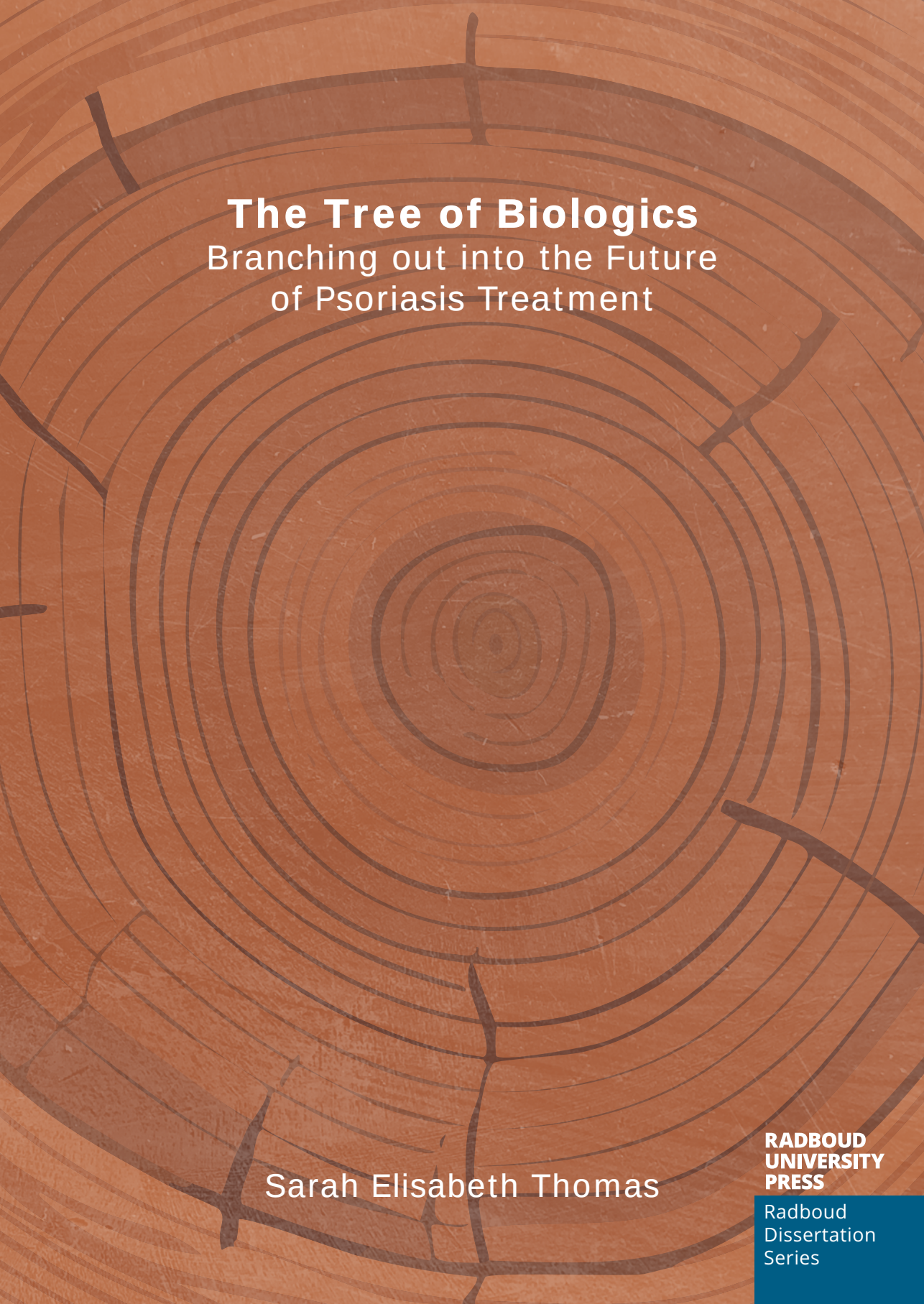

The Tree of Biologics

Branching out into the Future of Psoriasis Treatment

Sarah Elisabeth Thomas

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Sarah Thomas

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Branching out into the Future of Psoriasis Treatment

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on the authority of the Rector Magnificus prof. dr. J.M. Sanders,

according to the decision of the Doctorate Board

to be defended in public on

Thursday, March 6, 2025

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by

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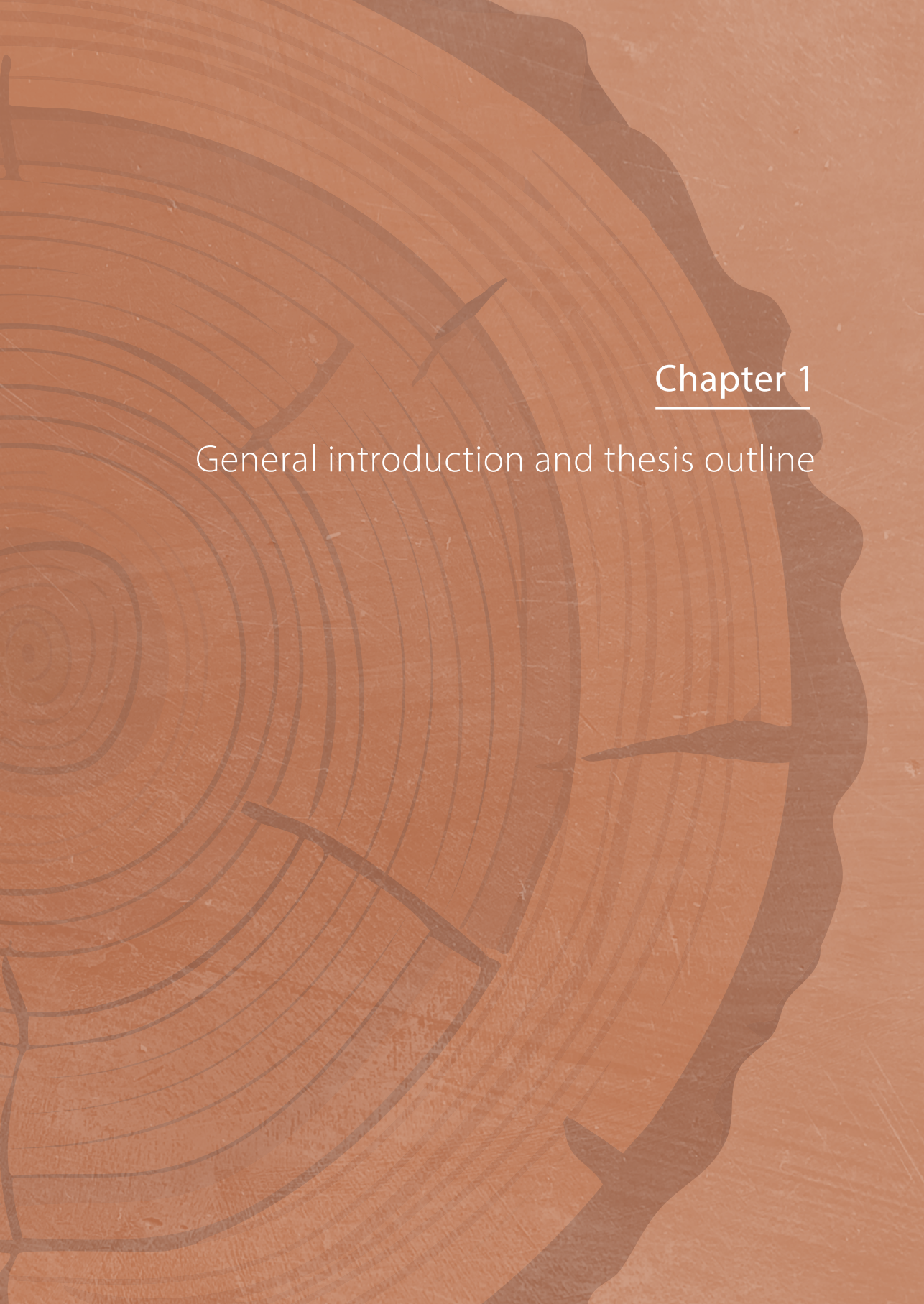

Chapter 1

General introduction and thesis outline

Introduction

The introduction of biologics for the treatment of psoriasis occurred 20 years ago. Since then, considerable research has been conducted on the effectiveness, safety, and patient satisfaction of these agents. However, knowledge gaps still exist. In recent years, new biologics have been introduced, prompting an examination of their placement in the overall treatment armamentarium. An important research methodology in this regard is the drug survival method. While many research groups publish in this field, there are significant opportunities for improvement in interpretation and execution of this methodology, which we aim to address through this thesis. Understudied populations in the context of biologics for psoriasis are two age groups at opposite ends of the spectrum: children and the elderly. In this thesis, we delve deeper into patient satisfaction, effectiveness, and safety within these groups using real-world data. Lastly, there is a noticeable increasing trend in the number of studies focusing on patients who either respond very well or very poorly to biologic treatment. An analysis of the influence of the various definitions addressing the extent of response used in these studies was lacking until the examination of this issue in this thesis. For a more comprehensive overview of the different objectives and research questions of this thesis, please refer to the last section of this introduction.

Psoriasis

This thesis focusses on psoriasis, a common chronic, inflammatory skin disease, consisting of red, scaly plaques. Most commonly involved sites are the elbows, knees, and scalp, but it can occur at any skin surface. Psoriasis greatly impacts people's quality of life, as the disease is associated with a physical, psychological and social burden.[1-3] It is associated with many diseases, such as psoriatic arthritis, obesity, cardiovascular diseases, and type 2 diabetes.[4-6] In 2014, the World Health Organization (WHO) recognized psoriasis as a serious non-communicable disease. The resolution highlighted that many people in the world suffer needlessly from psoriasis due to incorrect or delayed diagnosis, inadequate treatment, and insufficient access to care.[7]

History

Today, we possess extensive knowledge regarding the diagnosis of psoriasis. Scientific advancements have moved us forward significantly. However, this

understanding has not always existed. It took considerable time to discern how psoriasis distinguished itself and also to determine the nomenclature of the disease. The term 'psora', meaning 'an itchy rash', was the first term used by Hippocrates (460 - 377 BC), but was probably not used exclusively for psoriasis.[8] Psoriasis' first clinical description stems from Cornelius Celsius (25 BC – 45 AD), although he described it as impetigo.[9] Galen (129 – 216 AD) was the first to introduce the term psoriasis. For a long time, the prevailing belief centred on psoriasis as a condition primarily driven by keratinocytes. However, treatment of psoriasis with cyclosporin in the 1980s revealed an additional immunological dimension, implicating activated T cells and other immune cells in the pathogenesis.[10, 11] Subsequently, this recognition of immune mediation in addition to the involvement of keratinocytes sparked numerous advancements in the development of novel treatments for psoriasis.

Epidemiology

Epidemiological studies have been instrumental in enhancing our understanding of the global incidence and prevalence of psoriasis. However, there are still gaps in knowledge regarding the epidemiology of psoriasis, including trends over time and variations by age and gender. Studies on epidemiology were mostly conducted in high income countries.[12] Approximately 2-4% of the population in western countries is estimated to be affected by psoriasis.[13-16] Increased prevalence rates have been documented in regions with higher latitudes, and among individuals of Caucasian descent in contrast to those of other ethnic backgrounds.[17-19] Data on the incidence of psoriasis suggest a bimodal distribution for disease onset, with peaks occurring at the ages of 30-39 and 60-69 years.[12, 20] The prevalence in children (0 - 18 years of age) ranges from 0% to 1.37%.[16] There is no clear difference between the occurrence of psoriasis between male and female patients, although a slight male predominance has been reported in adults, and a slight female predominance in children.[16, 20]

Clinical features

Psoriasis exhibits various clinical manifestations, with plaque psoriasis being the predominant phenotype, accounting for 90% of cases. This form is identified by distinct red plaques covered in white to grey scales, leading to sensations of itch, pain, bleeding, or burning. The plaques may vary in size and thickness, demonstrating potential enlargement or central clearing. While any skin surface

can be impacted, common areas include the extensor sites of the elbows and knees, the lumbosacral region, and the scalp (**Figure 1**). Symmetrical patterns of occurrence are observed, and lesions may manifest at sites of trauma, known as the Koebner phenomenon. Anatomical variations of plaque psoriasis encompass scalp psoriasis, palmoplantar psoriasis, inverse psoriasis affecting skin folds, genital psoriasis, and nail psoriasis.

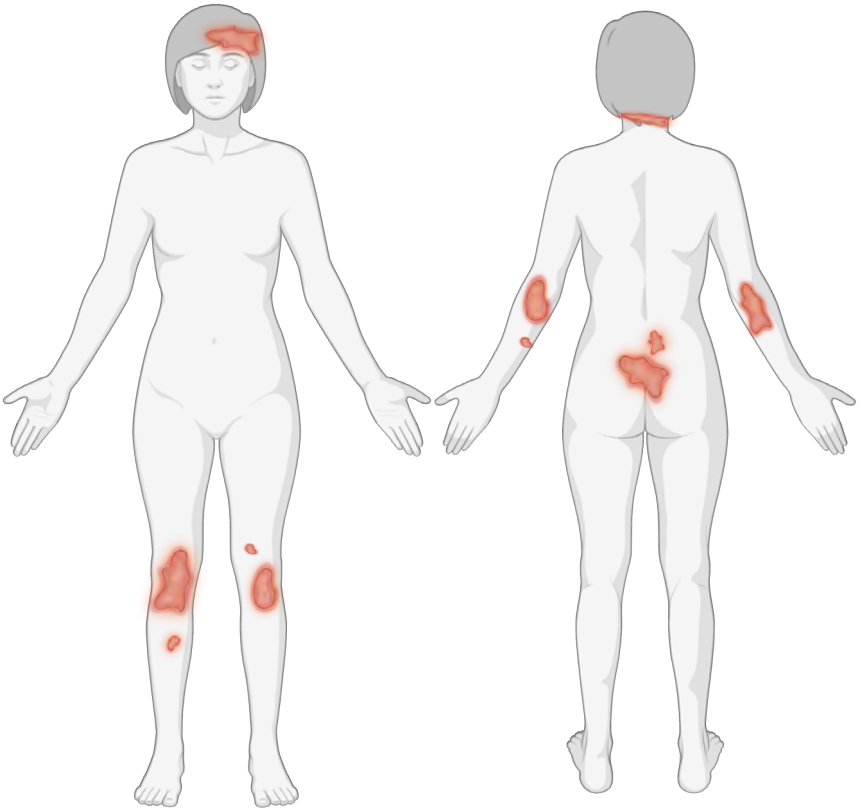

Figure 1 Common areas affected by psoriasis

Less common subtypes of psoriasis in adults include erythrodermic, guttate, and pustular psoriasis. Erythrodermic psoriasis involves the entire skin, while guttate psoriasis is characterized by numerous small, red, and scaly 'droplet-like' papules scattered across the body. Pustular psoriasis, although rare, manifests with sterile pustules and erythema in addition to psoriasis plaques, either generalized or localized to the palms and/or soles (known as palmoplantar pustulosis). Psoriasis, typically diagnosed through visual inspection, can sometimes require a skin biopsy in case of atypical presentation.

In paediatric patients with psoriasis, plaque psoriasis is also the predominant phenotype (up to 89%)[21-24], followed by guttate psoriasis (up to 30%)[24-27]. Diagnosing psoriasis in children presents greater challenges due to the typically thinner and smaller psoriatic plaques observed compared to adult patients. These plaques are commonly found on the face, scalp, and flexural areas. Lesions often exhibit less prominent scaling than in adult patients and tend to itch a lot. [28] Consequently, paediatric psoriasis may be mistaken especially for atopic dermatitis, but also for conditions such as, seborrheic dermatitis, pityriasis rosea, or dermatomycosis. [29] A recent diagnostic case-control accuracy study[30] tested the performance of consensus-agreed criteria for paediatric psoriasis and identified seven criteria that performed best: (i) scale and erythema in the scalp involving the hairline, (ii) scaly erythema inside the external auditory meatus, (iii) persistent well-demarcated erythematous rash anywhere on the body, (iv) persistent erythema in the umbilicus, (v) scaly erythematous plaques on the extensor surfaces of the elbows and/or knees, (vi) well-demarcated erythematous rash in the napkin area involving the crural fold and (vii) family history of psoriasis. Psoriasis commonly targets the skin, but can also involve the joints, and has been linked to several other medical conditions. Inflammation extends beyond the skin affected by psoriasis and has been observed to impact various organ systems. Consequently, there is a suggestion that psoriasis should be regarded as a systemic condition rather than solely a dermatological disorder. Approximately 25% of individuals with moderate-to-severe psoriasis develop Psoriatic Arthritis (PsA), compared to 16% of those with mild psoriasis. PsA, characterized by seronegative inflammatory arthritis involving peripheral joints, enthesitis, or dactylitis, shares immunological and pathophysiological features with psoriasis, leading to the registration of some therapies for both conditions. Prevalence data for juvenile Psoriatic Arthritis (JPsA) range from 0.7% to 10.5%, but are subject to difficulties in classification and diagnosis. [26, 31] Beyond PsA, psoriasis is linked to various other conditions such as cardiovascular disease, depression, Crohn's disease, and metabolic syndrome. However, the direction of causality in these associations remains unclear.

Pathogenesis

The pathogenesis of psoriasis is multifactorial, involving interactions between genetic susceptibility, immune dysregulation, epidermal hyperproliferation, angiogenesis, and environmental factors. The human leukocyte antigen (HLA) region on chromosome 6 is strongly associated with psoriasis. Variants of the HLA-C gene, particularly *HLA-C*06:02*, have been identified as major genetic risk factors

for psoriasis.[32] These genes encode proteins involved in antigen presentation and immune regulation, suggesting a crucial role for adaptive immune responses in psoriasis pathogenesis. Besides genetic susceptibility, environmental triggers are key in the manifestation of the disease. Various environmental factors have been identified as triggers, including stress, infections (specifically streptococcal), smoking, alcohol consumption, skin trauma (Koebner phenomenon), and certain medications (e.g. lithium, antimalarials, non-steroidal anti-inflammatory drugs).[33, 34] Although the exact mechanism of initiation of psoriasis has yet to be further elucidated, it is believed that the initial steps of pathogenesis include several innate immune cells, such as natural killer T cells, macrophages, keratinocytes, and plasmacytoid dendritic cells. These cells secrete cytokines (e.g., TNF-α, interleukin-1β, interferon-α, interferon-γ) which activate myeloid dendritic cells. Upon activation, myeloid dendritic cells travel to the lymph nodes where they secrete TNF-α, IL-12, and IL-23. These cytokines, alongside TGF-β1, prompt naive T cells to differentiate into Th1 and Th17 cells. Specifically, IL-12 and IL-23 facilitate the formation of Th1 and Th17 cells, respectively. As a result, Th1 cells produce TNF-α and IFN-γ, while IL-23 drives Th17 cells to release IL-17 and IL-22. Moreover, Th22 cells are stimulated to produce IL-22. This cascade of cytokine production propels a positive feedback loop that intensifies inflammatory responses (**Figure 2**). Such inflammation ultimately results in the thickening of the epidermis, the accumulation of immune cells like neutrophils and macrophages in the skin, and the formation of new blood vessels, contributing to the disease pathology.[35] A significant body of evidence now identifies IL-17, and therefore also its key regulator, IL-23, as the major players in psoriasis pathogenesis.[36, 37] The high efficacy of anti-IL-17 and anti-IL-23 therapies (biologics) in clinical trials further underscores the importance of this immunological axis.[38-43] In recent years, tissue-resident memory T cells, a particular subset of T cells, have garnered considerable interest. These cells are a type of memory T cells that do not recirculate, remaining in epithelial tissues for extended periods. Their activation can lead to the development of psoriasis. Several characteristics of psoriasis can be explained by their presence, including its sharply defined affected areas distinct from healthy skin and the tendency for psoriasis lesions to recur at previously affected locations.[44-46]

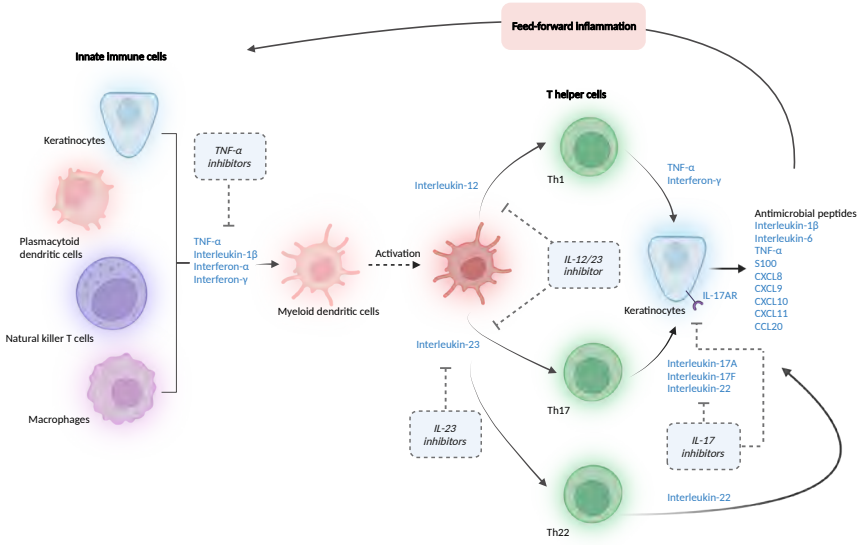

Figure 2 Immune pathogenesis of psoriasis. *TNF-α, tumour necrosis factor alfa; IL, interleukin; Th, T helper; CXCL, chemokine ligand; CCL, chemokine ligand*

Pharmacological treatment options

There are various treatment options for psoriasis, tailored to the severity of the condition (**Figure 3**). Before patients start a biologic, they have usually undergone multiple different treatments. The first step often involves topical therapy, such as corticosteroids, coal tar, vitamin D analogues, calcineurin inhibitors, emollients, or a combination of the aforementioned. Additionally, patients are often treated with phototherapy in the form of narrowband UVB or PUVA, which is effective, but less suitable for long-term use due to the risk of skin malignancies. For patients with moderate to severe psoriasis requiring systemic therapy, conventional systemic therapies like acitretin, cyclosporine, fumaric acid, and methotrexate are recommended.[47] In this chapter, only methotrexate will be further elaborated upon, as methotrexate is revisited later in this thesis. In some cases (e.g., contra-indications for conventional systemic agents, severe disease, or conception), it may be considered to bypass conventional systemic therapies and initiate biologics directly.

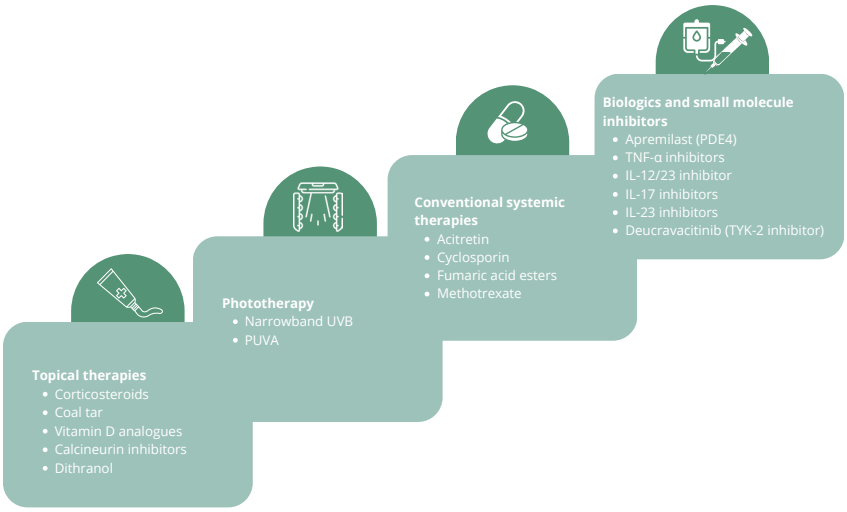

Figure 3 Pharmacological treatment options for psoriasis in adult patients. *UVB, ultraviolet B; PUVA, psoralen and ultraviolet A; PDE4, phosphodiesterase-4; TNF-α, tumour necrosis factor alfa; IL, interleukin; TYK-2, tyrosine kinase 2*

Conventional systemic therapies

Methotrexate

Methotrexate is a commonly used systemic treatment option for psoriasis and other inflammatory diseases. Methotrexate is a folic acid antagonist, inhibiting the conversion of folic acid to tetrahydrofolate by binding to the enzyme dihydrofolate reductase with higher affinity than the natural substrate. Since the conversion of folic acid is an essential step in the synthesis of nucleic acids during cell division, methotrexate inhibits the formation of new cells. The exact mechanism of action in psoriasis (but also in rheumatoid arthritis, psoriatic arthritis, chronic polyarthritis, and Crohn's disease) has not been elucidated. It may be due to an anti-inflammatory or immunosuppressive effect.[47, 48] Methotrexate is prescribed on a once-weekly basis, alongside folic acid supplements to mitigate side effects related to haematopoiesis and the gastrointestinal tract. Additionally, it is crucial to monitor for other significant side effects such as bone marrow suppression and liver fibrosis.

In paediatric patients with psoriasis, most conventional systemic treatments (including methotrexate) are not approved. This requires off-label prescription.[21, 49, 50] Available evidence is limited in comparison to evidence in adult patients. Based on the evidence at hand, methotrexate is considered the best option amongst the conventional systemic agents for paediatric patients.[21, 51 52, 53]

Biologics and small molecule inhibitors

Biologics are a class of medications, used in the treatment of psoriasis since 2005, that target specific inflammatory pathways involved in the disease. Their high effectiveness has revolutionized psoriasis treatment over the last two decades. Biologics are derived from living cells cultured in a laboratory and manufactured through recombined DNA techniques. Their nomenclature reflects their composition; receptor fusion proteins are denoted with the suffix '-cept', monoclonal antibodies with '-mab'. Fully human monoclonal antibodies typically end with '-umab', while combined antibodies utilize '-ximab' for chimeric antibodies and '-zumab' for humanized antibodies. Currently (2024), there are twelve different biologics available and EU approved for adult plaque psoriasis, which can be divided into four different classes based on their mode of action. A complete overview is presented in **Table 1**. The first available biologics for psoriasis were efalizumab (a monoclonal antibody against CD11a), and alefacept (a T cell CD2 receptor blocker). Efalizumab was introduced to the European market in 2003, but was withdrawn due to safety concerns. [54] Alefacept was approved in the United States in 2003, but withdrawn in 2011 as the sponsor chose to voluntarily withdraw it due to the availability of more effective and better tolerated biologics for psoriasis treatment. Currently available biologics target other cytokines or receptors.

The TNF-α inhibitors etanercept, infliximab, and adalimumab, and the IL-12/23-inhibitor ustekinumab were approved for the treatment of psoriasis in adults between 2004 and 2009 and are sometimes described as the first generation of biologics. Starting in 2015, a new class of biologic therapies, primarily focusing on IL-17, became available. This group includes secukinumab, ixekizumab, brodalumab, and bimekizumab. Subsequently, guselkumab became the first-in-class IL-23 inhibitor approved for treating moderate-to-severe psoriasis in 2017, followed by tildrakizumab and risankizumab. Furthermore, certolizumab pegol, another TNF-α blocker, received registration for psoriasis treatment in 2018. Certolizumab stands out as an exception due to its absence of placental transfer, making it a safe option for use in pregnant women. Over the period spanning 2015 to 2021, a total of eight new biologic therapies, with a focus mainly on IL-17 or IL-23 inhibition, have been approved for the management of psoriasis.

Biological treatment options for paediatric psoriasis patients have also been expanding over the last years. Currently approved biologics for paediatric patients are TNF-α-inhibitors etanercept and adalimumab, IL-12/23-inhibitor ustekinumab, and IL-17-inhibitors secukinumab and ixekizumab. Adalimumab is approved for

children aged >4 years, the other biologics for children aged >6 years. All EMA approved biologics for children are depicted in **Table 2**.

