on Safety of Adalimumab in Older Adults

Study characteristics		Results			
Author, year Study design	Treatment	Study Participants	Malignancies	Infections	
Chiricozzi et al, ²⁷ 2017 Retrospective	ADA 80mg ID, 40mg EOW	Mean age 48.4y±13.1 (range NR) n=16 (>65y) n=101 (≤65y)	NR	Cystitis was seen in 1/16 (6.3%) patient >65y, Epstein-Barr virus infection in 1/16 (6.3%) patient >65y, vs. 3/101 (3.0%) infections in patients ≤65y (p-value NR).	
Dommasch et al, ²⁸ 2019 Retrospective	ADA, dose NR	Mean age 46.1y±13.0 (IQR 39-57) n=449 (65-74y) 88 (≥75y) 6644(<65y)	NR	No significant increased risk of serious infections was seen in ADA users ≥65y compared to methotrexate users ≥65y PS-adjusted HR 1.80; 95%CI 0.54-5.98 for patients aged 65-74y, p=0.34 and PS-adjusted HR 0.66; 0.12-3.74 for patients ≥75y). No comparisons between age groups were made.	
Esposito et al, ¹⁸ 2012 Retrospective	ADA 80mg ID, 40mg EOW	Mean age 69.3y (SD NR, range 65-75) n=28 No age group comparisons were made.	NR	Dental infections were seen in 2/28 (7.1%) patients, mild upper respiratory infections were seen in 1/28 (3.5%) patients.	
Fiorentino et al, ³⁶ 2017 Prospective	ADA, dose NR	Mean age 59.9y±10.9 ^c (range NR) n=281 No age group comparisons were made.	No increased risk for malignancies was seen for all age patients after ≥12 months of mono- or combination therapy including ADA (OR, 1.37; 95%CI 0.93-2.02, p=1.099). A significant increased odds ratio for TNF-alpha inhibitors was seen when grouped (OR 1.54, 95%CI, 1.10- 2.15, p=0.01).	NR	

				Quality
	Cardiovascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	NR	Glycemic disorders were seen in 1/16 (6.3%) patient >65y, fatigue in 1/16 (6.3%) patient, and dyspnea in 1/16 (6.3%) patient; all of these AEs occurred in the same patients, as well as an infection. In total, 2/16 (12.5%) patients >65y experienced AEs compared with 13/101 (12.9%) patients ≤65y (p-value NR).	Mean/median FU NR; maximum 9y	B/6
	NR	NR	Median 257d (IQR 146-463)	A/7
	Atrial fibrillation was seen in 1/28 (3.5%) patient (SAE, patient withdrew).	Dyspnea was seen in 3/28 (10.7%) patients, weight gain ≥ 5kg in 2/28 (7.1%) patients, urticaria in 1/28 (1.1%) patient, headache in 1/28 (3.5%), and worsening of glaucoma in 1/28 (3.5%) patient. No significant difference in AEs were seen between ADA and ETA.	Mean/median FU NR, 3y for at least 17/28 (60.7%) patients (11/28 [39.3%] patients withdrew from treatment, time frame NR).	B/4
	NR	NR	Median 4.17y ^c (range NR, maximum 8.2y) Total patient-years: 48 870 ^c	A/6

eTable 5. Continued

Study characteristics		Results			
Author, year Study design	Treatment	Study Participants	Malignancies	Infections	
Napolitano et al, ³¹ 2016 Prospective	ADA, dose NR	Mean age >65y: 69.1y±7.7 ^c (n=24) ≤65y: 39.2y±14.7 ^c (n=78)	NR	Herpes zoster was seen in 1/24 (4.2%) patient >65y, compared with 1/78 (1.3%) patient ≤65y, p-value NR.	
Piaserico et al, ¹¹ 2014 Retrospective	ADA, dose NR	Mean age 71.3y±5 ^c (range 65-NR) n=18 No age group comparisons were made.	NR	The infection rate was 0.12/patient-year.	

Abbreviations: AE, adverse event; ADA, adalimumab; CI, confidence interval; d, days; EOW, every other week; ETA, etanercept; FU, follow-up; ID, initiation dose; IFX, infliximab; HR, hazard ratio; IQR, interquartile range; m, months; NR, not reported; OR, odds ratio; PS, propensity score; SAE, serious adverse event; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies; RoB, risk of bias; y, years.

^a Study quality was graded according to the STROBE criteria for observational studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials.^{8,9} A, >80% of criteria fulfilled; B, 50-80% of criteria fulfilled; C, <50% of criteria fulfilled.

^b Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{10,6} More detail is provided in in eTables 9 and 10.

^c including other treatment groups.

				Quality
	Cardiovascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
	NR for >65y.	No significant differences between age groups were seen when the incidence of adverse events in biologics were analyzed as a group (including ETA, IFX, ADA, UST and golimumab, p-value NR).	AEs as presented here were assessed at 6m.	B/5
	NR	The overall adverse events rate was 0.35/patient-year. No SAEs were reported in ADA users.	25.2 patient-years	B/5

eTable 6. Summary of Included Studies on Safety of Ustekinumab in Older Adults

Study characteristics		Results	
Author, year Study design	Treatment	Study Participants	Malignancies
Hayashi et al, ²³ 2014 Retrospective	UST 45mg ^c at wk0, wk4 and every 12wk for ≥1y. Dosage could be increased to 90mg in case of insufficient response (n=4).	Mean age 73.1y±7.4 (range 65-88) n=24 No age group comparisons were made.	NR
Megna et al, ²⁴ 2016 Retrospective	UST 45mg (<100kg) or 90mg (>100kg) at wk0, wk4 and every 12wk for ≥2y.	Mean age 70.3y±4.6 (range 65-79) n=22 No age group comparisons were made.	NR
Dommasch et al, ²⁸ 2019 Retrospective	UST, dose NR	Mean age 46.5y±12.8 (IQR 38-55) n=236 (65-74y) 60 (≥75y) 3789 (<65y)	NR
Fiorentino et al, ³⁶ 2017 Prospective	UST, dose NR	Mean age 59.9y±10.9 ^d (range NR) n=343 No age group comparisons were made.	No increased risk for malignancies was seen for all age patients after ≥12 months of mono- or combination therapy with UST versus no UST (OR, 0.98; 95%CI 0.63-1.53, p-value NR).

Abbreviations: AEs, adverse events; CI, confidence interval; d, days; FU, follow-up, HR, hazard ratio; IQR, interquartile range; NR, not reported; m, months; NR, not reported; OR, odds ratio; PS, propensity score; RoB, risk of bias; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies; UST, ustekinumab; wk, weeks; y, year.

^a Study quality was graded according to the STROBE criteria for observational studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials.^{8,9} A, >80% of criteria fulfilled; B, 50-80% of criteria fulfilled; C, <50% of criteria fulfilled.

^b Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{10,6} More detail is provided in eTables 9 and 10.

^c The corresponding author of the original article was contacted and verified the dosing regimen as presented here.

^d including other treatment groups.

				Quality
Infections	Cardiovascular AEs	Other AEs	Follow-up duration	Overall quality ^a /RoB ^b
Urinary tract infection was seen in 1/24 (4.2%) patient.	NR	Arthritis was seen in 2/24 (8.3%) patients (study drug was discontinued).	1y	B/5
No cases of serious infections were reported.	NR	Liver enzyme elevation was seen in 1/22 (4.5%) patient, and hyperglycemia in 1/22 (4.5%) patient.	2y	B/4
No significant increased risk of serious infections was seen in UST users ≥65y compared to methotrexate users ≥65y (PS-adjusted HR 2.12; 95%CI 0.39-11.61, p=0.39 for patients aged 65-74y, PS-adjusted HR for patients ≥75y could not be calculated due to low sample size). No comparisons between age groups were made.	NR	NR	Median 251d (IQR 146-437)	A/7
NR	NR	NR	Median 4.17y ^d (range NR, maximum 8.2y) Total patient-years: 48 870 ^d	A/6

eTable 7. Summary of Included Studies on Safety of Secukinumab in Older Adults

Study characteristics			Results					Quality
Author, year Study design	Treatment	Study Participants	Malignancies	Infections	Cardiovascular AEs	Other AEs	Follow- up duration	Overall quality/ RoB ^b
Körber et al, ²⁵ 2018 PHA: 3 RCTs	Secukinumab 300mg OW for wk0-4 and every 4wk for wk8-48	Mean age ≥65y: 69.3y (SD, range NR, n=67) <65y: 42.9y (SD NR, range 18-64, n=842)	NR	Infections were seen in 36/67 (53.7%) patients ≥65y vs. 527/839 (62.8%) patients <65y, (p≥0.05, not otherwise specified). Nasopharyngitis was seen in 13/67 (19.4%) patients ≥65y, vs. 219/839 (26.1%) patients <65y (p-value NR). Upper respiratory tract infections were seen in 4/67 (6.0%) patients ≥65y vs. 83/839 (9.9%) patients <65y (p-value NR).	Cardiac disorders were seen in 8/67 (11.9%) patients ≥65y vs. 24/839 (2.9%) patients <65y (p-value NR); mainly atrial fibrillation (1/67 [1.5%] patients ≥65y vs. 1/839 [0.1%] patients <65y, p-value NR), tachycardia (2/67 [3.0%] patients ≥65y vs. 3/839 [0.45%] patients <65y, p-value NR), and first-degree atrioventricular block (1/67 [1.5%] patients ≥65y vs. 4/839 [0.5%] patients <65y, p-value NR). Hypertension was seen in 7/67 (10.4%) patients ≥65y vs. 36/839 (4.3%) patients <65y (p-value NR).	In total, 55 (82.1%) patients ≥65y experienced adverse events vs. 719 (85.7%) patients <65y (p-value NR). AEs possibly related to the study drug were seen in 34.3% of patients ≥65y vs. 34.2% of patients <65y (n NR, p-value NR). Five (7.5%) patients ≥65y discontinued treatment due to AEs, vs. 36/839 (4.3%) patients <65y. SAEs possibly related to the study drug (type not specified): 4.5% patients ≥65y vs. 1.8% of patients <65y, p-value NR.	52wk	B/5

Abbreviations: NR, not reported; OW, once weekly; PHA, post-hoc analysis; RCT, randomized controlled trial; RoB, risk of bias; STROBE, Strengthening the Reporting of Observational Studies; w, weeks; y, year.

^a Study quality was graded according to the STROBE criteria for observational studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials.^{8,9} A, >80% of criteria fulfilled; B, 50-80% of criteria fulfilled; C, <50% of criteria fulfilled.

^b Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{6,10} More detail is provided in eTables 9 and 10.

eTable 8. Summary of Included Studies on Safety of Apremilast in Older Adults

Study characteristics		Results						Quality
Author, year Study design	Treatment	Study Participants	Malignancies	Infections	Cardiovascular AEs	Other AEs	Follow- up duration	Overall quality/ RoB ^b
Dommasch et al, ²⁸ 2019 Retrospective	Apremilast, dose NR	Mean age 51.4y±13.8 (IQR 42-61) n=201 (65-74y) 61 (≥75y) 1361 (<65y)	NR	No significant increased risk of serious infections was seen in apremilast users ≥65y compared to methotrexate users ≥65y (PS-adjusted HR 0.51; 95%CI 0.05-5.60, p=0.58 for patients aged 65-74y, PS- adjusted HR for patients ≥75y could not be calculated due to low sample size). No comparisons between age groups were made.	NR	NR	Median 169d (IQR 98-275)	A/7

Abbreviations: AEs, adverse events; d, days; IFX, infliximab; HR, hazard ratio; IQR, interquartile range; NR, not reported; PS, propensity score; RoB, risk of bias; SD, standard deviation; y, years.