In general, the safety profile of biologics is considered to be good. Most common side-effects for all biologics are upper respiratory tract infections and injection site reactions. [55-59] In that respect, patients should be carefully screened prior to and during treatment. Besides general side-effects, there are some class-specific contra-indications and concerns. TNF-α inhibitors are associated with an increased risk of viral infections, related to the role of TNF-α in the defense against intracellular infections. Additionally, caution is warranted in case of latent tuberculosis infections and TNF-α inhibitor use. [47, 60] Due to their role in the mucosal host defense against Candida albicans, IL-17-inhibitors are associated with reports of mucocutaneous candidiasis. [61-63] For IL-17-inhibitors, exacerbations of inflammatory bowel disease have also been documented, rendering it less preferable for patients with that particular comorbidity. [64, 65] Besides the generally shorter-term safety data from randomized controlled trials, real-world patient registries have provided us with more long-term safety data. [37] For older patients with psoriasis specifically, there is limited safety data available, primarily because they are frequently excluded from clinical trials. [66-68] **Chapter 3.1** delves into this issue.

One of the persistent challenges associated with prescribing and utilizing biologics for patients with psoriasis has been their high cost. [69, 70] This places a significant burden on healthcare budgets. In the Netherlands, prices can reach €23,000 for a biologic in a normal dose, per patient per year. High costs lead to lowered access to biologics, and patients being undertreated. When a patent of an originator biologic expires, biosimilars can enter the market. The manufacturing of biologics includes the use of living cells, which makes it impossible to create exact copies. [71] A biosimilar should be highly similar to the reference (originator) product, and have no clinically meaningful differences in terms of quality, safety, and efficacy. [72] There are currently several biosimilars available for infliximab, etanercept, and adalimumab. The first biosimilar of ustekinumab is approved by the EMA and expected to enter the market soon. [73] The expectation is that, as the market expands and competition intensifies, costs of biosimilars will further decrease. [74] Another way to reduce the costs of biologics might be dose reduction. Most patients chronically receive the standard dosing regimen as prescribed per label by the manufacturer. However, for etanercept, adalimumab, and ustekinumab in patients with stable low disease activity, a randomized non-inferiority trial showed that dose reduction was non-inferior with regards to quality of life, and that 53% successfully applied dose

reduction after 12 months.[75] For patients with psoriasis and stable low disease activity using IL-17- and IL-23-inhibitors, research on this topic is still ongoing.[76]

Besides the biologics, there is also a small molecule inhibitor (SMI) available for the treatment of psoriasis (apremilast). Due to their smaller size, SMI have the capacity to bind to a broader array of extracellular and intracellular targets in comparison to antibodies.[77] Apremilast is an oral selective phosphodiesterase-4 (PDE4) inhibitor.[78] Apremilast works intracellularly by impeding the degradation of cyclic adenosine monophosphate (cAMP). This action leads to heightened intracellular cAMP levels, consequently leading to diminished expression of proinflammatory mediators like TNF-α, IL-17 and IL-22 (**Figure 4**).[79]

Research on new targeted therapies is still ongoing and is mostly focused on tyrosine kinase 2 (TYK2) inhibition, and on IL-23 inhibition by intracellular peptides. Deucravacitinib, an oral SMI, is approved by the EMA and expected to enter the Dutch market soon.[80] Deucravaciticinib is a selective inhibitor of the TYK2 enzyme (belonging to the JAK family). TYK2 plays a role in the signalling IL-23, IL-12, and type I interferons (IFN). By blocking the release of these pro-inflammatory cytokines and chemokines involved in inflammatory and immune responses, deucravacitinib effectively reduces inflammation (**Figure 5**)

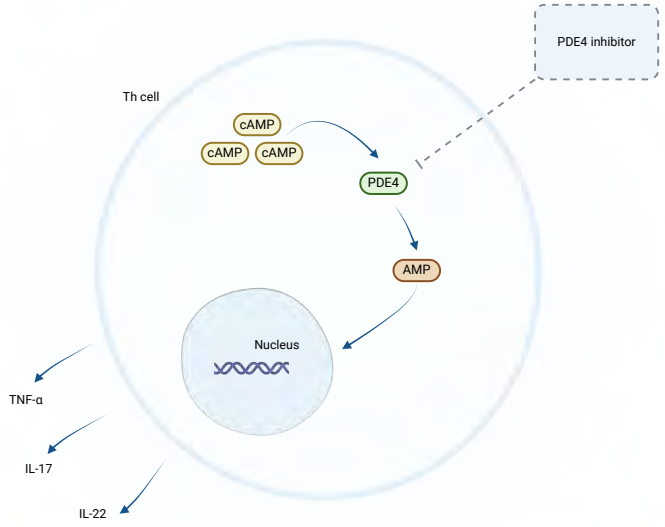

Figure 4 Working mechanism PDE4 inhibitor apremilast. *PDE4, phosphodiesterase-4; TNF-α, tumour necrosis factor alfa; IL, interleukin; Th, T helper; cAMP, cyclic adenosine monophosphate*

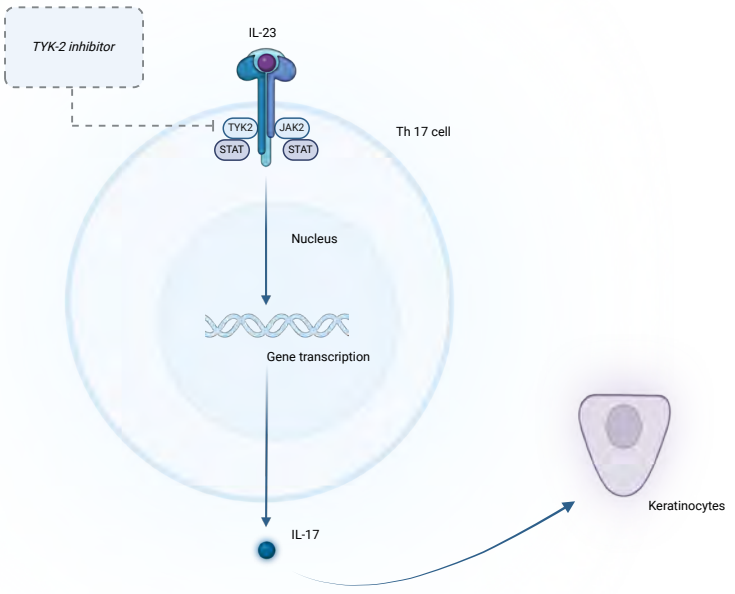

Figure 5 Working mechanism TYK-2 inhibitor deucravacitinib. *TYK-2, tyrosine kinase-2; IL, interleukin; Th, T helper; JAK2, janus kinase 2; STAT, signal transducer and activator of transcription*

Table 1 Biologic treatment options in adult patients

Target	Generic name	Brand name originator	Year of EMA approval	Mode of action	Dose
TNF-α	Etanercept[81]	Enbrel®	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[82]	Remicade®	2005	Chimeric IgG1κ monoclonal antibody binding TNF-α	5 mg/kg i.v. at week 0, 2 and 6, followed by every 8 weeks
	Adalimumab[83]	Humira®	2007	Human IgG1 monoclonal antibody binding TNF-α	80 mg s.c. initial dose, followed by 40 mg at week 1, and every (other) week thereafter
	Certolizumab pegol[84]	Cimzia®	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[85]	Stelara®	2009	Human IgG1κ 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 >100kg) at week 0 and 4, followed by ever 12 weeks
IL-17	Secukinumab[86]	Cosentyx®	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[87]	Taltz®	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
IL-17	Brodalumab[88]	Kyntheum®	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[89]	Bimzelx®	2021	Human IgG2 monoclonal antibody binding IL-17RA, thereby blocking IL-17a, IL-17a/f, IL-17F, IL-17c, and IL-17e (IL-25)	320 mg s.c. at week 0, 4, 8, 12, 16, followed by every 8 weeks

Table 1 Continued

Target	Generic name	Brand name originator	Year of EMA approval	Mode of action	Dose
IL-23	Guselkumab[90]	Tremfya®	2017	Human IgG1λ monoclonal antibody targeting the p19 subunit of IL-23	100 mg s.c. at week 0 and 4, followed by every 8 weeks
	Tildrakizumab[91]	Ilumetri®	2018	Human IgG1λ monoclonal antibody targeting the p19 subunit of IL-23	100 or 200 mg s.c. (depending on body weight ≥90kg or severe disease) at week 0 and 4, followed by every 12 weeks
	Risankizumab[92]	Skyrizi®	2019	Human IgG1λ monoclonal antibody targeting the p19 subunit of IL-23	150 s.c. at week 0 and 4, followed by every 12 weeks

Table 2 Biologic treatment options in paediatric patients

Target	Generic name	Brand name originator	Year of EMA approval	Mode of action	Dose
TNF-α	Etanercept[81]	Enbrel®	2009	Human TNF receptor p75 Fc fusion protein binding TNF, thereby acting as a competitive inhibitor of endogenous TNF-α	0.8 mg/kg (max 50 mg/dose) once weekly
	Adalimumab[83]	Humira®	2015	Human IgG1 monoclonal antibody binding TNF-α	Age 4-17 and 15-30 kg: 20 mg at week 0, followed at week 1 by 20 mg every 2 weeks Age 4-17 and ≥30 kg: 40 mg at week 0, followed at week 1 by 40 mg every 2 weeks
IL-12/23	Ustekinumab[85]	Stelara®	2015	Human IgG1κ monoclonal antibody, targeting the shared p40 subunit of IL-12 and IL-23	<60 kg: 0.75 mg/kg ≥60 kg to ≤100 kg: 45 mg >100 kg: 90 mg at weeks 0 and 4, and every 12 weeks thereafter
IL-17	Secukinumab[86]	Cosentyx®	2020	Human IgG1 monoclonal antibody selectively binding IL-17a	<50 kg: 75 mg ≥50 kg: 150 mg (may be increased to 300mg) at weeks 0, 1, 2, 3, and 4, and every 4 weeks thereafter
	Ixekizumab[87]	Taltz®	2020	Human IgG4 monoclonal antibody, selectively binding IL-17a	25 kg to ≤50 kg: 80 mg at week 0 and 40 mg every 4 weeks thereafter >50 kg: 160 mg at week 0 and 80 mg every 4 weeks thereafter

Real-world evidence

The majority of this thesis is based on real-world evidence/data (RWE). Given that the distinction between types of data is a recurring theme throughout this thesis, an explanation of the difference between research using randomized controlled trials (RCTs) and RWE is provided herein. Randomized Controlled Trials and RWE represent two distinct approaches to studying the effects and safety of medical interventions. RCTs are considered the gold standard in clinical research. In RCTs, participants are randomly assigned to either an intervention group, receiving the treatment being tested, or a control group, receiving either a placebo or standard treatment. This randomization helps to minimize biases and ensures that any differences observed between the groups can be attributed to the treatment being studied. [93, 94] RCTs are conducted under controlled conditions and often have strict inclusion and exclusion criteria, which can limit the generalizability of their findings to broader populations. Exploratory RCTs address the important question: does a drug work under ideal circumstances (efficacy). On the other hand, real-world data refers to data collected outside the constraints of a controlled clinical trial setting. Real-world data is derived from sources such as electronic health records and patient registries. Unlike RCTs, which have controlled environments and strict protocols, real-world data reflects the everyday clinical practice and experiences of patients in diverse healthcare settings. Real-world data provides insights into how treatments perform in real-world scenarios, including the outcomes, safety profile, and effectiveness of interventions in broader and more diverse patient populations. While RCTs offer high internal validity due to their rigorous design, real-world data offers the advantage of capturing outcomes in real-world settings, including long-term effectiveness, treatment adherence, and outcomes in populations not typically represented in clinical trials (such as older adults or those with multiple comorbidities). [67, 93, 95] Two specific subpopulations frequently omitted from clinical trials are children and older adults. In the case of paediatric RCTs, barriers like ethical considerations and the rarity of diseases pose limitations. [96] Conversely, for older adults, exclusion often stems directly from age limits and indirectly from the presence of comorbidities such as malignancies. [67] Real world data can thus address a different question compared to RCTs, namely: does a drug work in daily clinical practice (effectiveness). With the advent of international initiatives aimed at merging databases, it is anticipated that real-world registries will continue to evolve and significantly contribute to studying effectiveness, safety, and cost-effectiveness of treatments. [97] Given that RCTs and RWE tackle distinct issues, both are indispensable for the most comprehensive understanding of a drug's functionality. These two data sources are mutually reliant, with their combined analysis offering a more robust perspective.

For psoriasis, an increase in patient registries can be observed in recent years.[98] The majority of the data in this thesis originates from the BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry With Biologics) registry (https://biocapture.nl/). Since 2005, observational data on adult patients with psoriasis treated with biologics have been prospectively collected. Currently (2024), the network consists of 4 academic and 19 non-academic hospitals in the Netherlands and is still expanding. Data on patient characteristics, treatment and dosing, safety, effectiveness, and patient reported outcomes (e.g., dermatology related quality of life, treatment satisfaction) are collected in the BioCAPTURE registry. One chapter in this thesis is based on Child-CAPTURE data. The Child-CAPTURE registry is also a prospective, long-term registry for patients with psoriasis, although this registry focusses specifically on paediatric patients (<18 years), and includes data on all psoriasis treatments, instead of biologics solely. These registries provide us with valuable information on specific populations, such as older adults and children, which was explored in this thesis (**Chapter 3**).

Outcome measures

There is a broad range of outcome measures available to assess multiple aspects of psoriasis, including clinical severity, quality of life, patient-reported outcomes, and disease-specific symptoms and impacts.[99, 100] The wide array of outcome measures underscores the complexity of assessing patients with psoriasis and highlights the importance of utilizing combinations of measures when possible. Below, the outcome measures relevant to this thesis are outlined.

Psoriasis Area and Severity Index

The most frequently used outcome measure is the Psoriasis Area and Severity Index (PASI), introduced in 1978 as an outcome measure in a study on retinoids.[101] The PASI is a score ranging from 0 to 72, utilized to objectively measure the severity of psoriasis. A PASI >10 is generally classified as moderate to severe psoriasis.[102] To calculate the total PASI, the body is divided into four parts: the head, arms, trunk, and legs. The area that is affected by psoriasis of each body part is estimated. The existing psoriasis plaques are then also scored on erythema, induration, and scaling and multiplied by the area affected. Assessing psoriasis severity via the PASI is complex and requires experience, which makes it less ideal to use in daily clinical practice settings.[103] In research settings, the PASI is widely used. Relative PASI targets such as PASI75, PASI90, and PASI100 are often pursued in research, reflecting a 75%, 90%, and 100% reduction of the PASI compared to baseline. This is a point of critique on the use of relative PASI outcomes, as baseline PASI can

vary greatly between patients starting a drug especially in real-world practice. In **Chapter 2.1**, this topic is further elaborated on.

Patient Reported Outcome Measures

DLQI

The Dermatology Life Quality Index (DLQI) is a widely used questionnaire to assess the impact of skin diseases on patient's quality of life. It consists of ten questions covering various aspects such as symptoms, daily activities, leisure, work, personal relationships, and treatment. Each question is scored on a scale of 0 to 3, with higher scores indicating greater impairment of quality of life. [104] In research settings, the DLQI is often used as an outcome measure. Correlation studies between the objective disease severity (e.g., PASI) and subjective severity have shown that the objective measures alone do not capture the full impact of psoriasis. For certain patients, quality of life is significantly compromised despite having a low PASI assessed by a dermatologist. Conversely, some patients experience only mild impairment in quality of life despite having a high PASI. [105, 106] In children, an adapted version of the DLQI is used, called the Children's Dermatology Life Quality Index (CDLQI). [107] Data from the Child-CAPTURE cohort demonstrated that an improvement of the PASI score of 90% or greater led to the highest improvement in quality of life in children. [108]

Visual Analogue Scales

One of the challenges in managing paediatric psoriasis is accurately assessing and treating the subjective symptoms itch, pain, fatigue, and self-reported disease severity. The Visual Analogue Scale (VAS) is a tool that can be easily understood by children. Children are asked to report their burden (e.g., itch) on a scale ranging from "no itch at all" to "worst itch you can imagine". The VAS is a continuous scale, allowing for detailed measurement of symptoms and the ability to detect small changes over time. Only few studies have reported separate VAS for paediatric patients with psoriasis. [109-111] The VAS is explored in **Chapter 3.2** of this thesis.

Drug survival

Drug survival is an analysis methodology that encompasses various factors such as effectiveness, tolerability, safety, and patient satisfaction. Drug survival refers to the duration of time a patient continues to use a specific medication before discontinuing or switching to an alternative treatment. The majority of this thesis is based on studies using the drug survival methodology.

The commonly used approach for analysing the drug survival is Kaplan-Meier analysis, which estimates the probability of (drug) survival over time. In this method, the survival curve illustrates the proportion of patients still on drug at each time point. When a patient discontinues their drug, this is considered as an 'event' and the Kaplan-Meier curve declines (**Figure 6**). [112] The capacity to address censoring is a crucial aspect of Kaplan-Meier analysis, as it allows for the comprehensive integration of data from patients with varying follow-up durations into the model. [113]

Drug survival analysis enables us to assess how explanatory variables influence the likelihood of discontinuation of a drug. Consequently, we can pinpoint variables that forecast either prolonged or abbreviated drug survival. Multivariable Cox regression analysis is employed for this purpose. [114]

Over the last decades, the drug survival methodology has become increasingly popular in the field of Dermatology. A lot of studies report on overall drug survival, in which all discontinuation reasons are taken into account. However, in drug survival analyses, it is possible to specifically analyse an outcome of interest, e.g., discontinuation due to ineffectiveness. By analysing only ineffectiveness as an outcome, other discontinuation reasons that are not relevant to the performance of the drug itself, such as wish for pregnancy or financial reasons, are eliminated. [115, 116]

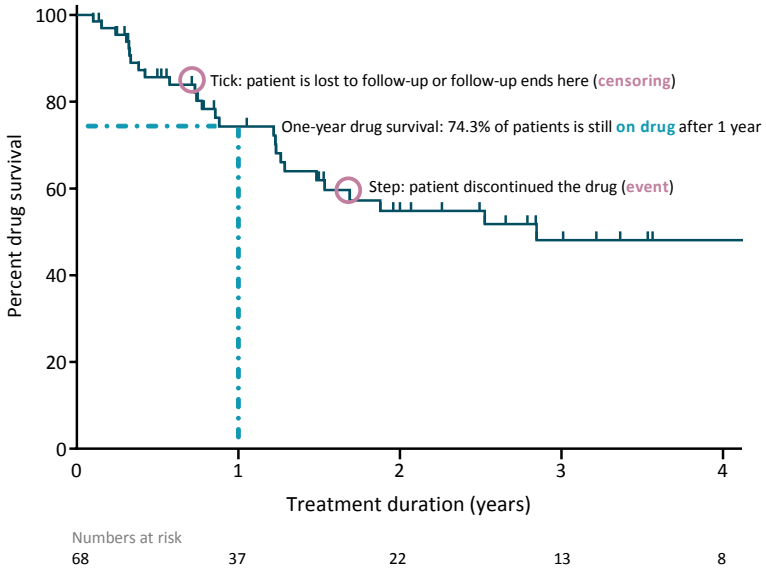

Figure 6 Kaplan-Meier drug survival methodology. *Adapted from van den Reek et al.* [113]

Aims and outline of this thesis

In this thesis, data from two prospective patient registries were combined with literature studies that encompass a broad scope of real-world and pharmacy/claims data on the treatment of psoriasis with biologics. With this approach, we attempted to give a comprehensive overview of the biologic landscape and the challenges that lie ahead.

The following overarching aims were identified:

- To explore and compare real-world drug survival and effectiveness of biologics for psoriasis
- To generate real-world evidence of treatment with biologics in children and older adults with psoriasis
- To study the influence of current definitions for super-response and multi-treatment resistance on psoriasis studies

To explore and compare real-world drug survival and effectiveness of biologics for psoriasis

The first aim is explored in **chapters 2.1, 2.2, 2.3,** and **2.4** by the following research questions:

- What is the comparative real-world effectiveness of the six most frequently used biologics (etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab, and guselkumab) in the BioCAPTURE cohort?
- What is the one- and two-year drug survival of guselkumab?
- What is the summarized drug survival of published studies on IL-17 and IL-23 inhibitors?
- What is the effectiveness of IL-23 inhibitors after switching from ustekinumab due to ineffectiveness?

To generate real-world evidence of treatment with biologics in children and older adults with psoriasis

The second aim of this thesis focuses on patients who are often under-represented and is explored in **chapters 3.2** and **3.3** by the following research questions:

- What is the extent of itch, pain, fatigue and disease severity in paediatric patients with psoriasis and how do methotrexate and biologics influence these complaints?

– What is the drug survival, effectiveness and safety of biologics in older adult patients compared to younger adult patients?

To study the influence of current definitions for super-response and multi-treatment resistance on psoriasis studies

The third aim of this thesis was studied by synthesizing different definitions of super-response and multi-treatment resistance used in psoriasis literature. The following research questions were explored in **chapters 4.1** and **4.2**:

– What are current definitions for super-response in literature and how do these definitions impact the composition of the super-responder group?
– What are current definitions for multi-treatment resistance in literature and how do these definitions impact the composition of the multi-treatment resistance group?

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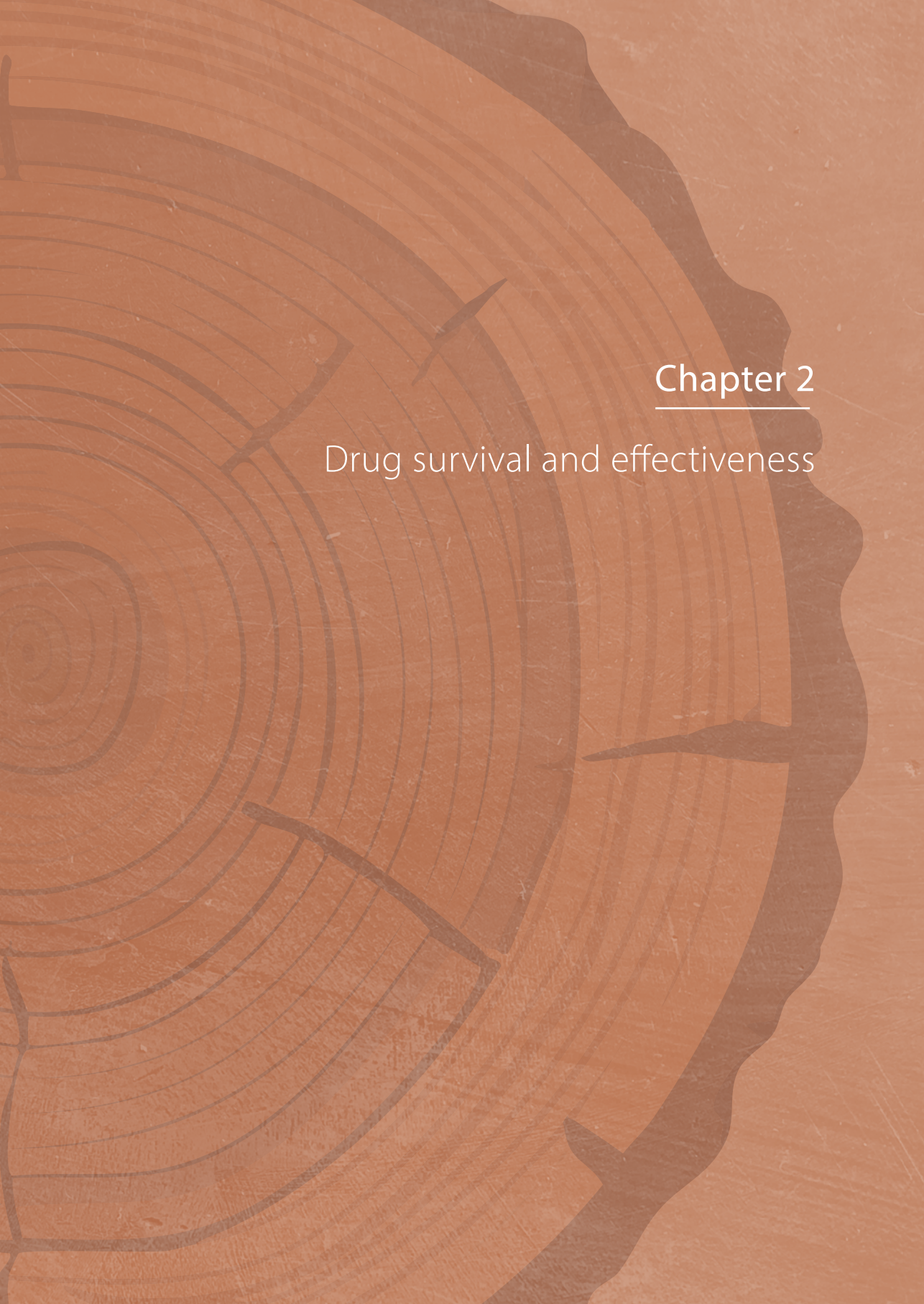

Chapter 2

Drug survival and effectiveness

2.1 Direct comparison of real-world effectiveness of biologics for psoriasis using absolute and relative PASI scores in a prospective multicentre cohort

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Abstract

Real-world evidence, directly comparing the effectiveness of interleukin (IL)17-inhibitors, IL-23-inhibitors, tumour necrosis factor alpha (TNF-α)-inhibitors and an IL-12/23-inhibitor in psoriasis, is scarce. The aim of this study was to directly compare the first-year effectiveness of biologic therapies for psoriasis, corrected for confounders. This prospective, multicentre cohort study assessed BioCAPTURE data on etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab, and guselkumab in 1,080 treatment episodes of 700 patients with psoriasis. The course of the mean absolute Psoriasis Area and Severity Index (PASI) and the proportion of patients who achieved PASI90/PASI75 were compared using linear mixed models and mixed logistic regression models respectively, corrected for baseline PASI, biologic naivety, and weight. Patients treated with adalimumab, ustekinumab, secukinumab, ixekizumab, or guselkumab all had a significantly lower mean PASI after 12 months compared with etanercept, and significantly higher overall odds of reaching PASI90 than those treated with etanercept. Patients treated with ixekizumab or guselkumab also had higher probabilities of reaching PASI90 than adalimumab, ustekinumab, and secukinumab. Relative to randomized controlled trials, the proportions of patients who reached PASI90/75 were lower in this real-world study.

Significance

Various biologics are currently available for treatment of psoriasis. However, studies directly comparing treatment effects of these biologics are scarce. Knowledge of the relative effectiveness of biologic therapies in daily practice will provide useful insights for physicians. Six biologics for psoriasis were compared: etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab, and guselkumab. Ixekizumab and guselkumab showed high effectiveness in daily practice, whereas etanercept seemed to be least effective. For all biologics, 90% reduction in baseline Psoriasis Area and Severity Index scores was reached less often in this real-world cohort than would be expected from randomized controlled trials.

Introduction

The development of biologic therapies has led to a breakthrough in psoriasis treatment. In network meta-analyses, the comparative efficacy of biologics has been outlined, based on data from RCTs.[1-4] However, in randomized controlled trials (RCTs), the "real-life" patient is not always adequately represented, due to, for example, the exclusion of patients with comorbidities, or those above a certain age limit.[5] Comparative effectiveness in daily practice has often been studied in tumour necrosis factor (TNF-α) inhibitors and ustekinumab[6-8], but is limited in newer generation biologics. Real-world data, directly comparing effectiveness of IL-17-inhibitors, IL-23-inhibitors, ustekinumab (IL-12/23-inhibitor) and TNF-α-inhibitors, are needed to supplement current evidence.