^a Study quality was graded according to the STROBE criteria for observational studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials.^{8,9} A, >80% of criteria fulfilled; B, 50-80% of criteria fulfilled; C, <50% of criteria fulfilled.

^b Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias Tool for randomized studies.^{10,6} More detail is provided in eTables 9 and 10.

eTable 9. Risk of Bias Assessment of Included Studies According to the Newcastle-Ottawa Scale⁹

Author, year	Selection		Comparability of cohorts				Outcome	
	Adequacy case definition	Representativeness of exposed cohort	Selection non-exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study	Assessment of Outcome	Follow-up duration	Follow-up Adequacy
Abe et al, 2007	NA	*	NA	*	*	NA	-	-
Almeyda et al, 1972**	NA	-	*	*	-	-	*	-
Bauer et al, 2017**	NA	-	NA	*	*	NA	-	-
Birnie et al, 1985**	NA	-	-	*	-	-	*	-
Borghi et al, 2015	NA	*	NA	*	*	NA	*	*
Chiricozzi et al, 2016	NA	*	NA	*	*	NA	*	-
Chiricozzi et al, 2017	NA	*	NA	*	*	NA	*	-
Dommasch et al, 2019	NA	*	NA	*	*	NA	*	-
Dickel et al, 2019	NA	*	NA	*	*	NA	*	-
Duhra et al, 1993**	NA	-	NA	-	*	NA	*	-
Esposito et al, 2012**	NA	-	NA	*	*	NA	*	-
Fairris et al, 1989**	NA	-	NA	*	*	NA	-	-
Fiorentino et al, 2017	*	*	*	*	NA	*	*	NA
Giunta et al, 2014	NA	*	NA	*	*	NA	*	-
Grossman et al, 1996**	NA	-	NA	*	*	NA	*	-
Hayashi et al, 2014	NA	*	NA	*	*	NA	*	-
Kaur et al, 1995**	NA	-	NA	*	*	NA	*	-

eTable 9. Continued

Selection			Comparability of cohorts				Outcome	
Author, year	Adequacy case definition	Representativeness of exposed cohort	Selection non-exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study	Assessment of Outcome	Follow-up duration	Follow-up Adequacy
Megna et al, 2016**	NA	-	NA	*	*	NA	*	-
Migliore et al, 2009	NA	*	NA	*	*	NA	*	-
Napolitano et al, 2016	NA	*	NA	*	*	NA	*	-
Nyfors et al, 1970**	NA	-	NA	*	*	NA	*	-
Nyfors, 1978**	NA	-	NA	*	*	NA	*	-
Piaserico et al, 2014	NA	*	NA	*	*	NA	*	-
Timonen et al, 1990	NA	*	NA	*	*	NA	*	-
Torii et al, 2016	NA	*	NA	*	*	NA	*	*
Veller Fornasa et al, 2003**	NA	-	NA	*	*	NA	*	-

NA, not applicable. * Criterion achieved - criterium not achieved. ** Results should be interpreted with caution; a high risk of selection bias was present in this study.

eTable 10. Risk of Bias Assessment of Included Studies According to the Cochrane Risk of Bias Tool⁸

Author, year	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting
Ohtsuki et al, 2003	?	+	?	?	-	-
Gordon et al, 2006	+	+	+	+	?	?
Körber et al, 2018	+	+	+	+	+	?
Menter et al, 2010	+	+	+	+	+	?
Militello et al, 2006	+	+	+	+	+	?

+ criterium achieved, ? unclear, – criterium not achieved

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CHAPTER 6

Summary and Discussion

Biologics allow patients with moderate to severe psoriasis to achieve adequate disease control, or even complete clearance.¹ To date, they are often used chronically in fixed dosages. Biologics are however expensive and impose a high burden on national healthcare budgets.² High costs also result in lower access to biologics in countries with limited healthcare resources.³ Moreover, selecting the right biologic for each individual patient is still not entirely possible yet.⁴ Insights into possibilities for more personalized treatment and solutions for more efficient use of biologics are therefore important. This thesis addresses several aspects of personalized treatment with biologics for patients with psoriasis, with a special focus on biologic dose reduction (DR) and its implementation. In this chapter, the main results from this thesis are summarized according to the research aims as posed in the introduction, followed by a discussion of the main findings, implications for clinical practice, and future perspectives. A graphical summary of the main findings and future perspectives regarding the road towards implementation of biologic dose reduction in psoriasis care is presented in **Figure 1**.

Aim 1. To gain insight in current practice and in perspectives of patients and healthcare providers towards biologic dose reduction in psoriasis

Dose reduction (DR) of biologics by means of interval prolongation between injections has proven to be (cost-)effective and safe in a substantial amount of psoriasis patients with stable and low disease activity.^{5, 6} By striving for the lowest effective dose, DR prevents overtreatment and enables more efficient use of biologics with decreasing healthcare costs.^{7, 8} Although several studies have shown the potential for safe DR of biologics, insight into current practice and attitudes of involved healthcare professionals was limited. Understanding such factors is nonetheless important as they can influence uptake of DR into practice.⁹⁻¹¹

In **chapter 2.1 and 2.2**, attitudes and behaviour regarding biologic DR for psoriasis among Dutch dermatologists and dermatologists worldwide were explored. First, an online survey was distributed amongst members of the Dutch Association for Dermatology and Venereology (in Dutch: NVDV) in October 2019, aimed at dermatologists and residents experienced in prescribing biologics. Based on this survey, another survey was developed and distributed by the International Psoriasis Council among their psoriasis expert councilors worldwide in July 2020. Results from both surveys revealed that DR was already applied by a majority of respondents: 78% out of 114 Dutch respondents and 70% out of 53 dermatologists from 23 countries worldwide. DR was most frequently applied for the 'older' biologics (e.g., adalimumab,

etanercept, ustekinumab, secukinumab). For the newer biologics, Dutch respondents frequently reported having too little experience with these agents to attempt DR. Of all Dutch respondents applying DR (n=89), 20% applied DR for ixekizumab (highest proportion) and 1% for tildrakizumab (lowest proportion). The international cohort was more progressive, with 35% of respondents applying DR for ixekizumab and guselkumab to 8% for tildrakizumab.

As can be concluded from both surveys, DR practice was heterogeneous. In the Netherlands, most respondents indicated to make a clinical estimation of disease activity before installation of DR instead of using disease activity scores. In contrast, the majority of the international cohort did use outcome measures as criteria to consider DR. Most international respondents indicated a 'PASI ≤ 1 or ≤ 2 , BSA ≤ 1 or ≤ 2 , or PGA ≤ 1 ' as criteria to initiate DR, together with at least one year treatment duration and stable low disease activity. In line with our results, another survey study also found that DR was performed among French dermatologists, in patients with cleared or almost cleared psoriasis.¹² The French cohort considered DR after one year of stable and low disease activity, and the most frequently reduced biologics were also adalimumab, etanercept, ustekinumab, and secukinumab.

In both cohorts, most important motivations for applying DR were similar, which were improving safety, cost savings, and applying DR upon patients request. On the other hand, Dutch and international respondents who already applied DR reported that lack of time, lack of experience with DR or with newer biologics in general, and lack of support limited the extent of applying DR. Among respondents who did not apply DR at all, Dutch respondents most frequently reported lack of guidance and limited experience with biologics as barriers to DR. At the time of conducting the surveys, the possibility of DR was only mentioned in few treatment guidelines and no clear criteria or dosing schedules were described.¹³⁻¹⁵ According to the majority of survey respondents however, there was a need for guidelines on DR substantiated with scientific evidence. Although not incorporated as answer option, Dutch participants also added lack of evidence on DR as free text suggestion. This answer was therefore incorporated as standard answer option in the international survey, where it was among the most frequently reported barriers to application of DR. Fear of anti-drug antibody formation was also among reported barriers by physicians, resulting from both surveys. More recent evidence showed however effectiveness and safety of DR for the investigated biologics (adalimumab, etanercept, ustekinumab) without risking increased immunogenicity.^{5, 16} As such, dissemination of this evidence seems highly relevant in order to address the reported barrier among dermatologists.

Surveys among dermatologists showed that ‘patients unwillingness to try DR’ was an important reason for not applying DR. Besides insight into healthcare professionals’ attitudes towards DR, the patients’ perspective should also be elucidated before assumptions regarding patient-relevant factors influencing application of DR are made.^{10, 17} In-depth explorations of perspectives of patients with psoriasis towards biologic DR were however lacking. Therefore, these perspectives were investigated in **chapter 2.3** by conducting a qualitative study. Qualitative research allows to gain a broad understanding of perspectives of the insider (e.g., patients), and is increasingly used in dermatology as it is particularly useful for dermatologic diseases which have major effects on patients’ quality of life.¹⁸ In this thesis, thematic analysis of interviews with 15 patients with psoriasis with different characteristics and treatment experiences showed that according to patients, minimizing medication use, lowering risks of adverse effects and lowering costs were among perceived advantages of biologic DR. Patients expressed also concerns about loss of disease control due to DR, and wanted fast access to flare treatment when needed. Addressing personalized information needs and involving patients in decision-making were deemed important for patients when considering DR.

When translating the patient interview results towards clinical practice, I learned that - according to patients - healthcare providers should acknowledge the impact of patients’ disease, address patients’ concerns related to DR, provide the possibility of resuming the standard dose, and facilitate prompt access to consultations in case of disease worsening. Although several factors such as shared-decision making might sound logical, results stretched that there might still be room for improvement according to patients. As such, adherence to the reported factors and uptake of these identified patient-relevant factors into guidelines could contribute to acceptance of DR among patients with psoriasis.

Aim 2. To investigate implementation of dose reduction of the first generation biologics for psoriasis in daily practice

Following the first RCT regarding DR of adalimumab, etanercept or ustekinumab (i.e., the CONDOR study),^{19, 20} we aimed to implement the DR strategy from this trial in daily practice (**chapter 3**). The DR strategy consisted of stepwise DR by means of injection interval prolongation leading to 67% and subsequently 50% of the standard dose, guided by disease activity (PASI) and impact on patients’ quality of life (DLQI) (e.g., ‘controlled’ DR). In case of PASI and/or DLQI >5, patients returned to the previous effective or standard dose. Trial results showed no differences in

persistent disease flares (PASI >5 for at least 3 months) between patients in the DR arm vs. patients using the standard dose, and DR was successful in 53% of patients. Moreover, DR was considered safe and resulted in substantial cost savings.^{8, 16, 19}

In **chapter 3.1**, results of a prospective daily practice evaluation regarding a one-step DR strategy of adalimumab, etanercept and ustekinumab were described. This strategy was based on the previous CONDOR study.²⁰ After obtaining first results of CONDOR, we started cautiously with implementing a one-step DR strategy in daily practice in Radboudumc, instead of two DR steps in CONDOR. Criteria for starting DR were less strict compared to the trial, as we aimed to explore possibilities and performance of the DR strategy in a less controlled environment. The one-step strategy led to 67% of the standard dose and was guided by disease activity (PASI) and patients' reported quality of life (DLQI). Patients could always return to the previous effective dose at their own request. Of 108 eligible patients, 80 started DR. Disease activity and dermatology related quality of life remained stable. After one year, 45 (67%) of 67 patients with one year of follow-up were still on a lower dose. This finding corresponded with the proportion of patients using a lower dose after one year in the CONDOR trial (68%).^{19, 21} No safety signals related to DR occurred, which was also in line with results from CONDOR. In our daily practice evaluation, direct medication costs for the total cohort were reduced by 23% after one year. Of note, exact cost savings would depend on type and price of the biologic. Although we evaluated a single step of DR, we now know from the final results of CONDOR that 34% of patients achieved the second step of DR to 50% of the original dose and as such, this second step should also be discussed with the patient.^{19, 21}

This daily practice observation showed that upon discontinuation of DR, 61% of patients who discontinued DR still had low PASI and/or DLQI scores but wished to resume the previous dose. This is in line with results from patient interviews in **chapter 2.3**, where patients indicated the possibility of resuming the standard dose when deemed necessary by the patient or the clinician as an important precondition for starting DR. Moreover, fear of psoriasis flares due to DR was indicated among barriers to DR by interviewed patients (**chapter 2.3**) but was also among most frequent reasons for patients refraining from participating in the daily practice study.

Results from the daily practice study also revealed that time-investment was needed to select eligible patients. This finding corresponds with survey results from **chapter 2**, where dermatologists indicated lack of time as barrier to application of DR. From the total outpatient clinic population (e.g., all patients on biologic treatment), the number needed to screen for one patient to start DR was 6. Patients needed to be screened several times in order to check if they reached stable and low disease activity and/or

6 months treatment duration. We installed a dedicated nurse to select these patients. The nurse also provided additional support by performing clinical scores and coaching patients. This resulted in a low threshold for patients to contact a dedicated healthcare provider in case of questions, and might have contributed to the success of the strategy.

While conducting several studies on biologic DR for psoriasis, we noticed that the question whether adequate treatment responses are regained when patients discontinue DR and resume the standard maintenance dose was largely unanswered up to then. **Chapter 3.2** describes the results from a follow-up analysis of patients included in CONDOR and our daily practice evaluation from **chapter 3.1**.^{19, 21, 22} Patients (n=59) who resumed the standard maintenance dose after DR of adalimumab, etanercept or ustekinumab were prospectively followed for 2 years. The standard dose was resumed in case of PASI and/or DLQI >5, or at the patients' own request despite low PASI or DLQI. During follow-up, most patients reached low disease activity again. One year after DR discontinuation, the median difference in PASI score compared with PASI before starting DR was 0 (IQR -0.8–0.7), and 0.3 (IQR -1.0–2.0) for patients who resumed the standard dose at their own request (n=19) vs. due to PASI and/or DLQI >5 (n=40). From the latter group, 17 patients had PASI scores >5 at the time of stopping DR, of which the majority (n=15, 88%) reached PASI ≤5 again after a median time of 4 months. Results demonstrated the importance of incorporating both disease activity measures and the patient perspective into criteria to guide DR, as either PASI as well as DLQI or the patients' wish could be the driving force for patients to resume the standard dose. Findings from this study are reassuring for patients and clinicians when considering DR and might serve as facilitating factor to overcome the barrier reported by dermatologists that patients might 'fear reduced effectiveness' as described in **chapter 2**.

After obtaining insight into current practice and perspectives of healthcare providers (**chapter 2**), and results regarding performance of a controlled DR strategy in daily practice (**chapter 3.1**), we conducted a pilot implementation study. In this study, we aimed to evaluate implementation of protocolized biologic DR in general dermatological practice (**chapter 3.3**). As implementation of innovations often include the complex process of influencing behaviour change, such pilot or feasibility studies of implementation are of added value. They can identify potential mechanisms of change and facilitate optimization of implementation strategies, in order to increase their impact.²³ In order to generate awareness and possibilities for further dissemination, various stakeholders including patient partners, dermatologists, researchers, and the Dutch Association for Dermatology and Venereology were involved in our studies on implementation of biologic DR.

In our pilot implementation study, a multicomponent implementation strategy was developed. This strategy aimed to target the collected barriers among healthcare providers to application of biologic DR, which resulted from the surveys in **chapters 2.1 and 2.2**.^{24, 25} By combining education, feedback, and development of local protocols, we involved healthcare providers in 3 general hospitals who were directed towards adoption of a disease activity guided, protocolized DR strategy based on the CONDOR study.¹⁹ Several implementation outcomes were evaluated, including implementation fidelity, feasibility, and adoption of the innovation.^{23, 26-28} Evaluation indicated feasibility of the developed implementation strategy, although some time-investment was needed. Analysis of interviews with involved healthcare providers provided insights into factors outside the scope of our implementation strategy which might contribute to successful implementation of biologic DR. These factors included practical issues such as availability of time and staff for support, uptake of DR into treatment guidelines, and supportive electronic health record systems with decision aids and options to calculate disease activity measures. Effect evaluation of actual uptake of the implemented innovation revealed that the proposed DR protocol was followed in the majority (85%) of patients on DR. Before the intervention period, 27 patients were already on a lowered dose. During the relatively short intervention period of 6 months, 26 extra patients (50% of patients eligible for DR) started DR.

Results from implementation studies often depend on the tested setting.¹⁰ As such, a consideration for future work could be to replicate our results in other or larger settings, or to perform a formal implementation study or a combined effectiveness-implementation hybrid trial.²³ Such hybrid trials comprise both testing effectiveness of an intervention on clinical outcomes, and conducting a pilot study for future implementation or testing a formed implementation strategy. Our used implementation strategy and identified additional factors influencing effective implementation of protocolized DR could form a basis for such future studies.

As described in **chapters 2.1 and 2.2**, lack of guidelines was among physician-reported barriers to application of biologic DR.^{24, 25} We also learned from these studies that DR was performed in daily practice, though practice was heterogeneous. Criteria for performing DR in guidelines were lacking and used DR strategies varied between studies.⁵ Therefore, we aimed to achieve consensus on criteria for biologic DR in psoriasis on a national level, supported by the existing evidence (**chapter 3.4**). Dutch dermatologists experienced in treating psoriasis patients with biologics were invited to participate in a modified online Delphi procedure by the Dutch Association for Dermatology and Venereology. Consensus was reached in 2 voting rounds

among 27 dermatologists on all 15 statements regarding criteria for the application of biologic DR by means of injection interval prolongation. Agreed criteria for DR eligibility and (dis)continuation included the following thresholds of disease activity measures: PASI ≤ 5 and/or PGA 0-2, in combination with DLQI ≤ 5 . Approved DR schedules for adalimumab and etanercept consisted of two subsequent steps, with injection interval prolongation leading to 67% and 50% of the standard dose. For ustekinumab, intermediate steps were added, resulting in four subsequent DR steps.

Within the Delphi process, no recommendations for DR schedules of the newer biologics (certolizumab pegol, IL-17 inhibitors (IL-17i), IL-23 inhibitors (IL-23i)) were provided due to the limited available scientific evidence on DR of these agents.⁵ Based on trial data showing high effectiveness rates of the IL-17i and IL-23i, including restoration of adequate treatment responses upon retreatment after treatment withdrawal,²⁹⁻³⁷ it could be assumed that DR will be possible for these biologics too. Among Delphi participants, it was eventually agreed that DR of the newer biologics could already be considered in individual patients.

Aim 3. To generate evidence on tightly controlled disease activity guided dose reduction for the newer biologics for psoriasis (IL-17 and IL-23 inhibitors)

The previous chapters of this thesis focused mainly on DR of the biologics adalimumab, etanercept, and ustekinumab. As these biologics were among the first generation biologics for psoriasis, the possibility of lowering biologic dosages was first explored for these agents. A scoping review of the literature in 2021 revealed that most studies regarding biologic DR for psoriasis up to then still included the first generation biologics (e.g., TNF- α inhibitors and ustekinumab).⁵ Among identified knowledge gaps was the limited amount of data on DR of the newer biologics (IL-17i and IL-23i).

In order to generate evidence on DR of the newer biologics, we designed a pragmatic, randomized, controlled, non-inferiority trial on DR of IL-17i and IL-23i in patients with psoriasis: the BeNeBio study (**chapter 4**). The BeNeBio study is a collaboration between the Netherlands and Belgium. Recruitment of patients started in August 2020 and was still ongoing at the time of writing this thesis (end of 2022). A total number of 244 adult psoriasis patients with stable low disease activity will be randomized between usual care or stepwise DR to achieve 67% and subsequently 50% of the original dose. Disease activity is monitored every 3 months by PASI and DLQI. Treatment is adjusted to the previous effective dose in case of increased PASI and/or DLQI, or at patients' request. At study start, all available IL-17i (secukinumab, ixekizumab, brodalumab) and IL-23i

(guselkumab, risankizumab, tildrakizumab) for psoriasis were included. During the recruitment phase of the study, a novel IL-17i entered the market in the Netherlands: bimekizumab, which was added to the study.^{38,39}

The BeNeBio study design was partly based on the previous CONDOR trial.²⁰ Follow-up of patients was prolonged from 12 months in CONDOR to 18 months in BeNeBio, in order to be able to assess DR of the included biologics with long injection intervals and to follow course of disease flares in case they occur. Moreover, another primary outcome was chosen based on lessons learned from CONDOR. In CONDOR, the primary outcome consisted of the difference in disease activity (PASI) between DR and usual care at study end. Disease activity would however possibly not differ between groups at study end, due to the tightly controlled strategy in which timely dose adjustments aim to prevent long-term disease worsening. Analysis of disease activity over time instead of a single time-point is as such more relevant in the context of DR studies.⁴⁰ In BeNeBio, the primary outcome was therefore defined as non-inferiority of the incidence proportion of persistent flares (PASI >5 for ≥ 3 months) in the DR group. Persistent flares were chosen because they have a larger impact on overall disease control than short flares, and are more informative than short-lived periods of increased psoriasis activity which are inherent to the nature of the disease.

After initiation of the BeNeBio study, more studies regarding DR of the IL-17i and IL-23i became available.⁴¹⁻⁴⁷ These studies varied however in used design, DR regimen and reported outcomes. Moreover, most studies had small sample sizes and were not all designed for investigating DR. In general, more studies were available on DR of the earlier available biologics (IL-17i) compared to the newer agents (IL-23i). Data showed promising results for possibilities of lowering IL-17i and IL-23i doses. However, larger and robust, randomized studies designed to investigate effectiveness of a formal DR strategy had not been carried out.