In RCTs, which typically include patients with high baseline Psoriasis Area and Severity Index (PASI) scores, efficacy outcomes are mostly reported as relative PASI-reduction compared with baseline (e.g., 75% and 90% PASI-reduction; PASI75 and PASI90). In a systematic review on short-term efficacy (10-16 weeks) of biologics, the proportions of PASI75 and PASI90 responders ranged up to 94.6% and 91.9% respectively.[9] Since reaching a relative PASI-target is highly dependent on the baseline value, patients with low PASI-scores at baseline may not achieve this, even though absolute treatment response may be excellent. In daily practice, baseline PASIs can be low, especially in patients switching therapies. Furthermore, patients may switch between biologics for reasons other than ineffectiveness (e.g. side-effects or trying to conceive). In addition to the relatively low baseline PASI, treatment results in "real-life" may be less favourable than in trials, due to the less controlled setting and the inclusion of patients with comorbidities and co-medication.[10] Altogether, this may impede achievement of PASI75/90 in daily practice.

This study analysed and directly compared the effectiveness of TNFα-inhibitors (etanercept and adalimumab), an IL-12/23-inhibitor (ustekinumab), IL-17-inhibitors (secukinumab and ixekizumab), and an IL-23-inhibitor (guselkumab) in patients with psoriasis from a prospective multicentre cohort, by reporting absolute and relative PASI measures, with confounder-correction.

Materials and methods

BioCAPTURE database

Data were extracted from the prospective, multicentre, Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE-registry, www.

biocapture.nl). This study contains data on patients with psoriasis treated with biological therapy in 3 academic and 14 non-academic centres in the Netherlands (2005 to 2021). According to our regional medical ethics committee, ethical approval was not necessary for this non-interventional study.

Data collection

A treatment episode (TE) represents the period of time in which a patient is continuously treated with a certain biologic. When treatment is discontinued or interrupted for ≥90 days, the current TE ends. Therefore, a single patient can have multiple TEs. Biologics for which <50 TEs were available, were not included in this study. For biologics with ≥50 TEs in the registry, TEs without a baseline PASI or a single follow-up PASI-score within the first year of treatment were excluded. Baseline PASI was defined as the PASI-score at the start of a TE, allowing a time window of 90 days prior, and until 7 days after the initiation of treatment. Baseline patient characteristics were collected and calculated for every TE.

In the first year of a new treatment episode, patients generally visit at baseline, week 6, week 12, and every 3 months thereafter. PASIs are measured at each visit. Since scheduling visits at exact time points is not feasible in a clinical setting, linear interpolation was used to estimate PASIs at 5 time-points: weeks 6, 12, 26, 39 and 52. PASIs measured in a range of 120 days from the intended time-points were used for interpolation. Interpolated PASIs were used to calculate PASI 0, ≤1, ≤3, ≤5, and PASI90, PASI75 or PASI50 at each time-point.

Statistical analysis

Statistical analyses were performed in SPSS version 25.0 (IBM, Armonk, NY, USA) or SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). A p-value < 0.05 was considered significant.

Baseline patient and treatment characteristics for the first TE per patient, and per biologic were displayed using descriptive statistics (mean ± standard deviation (SD), median and interquartile range (IQR), n (%)). Continuous variables were compared between treatment groups with one-way analysis of variance (ANOVA) in case of a parametric, and Kruskal–Wallis tests in case of a non-parametric distribution, respectively. For categorical variables, Pearson's $\chi 2$ test was used for comparisons.

Changes in mean Psoriasis Area and Severity Index

To investigate differences in PASI reduction between biologic treatments during the first year of treatment, a linear mixed model (LMM) analysis was performed in SPSS. LMM allows the implementation of repeated, correlated measures.

Furthermore, LMM can handle missing data (e.g. missing PASIs) adequately, and integrate all available data with flexible assumptions.[11] In this model, PASI was defined as dependent variable, and time from baseline visit (categorical, 5 time points), biologic treatment, and the interaction term between time and biologic treatment were key independent variables. The interaction term was included to analyse whether PASIs over time were different between patients on various types of biologics. To select possible confounders, baseline characteristics were tested univariately and incorporated into the multivariable model when the univariate p-value was <0.1, and their effect on the LMM was significant ($p \leq 0.05$). For every treatment group, estimated marginal means were calculated for each time-point to depict the course of the PASI during the first year of treatment. In post-hoc tests, all biologics were compared pairwise at all 5 time-points. The model assumptions were checked with residual plots (normality using a histogram, homoscedasticity with a scatterplot with residuals on the y-axis, and predicted values on the x-axis).

LMM analyses were repeated using PASIs complemented with last observation carried forward (LOCF) estimates. In this method, in case of early treatment termination ≤ 1 year, the last available PASI score is carried forward until 1 year. The LOCF method facilitates a more conservative approach compared with the as-treated analysis, as the last PASI-observation from patients who discontinue treatment due to ineffectiveness will continue to be taken into account.[12]

Proportion achieving PASI75 and PASI90

Data on PASI90 and PASI75 were analysed using a mixed logistic regression model (MLR), built in SAS. In this model, the dependent variable was dichotomous (PASI90 or PASI75 yes/no). Baseline characteristics that were identified as confounders in the LMM, were also set as fixed effects in the MLR. The MLR allowed for pairwise comparisons for each treatment with regards to reaching PASI90/PASI75, and calculation of odds ratios (OR). PASI90 and PASI75 analyses were repeated with imputing missing PASIs using LOCF.

Results

At data lock, 1,472 TEs of 871 patients (etanercept 340, adalimumab 485, ustekinumab 392, secukinumab 111, ixekizumab 76, guselkumab 68) were included. Infliximab, certolizumab-pegol, brodalumab, risankizumab and tildrakizumab were excluded, as < 50 TEs were available. After eliminating TEs without a baseline or single follow-up PASI, 1,080 TEs from 700 patients (etanercept 287 TEs (26.6%),

adalimumab 343 TEs (31.8%), ustekinumab 276 TEs (25.6%), secukinumab 75 TEs (6.9%), ixekizumab 55 TEs (5.1%), guselkumab 44 TEs (4.1%)) were included for analyses. Baseline patient characteristics, at the start of the first TE included (n = 700), are shown in Table 1. Table 2 reports baseline patient characteristics per biologic. After 1 year of treatment, 817 TEs (75.6%) were still ongoing, 127 TEs (11.8%) were discontinued due to ineffectiveness, 61 TEs (5.6%) due to adverse events, 24 TEs (2.2%) due to a combination of ineffectiveness and adverse events, 29 TEs (2.7%) were lost to follow up, 20 TEs (1.9%) were discontinued due to other reasons, and 2 TEs (0.2%) were discontinued because the patients had died.

Table 1 Baseline patient characteristics for unique patients

Baseline patient characteristics	**Unique patients N=700**
Age at start of biologic (yrs)	47.9 ± 13.2 Missing: 0
Gender (male)	438 (63.2%) Missing: 7
Height (cm)	175.6 ± 9.6 Missing: 66
Weight (kg)	87.3 [22.9] Missing: 17
BMI (kg/m2)	27.8 [7.1] Missing: 67
Positive family history of psoriasis (yes)	437 (66.3%) Missing: 41
Psoriatic arthritis (yes)	189 (30.8%) Missing: 86
Baseline PASI score (overall) Biologic naive patients (N=433) Biologic non-naive patients (N=267)	11.3 [8.7] 11.8 [8.6] 10.9 [9.5] Missing: 0

Mean ± SD, median [IQR], N (%).

The proportion of TEs in which patients were free from psoriasis (absolute PASI 0/PASI100) or in which an absolute PASI ≤ 1, ≤ 3, ≤ 5, and/or relative PASI90, PASI75 or PASI50 was reached during the first year of treatment, was visualized per group and per biologic (Figure 1). At baseline, 15.0% (n = 162) had an absolute PASI ≤ 5. After 1 year of treatment, 602 PASIs were available. At that time, 9.3% (n = 56) was free from psoriasis, and absolute PASI ≤ 1, ≤ 3 and ≤ 5 was reached by 21.3% (n = 128), 51.8% (n = 312) and 72.4% (n = 436), respectively. PASI90, PASI75 and PASI50 was reached by, respectively, 21.8% (n = 131), 46.2% (n = 278) and 77.2% (n = 465). The uncorrected course of the mean PASI is visualized in Figure S1.

Table 2 Baseline and treatment characteristics of the included TEs per biologic

Baseline TE characteristics	Etanercept N= 287 TEs	Adalimumab N= 343 TEs	Ustekinumab N= 276 TEs	Secukinumab N= 75 TEs	Ixekizumab N= 55 TEs	Guselkumab N= 44 TEs	p-value
Age at start of biologic (yrs)	47.7 ± 13.0 Missing: 0	49.4 ± 13.6 Missing: 0	48.5 ± 13.6 Missing: 0	50.2 ± 12.1 Missing: 0	49.9 ± 11.7 Missing: 0	50.5 ± 14.6 Missing: 0	0.443[a]
Gender (male)	171 (59.6%) Missing: 0	213 (62.2%) Missing: 1	165 (60.7%) Missing: 4	38 (51.4%) Missing: 1	32 (59.3%) Missing: 1	28 (63.6%) Missing: 0	0.647[b]
Height (cm)	174.0 [12.0] Missing: 31	175.0 [14.0] Missing: 13	176.0 [15.0] Missing: 16	174.0 [14.4] Missing: 1	176.8 [13.8] Missing: 3	178.0 [11.5] Missing: 5	0.208[c]
Weight (kg)	85.8 [22.8] Missing: 3	87.0 [23.3] Missing: 6	88.5 [22.8] Missing: 5	88.9 [25.9] Missing: 0	94.3 [25.0] Missing: 0	89.5 [29.0] Missing: 3	0.007[c]
BMI (kg/m2)	27.8 [7.3] Missing: 31	28.4 [7.2] Missing: 14	28.3 [7.6] Missing: 16	29.0 [7.5] Missing: 1	30.5 [9.4] Missing: 3	27.9 [8.1] Missing: 5	0.089[c]
Positive family history of psoriasis (yes)	190 (67.1%) Missing: 4	212 (65.4%) Missing: 19	184 (70.2%) Missing: 14	44 (62.9%) Missing: 5	32 (62.7%) Missing: 4	24 (63.1%) Missing: 6	0.736[b]
Psoriatic arthritis (yes)	83 (30.9%) Missing: 18	96 (32.0%) Missing: 43	72 (29.8%) Missing: 34	27 (38.0%) Missing: 4	23 (46.0%) Missing: 5	11 (32.4%) Missing: 10	0.274[b]
Duration of psoriasis until start of biologic (yrs)	20.8 [16.9] Missing: 0	19.6 [19.1] Missing: 12	18.6 [15.3] Missing: 12	22.8 [12.3] Missing: 2	21.6 [17.9] Missing: 0	21.2 [12.2] Missing: 4	0.120[c]
Biologic naive (yes)	164 (57.1%) Missing: 0	163 (47.5%) Missing: 0	93 (33.7%) Missing: 0	5 (6.7%) Missing: 0	4 (7.3%) Missing: 0	4 (9.1%) Missing: 0	<0.001[b]
Baseline PASI score	12.0 [8.4] Missing: 0	10.1 [8.1] Missing: 0	11.1 [10.3] Missing: 0	9.0 [6.5] Missing: 0	6.8 [5.9] Missing: 0	8.5 [8.8] Missing: 0	<0.001[c]

Mean ± SD, Median [IQR], N (%); [a] One-Way ANOVA [b] Chi-squared test, [c] Kruskal Wallis test

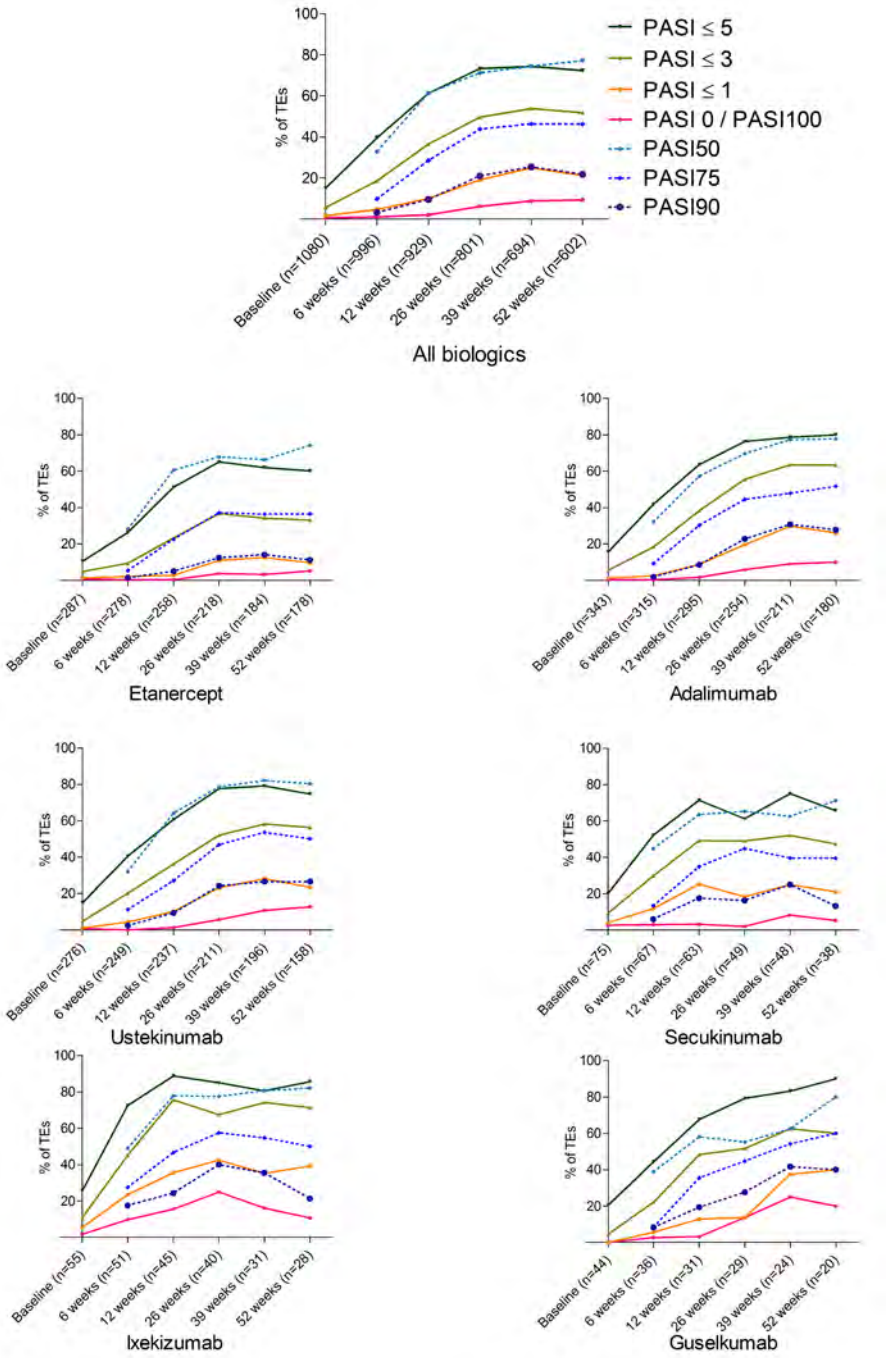

Figure 1 Percentage of TEs in which patients reached absolute PASI 0 / ≤1 / ≤3 / ≤5 or relative PASI100, PASI90, PASI75 or PASI50, displayed for all biologics combined and per biologic (as treated data).

Course of mean absolute PASI

Baseline PASI, body weight, and biologic naivety were identified as possible confounders, and set as fixed effects in the LMM. Since body mass index (BMI) is deducted from weight, to prevent multicollinearity, BMI was not included as a possible confounder. In estimating the marginal means, baseline PASI was set at 12.0, and weight at 90.0 kg for all biologics. Model assumptions were checked and reasonably met. Table S1 provides detailed information on the LMM output. Type III tests of fixed effects showed a significant effect for treatment, time, and the interaction between treatment and time. Figure 2 depicts the course of mean PASI according to LMM. Here, all biologics showed a rapid response in the first 3 months, after which the treatment effect stabilized. At 52 weeks, the mean PASIs for adalimumab (EMM 3.5, 95% confidence interval (95% CI) 2.9–4.0), ustekinumab (EMM 2.8, 95% CI 2.2–3.4), secukinumab (EMM 3.3, 95% CI 2.2–4.5), ixekizumab (EMM 1.3, 95% CI 0.0–2.7), and guselkumab (EMM 1.2, 95% CI 0.0–2.8) were significantly lower than for etanercept (EMM 5.0, 95% CI 4.4–5.5, all p-values < 0.013). Furthermore, mean PASI scores in ixekizumab were significantly lower than in adalimumab (p = 0.004), ustekinumab (p = 0.043) and secukinumab (p = 0.026). Mean PASI scores in guselkumab were significantly lower than in adalimumab (p = 0.009) and secukinumab (p = 0.035), and were almost significantly lower than in ustekinumab (p = 0.062). All p-values of pairwise comparisons are shown in Table S2. The LMM for the course of mean PASI was repeated with LOCF. LOCF analysis showed approximately the same direction of effects, with a significantly lower mean PASI in guselkumab than in ustekinumab (p = 0.027).

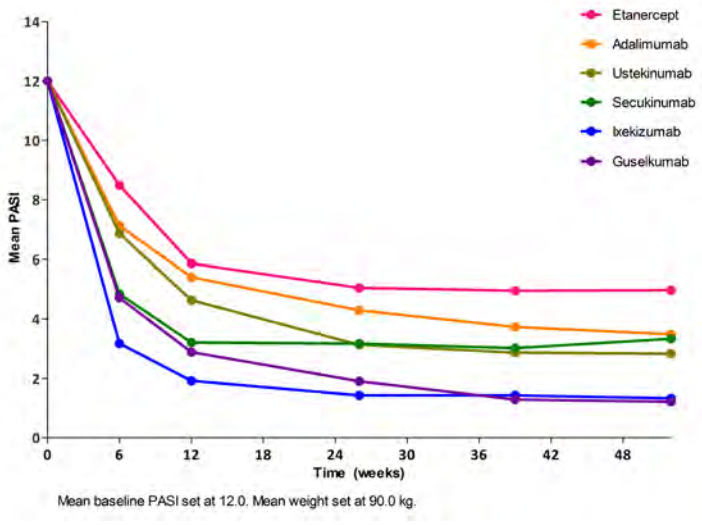

Figure 2 Mean PASI during the first year of treatment according to the linear mixed model, corrected for baseline PASI, body weight, and biologic naivety. *Baseline PASI was set at 12.0, body weight at 90 kg.*

Proportions of PASI75 and PASI90

To correct for confounders (baseline PASI, weight, and biologic naivety), proportions of TEs achieving PASI75 and PASI90 were analysed with a MLR model. The interaction term between time and type of biologic did not significantly contribute to the model ($p = 0.11$) and was therefore not incorporated. As a result, overall odds ratios (ORs) are presented instead of ORs for each time-point. Overall, adalimumab (OR 3.2 (95% CI 2.2–4.7) $p < 0.001$), ustekinumab (OR 4.2 (2.7–6.3) $p < 0.001$), secukinumab (OR 5.3 (2.8–6.3) $p < 0.001$), ixekizumab (OR 20.3 (10.7–38.5) $p < 0.001$), and guselkumab (OR 12.9 (6.2–27.0) $p < 0.001$) all had a significantly higher probability of reaching PASI90 than etanercept. Furthermore, ixekizumab and guselkumab both had a higher probability of reaching PASI90 than adalimumab (OR 6.3 (3.6–11.3) $p < 0.001$ and OR 4.0 (2.0–8.1) $p < 0.001$, respectively), ustekinumab (OR 4.9 (2.8–8.6) $p < 0.001$ and OR 3.1 (1.6–6.1) $p = 0.001$, respectively) and secukinumab (OR 3.8 (1.9–7.7) $p < 0.001$ and OR 2.4 (1.1–5.3) $p = 0.028$, respectively). Table S3 provides information on model output. Quantitative interpretation of ORs is difficult and therefore, the proportions of patients achieving PASI90/PASI75 were calculated based on the model and visualized for patients with average characteristics (e.g. baseline PASI 12, weight 90 kg). Split for biologic naivety, the proportion of TEs reaching PASI90 within the first year of treatment according to MLR is shown in Figure 3. Visualizations for PASI75 are shown in Figure S2. For ixekizumab, the odds of reaching PASI75 (OR 2.7 (1.3–5.3) $p = 0.005$), but not PASI90 (OR 1.57 (0.7–3.4) $p = 0.261$], were significantly higher compared with guselkumab. Analyses were repeated using the LOCF method, which showed similar results compared to the original analyses. Data on LOCF analyses for both LMM and MLR are available on request.

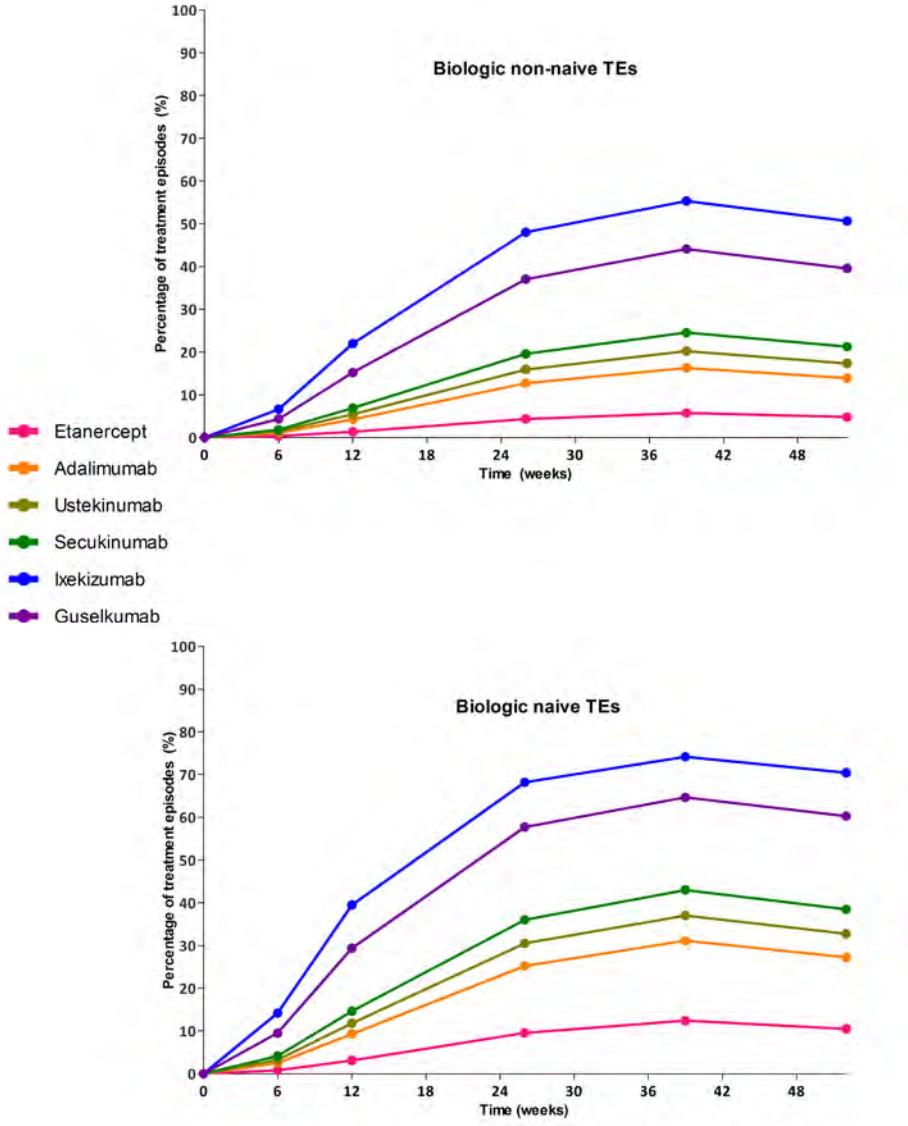

Figure 3 One-year PASI90 percentages based on the mixed logistic regression model, corrected for baseline PASI, body weight and biologic naivety. *Visualizations were made for patients with average characteristics (Baseline PASI 12.0, body weight 90 kg), and split for biologic naïve and non-naïve TEs)*

Discussion

This prospective study compared the effectiveness of 6 frequently used biologics: etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab and guselkumab (TNF-α-, IL-12/23-, IL-17-, and IL-23-inhibitors). For all TEs, 9.3% (n = 56) was free from psoriasis (PASI100) after 1 year. Absolute PASI ≤ 1, ≤ 3 and ≤ 5 was reached in 21.3% (n = 128), 51.8% (n = 312), and 72.4% (n = 436), and PASI90, PASI75 and PASI50 was reached by 21.8% (n = 131), 46.2% (n = 278) and 77.2% (n = 465) of TEs, respectively. Adjusted for baseline PASI, weight and biologic naivety, patients on adalimumab, ustekinumab, secukinumab, ixekizumab and guselkumab all had significantly lower PASI-scores after 1 year compared with etanercept. Furthermore, patients on ixekizumab had a significantly lower mean PASI after 1 year compared with adalimumab, ustekinumab and secukinumab. This was also the case for guselkumab compared with adalimumab and secukinumab. The overall, adjusted probability of reaching PASI90 was significantly higher for patients on adalimumab, ustekinumab, secukinumab, ixekizumab and guselkumab compared with patients on etanercept. Patients on ixekizumab and guselkumab also had a higher probability of reaching PASI90 than patients on adalimumab, ustekinumab, and secukinumab.

In systematic reviews and meta-analyses based on RCT data, higher success rates have been reported for IL-17- and IL-23-inhibitors as compared to TNF-α-inhibitors and ustekinumab, which is roughly in line with the current results. [3, 4, 13, 14] In real-world effectiveness studies, different biologics have been compared directly, but mostly from 1 or 2 different classes (e.g. TNF-α-inhibitors and ustekinumab) only. [6-8, 15-18] Real-world effectiveness studies on long-term (40-76 weeks) effectiveness of IL-17- and IL-23-inhibitors is accumulating. [17, 19-28] In most real-world effectiveness studies, however, relative PASI-targets were used, and the composition of the investigated population differed, e.g. regarding the proportion of biologic-naïve patients, which can explain differences with the current results. Yiu et. al[17] reported higher probabilities of reaching PASI ≤ 2 for secukinumab than for ustekinumab. Schwarz et. al[26] reported proportions of patients reaching PASI ≤ 2 for adalimumab, etanercept, secukinumab and ustekinumab between 51.8-89.6%, which was comparable with reaching PASI ≤ 5 in our cohort (60.1-80.0%). For all biologics in our RWE-cohort, relative PASI-targets, such as PASI90, were reached less often than in a Danish and Italian cohort (estimated PASI90 responses for etanercept, ustekinumab, adalimumab, secukinumab and ixekizumab ranged between 31.7% (etanercept) and 81.0% (ixekizumab)). However, baseline PASI-scores were not reported[28] or different timeframes for reaching PASI-targets were used[27], hampering direct comparisons.

In another study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) it has been demonstrated that in 90% of cases, absolute PASI ≤ 2 was in concordance with reaching PASI90.[29] In the current cohort, we observed that the proportion of patients who reached PASI90 was very similar to the proportion of patients who reached an absolute PASI ≤ 1 at each time-point, although no formal correlation analyses were performed. Discrepancies between these 2 studies are partly due to the difference in mean baseline PASI (15.4 in BADBIR vs. 12.0 in our cohort), as it is more difficult to reach a relative PASI improvement in case of low baseline scores. Therefore, patients with low PASI-scores at baseline may not achieve relative PASI outcomes, even though absolute treatment response may be excellent in practice. In most RCTs, a fixed percentage in PASI-reduction (e.g. PASI90) is still the primary outcome measure, although some studies have also reported absolute PASI-outcomes.[30-32] For instance, in the IXORA-S trial, the percentage of patients who reached an absolute PASI ≤ 5 on ixekizumab (88.2%, n = 120) was similar to our results (85.7%, n = 24), whilst the proportion of patients that reached PASI90 was markedly higher in their study (76.5%, n = 105) than in the current study (21.4%, n = 6) at week 52. Displaying absolute PASIs in addition to relative PASIs could lead to more robust comparisons between studies with different designs, either real-world effectiveness studies or RCTs.