As described above, recruitment and follow-up of patients in the BeNeBio study were still ongoing at the time of writing this thesis. Unfortunately, recruitment rates were behind schedule, mostly in Dutch sites. This might be explained by several factors. First, the COVID-19 pandemic occurred. This resulted in delayed study start in many hospitals and after the first waves of the pandemic, healthcare professionals were occupied with performing delayed or postponed care. In addition, in the beginning of the pandemic, many patients temporarily stopped their biologic due to concerns regarding increased risks of COVID-19 susceptibility and complications.⁴⁸ As a result, less patients were eligible for BeNeBio as patients should have used the standard dose

for at least 6 months before study participation. Moreover, patients and healthcare providers were forced to perform remote care. This might have resulted in less frequent clinic visits for patients, which was probably proceeded after the most urgent phases of the pandemic. Consequently, many patients were no longer used to visit the clinic every 3 months, which was nevertheless mandatory during the BeNeBio study. As such, the study design was less pragmatic than before the COVID-19 pandemic. Second, we noticed in several Dutch hospitals that the first generation biologics were still most frequently prescribed, partly due to the adoption of biosimilars of these biologics which have substantially lower prices. This may have resulted in lower numbers of eligible patients. Furthermore, patients on IL-17i or IL-23i were likely to have used one or more biologics before. These patients may more often refrain from study participation due to a fear of disease flares following DR, as described in **chapter 2.3**.

As the time between designing a study and actual performance will take time, not all factors limiting study performance can be taken into account. However, insight into factors influencing study feasibility could be of added value, as these factors could also influence future uptake of study results. Here, a possible solution could be to perform a feasibility study, although this may result in delay of conducting the actual trial. Another option could be to conduct a combined effectiveness-implementation hybrid trial, as I described in the previous section of this discussion.²³ Moreover, instead of conducting a classical trial, an adaptive trial design can be used which may result in a more efficient trial.⁴⁹ In such trials, pre-specified changes to the trial can be made based on planned and repeated analysis of accumulating data with maintenance of the trials' validity and integrity. This can result in earlier stop of recruitment to futile treatment arms, lowering of the sample size for less promising treatments, and earlier conclusions. Of course, such designs come with some challenges that should be addressed.⁴⁹

Aim 4. To explore possibilities for more personalized treatment with biologics, with focus on differences in treatment satisfaction between male and female patients, differences in risk of respiratory tract infections among biologics, and effectiveness and safety of biologics in patients of older age

In the last chapter, possibilities to personalize biological treatment for patients with psoriasis were explored, with focus on special groups and adverse effects. As selecting the right biologic for each patient is not entirely possible yet, effort remains needed to gain more insight into individualized treatment with biologics.

Treatment satisfaction

Previous studies on treatment with biologics for patients with psoriasis in daily practice showed that female patients discontinue their biologic treatment earlier than male patients.⁵⁰⁻⁵² Besides a higher risk of discontinuation of biologics due to side effects among females compared to males, reasons were not elucidated.^{50, 53-59} In **chapter 5.1**, we measured treatment satisfaction with the Treatment Satisfaction Questionnaire for Medication (TSQM) in a real-world cohort of psoriasis patients treated with biologics, and performed a confounder corrected, longitudinal analysis. In general, treatment satisfaction with biologics was high in both men and women. Over a period of one year, females reported significantly lower treatment satisfaction regarding the domains 'side effects' and 'global satisfaction' compared to males. The observed differences in treatment satisfaction might add to the underlying factors for a shorter biologic drug survival in women compared to men. In line with our results, lower treatment satisfaction in women was also reported in an Italian cohort and in a Swiss online survey study.^{60, 61}

As side effects were previously reported as reason for earlier biologic discontinuation among women, we also performed a post hoc analysis to evaluate incidence rates of serious adverse events (SAEs) and adverse events possibly related to biologic treatment. Women reported more adverse events in the context of biologic treatment compared to men (rate ratio 1.79; $P < 0.001$), with more fungal (rate ratio 2.20; $P = 0.001$) and herpes simplex infections (rate ratio 3.25; $P = 0.005$). Adjustment for gender-related adverse events (e.g., gynecological events) had no impact on significance rates. The number of SAEs did not differ between males and females (rate ratio 1.30; $P = 0.13$). This latter finding differed from a study which showed that females had higher odds of developing a serious infection (SI) compared to males when receiving systemic therapy for psoriasis.⁶²

Infections

Biologics have revolutionized treatment of patients with psoriasis. Biologics are very effective, but side effects can occur. The most frequently reported side effects of biologics are infections, especially respiratory tract infections (RTI).^{35, 63-68} The COVID-19 pandemic resulted in more attention for the risk of RTI among biologics users. However, limited real-world data on risk of RTI between biologics was available. For all types of serious infections (SI), studies have reported different results regarding risks of SI among patients with psoriasis treated with biologics, and comparisons between all available biologics are sparse.^{69-78 75, 78-80} More insight into the differential risk of infections between biologics could contribute to individualized treatment choices and accurate treatment decisions in case of an infection. Therefore, the differential effect

of currently available biologics on risk of RTI among psoriasis patients in a real-world setting was evaluated in **chapter 5.2**. Furthermore, the differential risk of all types of SI between biologics was explored, and an overview of SARS-CoV-2 infections during the pre-COVID-19 vaccine era was provided.

No differences in risk of RTI between adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, and guselkumab were observed in our confounder adjusted analysis. Among 1325 treatment episodes of 714 patients, the incidence rate of all SI was low (<2 per 100 patient years). For SI, no differential risk was found between biologics either in an explorative comparison. The low absolute number of SI in our cohort resulted in inadequate power to detect differences between biologics. However, the low SI rate observed in a large cohort poses the question if possible small differences only detectable in extremely large groups, would be clinically relevant.

Rates of SARS-CoV-2 infections in our cohort were comparable to the total Dutch population during 2020. We were however not able to investigate the impact of shielding behaviour. In a large, international survey among patients with psoriasis, it was observed that patients treated with targeted therapies reported greater risk-mitigating behaviour,⁸¹ which might explain the reported lower risk of adverse COVID-19 outcomes in this population.⁸² As a result of uncertainties regarding risk of severe COVID-19 infections in patients using immunosuppressants during the first stretch of the pandemic, more risk mitigating behaviour in our population might have resulted in the low rates of (severe) COVID-19 infections observed. However, a cross-sectional cohort study including patients from Radboudumc found no higher incidence of COVID-19 for psoriasis patients on biologics or conventional systemics compared to other treatments (e.g., topicals) when corrected for risk-mitigating behaviour and vaccination status.⁸³

When conducting observational studies, correction for possible confounders is critical. In **chapter 5.2**, we used a less conventional statistical method to select confounders: a Directed Acyclic Graph (DAG). This method can be used to select possible confounding variables based on theoretical assumptions about the causal relationship between variables.⁸⁴ Bias is minimized by considering the role of each variable in relation to the exposure and outcome, providing transparency in how variables are chosen, and preventing wrong interpretations of 'risk factors' as estimates for causality in multivariable analyses (e.g., so called Table 2 fallacy).^{84, 85}

Older patients

Another challenge for treatment with biologics in daily practice comprises treatment of older patients, due to the lack of inclusion of older patients in clinical trials and the special need for consideration of factors such as comedication, comorbidities, and frailty in this population.^{86, 87} This may even cause treatment hesitation among dermatologists when treating older patients, resulting in undertreatment.⁸⁸ In this thesis, the available evidence on effectiveness and safety of systemic treatment for psoriasis in patients 65 years or older was evaluated by means of a systematic literature review in **chapter 5.3**.

A total number of 31 articles with 39561 patients were included in the review, providing data on treatment with methotrexate, cyclosporin, acitretin, fumaric acid esters, etanercept, adalimumab, infliximab, ustekinumab, secukinumab, and apremilast. Overall, limited data on treatment effectiveness and/or safety in patients 65 years or older were available and quality of included studies was low. However, most systemic agents were effective in older as well as in younger patients. For acitretin, etanercept, adalimumab, and secukinumab, age group comparisons revealed comparative effectiveness in patients ≥ 65 years vs. in patients < 65 years. Therefore, with regards to effectiveness, age alone should not be a limiting factor in psoriasis treatment. Nevertheless, awareness of comorbidities and concomitant medication use is important, as treatment related adverse events might be associated with comorbidities which are more prevalent at higher age. Based on the results of this review, we found that this might specifically be the case for conventional systemic treatments such as cyclosporin and fumaric acid esters. However, a previous retrospective cohort study showed that increasing age was indeed associated with occurrence of causality assessed, treatment related adverse events, whereas comorbidities and polypharmacy were not.⁸⁹ In this study, 117 patients with 176 treatment episodes of methotrexate, dimethyl fumarate, acitretin, etanercept, adalimumab, or ustekinumab were included, and no significant differences in treatment related adverse events were observed between treatments. Reassuringly, serious adverse events were also rare in this study.⁸⁹ Recently, two studies analyzed drug survival - which is a composite measure of treatment success - of biological therapies in older patients, and indicated no differences in drug survival between patients < 65 and ≥ 65 years old.^{90, 91} Although current evidence suggests that age alone should not be a limiting factor in treating psoriasis with systemic therapies, future studies remain needed in order to accumulate evidence on (side-)effects of all available treatment options in the growing older population.

Main findings

Based on the results of this thesis, the following main findings can be concluded:

Aim 1. To gain insight in current practice and in perspectives of patients and healthcare providers towards biologic dose reduction in psoriasis.

- Surveys among Dutch and international dermatologists showed that biologic DR for patients with psoriasis is already applied in practice, although practice is heterogeneous. Cost reduction was an important motivating factor to apply DR. Factors hampering application of DR were patients' unwillingness, lack of time, and lack of support. Main barriers to application of DR were limited available scientific evidence, lack of guidance, limited experience with biologics or with DR, and risking disease flares or anti-drug antibody formation.
- Minimizing medication use, lowering risk of adverse effects, and lowering societal healthcare costs were among patients' motivations to consider DR. Patients also expressed concerns about loss of effectiveness due to DR.
- According to patients, healthcare providers should address patients' concerns, fulfil information needs, provide the possibility of resuming the standard dose, and involve patients in decision-making when considering DR.

Aim 2. To investigate implementation of dose reduction of the first generation biologics for psoriasis in daily practice.

- A one-step disease-activity guided DR strategy of adalimumab, etanercept and ustekinumab in daily practice lowered cumulative biologic doses and consequently, healthcare costs but required time-investment.
- Patients with psoriasis who resumed the standard maintenance dose after failure of adalimumab, etanercept or ustekinumab DR regained adequate treatment responses again.
- Education for healthcare providers and development of local protocols can promote uptake of protocolized DR of adalimumab, etanercept and ustekinumab in daily practice. Lack of time is the most important barrier to implementation of DR into daily practice.
- Among healthcare provider-reported factors to enhance further dissemination of DR into practice were the importance of incorporating DR into treatment guidelines, providing support for patients and performing shared-decision making, as well as availability of IT solutions such as decision aids and options to calculate clinical scores.
- Consensus was achieved among Dutch dermatologists on the following thresholds of disease activity measures to guide biologic DR: PASI ≤ 5 and/or

PGA 0-2, in combination with DLQI ≤ 5 . Agreed DR schedules for the biologics adalimumab, etanercept, and ustekinumab consisted of injection interval prolongation leading to 67% and 50% of the standard dose, with addition of 2 optional, intermediate steps in-between for ustekinumab.

- No consensus statements were defined regarding DR schedules for the newer biologics (IL-17i and IL-23i) due to limited available evidence, but it was agreed that DR for these biologics could be considered in individual patients.

Aim 3. To generate evidence on tightly controlled disease activity guided dose reduction for the newer biologics for psoriasis (IL-17 and IL-23 inhibitors).

- A pragmatic, randomized, controlled, non-inferiority trial on DR of IL-17i and IL-23i in patients with psoriasis was designed. Recruitment and follow up of patients in Belgium and the Netherlands was still ongoing at the time of writing this thesis.
- Results will inform us on effectiveness and safety of DR of the newer generations biologics for psoriasis.

Aim 4. To explore possibilities for more personalized treatment with biologics, with focus on differences in treatment satisfaction between male and female patients, differences in risk of respiratory tract infections among biologics, and effectiveness and safety of biologics in patients of older age.

- Women with psoriasis treated with biologics reported lower treatment satisfaction and more treatment-relevant adverse events compared to men. This might explain the earlier discontinuation with biological treatment of female compared to male patients.
- Although respiratory tract infections are among most frequently reported adverse events during biological treatment, we found no differential risk between the biologics adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and guselkumab in a real-world setting. This indicates that risk of respiratory tract infections should perhaps not be a discriminating factor when choosing between biologics.
- Among patients treated with adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and guselkumab, numbers of all types of serious infections were low. No increased risk of COVID-19 susceptibility was observed during the pre-vaccine era.
- Based on current literature, older age should not be a limiting factor in psoriasis management in itself. However, there is a need for more evidence on effectiveness and safety of systemic treatment for older adults with psoriasis.

Discussion, implications and future perspectives

What are optimal criteria to guide biologic dose reduction?

In this thesis, the road towards implementation of protocolized, disease activity guided or 'controlled' DR strategies for patients with psoriasis was investigated. I believe that guidance based on disease activity measures and patient reported outcomes is important, as the aim of DR should be to strive for the lowest, effective dose that patients as well as treating physicians agree upon. As demonstrated in **chapter 3.2**, by following a controlled DR strategy, timely action can prevent loss of adequate treatment responses. Guidance by means of clear criteria could also assist healthcare providers in performing biologic DR, as was shown in **chapter 3.3**.

An absolute PASI score of 5 was chosen to guide DR strategies across studies included in this thesis. This threshold for disease activity was based on prevailing national treatment targets and available evidence.^{5, 92} PASI 5 was also used to guide DR in the CONDOR trial,²⁰ of which results were further implemented in daily practice (**chapter 3**) and which served as a blueprint for development of a novel trial (**chapter 4**). In CONDOR, PASI 5 was chosen in the absence of a validated definition of psoriasis flares and was also supported by previous data which demonstrated that patients who remained on a biologic reached average PASI scores ≤ 5 at that time.⁹³ It can however be discussed if PASI 5 is still the right threshold to guide DR, as in the field of psoriasis, more stringent (e.g., 'lower') criteria were described in the past years to define low disease activity and treatment goals or targets.⁹⁴⁻⁹⁷ This resulted from the increased number of effective treatment options that became available, allowing patients with psoriasis to achieve (almost) complete clearance.¹ Of note, at the time of writing this thesis, no new treatment goals were defined in the Netherlands.

In our used criteria to guide biologic DR, upper limit thresholds were included which should be discriminated from treatment goals or targets. By using these upper limits of disease activity measures, we aim to select patients for DR with stable and low disease activity, with whom to discuss the option of DR. These upper limits also provide some room for application of DR in daily practice, as the accepted or reachable level of disease activity might differ between patients. For example, in our daily practice study (**chapter 3.1**), one patient wanted to start DR with PASI > 5 and DLQI 0, and four patients continued DR despite PASI > 5 . However, as low impact of the disease on patients' quality of life (DLQI < 5) is a prerequisite to start and continue DR in the proposed strategies, most patients initiating DR will have PASI scores well below 5, as can be seen from the included patients in the CONDOR trial (median PASI

at starting DR 1.8).¹⁹ Here, I would like to emphasize that the patients' perspective should always be taken into account, and that DR should be performed within a shared-decision making approach which was also indicated by interviewed patients in **chapter 2.3**.

It could nevertheless be that our used thresholds will need updates in case more stringent or lower thresholds for disease activity will be included in future treatment goals and guidelines. I think this might in particular account for the selection of patients with stable and low disease activity and not for definitions of disease flares. The need for adapting DR criteria will however also depend on results from future studies on real-world performance of available biologics and DR effects. A suggestion for future DR studies could be to assess at what PASI and DLQI scores patients return to the previous dose. Altogether, defining the most suitable criteria for DR should be considered as a dynamic process within the continuously changing treatment landscape.

Why is dose reduction possible and who can benefit?

Although previous literature demonstrated effectiveness of biologic DR in a substantial proportion of patients with psoriasis, underlying mechanisms that explain feasibility of DR are not fully elucidated. More insight in who can benefit would be valuable in daily practice. If it can be predicted which patients have higher risks to fail DR, these patients will not unnecessarily be exposed to DR. Within our DR strategies, a clinical and patient-centered approach was chosen and dosing schedules per biologic were based on previous clinical experiences and inspired by rheumatological studies. We did not incorporate other clinical factors such as comorbidities and treatment history into criteria to guide DR, although such factors are often considered when adjusting biological treatment. For instance, it has been demonstrated that patients with high BMI and patients with previous biologic exposure may have lower biologic drug survival.^{50, 98} Evidence towards factors influencing successful DR is however limited. Some small studies reported that factors predicting poorer response to biologics in general such as high BMI might also be considered as predictors for *unsuccessful* DR.^{5, 16, 19, 99-102} In the CONDOR study, many clinical variables (e.g., age, gender, smoking, BMI, disease duration, PsA, CRP, PASI, biologic naivety, biologic type) were tested for their predictive value in both univariate and multivariate models but showed no association with failure of DR.¹⁹ Therefore, we did not include this information into our DR strategies. In future research on DR, evaluation of possible predictors for successful DR remains important.

On a pharmacokinetic level, inter-individual variability exists leading to differences in biologic dose-response relationships between patients. Explanations can be found

in differences in clearance of biologics and anti-drug antibody (ADA) formation (i.e., immunogenicity). Clearance of biologics can be influenced by patient and disease characteristics such as body weight, degree of systemic inflammation, and presence of diabetes mellitus.^{103, 104} As standard dosing regimens do not account for pharmacokinetic variability between patients, fixed dosing might result in under- and overtreatment.⁷ This may in part explain the possibility of lowering the biologic dose in a subset of patients. The presence of dose-response relationships of biologics is the basis of therapeutic drug monitoring (TDM). TDM refers to the practice of measuring drug concentrations in order to allow tailored dose adjustments.¹⁰⁵ Before TDM can be implemented, assays for measuring drug levels and ADA should be developed when not already available and the right therapeutic window should be determined. In theory, TDM can also be used to guide DR. Within a proactive TDM approach, drug concentrations are regularly measured in patients, allowing dose optimization in order to achieve drug exposure targets associated with the desirable clinical response. However, by selecting patients with clinically low disease activity, TDM might not provide much benefit as patients already have reached the desirable clinical response. Moreover, it has been demonstrated that psoriasis patients with adequate treatment responses have varying drug levels.^{7, 16, 106, 107} In the light of DR, studies in both psoriasis and rheumatoid arthritis found that drug concentrations were not predictive of successful DR.^{16, 108} Previous studies provided however mostly data on the older biologics, and pharmacokinetics may differ between patients with low disease activity vs. patients with active disease. More research is therefore needed to determine inter-patient variability and pharmacokinetics of different biologics in different dosing regimens and how this influences clinical effectiveness.

Further insights into psoriasis pathogenesis may also provide a window of opportunity for more personalized dosing of biologics. It has been hypothesized that early intervention might modify the disease course of psoriasis. After psoriasis onset, a limited number of memory T-cells reside in the skin, but they accumulate over time. The expansion of these tissue-resident memory T-cells (TRMs) is thought to cause disease progression to a chronic state.¹⁰⁹ Moreover, TRMs may induce disease recurrence in response to triggers. When treated early with effective, targeted therapeutics, this process of ongoing recruitment of IL-17 producing T-cells may be halted. Consequently, this may lead to the possibility for long-term drug-free remission with lesser use of expensive biologics. In other immune-mediated inflammatory diseases, early treatment has been associated with improved outcomes.^{110, 111} For psoriasis, a trial regarding early treatment with guselkumab is ongoing at the time of writing this thesis.¹¹² Of note, within the context of such early treatment regimens, evaluation of cost-effectiveness seems of great importance as

early treatment might result in larger numbers of patients on biologics. It is currently unclear if this outweighs the possibility for use of lower dosages after early treatment or drug-free periods.

In conclusion, other potential approaches to enhance personalized dosing of biologics for psoriasis should be explored. Looking into options for more efficient use remains important, as risks of the cumulative dose of biologics remain unclear and new, expensive drugs are still being developed. Future studies could provide more insight in other forms of biologic DR as well, such as lowering the dose in mg instead of interval spacing, on demand dosing, and lowering the dose by skipping the induction scheme.^{44, 47} Eventually, results may also be translated to other immune-mediated inflammatory diseases.

Next steps for implementation of biologic dose reduction into practice

As described in **chapters 2 and 3** of this thesis, there is a need for guidelines on biologic DR substantiated by scientific evidence. Based on the results of this thesis, several recommendations can be done for actual guideline development. First, criteria to guide DR and dosing schedules per biologic should be practical. An example can be found in **chapter 3.4**, where we developed a clinical algorithm for application of DR based on consensus outcomes. Second, patient-relevant factors related to DR should be incorporated, as this will improve guidance of patients towards DR. Access to consultations and to the previous effective dose could be important for patients (**chapter 2.3**). I think patients should be informed on possible future DR *at treatment start*, preferably during the consultation and by means of a (online) patient information leaflet. As such, expectation management can be provided, which may result in increased awareness and confidence among patients.¹¹³⁻¹¹⁵ The treating clinician should address patients' concerns and pay attention to main issues that are important for patients as described in **chapter 2.3**. This will then lead to a shared decision. Of note, the Dutch Association for Dermatology and Venereology planned to add a chapter regarding biologic DR to the national psoriasis guideline in 2023-2024. For future research, evaluating uptake of guideline recommendations and assessing whether recommendations still fit with current practice could be of interest.

In the consensus of **chapter 3.4**, no recommendations were made regarding DR schedules for the newer biologics (IL-17i and IL-23i) as more evidence on DR of these classes needed to follow. For incorporation of innovations into guidelines, a certain level of evidence is also required. However, a point to consider here is the balance between current practice vs. quality and quantity of available evidence. It can be assumed that DR of the newer biologics is increasingly being applied in daily

practice, as in general these newer classes have high effectiveness rates, and results of our surveys in 2019-2020 among dermatologists indicated that DR was already applied for newer biologics as well at that time (**chapter 2**). In the light of current practice where DR is already performed, the expected (positive) results of possible trials, and the need for sustainable use of available resources (e.g., trials cost time and money), the question arises if (more) formal trials for DR remain needed, for instance when new biologics are being introduced.