A strength of this study is the high external validity due to the real-world practice environment and multicentre, prospective design of BioCAPTURE. LOCF analyses were performed, and led to very similar results compared with the as-treated analyses, showing robustness of the current results. A limitation was that fewer PASIs were available for ixekizumab and guselkumab, due to more recent regulatory approval, and fewer clinical visits due to COVID-19 restrictions. Due to a low number of patients on brodalumab (IL-17 inhibitor), risankizumab and tildrakizumab (IL-23 inhibitors), these relatively newer biologics could not be included in the current analyses. Furthermore, although we performed confounder-correction for baseline PASI, body weight and biologic naivety, residual confounding may still be present due to unmeasured factors.

This prospective, real-world study analysed the comparative effectiveness of the biologics etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab, and guselkumab in patients with moderate to severe psoriasis from the BioCAPTURE registry. Except for a nearly significant difference between the estimated mean PASI scores after 12 months in guselkumab vs ustekinumab (p = 0.062), ixekizumab and guselkumab showed better results compared with the other biologics for both absolute and relative PASI outcomes. However, the proportion of patients

who reached PASI90 was relatively low for all biologics, compared with what has been reported in RCTs and other real-world studies. As the therapeutic options for psoriasis continue to expand, ongoing comparative, real-world effectiveness research remains important. Absolute PASI could serve as a more robust outcome measure to compare outcomes of RCTs with real-world effectiveness studies. Replication by other large prospective daily practice cohorts will be key in verifying the current results.

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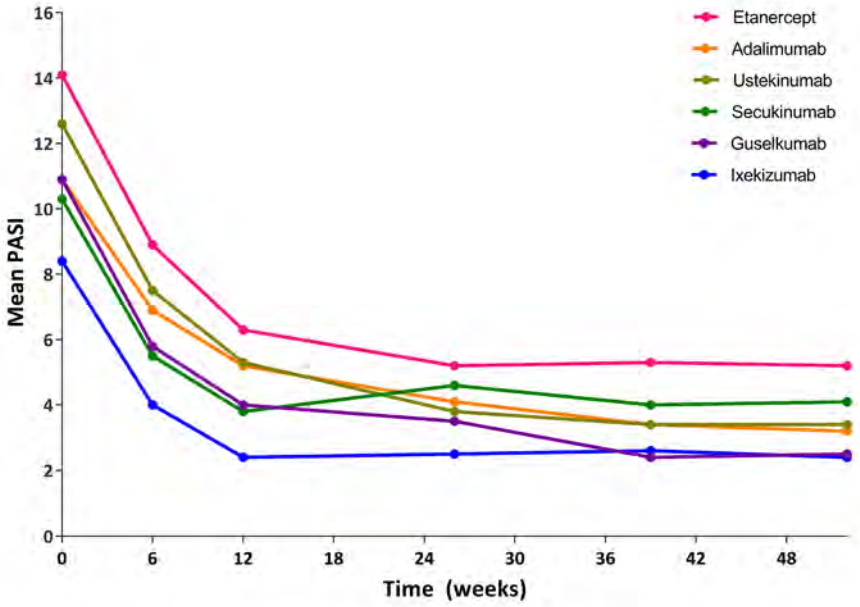
Supplementary content



	Etanercept			Adalimumab			Ustekinumab		
Time (weeks)	Mean	SD	N	Mean	SD	N	Mean	SD	N
0	14.1	8.6	287	10.9	5.9	343	12.6	7.5	276
6	8.9	6.1	278	6.9	4.8	315	7.5	5.2	249
12	6.3	4.6	258	5.2	4.8	295	5.3	4.7	237
26	5.2	5.2	218	4.1	4.8	254	3.8	4.5	211
39	5.3	5.1	184	3.4	4.4	211	3.4	4.0	196
52	5.2	4.2	178	3.2	3.2	180	3.4	3.2	158
	Secukinumab			**Ixekizumab**			**Guselkumab**		
Time (weeks)	Mean	SD	N	Mean	SD	N	Mean	SD	N
0	10.3	7.0	75	8.4	6.6	55	10.9	6.6	44
6	5.5	4.5	67	4.0	3.9	51	5.8	3.8	36
12	3.8	3.4	63	2.4	2.7	45	4.0	3.0	31
26	4.6	4.6	49	2.5	3.3	40	3.5	3.0	29
39	4.0	4.3	48	2.6	3.5	31	2.4	2.4	24
52	4.1	3.6	38	2.4	2.8	28	2.5	2.7	20

Figure S1 Mean PASI values per biologic from baseline until one year of treatment, uncorrected for confounders

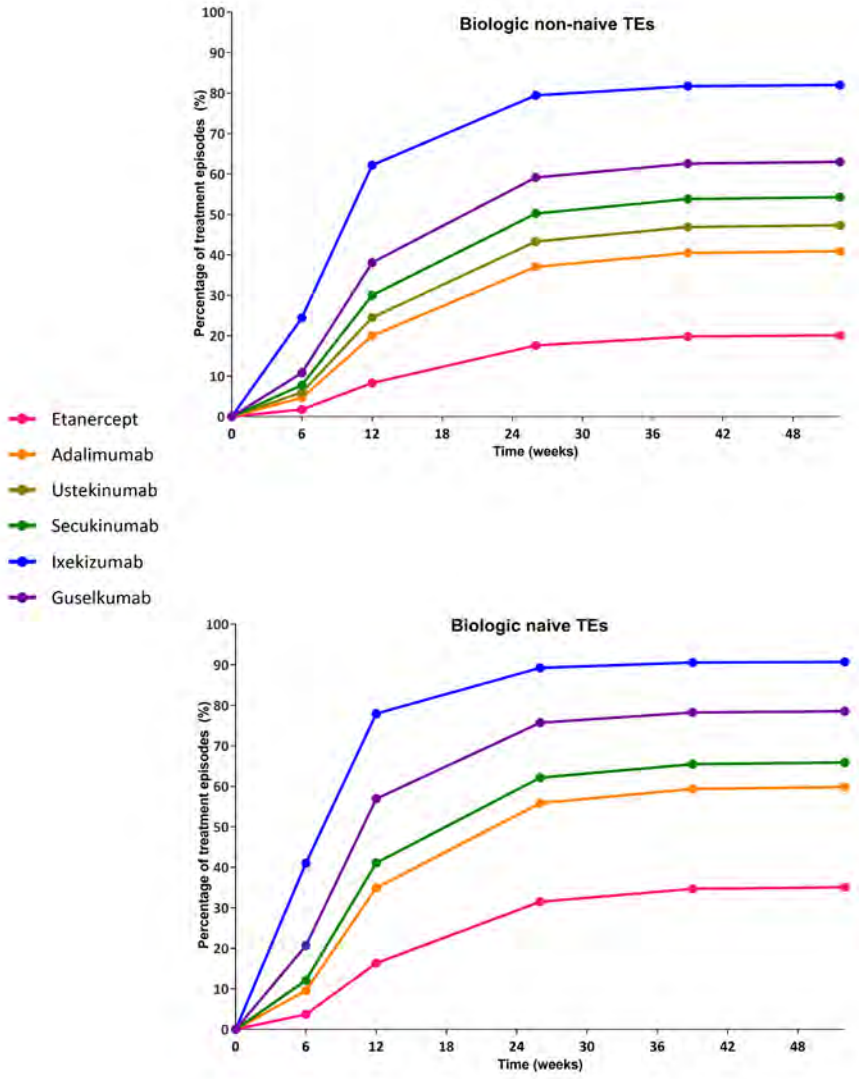


Figure S2 One-year PASI75 percentages based on the mixed logistic regression model, corrected for baseline PASI, body weight and biologic naivety. *Visualizations were made for patients with average characteristics (Baseline PASI 12.0, body weight 90 kg), and split for biologic naïve and non-naïve TEs)*

Table S1 Linear Mixed Model used to estimate mean PASI score outcomes during the first year of treatment with etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab of guselkumab, corrected for baseline PASI, body weight and biologic naivety (as treated analysis).

Variable	p-value type III tests of fixed effect	Estimate	p-value fixed effect	95% CI Lower limit	95% CI Upper limit
Intercept	0.000	-4.427702	0.000	-6.329307	-2.526097
Treatments	0.000				
Etanercept		3.757929	0.000	2.049523	5.466335
Adalimumab		2.272193	0.009	0.573177	3.971208
Ustekinumab		1.620188	0.062	-0.082394	3.322769
Secukinumab		2.121536	0.035	0.154272	4.088800
Ixekizumab		0.112474	0.916	-1.976219	2.201168
Guselkumab		0[a]	.	.	.
Time from baseline (weeks)	0.000				
6 weeks		3.498057	0.000	1.577841	5.418272
12 weeks		1.671940	0.096	-0.296819	3.640699
26 weeks		0.692337	0.492	-1.284600	2.669275
39 weeks		0.071865	0.945	-1.982074	2.125803
52 weeks		0[a]			
Baseline PASI	0.000	0.202064	0.000	0.180517	0.223612
Time * Treatment	0.030				
[Time=6weeks] * [Treatment=etanercept]		0.016469	0.987	-2.010184	2.043122
[Time=6weeks] * [Treatment=adalimumab]		0.138079	0.894	-1.884142	2.160300
[Time=6weeks] * [Treatment=ustekinumab]		0.531318	0.610	-1.508508	2.571144
[Time=6weeks] * [Treatment=secukinumab]		-1.988554	0.099	-4.349678	0.372571
[Time=6weeks] * [Treatment=ixekizumab]		-1.648522	0.195	-4.143202	0.846158
[Time=6weeks] * [Treatment=guselkumab]		0[a]			
[Time=12weeks] * [Treatment=etanercept]		-0.781220	0.460	-2.856062	1.293622
[Time=12weeks] * [Treatment=adalimumab]		0.245040	0.817	-1.825234	2.315315
[Time=12weeks] * [Treatment=ustekinumab]		0.127144	0.905	-1.960168	2.214455
[Time=12weeks] * [Treatment=secukinumab]		-1.800126	0.143	-4.210777	0.610524
[Time=12weeks] * [Treatment=ixekizumab]		-1.080056	0.407	-3.632595	1.472483
[Time=12weeks] * [Treatment=guselkumab]		0[a]			

Table S1 Continued

Variable	p-value type III tests of fixed effect	Estimate	p-value fixed effect	95% CI Lower limit	95% CI Upper limit
[Time=26weeks] * [Treatment=etanercept]		-0.617080	0.563	-2.706653	1.472494
[Time=26weeks] * [Treatment=adalimumab]		0.118864	0.911	-1.964123	2.201852
[Time=26weeks] * [Treatment=ustekinumab]		-0.395975	0.712	-2.496744	1.704794
[Time=26weeks] * [Treatment=secukinumab]		-0.856608	0.494	-3.310399	1.597183
[Time=26weeks] * [Treatment=ixekizumab]		-0.589748	0.654	-3.171611	1.992116
[Time=26weeks] * [Treatment=guselkumab]		0[a]			
[Time=39weeks] * [Treatment=etanercept]		-0.088340	0.936	-2.258320	2.081640
[Time=39weeks] * [Treatment=adalimumab]		0.176639	0.873	-1.987114	2.340392
[Time=39weeks] * [Treatment=ustekinumab]		-0.039461	0.972	-2.214888	2.135967
[Time=39weeks] * [Treatment=secukinumab]		-0.384529	0.765	-2.904127	2.135069
[Time=39weeks] * [Treatment=ixekizumab]		0.030054	0.983	-2.667935	2.728043
[Time=39weeks] * [Treatment=guselkumab]		0[a]			
[Time=52weeks] * [Treatment=etanercept]		0[a]			
[Time=52weeks] * [Treatment=adalimumab]		0[a]			
[Time=52weeks] * [Treatment=ustekinumab]		0[a]			
[Time=52weeks] * [Treatment=secukinumab]		0[a]			
[Time=52weeks] * [Treatment=ixekizumab]		0[a]			
[Time=52weeks] * [Treatment=guselkumab]		0[a]			
Body weight	0.000	0.039295	0.000	0.028475	0.050114
Experience with prior biologics	0.000				
Inexperienced (Biologic Naive)		-0.637151	0.000	-0.967776	-0.306526
Experienced (Biologic Non-Naive)		0[a]			

[a] This parameter is set to zero because it is redundant.

Abbreviations: PASI, Psoriasis Area and Severity Index; CI. confidence interval. Correction for multiple testing was not necessary, as type III tests showed a significant effect on treatment, time and the interaction between treatment and time.

Table S2 P-values of all pairwise comparisons according to the linear mixed model, corrected for baseline PASI, body weight, and biologic naivety

Biologic	Compared to	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
Etanercept	Adalimumab	*<0.001*	0.145	*0.027*	*0.001*	*<0.001*
	Ustekinumab	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
	Secukinumab	*<0.001*	*<0.001*	*0.001*	*0.001*	*0.013*
	Ixekizumab	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
	Guselkumab	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Adalimumab	Ustekinumab	0.411	*0.017*	*0.001*	*0.017*	0.101
	Secukinumab	*<0.001*	*<0.001*	*0.048*	0.227	0.818
	Ixekizumab	*<0.001*	*<0.001*	*<0.001*	*0.001*	*0.004*
	Guselkumab	*<0.001*	*<0.001*	*0.001*	*0.002*	*0.009*
Ustekinumab	Secukinumab	*<0.001*	*0.007*	0.944	0.792	0.448
	Ixekizumab	*<0.001*	*<0.001*	*0.007*	*0.041*	*0.043*
	Guselkumab	*0.002*	*0.016*	0.094	*0.047*	0.062
Secukinumab	Ixekizumab	*0.014*	0.070	*0.023*	0.055	*0.026*
	Guselkumab	0.864	0.695	0.138	0.057	*0.035*
Ixekizumab	Guselkumab	0.059	0.262	0.591	0.885	0.916

Table S3 Mixed Logistic Regression Model used to estimate the percentage of patients that reached PASI90 during the first year of treatment with etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab of guselkumab, corrected for baseline PASI, body weight and biologic naivety (as treated analysis).

Parameter	P-value Type III test	Estimate	P-value fixed effect	95%-CI Lower bound	95%CI Upper bound
Intercept		0.3831	0.4074	-0,52281	1,289012
Treatment	<0.0001				
Adalimumab		-0.2631	0.1391	-0,61159	0,085388
Etanercept		-1.4239	<.0001	-1,83942	-1,00838
Guselkumab		1.1350	0.0011	0,456252	1,813748
Ixekizumab		1.5852	<.0001	1,015428	2,154972
Secukinumab		0.2496	0.3962	-0,32684	0,826036
Ustekinumab		0	.		
Baseline PASI	<0.0001	0.05119	<0.0001	0,032137	0,07024316
Experience with biologics	<0.0001				
Biologic non-naive		-0.8403	<0.0001	-1.151156	-0.529444
Biologic naive		0	.		
Body weight	<0.0001	-0.01908	<0.0001	-0.02806856	-0.01009144
Time	<0.0001				
6 weeks		-2.6652	<0.0001	-3.121684	-2.208716
12 weeks		-1.2924	<0.0001	-1.634812	-0.949988
26 weeks		-0.1049	0.4990	-0.408896	0.199096
39 weeks		0.1876	0.2290	-0.117964	0.493164
52 weeks		0	.		

Abbreviations: PASI, Psoriasis Area and Severity Index; CI, confidence interval. Correction for multiple testing was not necessary as type III tests showed significant p-values for treatment and time.

2.2 Real-world data display long drug survival for guselkumab in patients with plaque psoriasis

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Guselkumab has been registered as the first interleukin23 (IL-23) inhibitor for treatment of psoriasis. Randomized controlled trials (RCT) have shown a favourable efficacy and safety profile for guselkumab.[1, 2] However, RCTs may not adequately reflect the real-world situation. [3] The primary objective of this, real-world observational multicentre study was to evaluate the one- and two-year drug survival (DS) of guselkumab, split for discontinuation due to ineffectiveness or side effects. A further aim was to elucidate predictors for a shorter guselkumab DS.

Methods and results

A detailed description of the methods is given in Appendix S1. Data from patients with plaque psoriasis treated with guselkumab were collected from the prospective BioCAPTURE registry (www.biocapture.nl) and retrospective data from 4 other centres in the Netherlands (timeframe 2020 to 2021). Temporary treatment interruptions for any reason were allowed if <90 days. This 90day gap was prolonged up to 1 year if patients discontinued due to fear of COVID19 or due to remission. In the Kaplan–Meier analyses, 3 separate DS curves were created with an event for discontinuation in general (all reasons), due to ineffectiveness or to sideeffects. Discontinuation due to an increase in musculoskeletal complaints in patients with psoriatic arthritis (PsA) was considered as an event in sideeffect analyses. Univariable and multivariable Cox regression models were used to identify factors affecting DS.

Participating centres and patient and treatment characteristics are shown in **Tables S1** and **S2**, respectively. A total of 195 patients (288.4 activelytreated patient years) were included; 110 (56.4%) were male, and 58 (29.7%) were biologic naive at guselkumab initiation. Forty (20.5%) patients had a rheumatologistconfirmed diagnosis of PsA. Six (3.1%) patients shortened the dosing interval, and 27 (13.8%) lengthened the interval.

Overall guselkumab DS rates after 1 and 2 years were 85.5% and 77.8%, respectively. One and 2year DS rates for discontinuation related to ineffectiveness were 92.8% and 88.7%, and for discontinuation related to sideeffects were 94.3% and 92.1%, respectively (**Figure 1**). The outputs of the Cox regression analyses are shown in **Table S3**.

The multivariable model showed a significant association between diabetes mellitus type 2 (DMt2) and a shorter DS (hazard ratio (HR) 3.69 (95% confidence

interval (95% CI) 1.14–11.98) (p = 0.030) due to ineffectiveness. Multivariable analyses for predictors of sideeffectrelated DS showed a significant association for a shorter DS in patients with PsA (HR 7.51 (95% CI 2.26–24.95) (p = 0.001)).

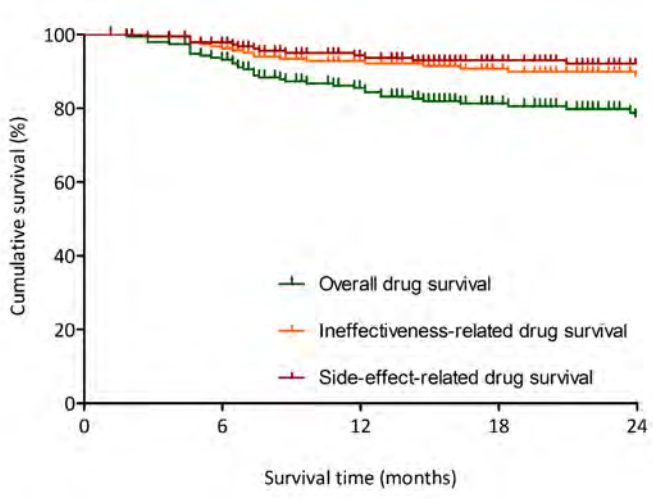

Figure 1 Kaplan Meier drug survival analysis of guselkumab during two years, split for reason of discontinuation

Discussion

This study shows that 1- and 2-year DS for guselkumab was high, both for discontinuation due to side-effects and ineffectiveness. The latter finding is notable, as in previous literature higher discontinuation rates due to ineffectiveness have been described for other types of biologics.[4] Previous studies on guselkumab DS in real-world settings have also reported high first-year DS (ranging from 68.0% [5] to 95.0% [6]), although sample size was often small, and the event definition and duration of follow-up varied. [5-11]

A substantial number of patients in this study (n = 27, 13.8%) used a lengthened dosing interval, which suggests that, for guselkumab, high therapeutic effectiveness can be maintained even on a lower dose. In ongoing studies on guselkumab for psoriasis, the use of a prolonged dosing interval is currently being evaluated.[12, 13]

Having PsA was associated with a shorter DS due to side effects. It should be noted that the association between side-effect-related discontinuation and PsA was

largely explained by patients with pre-existent PsA who experienced an increase in musculoskeletal complaints. In contrast, a systematic review on predictors of persistence for other biologics, described having PsA as predictive for longer survival.[14] Furthermore, we found an association between DMt2 and a higher risk of discontinuation due to ineffectiveness. In support of our findings, the Corrona psoriasis registry has previously reported that diabetes reduced the risk of achieving various biologic treatment goals.[15]

A strength of this study is the large study population, and high external validity due to the multicentre design. Due to the COVID-19 pandemic, there were fewer clinical visits during the study period and more treatment interruptions due to fear of COVID-19. These interruptions were handled differently (see Supplementary content), leading to a more realistic reflection of DS in non-COVID-19 time-frames.

In conclusion, this study found a high 1- and 2-year DS for guselkumab. Reassuringly, discontinuation due to ineffectiveness or side-effects was very uncommon. Having DMt2 was associated with a shorter DS due to ineffectiveness, whereas having PsA was associated with a shorter DS due to side effects. A substantial proportion of patients (14%) was able to prolong their dosing interval.

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Supplementary content

Table S1 Participating Centres

Centre	Setting	Data collection	Patient recruitment	Patients (N)
Radboudumc	Academic	Prospective	BioCAPTURE registry[a]	28
UMCG	Academic	Retrospective	Opt-out registry	31
Erasmus MC	Academic	Retrospective	Study-specific written informed consent	31
UMC Utrecht	Academic	Prospective	BioCAPTURE registry[a]	2
Maastricht UMC+	Academic	Prospective	BioCAPTURE registry[a]	1
Alrijne Ziekenhuis	Non-academic	Retrospective	Study-specific written informed consent	45
Medisch Centrum Leeuwarden	Non-academic	Retrospective	Study-specific written informed consent	24
ZGT Hengelo	Non-academic	Prospective	BioCAPTURE registry[a]	14
Bernhoven Ziekenhuis	Non-academic	Prospective	BioCAPTURE registry[a]	7
ZGT Almelo	Non-academic	Prospective	BioCAPTURE registry[a]	4
Amphia Ziekenhuis	Non-academic	Prospective	BioCAPTURE registry[a]	3
Catharina Ziekenhuis	Non-academic	Prospective	BioCAPTURE registry[a]	2
Slingeland Ziekenhuis	Non-academic	Prospective	BioCAPTURE registry[a]	1
St. Antonius ziekenhuis	Non-academic	Prospective	BioCAPTURE registry[a]	2

[a]All patients provided informed consent to participate in the BioCAPTURE registry.

Table S2 Patient and treatment characteristics

	N= 195
Gender (male)	110 (56.4%)
Age at psoriasis onset (years)	25.0 [23.0][a]
Age at guselkumab initiation (years)	49.4 ± 14.2
Psoriasis duration at guselkumab initiation (years)	18.0 [16.0][a]
PASI at guselkumab initiation	9.2 [9.3][b]
DLQI at guselkumab initiation	14.3 ± 8.0[c]
Weight	93.5 ± 18.0[d]
BMI	28.9 [7.2][e]
Family history of psoriasis	76 (39%)[b]
Comorbidities	
Psoriatic arthritis	40 (20.5%)
Diabetes mellitus type 2	26 (13.3%)
Hypertension	44 (22.6%)
Dyslipidemia	24 (12.3%)
Myocardial infarction (history of)	7 (3.6%)
Cerebrovascular incident or TIA (history of)	9 (4.6%)
Malignancy (history of)	12 (6.2%)
Non-melanoma skin cancer (history of)	7 (3.6%)
Inflammatory bowel disease	4 (2.1%)
Rheumatologic condition (other than PsA)	23 (11.8%)
Liver steatosis/fibrosis	25 (12.8%)
Kidney disease	6 (3.1%)
Hyperthyroidism	4 (2.1%)
Hypothyroidism	5 (2.6%)
Depression	25 (12.8%)
Treatment history	
Prior use of phototherapy	159 (81.5%)
Prior use of acitretin	32 (16.4%)
Prior use of cyclosporin	48 (24.6%)
Prior use of fumaric acid esters	122 (62.6%)
Prior use of methotrexate	156 (80.0%)
Prior use of apremilast	13 (6.7%)
Prior biologic use (yes)	137 (70.3%)
Prior use of TNF-a inhibitors	108 (55.4%)
Prior use of IL-12/23 inhibitor	97(49.7%)
Prior use of IL-17 inhibitor	61 (31.3%)
Prior use of IL-23 inhibitor	0 (0.0%)
0 prior biologics	58 (29.7%)
1 prior biologic	47 (24.1%)
2 prior biologics	33 (16.9%)

Table S2 Continued

	N= 195
3 prior biologics	23 (11.8%)
4 prior biologics	11 (5.6%)
5 prior biologics	16 (8.2%)
6 prior biologics	6 (3.1%)
7 prior biologics	0 (0.0%)
8 prior biologics	1 (0.5%)
Guselkumab dosing regimen	
Guselkumab dosing interval according to the label	162 (83.1%)
Use of a shortened dosing interval (higher dose)	6 (3.1%)
Use of a lengthened dosing interval (lower dose)	27 (13.8%)
Interruption of guselkumab for > 2 weeks	24 (12.3%)
Concomitant or bridging psoriasis medication*	**16 (8.2%)**
Methotrexate	
Bridging	4 (2.1%)
Concomitant	3 (1.5%)
Bridging and concomitant	5 (2.6%)
Acitretin	
Bridging	0 (0%)
Concomitant	1 (0.5%)
Bridging and concomitant	2 (1.0%)
Fumaric acid esters	
Bridging	1 (0.5%)
Reason for treatment discontinuation	
Ineffectiveness	17 (8.7%)
Side-effects$^{\Phi}$	12
Ineffectiveness + side-effects	1
Pregnancy wish	1
Fear of COVID-19	2
Other reasons	4
Unknown	1

Mean ± SD, median [IQR], N (%)

PASI; Psoriasis Area and Severity Index, DLQI; Dermatology Life Quality Index, BMI; Body Mass Index, TIA; Transient Ischaemic Attack, TNF-a; Tumour Necrosis Factor- alpha, IL; Interleukin.

[a] 31 missing, [b]71 missing, [c]148 missing, [d]84 missing, [e]91missing.

* The use of accompanying conventional systemic antipsoriatic therapies (methotrexate, acitretin, ciclosporin or dimethyl fumarates) was classified into bridging therapy or combination therapy. To be classified as bridging therapy, the conventional systemic had to be initiated prior to the start of guselkumab and continued for ≥28 but ≤90 days. To be classified as combination therapy, the conventional systemic was added at the start of or during guselkumab treatment and used for ≥28 days. Patients who initiated their systemic medication prior to guselkumab initiation but continued to use it for ≥90 days were assigned to a "bridging and combination therapy" group.

$^{\Phi}$ In patients who discontinued guselkumab due to side effects, 'musculoskeletal complaints' was the most common side effect leading to discontinuation (N=8). Six out of these 8 patients had a history of PsA.

Table S3 Determinants of guselkumab drug survival as computed by univariable and multivariable cox regression analysis. Variables with a p-value <0.2 in univariate analysis that were included in multivariable analyses are displayed in bold type.