Uptake of innovations in treatment guidelines does not guarantee actual implementation.⁹ Therefore, effort should be made to disseminate new guidelines. I believe that uptake can be improved by creating awareness and providing access to up-to-date information, for example by means of a 'living' guideline and/or an additional accessible toolbox with information and tools for assistance. This also connects with results from the implementation pilot in **chapter 3.3**. Successful implementation of innovations is however not only dependent on individual behaviour but also on organizational factors.¹¹ As described in this thesis, lack of time was a main identified barrier to implementation of biologic DR. This should be acknowledged when further implementing DR into practice, as it will influence actual uptake of recommendations. It will be difficult to create more time within busy practices, although installation of staff for support may eventually increase efficiency. I believe that limited extra time might be needed to educate patients and perform scores, especially when assisting tools are available. The required time-investment will probably be outweighed by the cost reduction due to DR. Even when drug prices decrease, for instance due to availability of biosimilars, DR will probably be cost-effective.⁸ In addition, it is important to avoid unnecessary drug exposure in patients with a chronic disease such as psoriasis. Involving stakeholders such as patients and clinicians, but also pharmacists and policy makers is therefore important when further implementing biologic DR on larger scales.

Another topic for future research would be to define criteria for biologic DR on an international level. As ideal criteria to guide DR could differ between countries due to differences in commonly used disease activity measures and differences in cultural and healthcare organizational aspects, our results might not be completely generalizable to other settings. However, results regarding DR safety and effectiveness from our DR studies and identified factors for successful implementation including patient-relevant factors could inform and inspire international practice as well.

Further possibilities for personalized and efficient use of biologics

Based on the results from **chapter 5**, it can be concluded that more insight into sex-

specific treatment with biologics and effectiveness and safety of current therapeutic options in patients of older age are still needed. Moreover, our data regarding risk of infections (**chapter 5.2**) provided reassuring results, but the question whether to continue or interrupt biologic treatment in case of an infection or elective surgery remains largely unanswered for patients with psoriasis. In order to answer remaining questions, use of real-world data seems highly important. Fortunately, real-world data is increasingly recognized as an important source of clinical evidence. For optimal use of real-world data, future work could focus on harmonizing analysis and reporting of observational data. As to date different methods are often used across real-world studies, comparisons of studies can be challenging. Furthermore, when accumulating data from different sources into large data sets (e.g., big data), other methods of data analysis including data-driven (e.g., machine learning) or longitudinal approaches could be utilized.¹¹⁶ Such modelling techniques can provide benefit, as they are able to include time-varying variables. Such techniques may more accurately reflect the real-world situation than techniques with a binary approach, as outcomes, exposures and characteristics such as comorbidities actually vary over time.¹¹⁷

Moreover, more insight in biomarkers related to treatment outcomes, sex differences, and disease mechanisms are also of added value for further treatment optimization. Merging different data sources including information on such biomarkers into big data sets could enable a more precise selection of treatment for the individual patient and lead to more economic use of expensive treatments. In order to do so, a multidisciplinary approach seems highly important.

Future research

Based on the discussion, several topics for future studies can be identified:

- Future studies can contribute to resolve remaining questions related to biologic DR. Topics of interest include insight in predictors for successful DR, performance of DR of the newer generations biologics, (very) long-term data on DR effectiveness, and reviewing criteria to guide DR strategies.
- Other options for personalized dosing of biologics including TDM approaches, early treatment, and 'as needed' regimens need further research as well.
- For implementation of biologic DR, uptake of DR into treatment guidelines is important. Together with an implementation toolkit including nationally available patient information, uptake of DR into practice can be enhanced. Evaluation of implementation on a larger, (inter)national scale is for future perspective.
- More insights in treatment responses of female and male patients could be explored, with the aim to provide answers to the higher discontinuation rates for women and lower perceived treatment satisfaction with biologics.

- Additional data is needed in order to answer the question whether biological treatment should be continued or interrupted in case of an infection.
- As the general population is ageing and the group of patients with psoriasis using biologics will age as well, more evidence on effectiveness and safety of biologics in patients of older age is warranted.
- Other topics of interest include more insights into treatment related biomarkers and possibilities for harmonizing methods of observational, real-world studies and for broader use of real-world data.

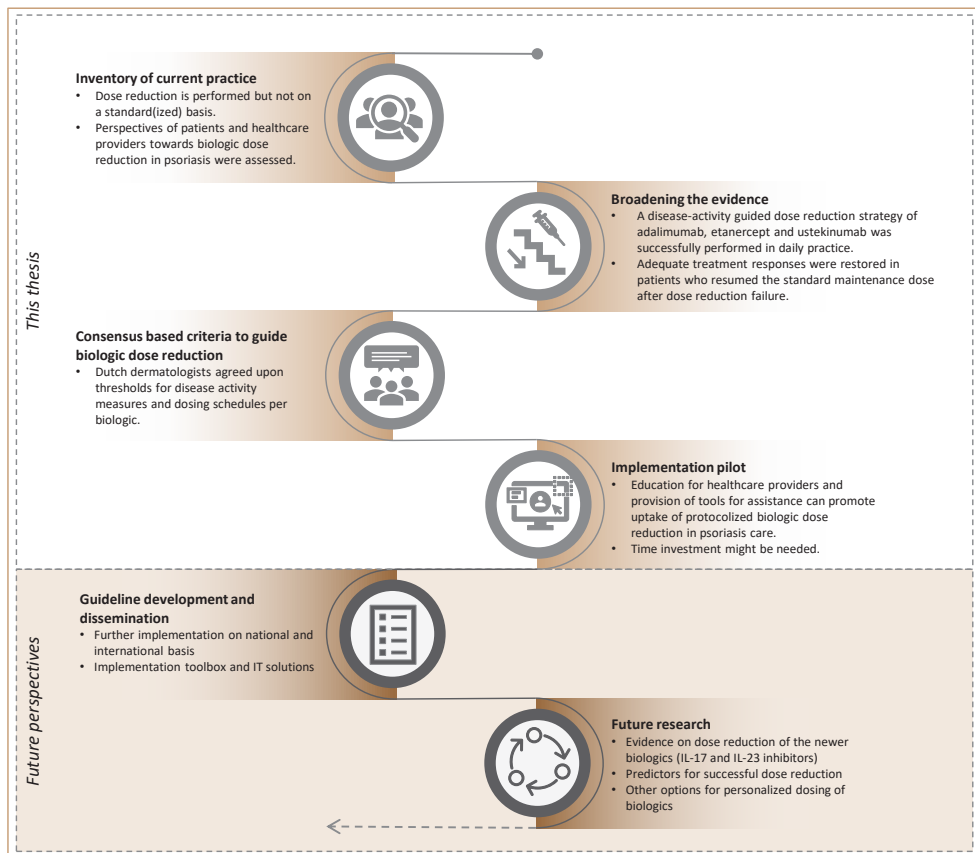


Figure 1. The road towards implementation of biologic dose reduction in psoriasis care.

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CHAPTER 7

Nederlandse Samenvatting

Op weg naar implementatie van dosisreductie van biologics voor patiënten met psoriasis

Psoriasis is een chronische ontstekingsziekte van de huid die bij ongeveer 500.000 mensen in Nederland voorkomt. Sinds 2003 zijn er zeer effectieve medicijnen beschikbaar gekomen voor mensen met matige-tot-ernstige psoriasis: biologics. Het gebruik van biologics heeft echter ook nadelen. Biologics zijn erg duur en kunnen gepaard gaan met bijwerkingen zoals infecties. Hoewel het aantal beschikbare biologics voor psoriasis nog steeds toeneemt, is het nog niet geheel mogelijk om het juiste middel voor de individuele patiënt te vinden. Daarnaast worden biologics vaak langdurig voorgeschreven in een standaarddosering. Eerder onderzoek liet zien dat niet elke patiënt deze standaarddosering nodig heeft om een goed effect van de behandeling te behouden. Verschillende studies hebben daarom al gekeken naar het verlagen van de dosering van een biologic nadat een goed behandel-effect is bereikt. Deze studies lieten zien dat dosisreductie mogelijk en veilig is bij patiënten met lage ziekteactiviteit, en dat zorgkosten dalen door het toepassen van dosisreductie. Toch zijn er nog verschillende vragen over dosisreductie van biologics bij psoriasis. In dit proefschrift worden verschillende aspecten van persoonsgerichte behandeling middels biologics voor mensen met psoriasis beschreven. De belangrijkste bevindingen van dit proefschrift worden hieronder samengevat per hoofdstuk.

Hoofdstuk 2. Het perspectief van patiënten en zorgverleners ten aanzien van dosisreductie van biologics bij psoriasis.

In hoofdstuk 2 werd inzicht verkregen in de stand van zaken omtrent dosisreductie in de dagelijkse praktijk middels vragenlijstonderzoek onder 114 Nederlandse dermatologen (hoofdstuk 2.1) en 53 dermatologen wereldwijd (hoofdstuk 2.2). Hieruit bleek dat dosisreductie al op redelijke schaal werd toegepast. De manier waarop men dosisreductie toepaste liep echter uiteen. Dermatologen vonden kostenbesparing een belangrijke motivatie voor het toepassen van dosisreductie. Redenen die ervoor zorgden dat dosisreductie niet werd toegepast waren tijdgebrek, de overtuiging dat patiënten het niet wilden, en onvoldoende ondersteuning. Dermatologen die überhaupt geen dosisreductie toepasten gaven hiervoor als redenen een gebrek aan wetenschappelijk bewijs, weinig ervaring met biologics en/of met dosisreductie, en het risico op ziekte opvlammingen of antistofvorming tegen de biologic. Er was behoefte aan een richtlijn over dosisreductie.

Vervolgens hebben we gekeken naar wat patiënten belangrijk vinden in het kader van dosisreductie. In hoofdstuk 2.3 werden 15 patiënten met psoriasis geïnterviewd.

Patiënten noemden het minimaliseren van medicatiegebruik, het verlagen van de kans op bijwerkingen, en het bijdragen aan lagere zorgkosten als voordelen van dosisreductie. Daarentegen kwam de angst voor opvlamming van psoriasis door het verlagen van de dosering naar voren. Het is voor patiënten belangrijk om te weten dat de dosering weer verhoogd kan worden als het niet goed gaat. De zorgverlener dient in te haken op eventuele zorgen van de patiënt, goede informatie te geven, en de patiënt te betrekken in de beslissing om dosisreductie toe te passen.

Hoofdstuk 3. Implementatie van dosisreductie van de eerste generatie biologics voor psoriasis (adalimumab, etanercept, ustekinumab) in de dagelijkse praktijk

In hoofdstuk 3 werd de toepasbaarheid en veiligheid van dosisreductie van de eerste generatie biologics voor psoriasis in de dagelijkse praktijk beschreven. In hoofdstuk 3.1 werd een 1-staps dosisreductiestrategie in de dagelijkse praktijk getest. Deze strategie was gebaseerd op een eerdere studie naar dosisreductie van de biologics adalimumab, etanercept en ustekinumab. In hoofdstuk 3.1 werd alleen de eerste stap dosisreductie (tot 67% van de standaarddosering) toegepast, in plaats van 2 stappen dosisreductie uit de eerdere studie (tot 67% en vervolgens tot 50%). De voorwaarde voor dosisreductie was dat de ziekteactiviteit en de impact van de psoriasis op de kwaliteit van leven van de patiënt laag waren bij start, en laag bleven gedurende de interventie. Na 1 jaar gebruikte 67% van deze patiënten nog steeds een lagere dosis. De ziekteactiviteit en impact op kwaliteit van leven bleven laag. Er was wel een tijdsinvestering nodig voor het selecteren van de geschikte patiënten voor dosisreductie.

In hoofdstuk 3.2 werd er gekeken naar patiënten uit voorgaande dosisreductie studies die teruggingen naar de standaarddosering. Er waren verschillende redenen om terug te gaan naar de standaarddosering: als de ziekteactiviteit of de impact van de psoriasis op de kwaliteit van leven te hoog werden, of als patiënten dit zelf wensten. Het merendeel van de patiënten die teruggingen naar de standaarddosering bereikte weer een lage ziekteactiviteit, oftewel een goed behandelresultaat. Deze bevinding is geruststellend voor patiënten en zorgverleners die dosisreductie overwegen.

Omdat nieuwe bevindingen niet altijd hun weg naar de praktijk vinden, is het belangrijk dat zogeheten implementatieonderzoek wordt verricht. In de implementatiestudie van hoofdstuk 3.3 werden zorgverleners in 3 algemene ziekenhuizen gestimuleerd om vaker dosisreductie toe te passen. Zij kregen voorlichting en er werden protocollen en patiëntfolders aangereikt. Uit interviews met deelnemende zorgverleners bleek dat gebrek aan tijd een belangrijke reden was

waardoor het niet lukt om dosisreductie toe te passen in de praktijk. Ondersteunend personeel voor begeleiding van patiënten kan hierbij helpen. Zorgverleners gaven aan opname van dosisreductie in behandelrichtlijnen en aanvullende ICT-oplossingen zoals beslishulpen in het patiëntendossier en opties voor het berekenen van ziekteactiviteitscores kunnen helpen bij het toepassen van dosisreductie. De resultaten lieten zien dat voorlichting en beschikbaarheid van protocollen ervoor kunnen zorgen dat zorgverleners vaker geprotocolleerde dosisreductie van biologics bij patiënten met psoriasis toepassen.

Om toepassing van dosisreductie in de dagelijkse praktijk te bevorderen en te harmoniseren, is het belangrijk om vast te stellen welke criteria relevant en noodzakelijk zijn om dosisreductie van biologics toe te passen. In hoofdstuk 3.4 werd consensus verkregen over 15 criteria voor het toepassen van dosisreductie onder 37 Nederlandse dermatologen. Er werd vastgesteld dat dosisreductie kan worden toegepast in overleg met de patiënt, en als ziekteactiviteit en impact op de kwaliteit van leven laag zijn. Daarnaast werd overeenstemming bereikt over het verlagen van de dosering van de biologics adalimumab en etanercept middels injectie-intervalverlenging in 2 stappen: tot 67% en vervolgens 50% van de standaarddosering. Voor ustekinumab werden 2 tussenstappen vastgesteld. De nieuwere biologics werden niet opgenomen in de consensus, omdat er weinig studies over dosisreductie van deze middelen beschikbaar waren. Er werd wel vastgesteld dat dosisreductie van deze nieuwere biologics voorzichtig kan worden toegepast in individuele gevallen.

Hoofdstuk 4. Dosisreductie van de nieuwe generatie biologics voor psoriasis (IL-17 en IL-23 remmers)

Er werd een pragmatische, gerandomiseerde, gecontroleerde, non-inferioriteitsstudie naar dosisreductie van de nieuwere generatie biologics voor psoriasis (IL-17 en IL-23 remmers) opgezet: de BeNeBio studie. BeNeBio is een samenwerking tussen Radboudumc en UZGent. In totaal nemen er 244 patiënten in 19 ziekenhuizen deel aan de studie. Tijdens het schrijven van dit proefschrift was de rekrutering en opvolging van patiënten nog gaande. Uiteindelijke resultaten zullen meer duidelijkheid geven over de effectiviteit en veiligheid van dosisreductie van de nieuwere generaties biologics voor patiënten met psoriasis.

Hoofdstuk 5. Persoonsgerichte behandeling van biologics voor psoriasis

Verskillende aspecten van persoonsgerichte behandeling van biologics voor psoriasis werden onderzocht in hoofdstuk 5. In hoofdstuk 5.1 werd gekeken naar het verschil in behandelingstevredenheid tussen mannen en vrouwen met psoriasis die werden behandeld met een biologic. Uit de resultaten bleek dat de behandelingstevredenheid hoog was, maar vrouwen rapporteerden een lagere behandelingstevredenheid dan mannen. Deze bevinding is een mogelijke verklaring voor de eerdere bevinding dat vrouwen eerder stoppen met een biologic.

Respiratoire infecties zijn de meest voorkomende bijwerkingen van biologics. In hoofdstuk 5.2 werd het verschil in risico op respiratoire infecties en alle soorten ernstige infecties tussen de verschillende biologics in de dagelijkse praktijk onderzocht. Hierbij werd geen verschil in risico op respiratoire infecties gevonden tussen de biologics adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab en guselkumab. Het aantal ernstige infecties was laag. Daarnaast werd er geen verhoogd risico op COVID-19 infecties gevonden in de tijd dat er nog geen vaccinaties beschikbaar waren.

Tot slot werd in hoofdstuk 5.3 een systematisch literatuuronderzoek gedaan naar effectiviteit en veiligheid van systemische behandelingen voor oudere patiënten met psoriasis. Over het algemeen waren er beperkte gegevens beschikbaar. Van de meeste systemische behandelingen bleek effectiviteit niet te worden beïnvloedt door leeftijd. Voor het medicijn ciclosporine werd wel een associatie gezien tussen hogere leeftijd en het optreden van meer bijwerkingen, met name nierfunctiestoornissen. Op basis van dit literatuuronderzoek zou leeftijd op zichzelf geen beperkende factor moeten zijn bij de behandeling van patiënten met psoriasis met systemische medicatie.



APPENDICES

List of abbreviations

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List of abbreviations

AE	Adverse Event
AEoSI	Adverse Event of Special Interest
ADA	Adalimumab OR Anti Drug Antibody
ADAMTSL5	ADAMTS like 5
BioCAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry with Biologics
BMI	Body Mass Index
BRO	Brodalumab
BSA	Body Surface Area
CCL-20	C-C Motif Chemokine Ligand 20
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CMO	Commissie Mensgebonden Onderzoek
CONDOR	CONtrolled DOse Reduction of biologics for psoriasis
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CVD	Cardiovascular disease
CXCL10	C-X-C motif chemokine 10
D	Day
DAG	Directed Acyclic Graph
DLQI	Dermatology Life Quality Index
DM	Diabetes Mellitus
DR	Dose Reduction
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Level
EMA	European Medicines Agency
EMM	Estimated Marginal Mean
EOW	Every Other Week
ETA	Etanercept
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GUS	Guselkumab
HBD-2	Human β -Defensin-2
HIV	human immunodeficiency virus
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life

ID	Initiation Dose
IFN	Interferon
IFX OR INF	Infliximab
IgG	Immunoglobulin G
IMID	Immune Mediated Inflammatory Diseases
iMTA	institute for Medical Technology Assessment
IL	Interleukin
IL-17i	Interleukin-17 inhibitor
IL-23i	Interleukin-23 inhibitor
IPC	International Psoriasis Council
IQR	Inter Quartile Range
IRR	Incidence Rate Ratio
ITT	Intention-To-Treat
IV	Intravenous
IXE	Ixekizumab
JAK	Janus Kinase
LMM	Linear Mixed Model
LOCF	Last Observation Carried Forward
LTBI	Latent Tuberculosis Infection
M	Month
MACE	Major Adverse Cardiac Event
MCQ	Medical Consumption Questionnaire
Mg	Milligram
MTX	Methotrexate
N	Total number of individuals or observations
NA	Not applicable
NET	Neutrophil Extracellular Trap
Nmsc	Non-melanoma skin cancer
NR	Not Reported
NRI	Non-Responder Imputation
NRS	Numeric rating scale
NVED	Nederlandse Vereniging voor Experimentele Dermatologie
OR	Odds Ratio
OW	Once Weekly
PASI	Psoriasis Area and Severity Index
PASI75	75% reduction in PASI compared to baseline
PASI90	90% reduction in PASI compared to baseline
PASI100	100% reduction in PASI compared to baseline
PCQ	Productivity Cost Questionnaire

PGA	Physician Global Assessment
PHA	Post Hoc Analysis
PK	Pharmacokinetic
PsA	Psoriatic arthritis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient Reported Outcome
PY	Patient-Years
QALY	Quality Adjusted Life Years
QoL	Quality of life
Q10D	Every 10 days
QW	Every week
Q2W	Every 2 weeks
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RIHS	Radboud Institute for Health Sciences
RoB	Risk Of Bias
RTI	Respiratory Tract Infection
RWE	Real world evidence
SAE	Serious Adverse Event
S.c.	Subcutaneous
SC	Steering Committee
SD	Standard Deviation
SDM	Shared Decision-Making
SEC	Secukinumab
SF-36	Short Form-36
SI	Serious Infection
SPSS	Statistical Package for Social Sciences
SRQR	Standards for Reporting Qualitative Research
STAT	Signal Transducer and Activator of Transcription
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
TE	Treatment Episode
Th cell	T-helper cell
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor Inhibitor
TRM	Tissue Resident Memory

TSQM	Treatment Satisfaction Questionnaire for Medication
TW	Twice Weekly
TYK	Tyrosine Kinase
UC	Uncontrolled OR Usual Care
UST	Ustekinumab
UV	Ultraviolet
VAS	Visual Analogue Scale
Wk	Week
Y	Year

List of publications

Publications related to this thesis

van der Schoot LS, Janssen JJ, Bastiaens MT, de Boer-Brand A, Christiaansen-Smit C, Enomoto DNH, Hovingh R, Tupker RA, Seyger MMB, Verhoef LM, van den Reek JMPA, de Jong EMGJ. Steps towards implementation of protocolized dose reduction of adalimumab, etanercept and ustekinumab for psoriasis in daily practice. *Journal of Dermatological Treatment*. 2023 Dec;34(1):2186728.

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van der Schoot LS, Groenewoud JMM, van Gelder MHJ, Otero ME, Arnold WP, Berends MAM, de Bruin-Weller MS, Dodemont SRP, Kleinpenning MM, Koetsier MIA, Kop EN, Körver JEM, Kuijpers ALA, van Lümig PPM, Mommers JM, Njoo MD, Ossenkoppele PM, Tupker RA, Visch MB, Weppner-Parren LJMT, de Jong EMGJ, van den Reek JMPA. Risk of respiratory tract infections and serious infections in psoriasis patients treated with biologics: results from the BioCAPTURE registry. *JEADV Clinical Practice*. 2022;1– 14.

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van Muijen ME*, **van der Schoot LS***, Bovenschen HJ, Dodemont SRP, van Lümic PPM, van Enst WA, van den Reek JMPA, de Jong EMGJ. Dosisvermindering van biologics voor psoriasis: houding en gedrag van Nederlandse dermatologen. *Nederlands Tijdschrift voor Dermatologie en Venereologie*. 2021;31(1):22-26. *Authors contributed equally.

van Winden MEC, **van der Schoot LS**, van de L'Isle Arias M, van Vugt LJ, van den Reek JMPA, van de Kerkhof PCM, de Jong EMGJ, Lubeek SFK. Effectiveness and Safety of Systemic Therapy for Psoriasis in Older Adults: A Systematic Review. *JAMA Dermatology*. 2020 Nov;156(11):1229-1239.

van der Schoot LS, van den Reek JMPA, Groenewoud JMM, Otero ME, Njoo MD, Ossenkoppele PM, Mommers JM, Koetsier MIA, Berends MAM, Arnold WP, Peters B, Andriessen MPM, Den Hengst CW, Kuijpers ALA, de Jong EMGJ. Female patients are less satisfied with biological treatment for psoriasis and experience more side-effects than male patients: results from the prospective BioCAPTURE registry. *Journal of the European Academy of Dermatology and Venereology*. 2019 Oct;33(10):1913-1920.