	Event=discontinuation due to ineffectiveness Hazard ratio [95% CI]		Event = discontinuation due to side effects. Hazard ratio [95% CI]	
	Univariable analysis	**Multivariable analysis**	**Univariable analysis**	**Multivariable analysis**
Age	0.999 [0.967-1.032] (p=0.954)		1.007 [0.969-1.046] (p=0.733)	
Higher age at start guselkumab	1.001 [0.968-1.034] (p=0.964)		1.007 [0.968-1.046] (p=0.737)	
Higher age at psoriasis onset	1.008 [0.974-1.044] (p=0.632)		0.997 [0.957-1.039] (p=0.893)	
Sex (male)	1.115 [0.448-2.980] (p=0.766)		1.174 [0.384-3.588] (p=0.779)	
Diagnosis of psoriatic arthritis	1.711 [0.594-4.924] (p=0.320)		**7.511 [2.261-24.950] (p=0.001)**	7.511 [2.261-24.950] (p=0.001)
Biologic naivety	**0.292 [0.067-1.269] (p=0.100)**		**0.194 [0.025-1.489] (p=0.115)**	
Higher baseline PASI score	0.975 [0.908-1.046] (p=0.479)		0.920 [0.822-1.030] (p=0.149)[a]	
Higher BMI	1.026 [0.907-1.162] (p=0.679)		0.887 [0.759-1.037] (p=0.134)[a]	
Higher weight	1.005 [0.971-1.041] (p=0.773)		0.978 [0.942-1.015] (p=0.236)	
Family history of psoriasis	**0.492 [0.165-1.464] (p=0.202)**		1.799 [0.363-8.920] (p=0.472)	
History of DM type 2	**3.664 [1.375-9.767] (p=0.009)**	3.687 [1.135-11.984] (p=0.030)	0.605 [0.079-4.654] (p=0.629)	
History of Hypertension	0.396 [0.091-1.724] (p=0.217)		0.569 [0.126-2.567] (p=0.463)	
History of Depression	0.418 [0.056-3.143] (p=0.397)		0.591 [0.077-4.549] (p=0.614)	
Liver steatosis/fibrosis	0.864 [0.199-3.761] (p=0.846)		1.241 [0.275-5.601] (p=0.779)	

PASI; Psoriasis Area and Severity Index, BMI; Body Mass Index, DM; Diabetes Mellitus.

[a]*Baseline PASI score and BMI were not incorporated in the multivariable model for side-effect-related survival of the original data, due to the high number of missing values. In sensitivity analysis using pooled imputed data, Baseline PASI and BMI were included in the multivariable model. Results of sensitivity analyses were similar to outcomes for the original data.*

Supplementary Methods

Materials and methods

Data collection

In this observational, multicentre study, prospective data from the BioCAPTURE database (www.biocapture.nl) was combined with retrospective data collected from 4 other centres in the Netherlands. Patients provided written informed consent for inclusion in the BioCAPTURE registry, or written informed consent for retrospective data collection for this specific study (CMO Radboudumc, dossier 2020-6187). In one academic centre (University Medical Centre Groningen; UMCG), an opt-out approach was used: written informed consent was not required, as only retrospective pseudonymized data from regular care were collected, and the study was granted exemption from reviewing by the institutional review board from the UMCG.

All adult patients with plaque psoriasis that were treated with guselkumab in a daily practice setting were eligible for inclusion. Patients were actively recruited between November 2020 and July 2021. Inclusion was allowed during the entire study period, leading to various lengths in follow-up duration. Patients were eligible for inclusion if they started guselkumab for psoriasis in a daily practice setting, and had at least 1 follow-up visit after guselkumab initiation before July 1st, 2021. If patients also suffered from psoriatic arthritis (PsA), plaque psoriasis had to be the main reason for prescribing biological therapy. All PsA diagnoses were confirmed by a rheumatologist.

Patient and treatment characteristics

Pseudonymized data on baseline patient characteristics, medication history, guselkumab start- and stop dates, disease parameters during guselkumab treatment (Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI)) and reasons for guselkumab discontinuation were collected. Data were stored in Castor, a cloud-based electronic data management platform in compliance with Good Clinical Practice (GCP) standards (www.castoredc.com). Reasons for discontinuation of treatment were classified as: ineffectiveness, side effects, pregnancy wish, other reasons, a combination of the aforementioned reasons, or for unknown reasons. Increase of musculoskeletal complaints in patients with PsA was classified as possible side effect. Treatment deviations from per-label guselkumab dosing (100 mg guselkumab at week 0, 4, and every 8 weeks thereafter) were recorded in case of treatment interruptions and/or application of an altered dosing regimen. Treatment interruptions <2 weeks were not recorded.

Outcome definitions for statistical analysis

A treatment episode (TE) was defined as the period in which the patient actively used guselkumab. When guselkumab was interrupted for ≥ 90 days, the TE ended. Two special circumstances were applicable to this cohort, for which this rule was adapted. Firstly, in case of treatment interruptions due to fear of COVID-19, TEs were viewed as continuous as long as I) both patient and doctor had the intention to continue guselkumab, II) no new systemic anti-psoriasis treatment was started, and III) guselkumab was re-initiated within 1 year from interruption. Furthermore, a second group showed very good response, for which time between doses was prolonged beyond the 90 days window. The first two criteria mentioned above were also applied to this group. In patients with multiple guselkumab TEs, only the first TE was used for analysis. Active guselkumab users were censored at the moment of the last contact with their treating physician (either clinic visit or by phone), or after 2 years of follow-up. The use of accompanying conventional systemic antipsoriatic therapies (methotrexate, acitretin, ciclosporin or dimethyl fumarates) was classified into bridging therapy or combination therapy. To be classified as bridging therapy, the conventional systemic had to be initiated prior to the start of guselkumab and continued for ≥28 but ≤90 days. To be classified as combination therapy, the conventional systemic was added at the start of or during guselkumab treatment and used for ≥28 days. Patients who initiated their systemic medication prior to guselkumab initiation but continued to use it for ≥90 days were assigned to a "bridging and combination therapy" group.

Statistical analyses

Descriptive statistics were used to display patient and treatment characteristics (mean ± standard deviation (SD), median and interquartile range [IQR], N (%)). To generate survival curves, survival analysis was performed using Kaplan-Meier estimates. In the primary analysis, three separate survival curves were created with an event for discontinuation in general (I), due to ineffectiveness (II) or due to side effects (III). Overall survival (I), covered discontinuation due to any reason, including pregnancy, 'unknown' and 'other reasons'. If a patient discontinued guselkumab due to a combination of both ineffectiveness and side effects, discontinuation was taken into account in all three analyses. In univariate Cox-regression analyses, the following clinically relevant baseline characteristics were tested for a possible association with drug survival related to ineffectiveness- or side effects: age, age at guselkumab initiation, age at psoriasis diagnosis, sex, history of biologic use, baseline PASI, weight, body mass index (BMI), family history of psoriasis, psoriatic arthritis (PsA), diabetes mellitus (DM) type 2, hypertension, depression and liver steatosis/fibrosis. These variables were only analysed for ineffectiveness- or side-

effect-related survival, as some reasons for discontinuation in the overall survival curve are not (e.g. pregnancy) or may not be (e.g. 'unknown reasons') related to the effects of guselkumab. Potential predictor variables that had a p-value ≤0.2 in univariate analysis were entered in a multivariate Cox regression model with backward selection to identify factors affecting drug survival prognosis. Multivariable Cox regression models were repeated with imputed data (multiple imputation, N=10) of baseline variables in case of large numbers of missing values. Analyses were performed in SPSS version 25.0 (IBM, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

2.3 Drug survival of IL-17 and IL-23 inhibitors for psoriasis: a systematic review and meta-analysis

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Abstract

Background and Objective

The most recently approved biologics for moderate-to-severe psoriasis are the interleukin (IL)-17 and IL-23 inhibitors. Drug survival is a frequently used outcome to assess drug performance in practice. An overview of the available drug survival studies regarding IL-17 and IL-23 inhibitors is lacking. Therefore, our objective was to assess the drug survival of IL-17 and IL-23 inhibitors for psoriasis.

Methods

A search of PubMed, Embase, Cochrane Library and Web of Science was conducted (last search 27 December, 2023). Inclusion criteria were (1) cohort study (2) patients aged ≥ 18 years with plaque psoriasis, and (3) evaluation of drug survival of at least one of the IL-17 and IL-23 inhibitors. Exclusion criteria were: primary focus on patients with psoriatic arthritis, fewer than ten study subjects, and another language than English.

The Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline was followed. Survival probabilities at monthly intervals were extracted from Kaplan-Meier curves using a semi-automated tool. Data were pooled using a non-parametric random-effects model to retrieve distribution-free summary survival curves. Summary drug survival curves were constructed per biologic for different discontinuation reasons: overall, ineffectiveness and adverse events, and split for the effect modifier biologic naivety. Results were analysed separately for registry/electronic health record data and for pharmacy/claims data.

Results

A total of 69 studies aggregating drug survival outcomes of 48,704 patients on secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab were included. Summary drug survival estimates of registry/electronic health record studies for overall, ineffectiveness and adverse event related drug survival were high (all point estimates ≥0.8 at year 1) for included biologics, with highest estimates for guselkumab and risankizumab. All estimates for drug survival were higher in biologic naive than in experienced patients. Estimates of pharmacy/claims databases were substantially lower than estimates from the primary analyses based on registry/electronic health record data.

Conclusions

This meta-analysis showed that the investigated IL-17 and IL-23 inhibitors had high drug survival rates, with highest rates for guselkumab and risankizumab drug survival. We showed that effect modifiers such as biologic naivety, and the source of data used (registry/electronic health record data vs. pharmacy/claims databases) is relevant when interpreting drug survival studies.

Key Points

- Many drug survival studies on interleukin-17 and interleukin-23 inhibitors have emerged. This meta-analysis provides an extensive and inclusive overview of all currently available drug survival data on these biologics.
- Interleukin-17 and interleukin-23 inhibitors demonstrated high drug survival rates in psoriasis treatment, with highest rates for guselkumab and risankizumab.
- Data from registry/electronic health records provided more information and had less risk of bias than pharmacy/claims databases in the context of drug survival.

Introduction

In patients with psoriasis, interleukin (IL)-17 and IL-23 play a major role in the pathogenesis of the disease.[1] The most recently developed biologics for psoriasis target the IL-17 and IL-23 pathway. Four IL-17 inhibitors (secukinumab, brodalumab, ixekizumab, bimekizumab) and three IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab) are currently approved by the European Medicines Agency and US Food and Drug Administration. These drugs showed very good results in randomised clinical trials.[2-4] However, this does not necessarily reflect their effectiveness in daily practice. Clinical trials are known for their strict inclusion and exclusion criteria, creating a homogeneous study population. This can impair the generalisability of trial results to the real-world population, which is often more heterogeneous.[5] In addition, differences in adherence to medication can lead to variations between outcomes of clinical trials and the real world.[6] To evaluate treatment in a real-world setting, drug survival, also known as "drug retention" or "drug persistence", is a commonly used measure. Drug survival is defined as the time that patients remain on the prescribed drug and is visualised using Kaplan-Meier curves. The outcomes of drug survival analyses can give insights in the number of patients discontinuing their treatment, but also in the reasons for discontinuation in daily practice. Main reasons for discontinuation are ineffectiveness and side effects. In addition, various patient-related variables can affect drug survival such as sex, body mass index, the presence of psoriatic arthritis or prior experience with other biologics.[7]

Previously published systematic reviews on drug survival in patients with psoriasis focused on tumour necrosis factor-α inhibitors and the IL-12/23 inhibitor ustekinumab, except for Mourad et al.[8-10], who included secukinumab, ixekizumab and guselkumab. Since that time, two more IL-17-inihibitors and two more IL-23 inhibitors have become available, resulting in many new publications on drug survival of IL-17- inhibitors and IL-23-inhibitors. A review and meta-analysis on the drug survival of the newer biologics (IL-17 and IL-23 inhibitors) are not yet available. The advanced methodology used in this meta-analysis summarised the total course of drug survival curves. This provides more robust and precise summary drug survival estimates that enhance the reliability of findings. For patient-tailored treatment, a comprehensive overview of the newer biologics is essential in making evidence-based choices among the newer biologics available for psoriasis.

Methods

A systematic review and meta-analysis of real-world evidence on drug survival of IL-17 and IL-23 inhibitors for the treatment of psoriasis was conducted. The literature search and reporting were done according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline checklists.[11-13] The study protocol was registered in PROSPERO (CRD42021297356).

Literature search

A literature search of PubMed, EMBASE, Cochrane Library, and Web of Science was developed with the help of an institutional librarian and conducted by two authors (ST and LB, last search December 27, 2023) to identify eligible studies. The search terms included several alternatives for drug survival analysis, such as 'Kaplan-Meier estimate', 'drug adherence', 'drug failure', 'drug retention', 'drug persistence', and 'drug discontinuation', combined with synonyms for psoriasis and the available biologics. The full search strategy can be viewed in **Table S1**.

Study selection

Two authors (S.T./L.B.) independently screened and selected relevant studies by using the Rayyan web-tool.[14] Inclusion criteria were (1) the design was cohort study, (2) the study subjects were patients aged ≥18 years with plaque psoriasis, and (3) drug survival of at least one of the following biologics was described: secukinumab (SEC), ixekizumab (IXE), brodalumab (BRO), risankizumab (RIS), guselkumab (GUS), or tildrakizumab (TIL). Exclusion criteria were (1) studies with a primary focus on patients with psoriatic arthritis (e.g., selected from a rheumatological cohort) (2) studies with fewer than ten study subjects, and (3) studies in another language than English.

When a full text version was not available, or in case of other crucial missing data, authors of the specific study were contacted. All studies were carefully screened for overlapping patient populations and authors were contacted in case of doubt. In case of no response, only the cohort with the longest follow-up was analysed. Complex decisions regarding whether to include specific outcomes of separate studies were deliberated within the study team (ST, MS, EJ, JR).

Data extraction

The following data were extracted by ST and LB and implemented in a pre-designed data-extraction spreadsheet: study design, author, year of publication, location,

time frame, study design, setting, information source (electronic health records [EHR]/registry data; or pharmacy/claims data), patient population size, follow-up period, patient characteristics (age, sex, body mass index, age at onset of psoriasis, disease duration, baseline Psoriasis Area and Severity index score, presence of concomitant psoriatic arthritis) percentage biologic naive patients, type of biologic treatment (IL-17 or IL-23 inhibitor), dosage, treatment regime, treatment duration. Drug survival was depicted as overall drug survival, ineffectiveness related drug survival, adverse event related drug survival, and drug survival for biologic-naive or experienced patients.

Methodological Quality Assessment

The quality of the included studies was assessed with the Quality in Prognostic Studies (QUIPS) tool and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.[15, 16] The QUIPS tool was partly adjusted in discussion with the study group to fit the study methodology of drug survival analyses (see **Appendix S1**). Two authors (ST/LB) independently evaluated each domain for all articles, resulting in an overall risk of bias (RoB) score per domain. In case of disagreement, a third author (JR) was consulted. The quality of evidence was also summarised using the Quality Rating Scheme for Studies and Other Evidence, a modification from the Oxford Centre for Evidence-Based Medicine.

Statistical analysis

As we considered summary drug survival curves most informative to compile drug survival studies, we used a non-parametric random effects model to retrieve a distribution-free summary drug survival curve described in detail by Combescure et al.[17] This method obtains a distribution-free summary drug survival curve by expanding the product limit estimator of drug survival for aggregated drug survival data. The extension of DerSimonian- and Laird methodology for multiple outcomes was applied to account for between study heterogeneity.[17] The I^2 statistic was used to measure the between-study variability of the arcsine transformed conditional survival estimates.[18] In contrast to a meta-analysis of drug survival at a single point in time, the homogeneity assumption is that the conditional drug survival probabilities are equal in the studies for any time *t*.

The main advantage of this approach over meta-analyses of drug survival probabilities at a single timepoint lies in the ability to use full drug survival curves. The estimated pooled drug survival at time *t* includes all studies, also studies ended before *t*, because the conditional drug survival probabilities before *t* are estimated with these same studies.

Summary drug survival curves with 95% confidence intervals (CIs) [based on Greenwood's formula] were estimated from the drug survival rates and the numbers-at-risk extracted from studies included in the meta-analysis. Drug survival probabilities at each timepoint were extracted using a semi-automated tool (Webplotdigitizer Version 4.5; https://automeris.io/WebPlotDigitizer/) at monthly intervals. The numbers of at-risk participants during different time intervals were calculated using the method previously described by Williamson et al. [19] and Tierney et al. [20] Heterogeneity was measured using I^2 values and Cochran's Q statistic. Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) with package 'MetaSurv'.

Summary drug survival (pooled) curves of all separate biologics were constructed for different discontinuation reasons (events): overall drug survival, ineffectiveness related drug survival, and adverse event related drug survival. As biologic naivety has shown to be an important variable influencing drug survival, drug survival data on biologic-naïve and biologic-experienced patients were also extracted if available. [21] In case no Kaplan-Meier curve was available, and drug survival rates were only described at specific timepoints in the text or tables, these rates were extrapolated to earlier timepoints and incorporated in sensitivity analyses but not in the primary analyses. Additionally, separate sensitivity analyses were performed excluding studies which were classified as high risk of bias in the QUIPS tool and as serious risk of bias in the ROBINS-I tool.

Studies based on data from registry/EHR databases and studies using pharmacy/claims data were analysed as separate groups as the underlying information leading to drug survival was different and might influence drug survival. In registry/EHR studies, drug survival is not derived from data on insurance claims, but from the medical records (e.g., patient registry data/medical record investigations). The actual use by the patient, reason for discontinuation (including being lost to follow up), temporary dose changes and definitive discontinuation dates are recorded in registry/EHR databases, whereas they are mostly not recorded in pharmacy/claims databases. Albeit being less precise on these issues, pharmacy/claims databases lead to information in large groups of patients. Therefore, summary drug survival curves were constructed separately for (I) registry/EHR data and (II) pharmacy/claims data.

An overview of which study was included in each outcome can be found in Table S10. Additionally, in all Figure legends the references of the included studies for that specific outcome were stated.

Direct comparison summary drug survival estimates

Summary drug survival estimates from the meta-analyses were directly compared at 1, 2, and 3 years between the different biologics for the overall drug survival and ineffectiveness-related drug survival using the methodology described by Klein et al.[22], and presented as differences in drug survival estimates with 95% CIs.

Results

Study characteristics

The literature search resulted in 2299 records, after screening for duplicates 1615 unique records remained. Of these, 127 full-text articles were assessed for eligibility, resulting in 69 articles included in this review (**Figure 1, Appendices S2 and S3**).

Quality Assessment

An overview of the quality assessment per domain using the QUIPS and ROBINS-I tool is provided in **Tables S3 and S4**. All studies that were assessed as high risk of bias in the QUIPS tool[23-74] and as serious risk of bias in the ROBINS-I tool[28, 31, 36, 45, 47, 52, 54-57, 60, 63, 66, 67, 69, 73, 75, 76] were excluded in separate sensitivity analyses. Results of the separate sensitivity analyses were in line with results of the main analyses and shown in **Tables S7 and S8**. Excluding studies marked as serious risk of bias using the ROBINS-I tool, summary survival estimates of registry/EHR studies were very similar. Pharmacy/claims database studies all had to be excluded because of their serious risk of bias assessment according to the ROBINS-I tool. When using the QUIPS tool to assess the risk of bias, many studies had to be excluded and summary survival estimates slightly changed in both directions. However, in general results were still in line with the main analyses.

Using the Quality Rating Scheme for Studies and Other Evidence, most studies were rated with a 3: 'case-control studies; retrospective cohort study' (**Table S5**).

Systematic review and meta-analysis

Forty-seven articles reported on SEC (23,960 patients), 31 on IXE (12,446 patients), 13 on BRO (2353 patients), 24 on GUS (8174 patients), 7 on RIS (1427 patients), and 4 on TIL (304 patients). In total 48,704 patients were included in this literature review. The characteristics from the included studies are given in **Table S2**.

As stated, studies based on drug survival from registry/EHR data and studies using pharmacy/claims data were analysed separately.

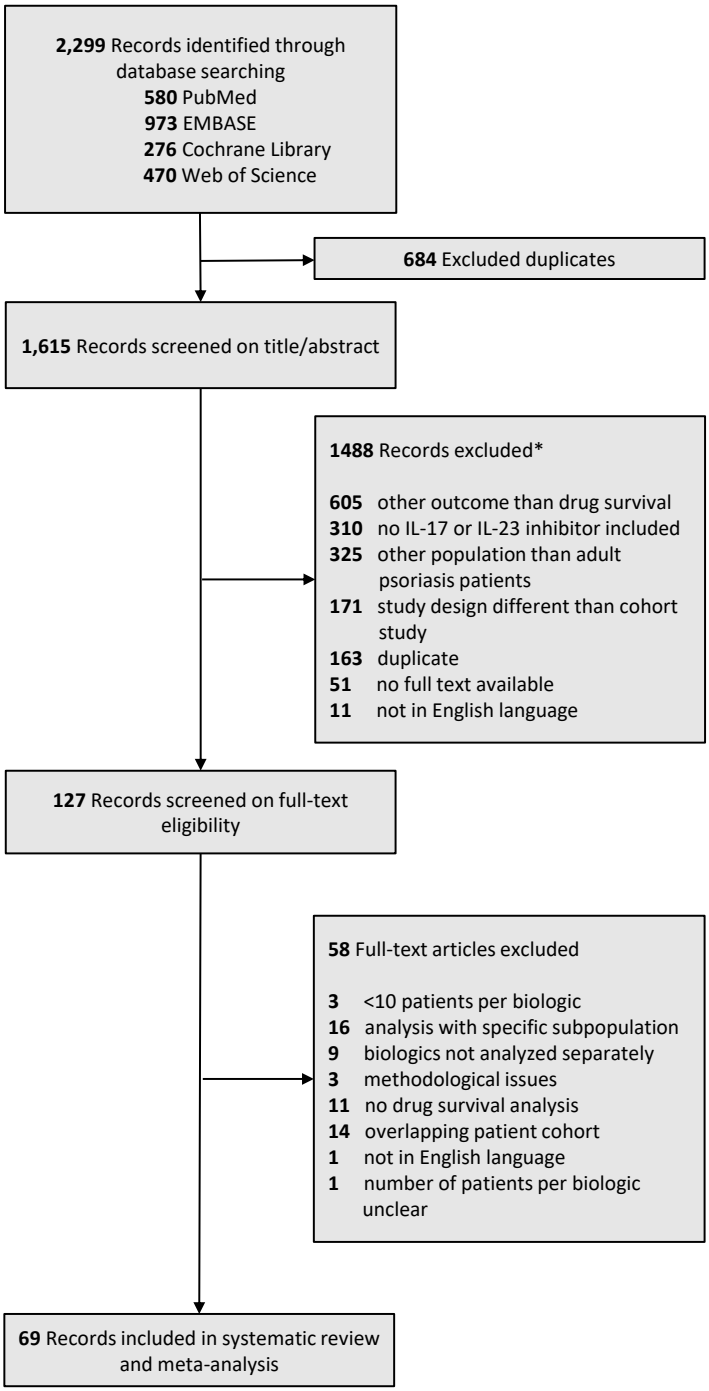

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram
*Some studies were classified with more than one exclusion reason

Table 1 Summary drug survival estimates (95% confidence intervals) per drug survival outcome

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Registry/EHR data						
Overall drug survival						
Studies included	26[24-26, 33, 34, 39-41, 44, 46, 48, 50, 51, 53, 62, 64, 68, 70, 72, 74, 80-85]	15[23, 32, 33, 39, 40, 42-44, 46, 49, 62, 70, 81, 84, 85]	8[39, 40, 58, 62, 84-87]	14[29, 30, 33, 35, 37, 43, 44, 50, 59, 70, 84, 85, 88, 89]	5[27, 50, 84, 85, 90]	4[27, 50, 84, 91]
Patients included	6903	3101	1801	2641	1140	304
Heterogeneity, I^2 (%)	28.5	15.1	16.8	0.0	0.0	0.0
Year 1	0.81 (0.77-0.85)	0.79 (0.73-0.86)	0.81 (0.72-0.90)	0.87 (0.83-0.92)	0.91 (0.88-0.95)	0.80 (0.71-0.91)
Year 2	0.66 (0.61-0.72)	0.67 (0.60-0.75)	0.71 (0.60-0.83)	0.81 (0.75-0.86)	0.88 (0.83-0.93)	0.47 (0.24-0.94)
Year 3	0.53 (0.46-0.62)	0.61 (0.54-0.70)	0.62 (0.51-0.77)	0.77 (0.72-0.83)	0.86 (0.80-0.92)	NA
Year 5	0.38 (0.28-0.50)	0.55 (0.47-0.65)	NA	0.75 [0.69-0.81)	NA	NA
Ineffectiveness related drug survival						
Studies included	6[24, 34, 65, 71, 77, 83]	3[23, 71, 77]	1[71]	3[71, 77, 89]	1[71]	0
Patients included	4070	1660	116	1323	118	0
Heterogeneity, I^2 (%)	0.0	0.0	NA	0.0	NA	NA
Year 1	0.87 (0.83-0.92)	0.91 (0.86-0.96)	0.93[a]	0.93 (0.92-0.95)	0.96[a]	NA
Year 2	0.74 (0.70-0.79)	0.83 (0.75-0.93)	0.88[a]	0.90 (0.87-0.93)	NA	NA
Year 3	0.64 (0.58-0.70)	0.82 (0.73-0.90)	NA	0.89 (0.86-0.92)	NA	NA
Year 5	0.60 (0.53-0.69)	0.72 (0.64-0.81)	NA	0.87 (0.84-0.91)	NA	NA
Adverse event related drug survival						
Studies included	3[24, 77, 83]	2[23, 77]	0	2[77, 89]	0	0
Patients included	2995	1009	0	925	0	0
Heterogeneity, I^2 (%)	0.0	0.0	NA	0.0	NA	NA
Year 1	0.93 (0.90-0.96)	0.94 (0.90-0.98)	NA	0.95 (0.91-0.98)	NA	NA
Year 2	0.89 (0.85-0.93)	0.88 (0.85-0.91)	NA	0.90 (0.84-0.96)	NA	NA

Table 1 Continued

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Drug survival split for biological naivety						
Studies included Biologic naïve patients	16[26, 39, 40, 44, 46, 51, 55, 60, 68, 70, 72, 75, 81, 83, 85, 92]	9[39, 40, 44-46, 81, 85, 92, 93]	3[40, 85, 92]	7[29, 37, 44, 47, 85, 88, 92]	1[85]	0
Patients included	1669	614	215	410	13	0
Heterogeneity, I^2 (%)	0.0	0.0	0.0	0.0	NA	NA
Year 1	0.86 (0.82-0.89)	0.83 (0.77-0.89)	0.84 (0.73-0.97)	0.83 (0.76-0.91)	1.00[a]	NA
Year 2	0.72 (0.67-0.77)	0.68 (0.60-0.76)	0.67 (0.50-0.92)	0.74 (0.66-0.83)	NA	NA
Year 3	0.58 (0.51-0.66)	0.57 (0.48-0.68)	NA	0.69 (0.59-0.80)	NA	
Studies included Biologic experienced patients	16[26, 39, 40, 44, 46, 51, 55, 60, 68, 70, 72, 75, 81, 83, 85, 92]	9[39, 40, 44-46, 81, 85, 92, 93]	4[39, 40, 85, 92]	7[29, 37, 44, 85, 88, 92, 93]	1[85]	0
Patients included	2727	1183	289	547	48	0
Heterogeneity, I^2 (%)	7.5	0.0	0.0	0.0	NA	NA
Year 1	0.77 (0.72-0.83)	0.72 (0.65-0.80)	0.72 (0.66-0.80)	)0.81 (0.74-0.89)	0.95[a]	NA
Year 2	0.60 (0.53-0.67)	0.55 (0.47-0.65)	0.62 (0.52-0.73)	0.72 (0.62-0.83)	NA	NA
Year 3	0.48 (0.39-0.58)	0.47 (0.38-0.60)	0.51 (0.41-0.63)	0.62 (0.52-0.74)	NA	NA
	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Pharmacy/claims databases						
Overall drug survival						
Studies included	10[28, 52, 54, 56, 61, 63, 66, 67, 69, 73]	7[28, 52, 54, 56, 61, 69, 73]	2[69, 94]	4[28, 54, 67, 69]	1[69]	0
Patients included	10687	5171	476	4832	327	0
Heterogeneity, I^2 (%)	72.7	62.9	0.0	86.9	NA	NA

Table 1 Continued

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Year 1	0.67 (0.61-0.75)	0.69 (0.58-0.82)	0.65 (0.57-0.74)	0.80 (0.63-1.00)	0.90[a]	NA
Year 2	0.49 (0.41-0.59)	0.54 (0.43-0.68)	0.53 (0.42-0.69)	0.66 (0.47-0.92)	NA	NA
Year 3	0.41 (0.33-0.51)	0.45 (0.33-0.61)	0.47 (0.36-0.62)	0.57 (0.35-0.92)	NA	NA
Drug survival split for biological naivety						
Studies included Biologic naïve patients	5[28, 36, 67, 73, 76]	4[28, 31, 73, 76]	1[73]	2[28, 67]	0	0
Patients included	3670	3133	195	1980	0	0
Heterogeneity, I^2 (%)	40.9	87.4	NA	13.7	NA	NA
Year 1	0.66 (0.54-0.79)	0.70 (0.46-1.00)	0.72[a]	0.76 (0.66-0.86)	NA	NA
Year 2	0.49 (0.35-0.68)	0.58 (0.33-1.00)	0.64[a]	0.67 (0.48-0.94)	NA	NA
Year 3	0.40 (0.27-0.59)	0.48 (0.24-0.98)	0.61[a]	0.64 (0.41-0.98)	NA	NA
Studies included Biologic experienced patients	4[28, 67, 73, 76]	4[28, 31, 73, 76]	1[73]	2[28, 67]	0	0
Patients included	3969	3512	122	1813	0	0
Heterogeneity, I^2 (%)	4.6	79.8	NA	0.0	NA	NA
Year 1	0.55 (0.42-0.71)	0.61 (0.40-0.92)	0.66[a]	0.72 (0.62-0.83)	NA	NA
Year 2	0.36 (0.24-0.56)	0.45 (0.23-0.85)	0.55[a]	0.60 (0.44-0.81)	NA	NA
Year 3	0.25 (0.16-0.39)	0.34 (0.18-0.64)	0.52[a]	0.53 (0.33-0.83)	NA	NA

[a] Drug survival estimate instead of summary drug survival estimate

(I) For registry/EHR data, several drug survival outcomes were analysed based on the available studies per agent. Our literature search yielded studies on overall drug survival for SEC, IXE, BRO, GUS, RIS, and TIL, for drug survival split for biologic naivety for SEC, IXE, BRO, GUS, and RIS, and for ineffectiveness related drug survival for SEC, IXE, BRO and GUS, and for adverse event related drug survival for SEC, IXE, and GUS. Regarding the separate biologics, SEC had the most available registry/EHR studies (34), followed by IXE (21), GUS (20), BRO (10), RIS (6) and TIL (4).

(II) In pharmacy/claims databases, discontinuation reasons were missing hence only overall drug survival studies were identified. A meta-analysis of pharmacy/claims database studies could be performed for SEC, IXE, BRO, and GUS as these drugs had multiple studies available. Results split for biologic naivety of patients on SEC, IXE and GUS could also be included to construct summary drug survival curves.

Registry/EHR data

The registry/EHR data extracted were provided by medical records (42 studies; 11,365 patients) and patient registries (13 studies; 10,154 patients) from 29 different countries, mainly located in Europe. In **Table 1**, summary (drug) survival estimates (SSE) with 95% CIs per biologic regarding overall drug survival, ineffectiveness related drug survival, adverse event related drug survival and drug survival split for biologic naivety at 1, 2, 3, and 5 years of treatment are provided. Summary survival estimates for overall, ineffectiveness-related and adverse event-related drug survival were high for all included biologics (for instance, SSE all ≥0.8 at year 1) (see **Table 1**, **Figure 2** and **3**). All estimates for biologic naive patients were higher than the estimates of the same biologic for the experienced patients. For example, for IXE naive versus experienced at year 1, SSE were 0.83 (95%CI 0.77-0.89) and 0.72 (95%CI 0.65-0.80), respectively. Risankizumab showed the highest SSE for overall drug survival at years 1, 2, and 3 (all SSE >0.86). Overall drug survival contained data on all biologics, whereas in the differentiated analyses (such as ineffectiveness, adverse events, and biologic naivety) not all biologics were represented, especially RIS and TIL. These differentiated analyses showed that GUS consistently had the highest SSE on almost all drug survival outcomes; for example, the GUS SSE was 0.87 (95%CI 0.84-0.91) for 5-year ineffectiveness related drug survival (**Table 1**). The only exception was SEC drug survival which was highest in biologic naive patients at year 1 with an SSE of 0.86 (95%CI 0.82-0.89). Summary drug survival estimates of the IL-17-inhibitors SEC, IXE, and BRO were similar to each other for the 1-year and 2-year overall drug survival and ineffectiveness related drug survival. One-year and 2-year adverse event related drug survival of IL-17-inhibitors (SEC, IXE) was similar to that of GUS (SSE GUS 1 and 2 year 0.95

(95%CI 0.91-0.98) and 0.90 (95%CI 0.84-0.96)). The summary drug survival curves of the meta-analysis for adverse event related drug survival and for drug survival split for biologic naivety are displayed in **Figures S1, S2** and **S3**. Heterogeneity between studies was low (I^2<29%), see **Table 1.**

Results of the sensitivity analyses, in which also studies where no Kaplan-Meier curves were provided[38, 47, 55, 77] were included, were very similar to the primary analyses, see **Table S6.**

Pharmacy/claims data

Table 1 also shows drug survival data (SSE from the meta-analysis or separate Kaplan-Meier drug survival estimates) for SEC, IXE, BRO and GUS from pharmacy/claims databases. Fourteen pharmacy/claims database studies (27,521 patients) could be included from 9 different countries, most of which were conducted in North America). In **Figures S4, S5** and **S6**, a visualisation of summary drug survival curves is provided (SEC, IXE, BRO, GUS, RIS). SSE of pharmacy/claims data for 1- and 2-year overall drug survival were low compared to SSE from registry/EHR data (e.g., 1-year and 2-year overall SSE for SEC pharmacy/claims data of 0.67 (95%CI 0.61-0.75) and 0.49 (95%CI 0.41-0.59) versus 0.81 (95%CI 0.77-0.85) and 0.66 (95%CI 0.61-0.72) in registry/EHR data, respectively). Heterogeneity between studies varied greatly (range I^2 0%-87%), see **Table 1**.

The drug survival percentages of the sensitivity analysis using extrapolation of point estimates[31, 57] for pharmacy/claims databases are also reported in **Table S6**.

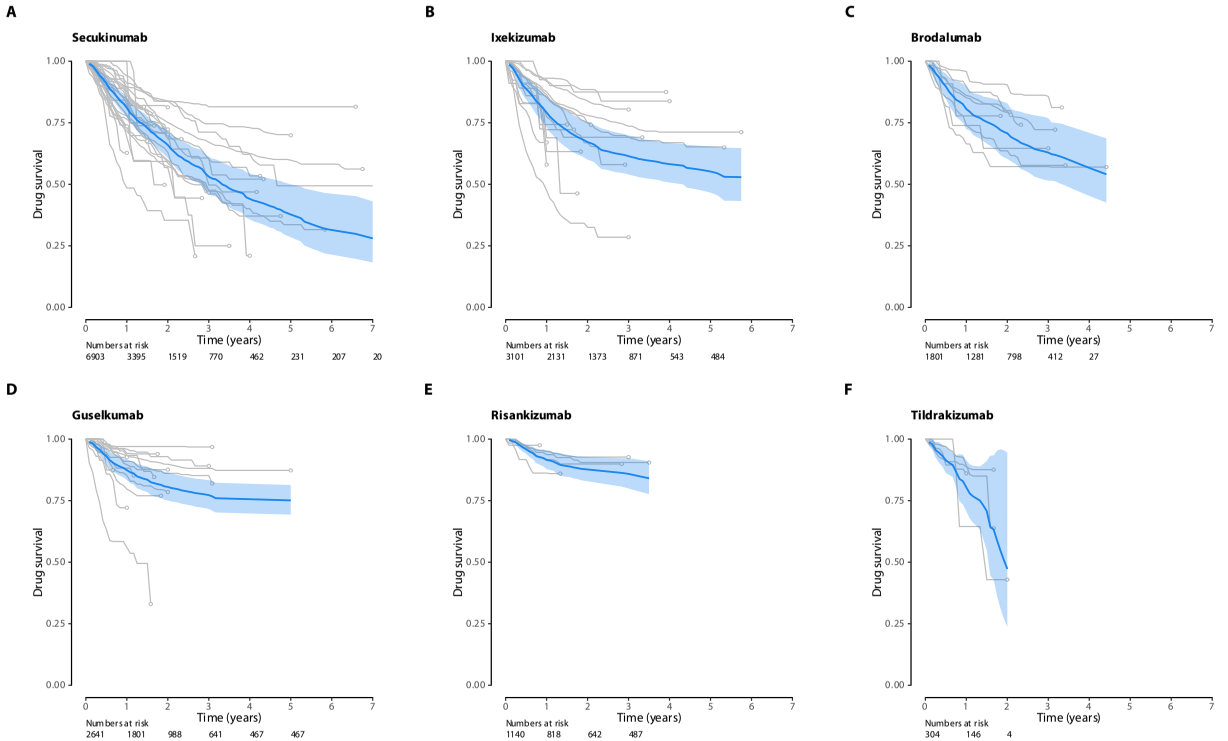

Figure 2 Non-parametric random effects summary drug survival curves with 95% confidence intervals for overall survival.

Summary drug survival curves in blue, separate studies in grey. A: secukinumab[24-26, 33, 34, 39-41, 44, 46, 48, 50, 51, 53, 62, 64, 68, 70, 72, 74, 80-85], B: ixekizumab[23, 32, 33, 39, 40, 42-44, 46, 49, 62, 70, 81, 84, 85], C: brodalumab[39, 40, 58, 62, 84-87], D: guselkumab[29, 30, 33, 35, 37, 43, 44, 50, 59, 70, 84, 85, 88, 89], E: risankizumab[27, 50, 84, 85, 90], F: tildrakizumab[27, 50, 84, 91]. The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

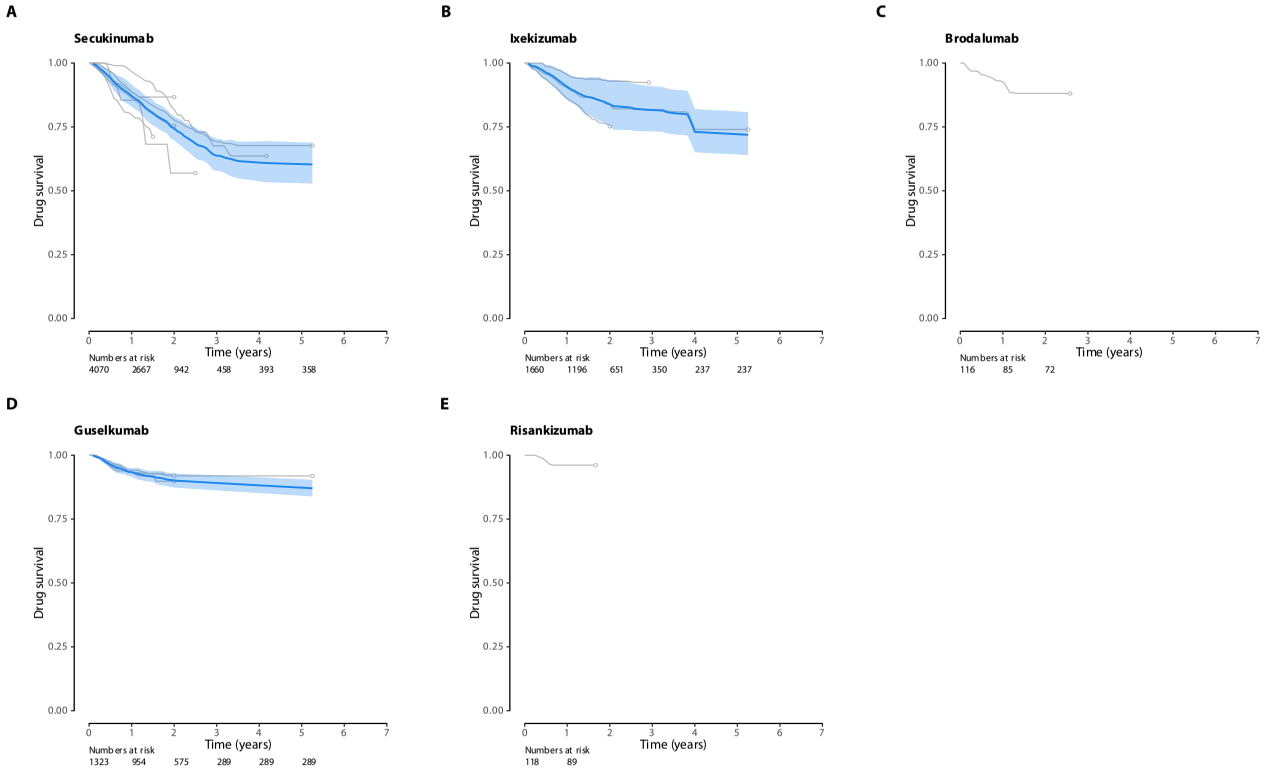

Figure 3 Non-parametric random effects summary drug survival curves with 95% confidence intervals for ineffectiveness related drug survival.

Summary drug survival curves in blue, separate studies in grey. A: secukinumab[24, 34, 65, 71, 77, 83], B: ixekizumab[23, 71, 77], C: brodalumab[71] (drug survival estimate instead of summary drug survival estimate), D: guselkumab, E: risankizumab[71] (drug survival estimate instead of summary drug survival estimate). The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

Direct comparison summary drug survival estimates

Risankizumab had statistically significantly higher SSE for the overall drug survival at years 1, 2, and 3, compared to SEC and IXE, and higher rates at year 2 and 3 compared to BRO (estimated differences and 95% confidence intervals SEC-RIS at year 1, 2, and 3; -0.11 (95%CI -0.17, -0.04), -0.22 (95%CI -0.32, -0.12), and -0.33 (95%CI -0.49, -0.17), respectively, IXE-RIS at years 1, 2, and 3; -0.12 (95%CI -0.21, -0.03), -0.21 (95%CI -0.33, -0.08), and -0.24 (95%CI -0.39, -0.10), respectively, BRO-RIS at year 2 and 3; -0.17 (95%CI -0.34, -0.00), and -0.23 (95%CI -0.44, -0.02), respectively). Guselkumab also had statistically significantly higher SSE for the overall drug survival at years 2 and 3, compared with SEC and IXE (estimated difference and 95%CI SEC-GUS at years 2 and 3; -0.15 (95%CI -0.25, -0.04) and -0.24 (95%CI -0.40, -0.08), respectively, IXE-GUS at years 2 and 3; -0.13 (95%CI -0.27, -0.00) and -0.16 (95%CI -0.31, -0.00), respectively), and higher rates at years 1, 2, and 3 for ineffectiveness related drug survival compared with SEC (estimated difference and 95%CI SEC-GUS at years 1, 2, and 3; -0.06 (95%CI -0.11, -0.01), -0.16 (-95%CI 0.23, -0.09), and -0.25 (95%CI -0.36, -0.15), respectively). At 3 years, the ineffectiveness related drug survival of IXE was significantly higher than that of SEC (estimated difference and 95%CI -0.18 (-0.32, -0.03)). An overview of all pairwise comparisons is displayed in **Table 9**.

Discussion

This systematic review and meta-analysis was performed to investigate the drug survival of IL-17 and IL-23 inhibitors in patients with psoriasis. A total of 69 studies including 48,704 patients were systematically reviewed to assess the drug survival of IL-17 and IL-23 inhibitors. Detailed summary drug survival curves were constructed to provide insight into the drug survival curves per drug over time, analysed separately for different discontinuations reasons (ineffectiveness and adverse events) and biologic naivety. Summary drug survival estimates, also for ineffectiveness related drug survival, were similar for SEC, IXE and BRO, but ineffectiveness related drug survival of IXE was significantly higher than drug survival of SEC at 3 years, indicating that patients on IXE are less likely to discontinue their drug because of ineffectiveness than patients on SEC. Risankizumab had the highest SSE for overall drug survival at 1, 2, and 3 years. Guselkumab had the highest SSE at 1, 2, and 3 years for almost all differentiated (e.g. ineffectiveness-related and adverse event-related drug survival) outcomes compared with the other biologics. Note that in the differentiated outcomes, such as ineffectiveness related drug survival, not all biologics were consistently present. In line with

previous findings, drug survival for biologic-naive patients was superior to that of biologic-experienced patients. Estimates of drug survival based on pharmacy/claims databases were substantially lower, indicating worse performance of these drugs compared to the analyses based on registry/EHR data. By utilising the method by Combescure et al. in our meta-analysis, we were able to implement drug survival probabilities from each month of the full reported follow-up duration, constructing precise drug survival estimates.

In previous systematic reviews and meta-analyses on the efficacy of biologics for the treatment of psoriasis, favourable outcomes have been reported. [8-10] However, analyses were performed at specific timepoints (e.g. at 1 and 2 years), which results in an under-representation of studies reporting drug survival at other timepoints. As stated, to overcome this limitation the Combescure method was used, which permits inclusion of the full drug survival curves. Mourad and Gniadecki performed a comparative meta-analysis of hazard ratios specifically for the drug survival of biological treatment. The 2- and 5-year drug survival data at that time were insufficient to compare drug survival for the IL-17 and IL-23 inhibitors yet. Their 1-year pairwise comparisons showed a superiority of SEC over IXE. [10] Prior extensive reviews on the drug survival of tumour necrosis factor-α inhibitors and ustekinumab reported lower pooled annual drug survival rates for the tumour necrosis factor-α inhibitors etanercept, adalimumab, and infliximab after 1 (all <0.74) and 3 years (all <0.54) compared to our IL-17 and IL-23 rates (all point estimates ≥0.8). For ustekinumab, similar drug survival rates to our results for SEC, IXE and BRO were reported. GUS and RIS overall drug survival rates in our study were substantially higher than previously reported etanercept, adalimumab, infliximab, and ustekinumab rates up to five years. [8, 9] Guselkumab and RIS drug survival rates were also statistically significantly higher than SEC, IXE and BRO rates in this meta-analysis, which is possibly related to the upstream effect of IL-23 inhibitors in the IL-23/IL-17 cytokine pathway. [78]

Remarkably, summary drug survival estimates of pharmacy/claims databases were noticeably lower than these estimates from registry/EHR databases (e.g., 2-year overall summary drug survival estimate for SEC pharmacy/claims data of 0.49 (95%CI 0.41-0.59) vs. 0.66 (95%CI 0.61-0.72) in registry/EHR data), and the I^2 statistic for heterogeneity was higher in pharmacy/claims database studies compared with registry/EHR studies. As the total number of patients in the many registry/EHR studies is comparable to the total number of patients in the pharmacy/claims studies, the difference in drug survival outcomes is not likely explained by a difference in precision of the estimate. In pharmacy/claims database studies,

the administrative claims for medication are used, and the actual medication use of the patient is not verified at a physician and patient level. Missing information on the cause of discontinuation and the exact date of discontinuation might pose possible hazards in the interpretation of data from pharmacy/claims databases. Events that are not related to the drug performance, for example, insurance issues, relocation, or factors such as family planning, cannot be distinguished from drug related issues. As for detailed drug survival analyses, the nature and timing of discontinuation events are utterly important and may outweigh the advantage of including large populations from claims databases. Moreover, especially for claims databases, results are generalisable to the insured population, but not necessarily to uninsured patients, or patients with other insurance types.

The study's literature search was constrained to English-language publications, potentially introducing language bias. Drug survival studies reporting on bimekizumab were not yet available. Tildrakizumab was included in our study, however at the time of our search, only short-term follow-up drug survival studies were available. RoB assessments using the QUIPS and ROBINS-I tool led to a subset of studies with high/serious RoB, which were excluded in separate sensitivity analyses. There were no studies which could be classified as low RoB using both tools, this should be taken into consideration when interpreting results. Furthermore, most studies included in this review reported on overall drug survival. It should be kept in mind that several discontinuation reasons underlie this outcome which may not all be related to the performance of the drug itself, like wish for pregnancy or financial reasons. [77, 79] The coverage and reimbursement policies of health insurance plans and formularies can influence drug survival rates. Restrictions imposed by insurance companies, such as prior authorisation requirements or limited formulary options, may create barriers to accessing certain medications. Patients who face difficulties in obtaining insurance coverage for a prescribed medication may be more likely to discontinue treatment. This further underscores the importance of drug survival analyses with a focus on specific discontinuation reasons (ineffectiveness, adverse events). It is crucial to register financial reasons separately in order to prevent them from influencing drug survival rates with regard to ineffectiveness and adverse events. In future studies, we would strongly encourage reporting drug survival separately for different discontinuation reasons (instead of combining all reasons in an overall drug survival) and effect modifiers.

Furthermore, we want to highlight that a given drug is always both prescribed and discontinued in a landscape of competing drugs. The quantity of available alternatives likely affects the decisions made by doctors. When the selection of

alternative options is restricted, doctors are likely more inclined to maintain their patients on a specific drug. In contrast, when many treatment options are available, treating physicians as well as patients could decide easier for switching to a consecutive biological treatment. In addition to doctors adjusting their prescription practices, patients' perspectives can also evolve, as they might strive for higher therapeutic objectives, potentially leading to earlier consideration of switching. In the current study timeframe however, there were consistently multiple 'older' biologic alternatives (such as ustekinumab, adalimumab, etanercept, infliximab) as well as the small-molecule apremilast available alongside the newest biologics included, which also entered the market rapidly during the studied period. The number of patients who continued with their IL-17/IL-23 inhibitor because there were no alternatives available was considered very low, thereby minimising the potential impact of drug availability on our findings.

This meta-analysis showed that investigated IL-17 and IL-23 inhibitors had high drug survival rates, with highest rates for GUS and RIS drug survival. Attention for effect modifiers (biologic naivety), and source of data (registry/EHR data vs. pharmacy/claims databases) is relevant when interpreting drug survival studies.

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Supplementary content

Figure S1 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for adverse event related drug survival

Figure S2 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for drug survival of biologic naïve patients

Figure S3 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for drug survival of biologic experienced patients

Figure S4 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for the overall drug survival using pharmacy/claims data

Figure S5 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for drug survival of biologic naïve patients using pharmacy/claims data

Figure S6 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for drug survival of biologic experienced patients using pharmacy/claims data

Table S1 Full search strategy

Table S2 Baseline and treatment characteristics of included cohorts

Table S3 Risk of bias assessment using the QUIPS tool

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Table S5 Risk of bias assessment using the Oxford Rating Scheme for Studies and Other Evidence

Table S6 Summary drug survival estimates for overall drug survival, sensitivity analysis using extrapolation

Table S7 Summary drug survival estimates for overall drug survival, sensitivity analysis excluding high risk of bias studies according to QUIPS

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Table S9 Comparison of summary drug survival estimates

Table S10 Inclusion and exclusion reasons per meta-analysis outcome: see supplementary content online

Appendix S1 Modified QUIPS tool

Appendix S2 List of included articles

Appendix S3 List of excluded articles based on full-text screening for eligibility

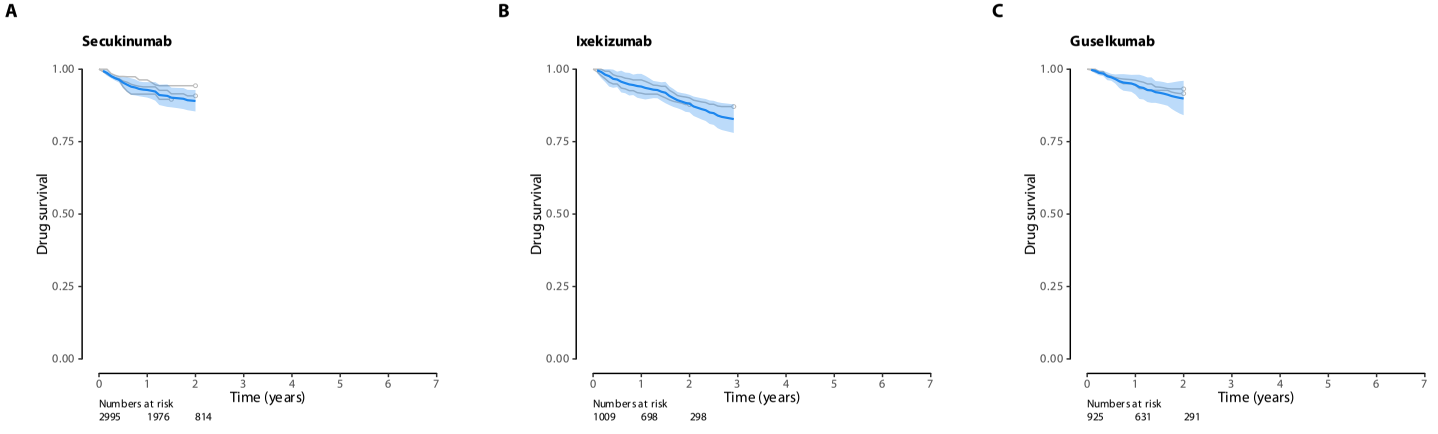

Figure S1 Non-parametric random effects summary drug survival curves with 95% confidence intervals for adverse event related drug survival.