*Authors contributed equally.

Publications not related to this thesis

van der Schoot LS, van Muijen ME, van den Reek JMPA, de Jong EMGJ. Dosisreductie van biologics bij psoriasis: stand van zaken en perspectieven. *Nederlands Tijdschrift voor Dermatologie en Venereologie*. 2021;31(7):16-19.

van der Schoot LS, van den Reek JMPA. Data-driven prediction of biologic treatment responses in psoriasis: steps towards precision medicine. *British Journal of Dermatology*. 2021 Oct;185(4):698-699.

Research data management

This thesis is based on data from human clinical studies (**chapters 3.1, 3.2, 3.3, 4.1, 5.1, 5.2**), literature study (**chapter 5.3**), and surveys or interviews among dermatologists and patients (**chapters 2, 3.3, 3.4**). All studies were conducted in accordance with the principles of the Declaration of Helsinki. The BeNeBio study (**chapter 4.1**) was subject to the Medical Research Involving Human Subjects Act (WMO) and was conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands (METC Oost-Nederland) has given approval to conduct the studies (**chapters 3.1, 3.2, 4.1, 5.1, 5.2**), or waived ethical approval due to the nature of the study (**chapters 2.1, 2.2, 2.3, 3.3, 3.4**). Written informed consent was obtained from all participating patients or healthcare providers across studies, excluding **chapters 2.1 and 2.2**. In **chapters 2.1 and 2.2**, no personal data from participating dermatologists was collected when conducting the surveys. Participants were however informed that their results would be used for external publication.

Patient data from BioCAPTURE (**chapters 3.1, 3.2, 5.1, 5.2**) and from **chapters 3.3 and 4.1** were pseudonymized and collected through electronic Case Report Forms (eCRF) by use of the web-based data management system Castor EDC (Amsterdam, The Netherlands). An audit trail was kept in Castor to provide evidence of all activities that altered the original data. In **chapters 2.1 and 2.2**, survey data was collected anonymously by using the password-protected web-based survey system Qualtrics (XM 2020, Provo, UT, USA). Data from **chapter 3.4** were anonymously collected by the use the password-protected web-based survey system Survio (www.survio.com). All data were later converged from the database into SPSS (IBM, Armonk, NY, USA) for analysis. Qualitative data from **chapters 2.3 and 3.3** was collected through audio-recordings of telephone interviews. Anonymous audio data was transcribed verbatim and analyzed using Atlas.ti software.

All data is stored on the local department server (H:\Research\Data) and when applicable in Castor EDC. Datasets of **chapters 5.1 and 5.2** are also stored in the BioCAPTURE workspace in the Digital Research Environment Azure (DRE), with access for BioCAPTURE study staff. To ensure interpretability of the data, all filenames, primary and secondary data, metadata, descriptive files and program code and scripts used to provide the final results are documented along with the data. Privacy of participants is warranted by use of encrypted and unique individual subject codes. Codes were stored separately from the study data at the local department

server (H:\SleutelsResearch) and were password secured and only accessible by the principle investigator, sub investigator, study coordinator, and monitor. Paper data including informed consent forms (**chapters 2.3, 3.1, 3.2, 4.1, 5.1, 5.2**) were stored in locked cabinets at the Dermatology department of the Radboudumc. These data will be transferred to the departments archive after publication of the study. In **chapter 3.3**, patient data were collected in participating hospitals. Written informed consents and patient identification keys are stored by the sub-investigators in their respective hospitals. Data is only accessible by study team members working at the Radboudumc and sub-investigators at participating study sites for **chapters 3.3, 4.1**.

All data will be saved for 15 years after completion of the studies, except for trial data from the BeNeBio study (**chapter 4.1**) which will be kept for 20 years. Using patient data from **chapters 3.1, 3.2, 5.1, 5.2** in future research is only possible with renewed permission by the patient as recorded in the informed consent. Results of **chapters 2.1, 2.2, 2.3, 3.1, 3.2, 3.3, 3.4, 4.1, 5.2** are publicly available through open access publication. The original datasets are available from the corresponding author upon reasonable request.

PhD portfolio

Department: Dermatology

PhD period: 01/12/2019 – 31/12/2022

PhD Supervisor(s): Prof. dr. E.M.G.J. de Jong

PhD Co-supervisor(s): Dr. J.M.P.A. van den Reek

Training activities	Hours
Courses	
ZonMw - Opleidingsmiddag Zorgevaluatie en Gepast Gebruik (2020)	4
Radboudumc - Pubmed II Course (2020)	3
Radboudumc - eBROK Course (2020)	26
RIHS - Introduction Course for PhD candidates (2020)	15
RU - Statistics for PhD candidates by using SPSS (2020)	56
RU - Scientific writing for PhD Candidates (2020)	84
Radboudumc - Scientific Integrity Course (2021)	20
RIHS - Workshop: How to perform a peer review (2021)	1.5
RIHS - Workshop: How to write a rebuttal (2021)	1
RIHS - Workshop: Excel (2021)	1
Coursera - Qualitative Data Collection Methods (2021)	16
Radboudumc - Introductie cursus Kwalitatief Onderzoek in de Gezondheidszorg (2021)	16
Janssen-Cilag - Speakers Training (2021)	3
Radboudumc - Workshop: How to Sell Your Science	4
Radboudumc - Career Development Workshop (2022)	16
Radboudumc - Ogen Wijd Open (2022)	40
Seminars	
Dermatology - various clinical seminars (2020-2022)	6
Department of Dermatology - Journal Club and Research Updates (2019-2022)	30
Radboudumc - Grand Round: AI in de zorg (2020)	1
Radboudumc - Research integrity round: the dark side of science (2021)	1
Janssen-Cilag - EADV review 2021 (oral presentation) (2021)	4
RIHS - Webinar: Open Access (2020)	1
RIHS - Webinar: Social Media (2020)	1
ZonMw - Webinar: Inclusies voorop (2020)	1.5
BioCAPTURE - Annual network meetings (oral presentation) (2020-2021)	4
RIHS - Webinar: Mental Health & Wellbeing (during COVID-19) (2021)	1
Stichting Medical Business - Webinar: Zorg en Politiek (2021)	2
Stichting Medical Business - Webinar: implementeren (2021)	2
Stichting Medical Business - Masterclass: Geldstromen in de zorg & Healthy hospitals (2021)	4
Psoriasispatiënten Nederland - Webinar: Personalized care (oral presentation) (2021)	3
ZonMw - Webinar: Implementeren van start tot finish (2021)	1
Eli Lilly - Masterclass Dermatology (oral presentation) (2021)	2
Radboudumc - Research Integrity Round: the challenges of collaboration with profit and non-profit organisations (2022)	1.5
ZonMw - Webinar: Week van de Implementatie (2022)	2
Radboudumc - Research Integrity Round: Research Integrity in times of crisis: Juggling slow and fast science (2022)	1.5
Radboudumc - Research Integrity Round: publication ethics: Promises, problems and perspectives (2022)	1.5
MedNet - Masterclass Psoriasis (2022)	1
RIHS - Lecture: Sustainable Science (2022)	1
Radboudumc - Research Rounds: Inflammatory Diseases (oral presentation) (2022)	1

Training activities	Hours
Conferences	
Nederlandse Vereniging Experimentele Dermatologie (NVED) - Annual meeting (2020)	16
NVDV - Dermatologendagen virtual conference (poster presentation) (2020)	16
ZonMw - Congres Goed Gebruik Geneesmiddelen virtual conference (2021)	6
Eilanddagen Dermatologie (2021)	6
European Academy of Dermatology and Venereology (EADV) - virtual conference (oral presentation) (2021)	24
Psoriasis from Gene to Clinic - virtual conference (poster presentation) (2021)	16
Erasmusmc - Into Inflammation conference (2021)	16
ZonMw - Congres Goed Gebruik Geneesmiddelen (poster presentation) (2022)	7
RIHS - PhD Retreat (2022)	16
Nederlandse Vereniging Experimentele Dermatologie (NVED) - Annual meeting (poster presentation) (2022)	16
European Academy of Dermatology and Venereology (EADV) congress (poster presentation) (2022)	24
Other	
RU - Writing coaching (2022)	8
NVDV - Werkgroep lid richtlijnherziening Psoriasis (2021-2022)	20
Peer review for several dermatological journals (2021-2022)	12
Teaching activities	
Supervision of internships / other	
Supervision master students/physician assistant in training during consulting hours	80
Supervision research internship master medical student (2020)	50
Radboudumc – Meet the PhD project (2022)	5
Supervision research internship master medical student (2022)	50
Total	767.5

Curriculum Vitae

Lara van der Schoot werd geboren op 25 september 1993 in Eindhoven en woonde gedurende haar jeugd in Oirschot. Na het behalen van haar VWO diploma aan het Heerbeeck College Best begon zij in 2011 aan de studie geneeskunde aan de Radboud Universiteit Nijmegen. Na een fulltime bestuursjaar bij de Medische Faculteits Vereniging Nijmegen (MFVN) in 2013-2014 behaalde zij haar bachelor diploma in 2015. Tijdens de master geneeskunde was zij actief in de medezeggenschap als lid van de facultaire studentenraad en student-lid van de UMC Raad van het Radboudumc. In 2018 sloot zij haar studie af met een coschap tropengeneeskunde in Tanzania en een wetenschappelijke stage op de afdeling dermatologie in het Radboudumc. Alhier werd haar interesse voor het doen van wetenschappelijk onderzoek gewekt.



Na het behalen van haar masterdiploma in november 2018 startte zij als arts-onderzoeker richtlijnontwikkeling bij de Nederlandse Vereniging voor Dermatologie en Venereologie, waar haar enthousiasme voor het volgen van een PhD-traject werd vergroot. In december 2019 startte Lara met een promotietraject op de afdeling dermatologie van het Radboudumc te Nijmegen onder begeleiding van prof. Dr. E.M.G.J. de Jong en dr. J.M.P.A. van den Reek. Tijdens haar promotietraject deed zij onderzoek naar dosisreductie van biologics bij patiënten met psoriasis. Hierbij werkte zij onder andere nauw samen met collega's uit Gent, België in het kader van de BeNeBio studie, een gerandomiseerde, multicenter studie naar dosisreductie van IL-17 en IL-23 remmers bij patiënten met psoriasis in Nederland en België. Zij combineerde haar eigen onderzoek met het behandelen van patiënten met psoriasis op het gespecialiseerde biologics spreekuur van de afdeling dermatologie van het Radboudumc te Nijmegen.

Lara is per januari 2023 werkzaam als arts-niet-in-opleiding-tot-specialist (ANIOS) bij de afdeling dermatologie van het Radboudumc te Nijmegen. Per februari 2024 start zij met de opleiding tot dermatoloog op dezelfde afdeling.

Dankwoord

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