Summary drug survival curves in blue, separate studies in grey. A: secukinumab[1-3], B: ixekizumab[3, 4], C: guselkumab[3, 5]. The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

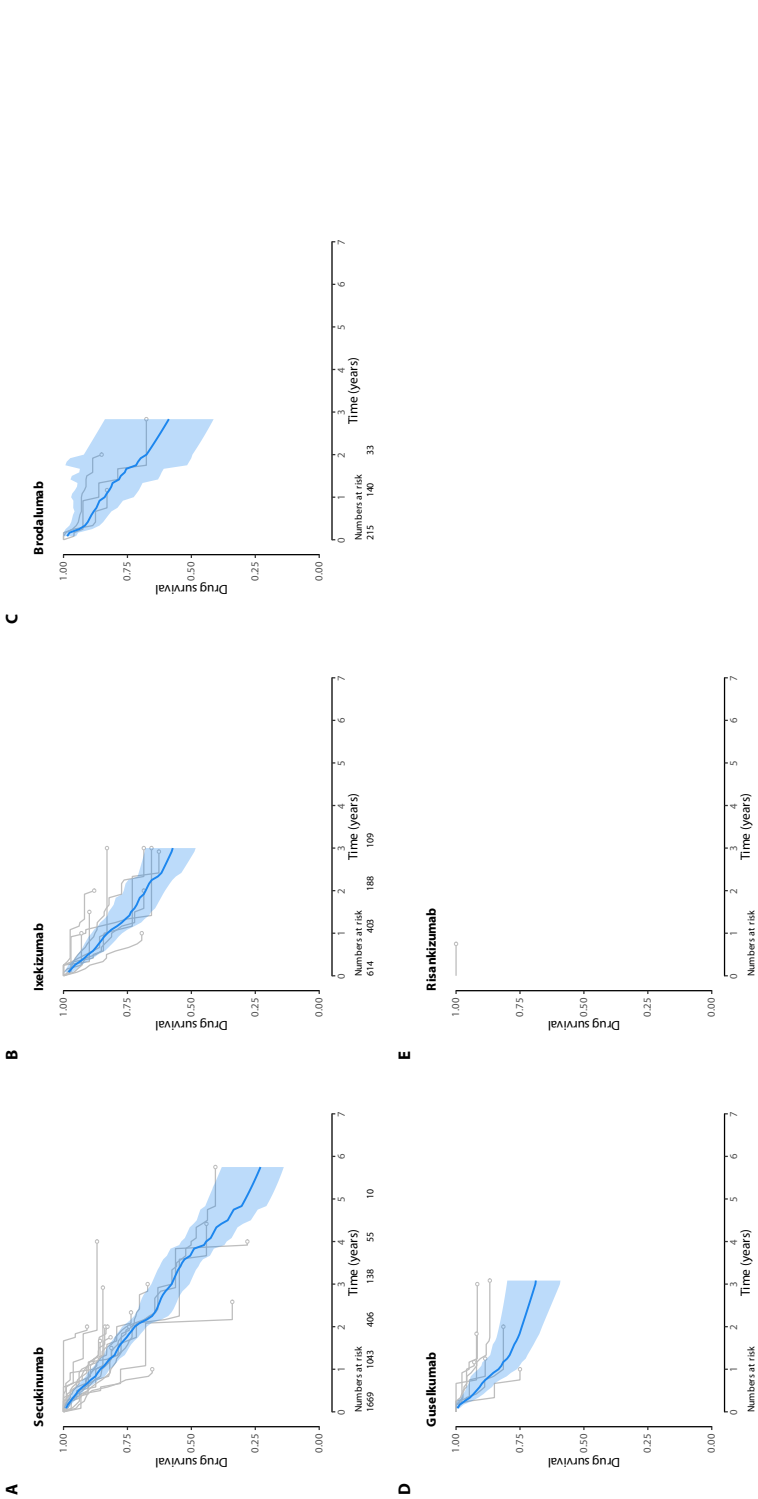

Figure S2 Non-parametric random effects summary drug survival curves with 95% confidence intervals for drug survival of biologic naïve patients

Summary drug survival curves in blue, separate studies in grey. A: secukinumab[2, 6-20], B: ixekizumab[7, 9-13, 20-22], C: brodalumab[7, 12, 20, 23-26], D: guselkumab[7, 11, 20], E: risankizumab[20] (drug survival estimate instead of summary drug survival estimate) The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

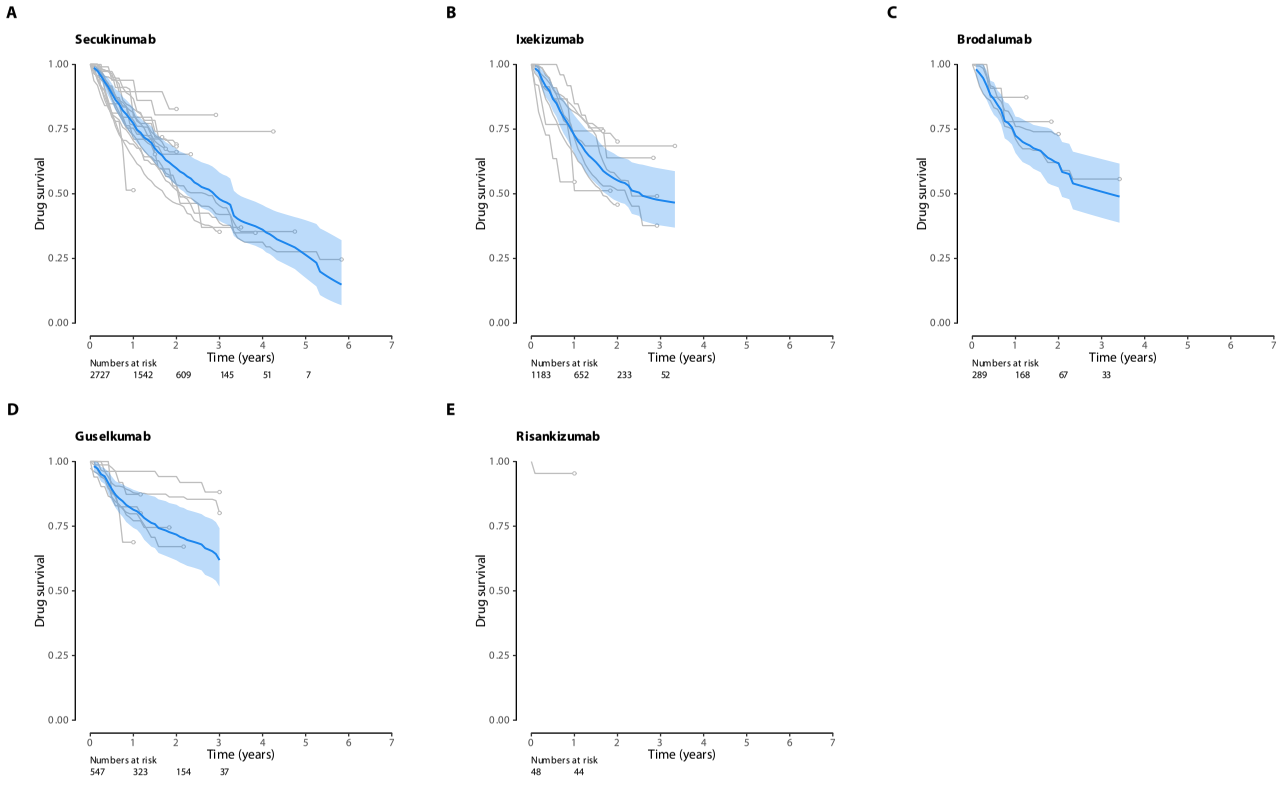

Figure S3 Non-parametric random effects summary drug survival curves with 95% confidence intervals for drug survival of biologic experienced patients

Summary drug survival curves in blue, separate studies in grey. A: secukinumab[2, 6-20], B: ixekizumab[7, 9-13, 20-22], C: brodalumab[7, 10, 11, 20], D: guselkumab[7, 12, 20, 21, 23, 24, 26], E: risankizumab[20] (drug survival estimate instead of summary drug survival estimate). The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

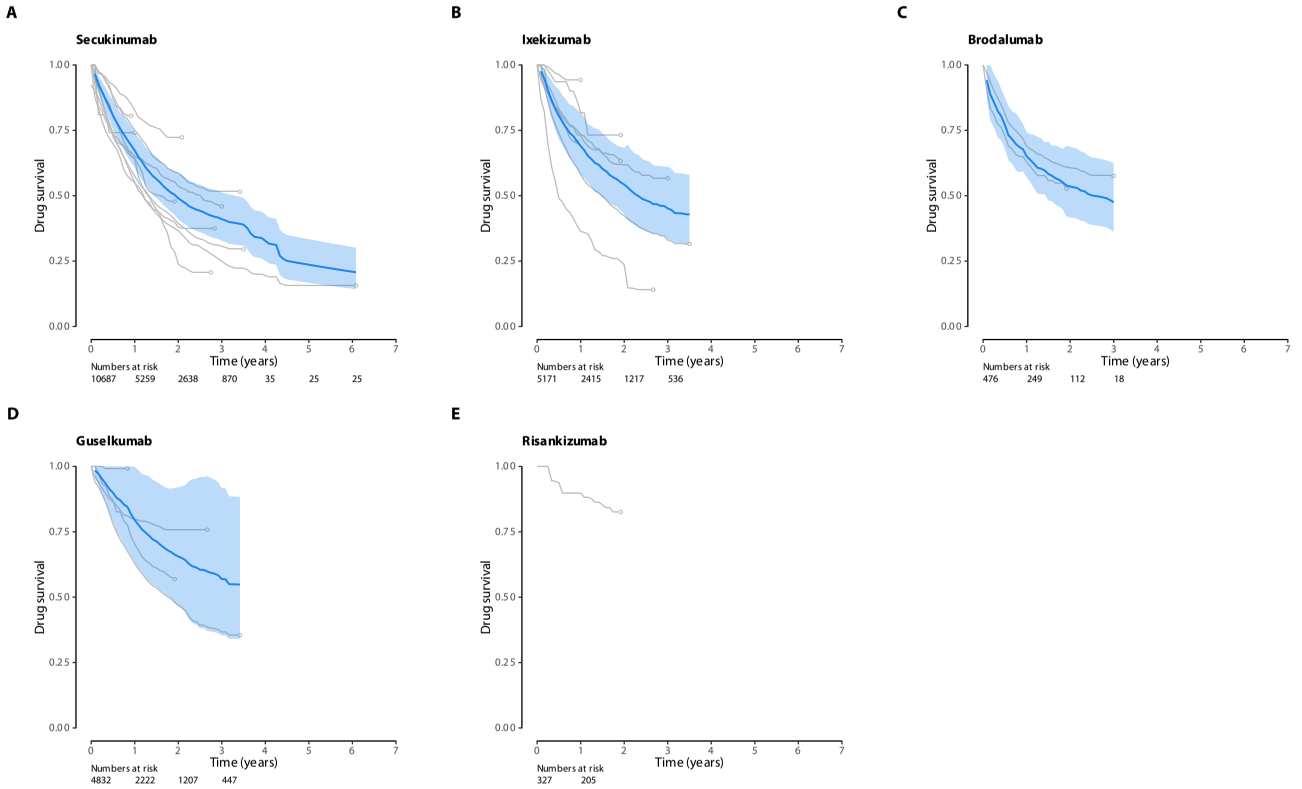

Figure S4 Non-parametric random effects summary drug survival curves with 95% confidence intervals for the overall drug survival using pharmacy/claims data. Summary drug survival curves in blue, separate studies in grey. A: secukinumab[27-36], B: ixekizumab[27-31, 35, 36], C: brodalumab[35, 36], D:guselkumab[27, 29, 34, 35], E: risankizumab[35] (drug survival estimate instead of summary drug survival estimate). The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

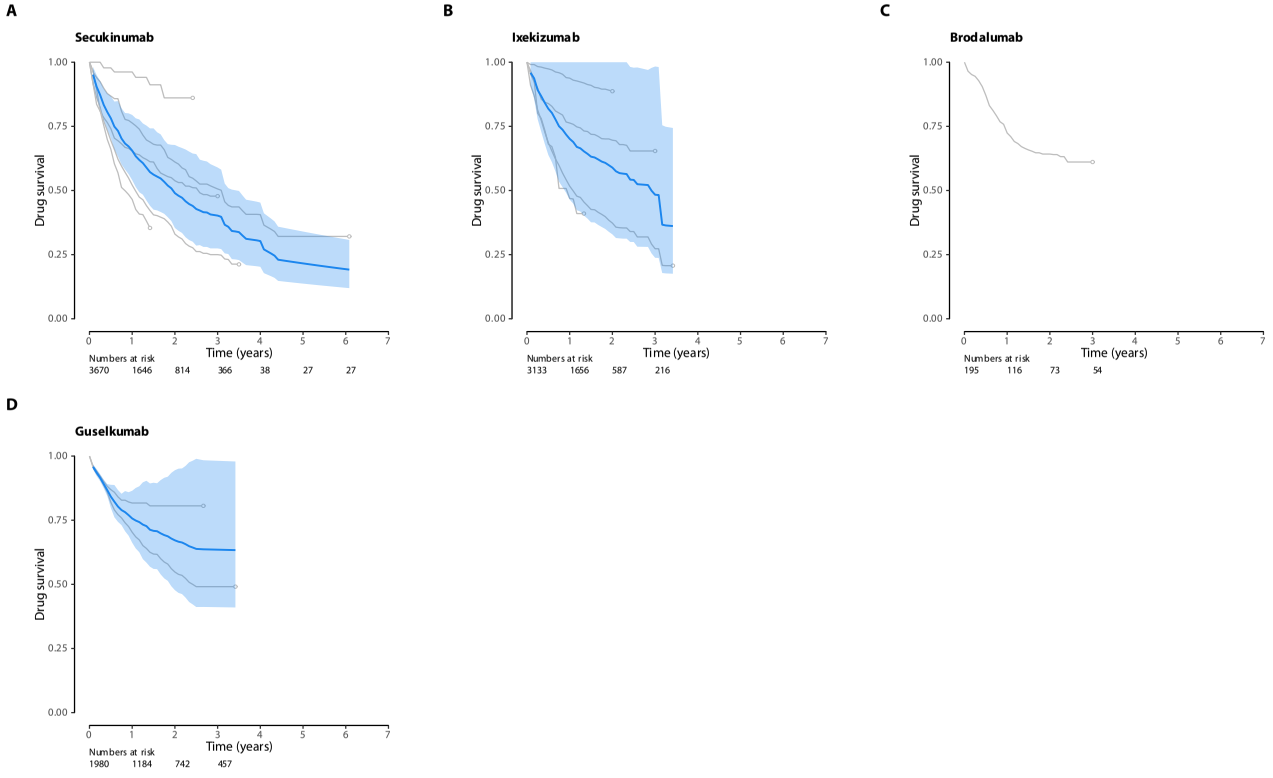

Figure S5 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for drug survival of biologic naïve patients using pharmacy/claims data

Summary drug survival curves in blue, separate studies in grey. A: secukinumab[27, 34, 36-38], B: ixekizumab[27, 36, 38, 39], C: brodalumab[36] (drug survival estimate instead of summary drug survival estimate), D: guselkumab[27, 34]. The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

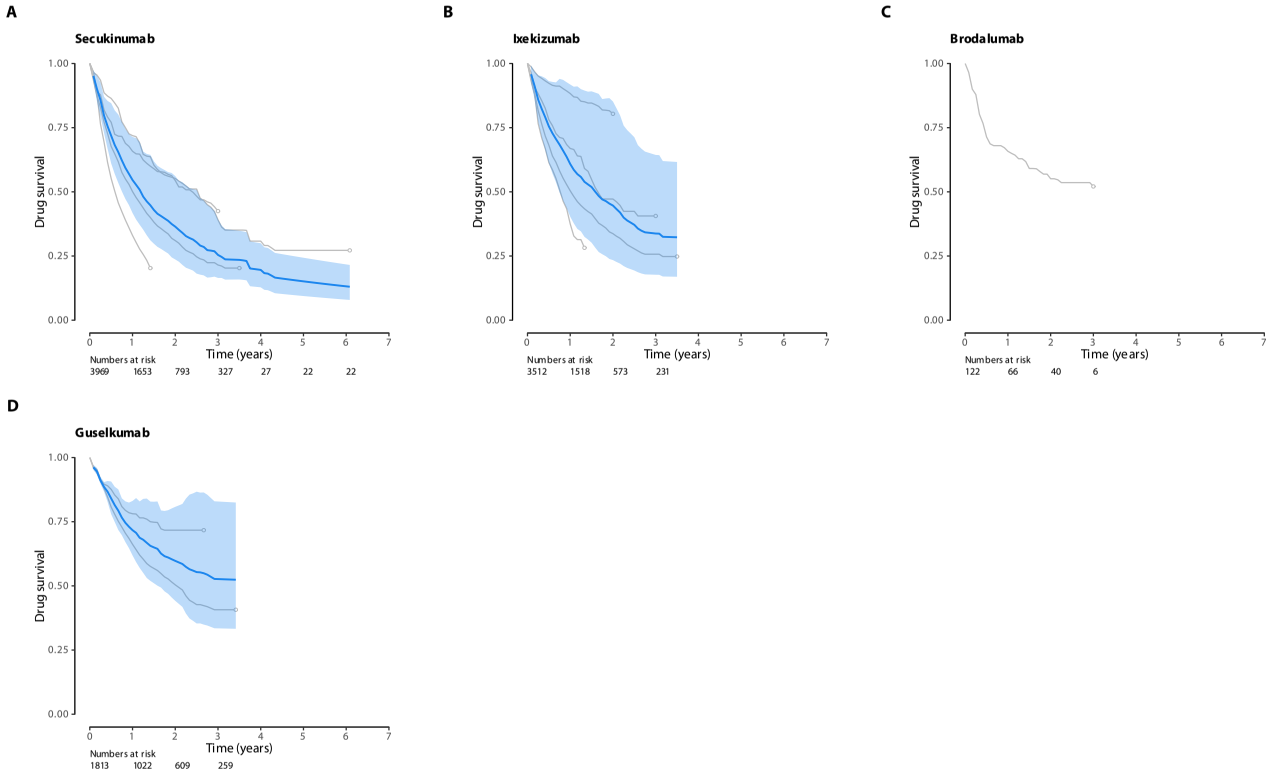

Figure S6 Non-parametric random effects summary drug survival curves with 95% confidence intervals (in blue) for drug survival of biologic experienced patients using pharmacy/claims data

Summary drug survival curves in blue, separate studies in grey. A: secukinumab[27, 34, 36, 38], B: ixekizumab[27, 36, 38, 39], C: brodalumab[36] (drug survival estimate instead of summary drug survival estimate), D: guselkumab[27, 34]**.** The numbers of at-risk patients in the whole cohort at the beginning of each year are reported.

Table S1 Full search strategy

Pubmed	EMBASE	Cochrane Library	Web of Science
psoriasis [MeSH] OR psorias* [tiab]	Psoriasis/ OR psoriasis vulgaris/ OR psorias*.ti.kf	[mh Psoriasis] OR Psorias*:ti.ab.kw	TI=(Psoriasis OR OR Psoriases)
biological therapy [Mesh:NoExp] OR biological products [Mesh:NoExp] OR biosimilar pharmaceuticals [Mesh] OR secukinumab [Supplementary Concept] OR ixekizumab [Supplementary Concept] OR brodalumab [Supplementary Concept] OR risankizumab [Supplementary Concept] OR guselkumab [Supplementary Concept] OR tildrakizumab [Supplementary Concept] OR Interleukin-23/antagonists and inhibitors [Mesh] OR Interleukin 23 subunit p19 [Mesh] OR Interleukin-17/antagonists and inhibitors [Mesh] OR biologic* [tiab] OR biosimilar* [tiab] OR "IL 23 inhibitor*" [tiab] OR "IL 17 inhibitor*" [tiab] OR "Interleukin 23 inhibitor*" [tiab] OR "Interleukin 17 inhibitor*" [tiab] OR "IL 23 blocker*" [tiab] OR "IL 17 blocker*" [tiab] OR	biological therapy/ OR biological product/ OR biosimilar agent/ OR secukinumab/ OR ixekizumab/ OR brodalumab/ OR risankizumab/ OR guselkumab/ OR tildrakizumab/ OR Interleukin 23 antibody/ OR Interleukin 23p19/ OR Interleukin 17 antibody/ OR biologic$.ab.ti.kf OR biosimilar$.ab.ti.kf OR IL 23 inhibitor$.ab.ti.kf OR IL 17 inhibitor$.ab.ti.kf OR Interleukin 23$.ab.ti.kf OR Interleukin 17 inhibitor$.ab.ti.kf OR IL 23 blocker$.ab.ti.kf OR IL 17 blocker$.ab.ti.kf OR Interleukin 23 blocker$.ab.ti.kf OR Interleukin 17 blocker$.ab.ti.kf OR IL 23 antagonist$.ab.ti.kf OR IL 17 antagonist$.ab.ti.kf OR Interleukin 23 antagonist$.ab.ti.kf OR Interleukin 17 antagonist$.ab.ti.kf OR Anti IL 23.ab.ti.kf OR Anti IL 17$.ab.ti.kf OR	[mh^"Biological Therapy"] OR [mh^"Biological Products"] OR [mh "Biosimilar Pharmaceuticals"] OR [mh "Interleukin 23"/AI] OR [mh "Interleukin 23 subunit p19"] OR [mh "Interleukin 17"/AI] OR "IL 23 inhibitor*":ti.ab.kw OR "IL 17 inhibitor*":ti.ab.kw OR "Interleukin 23*":ti.ab.kw OR "Interleukin 17 inhibitor*":ti.ab.kw OR "IL 23 blocker*":ti.ab.kw OR "Interleukin 23 blocker*":ti.ab.kw OR "IL 23 antagonist*":ti.ab.kw OR "IL 17 antagonist*":ti.ab.kw OR "Interleukin 23 antagonist*":ti. ab.kw OR "Interleukin 17 antagonist*":ti. ab.kw OR "Anti IL 23":ti.ab.kw OR "Anti IL 17*":ti.ab.kw OR "Interleukin 23 subunit p19":ti.ab.kw OR secukinumab:ti.ab.kw OR cosentyx:ti.ab.kw OR ixekizumab:ti.ab.kw OR taltz:ti.ab.kw OR brodalumab:ti.ab.kw OR kyntheum:ti.ab.kw OR	TS=(biologic* OR biosimilar* OR "IL 23 inhibitor*" OR "IL 17 inhibitor*" OR "Interleukin 23 inhibitor*" OR "Interleukin 17 inhibitor*" OR "IL 23 blocker*" OR "IL 17 blocker*" OR "Interleukin 23 blocker*" OR "Interleukin 17 blocker*" OR "IL 23 antagonist*" OR "IL 17 antagonist*" OR "Interleukin 23 antagonist*" OR "Interleukin 17 antagonist*" OR "Anti IL 23" OR "Anti IL 17*" OR "Interleukin 23 subunit p19" OR secukinumab OR cosentyx OR ixekizumab OR taltz OR brodalumab OR kyntheum OR siliq OR risankizumab OR skyrizi OR guselkumab OR tremfya OR

Table S1 Continued

Pubmed	EMBASE	Cochrane Library	Web of Science
"Interleukin 23 blocker*" [tiab] OR "Interleukin 17 blocker*" [tiab] OR "IL 23 antagonist*" [tiab] OR "IL 17 antagonist*" [tiab] OR "Interleukin 23 antagonist*" [tiab] OR "Interleukin 17 antagonist*"[tiab] OR "Anti IL 23" [tiab] OR "Anti IL 17*" [tiab] OR "Interleukin 23 subunit p19" [tiab] OR secukinumab [tiab] OR cosentyx [tiab] OR ixekizumab [tiab] OR taltz [tiab] OR brodalumab [tiab] OR kyntheum [tiab] OR siliq [tiab] OR risankizumab [tiab] OR skyrizi [tiab] OR guselkumab [tiab] OR tremfya [tiab] OR tildrakizumab [tiab] OR ilumetri [tiab] OR ilumya [tiab]	Interleukin 23 subunit p19.ab.ti.kf OR secukinumab.ab.ti.kf OR cosentyx.ab.ti.kf OR ixekizumab.ab.ti.kf OR taltz.ab.ti.kf OR brodalumab.ab.ti.kf OR kyntheum.ab.ti.kf OR siliq.ab.ti.kf OR risankizumab.ab.ti.kf OR skyrizi.ab.ti.kf OR guselkumab.ab.ti.kf OR tremfya.ab.ti.kf OR tildrakizumab.ab.ti.kf OR ilumetri.ab.ti.kf OR ilumya.ab.ti.kf	siliq:ti.ab.kw OR risankizumab:ti.ab.kw OR guselkumab:ti.ab.kw OR tremfya:ti.ab.kw OR tildrakizumab:ti.ab.kw OR ilumya:ti.ab.kw	tildrakizumab OR ilumetri OR ilumya)

Table S1 Continued

Pubmed	EMBASE	Cochrane Library	Web of Science
"Survival Analysis"[Mesh:NoExp] OR "Kaplan-Meier Estimate"[Mesh] OR "Medication Adherence"[Mesh] OR "Proportional Hazards Models" [Mesh] OR "Kaplan-Meier"[tiab] OR "Survival Analys*"[tiab] OR "drug survival" [tiab] OR "drug adherence" [tiab] OR "drug failure" [tiab] OR "drug discontinuation" [tiab] OR "drug persistence" [tiab] OR "drug retention" [tiab] OR "medication adherence" [tiab] OR "medication discontinuation" [tiab] OR "medication failure" [tiab] OR "medication persistence" [tiab] OR "medication retention" [tiab] OR "therapy adherence" [tiab] OR "therapy discontinuation" [tiab] OR "therapy failure" [tiab] OR "therapy retention" [tiab] OR "therapy persistence" [tiab] OR Cox multivariate analys* [tiab] OR Cox regression [tiab] OR Cox survival analys* [tiab] OR Proportional hazard* [tiab]	survival analysis/ OR kaplan meier method/ OR medication compliance/ OR proportional hazards model/ OR Kaplan-Meier*.ti.ab.kf. OR Survival Analys*.ti.ab.kf. OR drug survival.ti.ab.kf. OR drug adherence.ti.ab.kf. OR drug failure.ti.ab.kf. OR drug discontinuation.ti.ab.kf. OR drug persistence.ti.ab.kf. OR drug retention.ti.ab.kf. OR medication adherence.ti.ab.kf. OR medication discontinuation.ti.ab.kf. OR medication failure.ti.ab.kf. OR medication persistence.ti.ab.kf. OR medication retention.ti.ab.kf. OR therapy adherence.ti.ab.kf. OR therapy discontinuation.ti.ab.kf. OR therapy failure.ti.ab.kf. OR therapy retention.ti.ab.kf. OR therapy persistence.ti.ab.kf. OR Cox multivariate analys*.ti.ab.kf. OR Cox regression.ti.ab.kf. OR Cox survival analys*.ti.ab.kf. OR Proportional hazard*.ti.ab.kf.	[mh ^Survival Analysis] OR [mh ^Kaplan-Meier Estimate] OR [mh ^Medication Adherence] OR [mh ^Proportional Hazards Models] OR Kaplan-Meier*:ti.ab.kw OR Survival Analys*:ti.ab.kw OR drug survival:ti.ab.kw OR drug adherence:ti.ab.kw OR drug failure:ti.ab.kw OR drug discontinuation:ti.ab.kw OR drug persistence:ti.ab.kw OR drug retention:ti.ab.kw OR medication adherence:ti.ab.kw OR medication discontinuation:ti.ab.kw OR medication failure:ti.ab.kw OR medication persistence:ti.ab.kw OR medication retention:ti.ab.kw OR therapy adherence:ti.ab.kw OR therapy discontinuation:ti.ab.kw OR therapy failure:ti.ab.kw OR therapy retention:ti.ab.kw OR therapy persistence:ti.ab.kw OR Cox multivariate analys*:ti.ab.kw OR Cox regression:ti.ab.kw OR Cox survival analys*:ti.ab.kw OR Proportional hazard*:ti.ab.kw	TS=("survival analys*" OR "Kaplan-Meier*" OR "Proportional Hazard*" OR "drug survival" OR "drug adherence" OR "drug failure" OR "drug discontinuation" OR "drug persistence" OR "drug retention" OR "medication adherence" OR "medication failure" OR "medication discontinuation" OR "medication persistence" OR "Medication retention" OR "therapy adherence" OR "therapy failure" OR "therapy discontinuation" OR "therapy persistence" OR "therapy retention")
Hits	**Hits**	**Hits**	**Hits**
Hits: 580	**Hits: 973**	**Hits: 276**	**Hits: 470**

At the start of this study bimekizumab was registered for a very short period of time, and therefore not included in the literature search.

Table S2 Baseline characteristics of the included studies

EHR/registry data				
Study	**Country**	**Data source**	**IL-17/IL-23 agent**	**Sample size**
Caldarola et al. 2021[1]	Italy	Medical records	SEC	122
			IXE[a]	*123*
Caldarola et al. 2023[4]	Italy	Medical records	IXE	306
Caldarola et al. 2023[40]	Italy	Medical records	RIS	112
Chatzimichail et al. 2021[41]	Germany	Medical records	SEC	68
Costa de Lima et al. 2021[42]	Brazil	Medical records	SEC	13
Dapavo et al. 2021[7]	Italy	Medical records	*SEC*[a]	*49*
			IXE[a]	*63*
			BRO	49
			GUS	46
Dauden et al. 2020[6]	Spain	Medical records	SEC	384
Egeberg et al. 2022[21]	Denmark	Patient registry	SEC	741
			IXE	170
			GUS	68
Elgaard et al. 2023[43]	Denmark	Medical records	*GUS*[a]	*29*
			TIL	14
			RIS	37
Elgaard et al. 2023[44]	Denmark	Medical records	BRO	83
Foley et al. 2022[8]	Australia and New Zealand	Patient registry	SEC	294
Galluzzo et al. 2023[23]	Italy	Medical records	GUS	122
Gargiulo et al. 2023[45]	Italy	Medical records	BRO	606
Gerdes et al. 2022[46]	Germany	Patient registry	GUS	303
Gooderham et al. 2021[47]	Canada	Medical records	SEC	310
			IXE	135
			GUS	137
Goon et al. 2020[48]	UK	Medical records	SEC	122
Graier et al. 2020[9]	Austria	Patient registry	SEC	390
			IXE	406
Gulliver et al. 2020[49]	Canada	Medical records	IXE	38
Herranz-Pinto et al. 2023[50]	Spain	Medical records	GUS	69
Hugo et al. 2023[24]	Czech Republic	Patient registry	GUS	333
Iznardo et al. 2021[51]	Spain	Medical records	SEC	78
			IXE	60
			GUS	43

Mean age (years)	Mean BMI	Mean baseline PASI	Male sex (%)	PsA (%)	Biologic naïve (%)
55.5±14.1	26.9±3.4	14.7±7.9	54.9	22.9	59.8
53.5±12.4	*26.2±4.1*	*15.3±6.6*	*53.7*	*15.4*	*50.4*
53.9±14.1	28.0±5.0	17.0±7.4	66.4	40.9	43.2
48.0 (39.5-57.0)[b]	27.0 (24.0-29.5)[b]	15.2 (10.0-20.0)[b]	63.4	25.9	42.0
48.9±15.1	NA	NA	67.6	42.6	58.8
NA	NA	NA	NA	NA	NA
55	*28*	*14.6*	*51.0*	*36.7*	*59.2*
55	*29*	*20.2*	*52.2*	*34.9*	*47.1*
52	27	12.0	68.3	36.7	51.0
49	24	11.5	73.5	23.9	45.7
47.6±12.5	NA	14.3	62.7	30.0	31.0
45.8±14.1	30.0±7.0	9.3±7.3	60.7	23.4	47.5
49.0±13.6	31.5±7.3	7.2±6.7	62.4	22.9	15.3
47.8±12.5	32.6±7.7	8.6±7.2	63.7	32.4	0.0
45.9±13.8	*33.0±7.8*	*9.7±8.0*	*58.6*	*44.8*	*0.0*
46.2±5.1	31.3±4.7	9.7±3.7	85.7	14.3	7.1
50.5±12.8	29.6±5.5	5.8±4.9	56.8	18.9	8.1
49.2 (17-87)[c]	30.3±6.2	10.9±6.9	59.0	21.7	9.6
48.4±12.8	30.8±6.6	13.0±10.5	59.4	29.6	35.6
51.5±14.6	28.6±6.1	16.2±12.9	52.6	11.5	35.2
52.6±14.9	26.7±4.7	14.4±7.3	67.8	21.5	49.0
49.7±13.8	29.7±6.3	16.4±10.8	63.7	27.7	48.8
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
48.5±16.0	NA	14.0±4.8	59.8	NA	NA
47.5±17.7	27.5	NA	58.7	42.1	37.7
45.2±13.7	28.9	NA	68.2	40.6	47.8
51.6±10.5	NA	10.8±7.9	50.0	60.5	15.8
50.7±14.6	28.3±6.0	10.0±6.0	71.0	35.0	41.0
50.3±13.3	30.3±6.6	16.0±7.7	66.7	21.0	51.4
53.0±14.7	NA	NA	67.0	31.0	47.0
56.0±14.0	NA	NA	58.0	37.0	25.0
50.0±21.5	NA	NA	56.0	30.0	9.0

Table S2 Continued

EHR/registry data				
Study	**Country**	**Data source**	**IL-17/IL-23 agent**	**Sample size**
Kishimoto et al. 2021[10]	Japan	Medical records	SEC	38
			IXE	26
			BRO	12
Kojanova et al. 2022[11]	Czech republic	Patient registry	SEC	490
			IXE	275
			BRO	298
Lee et al. 2019[52]	USA	Medical records	SEC	48
Lee et al. 2019[53]	USA	Medical records	IXE	22
Lee et al. 2020[54]	USA	Medical records	GUS	12
			IXE	19
Li et al. 2022[12]	China	Medical records	SEC	175
			IXE	70
			GUS	36
Lockshin et al. 2021[22]	USA and Canada	Patient registry	IXE	552
Lunder et al. 2019[13]	Slovenia	Patient registry	SEC	340
			IXE	98
Lytvyn et al. 2021[25]	Canada	Medical records	GUS	264
Malkönen et al. 2022[26]	Finland	Medical records	GUS	181
Mashor et al. 2022[55]	Malaysia	Medical records	SEC	11
Mastorino et al. 2023 (JEADV)[56]	Italy	Medical records	IXE	189
Mastorino et al. 2023 (DDG)[57]	Italy	Medical records	SEC	256
			IXE[a]	*189*
			BRO[a]	*203*
			GUS	74
			TIL	99
			RIS	236
Mendes-Bastos et al. 2022[14]	Portugal	Medical records	SEC	285
Nguyen et al. 2023[58]	Vietnam	Medical records	SEC	232
Ortolan et al. 2022[15]	Italy	Medical records	SEC	62
Rompoti et al. 2019[59]	Greece	Medical records	SEC	67
Rompoti et al. 2022[60]	Greece	Medical records	BRO	91
Ruiz-Villaverde et al. 2020[61]	Spain	Medical records	GUS	87
Ruiz-Villaverde et al. 2020[16]	Spain	Medical records	SEC	171
Ruiz-Villaverde et al. 2022[62]	Spain	Medical records	TIL	61

Mean age (years)	Mean BMI	Mean baseline PASI	Male sex (%)	PsA (%)	Biologic naïve (%)
52.2±15.2	25.2±2.8	NA	82.0	34.0	39.0
50.2±17.5	24.8±3.7	NA	69.0	31.0	50.0
53.8±18.1	25.0±3.2	NA	58.0	25.0	0.0
51.0±12.8	29.6±6.1	16.4±7.9	58.1	45.2	41.4
52.5±12.6	29.8±6.0	15.5±6.9	55.3	40.0	29.1
48.8±13.3	29.9±6.3	17.0±7.0	66.9	15.5	49.7
47.2±13.0	NA	NA	45.8	25	6.3
48.4±12.3	NA	NA	63.6	31.8	0.0
45.9±11.5	NA	NA	58.3	8.3	0.0
49.4±12.8	NA	NA	63.2	31.6	0.0
43.1±13.6	24.2±3.9	16.9±7.0	68.0	11.4	81.7
42.9±13.4	24.9±4.0	16.0±6.2	81.4	8.6	82.9
41.0±9.8	25.8±3.9	17.6±4.8	77.8	5.6	55.6
50.0±13.6	NA	8.9±8.2	54.2	58.9	20.7
50.7±12.6	28.8±5.6	15.8±9.5	59.4	20.0	48.5
51.0±13.4	27.8±5.0	18.0±13.5	64.0	12.0	51.0
50.3±14.3	NA	10.9±8.5	58.7	25.4	NA
52.2 (40.5-62.5)[b]	30.3 (26.0-36.4)[b]	7.0 (5.0-10.2)[b]	64.8	21.6	43.6
38.2±10.8	27.3±7.1	26.7±13.3	54.5	54.5	NA
56.1±4.1	28.1±5.6	17.8±7.0	65.1	39.7	64.0
57.5±14.5	27.5±5.4	15.8±5.6	64.0	34.0	63.0
56.1±14.09	*28.1±5.6*	*17.8±7.0*	*65.0*	*40.0*	*64.0*
53.0±16.0	*27.0±4.8*	*13.6±6.2*	*73.0*	*27.0*	*60.0*
46.6±16.7	24.2±4.8	11.0±6.4	58.0	24.0	65.0
57.5±17.3	26.5±5.4	9.8±3.4	59.0	25.0	88.0
52.0±15.2	26.8±6.2	14.8±7.2	63.0	13.0	56.0
48.4±13.4	27.7±4.5	16.6 (11.8-24.0)[b]	58.3	24.8	51.3
39.0 (30.0-52.3)[c]	23.5 (21.4-25.9)[c]	22.0 (16.2-29.4)[c]	68.1	12.9	95.3
54.7±14.6	27.4±4.7	10.8±5.6	61.0	0.0	NA
48.6±12.8	29.0 (25.5-32.7)[b]	133 (7.3-21.5)[b]	75.3	38.2	42.9
52.5 (18-77)[b]	28.9(19.5-40.5)[b]	10.3±6.2	63.7	25.3	51.6
49.9±14.6	NA	NA	60.9	13.8	NA
NA	NA	NA	45.0	37.4	32.2
49.5±13.9	29.0[c]	10.7±5.5	49.2	34.4	4.9

Table S2 Continued

EHR/registry data				
Study	**Country**	**Data source**	**IL-17/IL-23 agent**	**Sample size**
Schots et al. 2022[63]	Belgium	Medical records	SEC[d]	59
			IXE[d]	49
			BRO[d]	17
Sotiriou et al. 2019[64]	Greece	Medical records	SEC	42
Sotiriou et al. 2022[65]	Greece	Medical records	SEC	172
Tada et al. 2023[17]	Japan	Medical records	SEC	123
Thein et al. 2023[18]	Denmark	Patient registry	SEC	852
			IXE	258
			GUS	106
Torres et al. 2019[19]	Europe	Medical records	SEC	330
Torres et al. 2021[66]	Europe and USA	Medical records	SEC	911
			IXE	651
			BRO	116
			GUS	398
			RIS	118
Torres et al. 2022[67]	Europe, Canada	Medical records	SEC	1542
			IXE	1073
			BRO	549
			GUS	879
			TIL	130
			RIS	693
Van den Reek et al. 2018[2]	Netherlands	Patient registry	SEC	196
Van Muijen et al. 2022[5]	Netherlands	Patient registry	GUS	195
Wang et al. 2021[68]	China	Medical records	SEC	66
Yanase et al. 2023[20]	Japan	Patient registry	SEC	217
			IXE	137
			BRO	145
			GUS	104
			RIS	62
Yiu et al. 2022[3]	UK and Ireland	Patient registry	SEC	2677
			IXE	703
			GUS	730

Mean age (years)	Mean BMI	Mean baseline PASI	Male sex (%)	PsA (%)	Biologic naïve (%)
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
50.8	28.7	NA	NA	42.1	NA
56.2±17.9	NA	NA	62.0	31.3	34.9
54.9±13.9	24.6±4.7	9.2±7.4	67.5	25.2	47.2
46.6±14.3	NA	NA	59.4	26.5	23.0
48.9±14.0	NA	NA	58.5	25.2	31.0
47.6±13.3	NA	NA	58.5	28.3	NA
51.9±14.6	NA	NA	68.0	21.5	47.6
49.3±13.8	28.0±5.6	13.8±7.7	60.0	41.8	42.6
50.2±13.1	28.4±5.5	13.3±8.0	62.7	43.0	42.7
51.3±14.1	29.6±6.6	14.2±7.3	69.8	28.0	39.7
51.2±14.3	28.8±5.5	12.7±6.9	58.5	27.1	33.9
50.9±14.7	28.6±6.5	12.1±7.6	62.7	38.1	43.2
53.2±13.6	27.8±5.5	14.8±7.7	61.0	35.0	52.5
52.7±14.1	27.9±5.2	13.8±8.0	61.7	33.5	48.2
52.1±14.3	28.2±5.5	14.2±6.9	62.5	20.2	47.4
52.8±14.6	28.2±5.7	12.5±6.9	57.6	18.3	39.6
52.6±16.1	27.2±4.8	13.0±6.9	60.0	10.0	53.8
50.5±15.4	27.9±5.5	13.4±7.6	60.9	15.1	41.0
48.9±13.6	28.7 (17.8-48.3)[b]	10.9 (1.8-45.4)[b]	60.7	23.5	16.8
49.4±14.2	28.9 [7.2][b]	9.2 [9.3][b]	56.4	20.5	29.7
40.1±11.6	24.7±4.7	15.6±9.0	78.8	NA	NA
55.4±14.3	NA	NA	73.0	38.8	32.7
54.9±13.1	NA	NA	81.0	41.0	31.4
55.5±13.4	NA	NA	77.0	29.6	29.0
56.1±15.9	NA	NA	71.0	35.0	15.4
57.2±13.6	NA	NA	77.0	22.4	21.0
47.0 (37.0-56.0)[b]	31.0 (27.1-36.2)[b]	12.2 (8.0-17.5)[b]	57.3	34.4	35.8
46.0 (36.0-56.0)[b]	31.4 (27.3-36.7)[b]	11.4 (6.8-16.8)[b]	56.0	41.0	18.2
48.0 (36.0-56.0)[b]	31.6 (27.5-37.7)[b]	11.0 (7.0-16.0)[b]	56.4	26.0	23.6

Table S2 Continued

Pharmacy/claims data				
Study	**Country**	**Data source**	**IL-17/IL-23 agent**	**Sample size**
Study	Country	Data source	IL-17/IL-23 agent	Sample size
Fitzgerald et al. 2023[27]	USA	Claims database	SEC	6123
			IXE	3728
			GUS	3408
Gulliver et al. 2023[39]	Canada	Claims database	IXE	1891
Hendrix et al. 2020 [38]	USA	Claims database	SEC	908
			IXE	466
Huang et al. 2022[37]	Taiwan	Claims database	SEC	52
Mucherino et al. 2023[28]	Italy	Claims database	SEC	183
			IXE	141
Oh et al. 2022[29]	Korea	Claims database	SEC	738
			IXE	116
			GUS	679
Pilon et al. 2022[30]	Canada	Claims database	SEC	1807
			IXE	535
Pina Vegas et al. 2022[69]	France	Claims database	SEC	2133
			IXE	502
			BRO	76
Schmitt-Egenolf et al. 2021[31]	Sweden	Claims database	SEC	394
			IXE	50
Shalom et al. 2019[32]	Israel	Claims database	SEC	261
Sruamsiri et al. 2018[33]	Japan	Claims database	SEC	21
Sullivan et al. 2023[34]	Australia	Claims database	SEC	305
			GUS	385
Tada et al. 2023[35]	Japan	Claims database	SEC	366
			IXE	279
			BRO	159
			GUS	360
			RIS	327
Wang et al. 2023[36]	Japan	Claims database	SEC[d]	489[e]
			IXE[d]	322[e]
			BRO[d]	317[e]

SEC. secukinumab; IXE. ixekizumab; RIS. risankizumab; BRO. brodalumab; GUS. guselkumab; TIL. tildrakizumab; a Not included due to overlapping patient populations; b Median [IQR] or (range); c SD missing; d Baseline characteristics were not available per biologic type; e Numbers were obtained from Kaplan-Meier curve.

Mean age (years)	Mean BMI	Mean baseline PASI	Male sex (%)	PsA (%)	Biologic naïve (%)
Mean age (years)	Mean BMI	Mean PASI	Male sex (%)	PsA (%)	Biologic naïve (%)
49.4±11.7	NA	NA	54.2	54.2	44.5
49.1±11.6	NA	NA	50.3	38.3	41.8
47.4±12.5	NA	NA	47.1	16.7	52.2
52.3±13.3	NA	14.3±8.1	61.4	NA	63.9
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
43.5 (34.0-57.5)[b]	NA	NA	84.6	NA	NA
48.9±15.2	NA	NA	66.7	NA	NA
46.9±13.8	NA	NA	65.2	NA	NA
45.8±13.2	NA	NA	69.2	22.1	56.9
44.8±13.8	NA	NA	66.4	21.6	61.
47.7±12.5	NA	NA	70.0	26.8	57.0
49.0±14.6	NA	NA	50.7	28.7	71.4
49.0±14.6	NA	NA	50.7	28.7	71.4
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
42.6±14.0	NA	NA	60.5	2.7	45.8
39.8±14.4	NA	NA	60.8	0.0	11.8
52.2±14.2	NA	NA		58.6	3.1
45.4	NA	NA	66.7	NA	61.9
NA	NA	NA	53.2	NA	52.1
NA	NA	NA	57.9	NA	52.2
47.7±12.1	NA	NA	65.8	NA	NA
49.3±10.7	NA	NA	72.8	NA	NA
48.3±12.1	NA	NA	78.6	NA	NA
50.1±11.	NA	NA	60.8	NA	NA
47.7±11.5	NA	NA	76.1	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA

Table S3 Risk of bias assessment using the modified Quality in Prognostic Studies (QUIPS) tool

Study	Study participation	Study Attrition	Prognostic factor measurement	Outcome measurement	Statistical Analysis and reporting	Risk of bias
Caldarola – Dermatol Ther	low	low	moderate	moderate	low	moderate
Caldarola Expert Opin Biol Ther 2021	low risk	moderate	moderate	moderate	low	high
Caldarola Expert Opin Biol Ther 2023	low risk	moderate	moderate	moderate	low	high
Chatzimichail	low	low	moderate	moderate	moderate	moderate
Costa de Lima	moderate	low	moderate	moderate	moderate	high
Dapavo	low	high	moderate	low	moderate	moderate
Dauden	low	moderate	moderate	moderate	low	high
Egeberg	low	high	moderate	moderate	low	moderate
Elgaard – Drugs in R&D	low risk	low	moderate	moderate	low	moderate
Elgaard et al. – J Dermatol Treat	moderate risk	low	moderate	moderate	low	high
Fitzgerald	low	moderate	high	moderate	low	high
Foley	low	moderate	moderate	high	low	moderate
Gerdes	low	moderate	moderate	moderate	low	high
Galluzzo	low risk	moderate	moderate	moderate	low	high
Gargiulo	low risk	low	moderate	moderate	low	moderate
Gooderham	moderate	low	moderate	moderate	low	high
Goon	moderate	moderate	moderate	moderate	moderate	high
Graier	low	low	moderate	moderate	low	moderate
Gulliver - Journal Dermatol Treat	moderate	high	moderate	moderate	high	high
Gulliver – Dermatol Ther	low	high	high	high	low	high

Table S3 Continued

Study	Study participation	Study Attrition	Prognostic factor measurement	Outcome measurement	Statistical Analysis and reporting	Risk of bias
Hendrix	moderate	low	high	moderate	low	moderate
Herranz-Pinto	low risk	moderate	moderate	moderate	low	high
Huang	low	high	high	moderate	moderate	high
Hugo	low risk	moderate	moderate	moderate	low	high
Iznardo	moderate	high	high	moderate	moderate	high
Kishimoto	low	moderate	moderate	moderate	moderate	high
Kojanova	moderate	low	moderate	moderate	low	high
Lee – J Am Acad Dermatol	high	moderate	high	moderate	moderate	high
Lee – J Dermatol Treat 2019	high	moderate	moderate	moderate	high	high
Lee – J Dermatol Treat 2020	high	moderate	moderate	moderate	high	high
Li	low risk	moderate	moderate	moderate	low	high
Lockshin	low	moderate	moderate	moderate	low	high
Lunder	low	high	moderate	moderate	moderate	high
Lytvyn	moderate	moderate	moderate	moderate	moderate	high
Malkonen	low	low	moderate	high	low	moderate
Mashor	moderate	moderate	moderate	moderate	moderate	high
Mastorino - DDG	low	high	moderate	moderate	low	high
Mastorino - JEADV	low	high	moderate	moderate	moderate	high
Mendes-Bastos	moderate	moderate	high	high	low	high
Mucherino	low	moderate	high	high	low	high
Nguyen	low	moderate	moderate	moderate	low	high

Table S3 Continued

Study	Study participation	Study Attrition	Prognostic factor measurement	Outcome measurement	Statistical Analysis and reporting	Risk of bias
Ortolan	moderate	moderate	moderate	moderate	moderate	high
Oh	low	high	high	moderate	low	high
Pilon	low	high	high	high	low	high
Pina Vegas	moderate	moderate	high	high	low	high
Rompoti - JEADV 2019	low	high	moderate	moderate	low	moderate
Rompoti – JEADV 2022	low	high	moderate	moderate	moderate	high
Ruiz Villaverde -Dermatol Ther	moderate	moderate	moderate	moderate	low	high
Ruiz Villaverde – Int J Dermatol	moderate	low	moderate	moderate	low	high
Ruiz Villaverde – J Clin Med	low risk	high	moderate	moderate	low	moderate
Schmitt Egenolf	low	moderate	moderate	moderate	low	high
Schots	moderate	Low	moderate	moderate	low	high
Shalom	moderate	low	moderate	moderate	low	high
Sotiriou - JEADV 2019	moderate	moderate	moderate	moderate	low	high
Sotiriou – JEADV 2022	moderate	high	moderate	moderate	low	high
Sruamsiri	low	moderate	high	high	low	high
Sullivan	low	moderate	high	moderate	low	high
Tada – Dermatol Ther	low risk	moderate	moderate	moderate	low	high
Tada – J Dermatol	low	moderate	high	high	low	high
Thein	low risk	high	moderate	moderate	low	high
Torres 2019	low	high	moderate	moderate	low	high
Torres – Am J Clin Derm 2021	low	moderate	moderate	moderate	moderate	high

Table S3 Continued

Study	Study participation	Study Attrition	Prognostic factor measurement	Outcome measurement	Statistical Analysis and reporting	Risk of bias
Torres – J Am Clin Derm 2022	low risk	low	moderate	moderate	low	moderate
van Muijen	low	low	moderate	moderate	low	moderate
van den Reek	low	low	moderate	low	low	low
Wang – Dermatol Ther	moderate	high	moderate	moderate	low	high
Wang – J Dermatol Treat	low	high	high	moderate	low	high
Yanase	low risk	low	moderate	moderate	low	moderate
Yiu	low	low	moderate	low	low	low

Table S4 Risk of bias assessment using the ROBINS-I tool

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of Bias
Caldarola - Expert Opin Biol Ther - 2021	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Caldarola - Expert Opin Biol Ther - 2023	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Caldarola - Dermatol Ther	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Chatzimichail	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Costa de Lima	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Dapavo	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Dauden	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Egeberg	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Elgaard - Drugs in R&D	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Elgaard - J Dermatol Treat	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Fitzgerald	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Foley	Moderate	Low	Low	Low	Moderate	Low	Serious	Serious
Galluzzo	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Gargiulo	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Gerdes	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Gooderham	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Goon	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Graier	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Gulliver – J Dermatol Treat	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Table S4 Continued

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of Bias
Gulliver – Dermatol Ther	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Hendrix	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Herranz-Pinto	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Huang	Moderate	Low	Low	Serious	Moderate	Moderate	Low	Serious
Hugo	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Iznardo	Moderate	Low	Moderate	Low	Low	Low	Moderate	Moderate
Kishimoto	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Kojanova	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Lee - J Dermatol Treat - 2019	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Lee - J Am Acad Dermatol	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Lee - J Dermatol Treat - 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Li	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Lockshin	Moderate	Low	Moderate	Low	Low	Low	Serious	Serious
Lunder	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Lytvyn	Moderate	Low	Low	Low	Low	Low	Serious	Serious
Malkonen	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Mashor	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Mastorino - DDG	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Mastorino - JEADV	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate

Table S4 Continued

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of Bias
Mendes-Bastos	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Mucherino	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Nguyen	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Oh	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Ortolan	Moderate	Low	Moderate	Low	Low	Low	Serious	Serious
Pilon	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Pina Vegas	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Rompoti - JEADV - 2019	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Rompoti - JEADV - 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Ruiz-Villaverde - Dermatol Ther	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Ruiz-Villaverde - Int J Dermatol	Moderate	Low	Low	Low	Low	Low	Serious	Serious
Ruiz-Villaverde - J Clin Med	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Schmitt-Egenolf	Moderate	Low	Low	Serious	Moderate	Moderate	Low	Moderate
Schots	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Shalom	Moderate	Low	Low	Serious	Moderate	Moderate	Low	Serious
Sotiriou - JEADV - 2019	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Sotiriou - JEADV - 2022	Moderate	Low	Moderate	Moderate	Moderate	Low	Low	Moderate
Sruamsiri	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Sullivan	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Tada - Dermatol Ther	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious

Table S4 Continued

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of Bias
Tada - J Dermatol	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Thein	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Torres - J Am Acad Dermatol	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
Torres - Am J Clin Derm - 2021	Moderate	Low	Moderate	Moderate	Moderate	Low	Low	Moderate
Torres - Am J Clin Derm - 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
van Muijen	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
van den Reek	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
Wang - Dermatol Ther	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
Wang – J Dermatol Treat	Moderate	Low	Moderate	Serious	Moderate	Moderate	Low	Serious
Yanase	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Yiu	Moderate	Low	Moderate	Moderate	Moderate	Low	Low	Moderate

Table S5 Risk of bias assessment using the Oxford Rating Scheme for Studies and Other Evidence

Author	Quality Rating Scheme for Studies and Other Evidence	
Caldarola – Dermatol Ther	3	Case-control studies; retrospective cohort study
Caldarola - Expert Opin Biol Ther 2023	3	Case-control studies; retrospective cohort study
Chatzimichail	3	Case-control studies; retrospective cohort study
Costa de Lima	3	Case-control studies; retrospective cohort study
Dapavo	3	Case-control studies; retrospective cohort study
Dauden	3	Case-control studies; retrospective cohort study
Egeberg	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Elgaard - Drugs in R&D	3	Case-control studies; retrospective cohort study
Elgaard - J Dermatol Treat	3	Case-control studies; retrospective cohort study
Fitzgerald	3	Case-control studies; retrospective cohort study
Foley	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Galluzzo	3	Case-control studies; retrospective cohort study
Gargiulo	3	Case-control studies; retrospective cohort study
Gerdes	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Gooderham	3	Case-control studies; retrospective cohort study
Goon	3	Case-control studies; retrospective cohort study
Graier	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Gulliver - Dermatol Ther	3	Case-control studies; retrospective cohort study
Gulliver - J Derm Treat	3	Case-control studies; retrospective cohort study
Hendrix	3	Case-control studies; retrospective cohort study
Herranz-Pinto	3	Case-control studies; retrospective cohort study
Huang	3	Case-control studies; retrospective cohort study
Hugo	3	Case-control studies; retrospective cohort study
Iznardo	3	Case-control studies; retrospective cohort study
Kishimoto	3	Case-control studies; retrospective cohort study
Kojanova	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Lee - J Am Acad Dermatol	3	Case-control studies; retrospective cohort study
Lee - J Dermatol Treat - 2019	3	Case-control studies; retrospective cohort study
Lee - J Dermatol Treat - 2020	3	Case-control studies; retrospective cohort study
Li	3	Case-control studies; retrospective cohort study
Lockshin	2	Well-designed controlled trial without randomization; prospective comparative cohort trial

Table S5 Continued

Author	Quality Rating Scheme for Studies and Other Evidence	
Lunder	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Lytvyn	3	Case-control studies; retrospective cohort study
Malkonen	3	Case-control studies; retrospective cohort study
Mashor	3	Case-control studies; retrospective cohort study
Mastorino - DDG	3	Case-control studies; retrospective cohort study
Mastorino - JEADV	3	Case-control studies; retrospective cohort study
Mendes-Bastos	3	Case-control studies; retrospective cohort study
Mucherino	3	Case-control studies; retrospective cohort study
Nguyen	3	Case-control studies; retrospective cohort study
Oh	3	Case-control studies; retrospective cohort study
Ortolan	3	Case-control studies; retrospective cohort study
Pilon	3	Case-control studies; retrospective cohort study
Pina Vegas	3	Case-control studies; retrospective cohort study
Rompoti - JEADV - 2019	3	Case-control studies; retrospective cohort study
Rompoti - JEADV - 2022	3	Case-control studies; retrospective cohort study
Ruiz-Villaverde - Dermatol Ther	3	Case-control studies; retrospective cohort study
Ruiz-Villaverde - Int J Dermatol	3	Case-control studies; retrospective cohort study
Ruiz-Villaverde - J Clin Med	3	Case-control studies; retrospective cohort study
Schmitt Egenolf	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Schots	3	Case-control studies; retrospective cohort study
Shalom	3	Case-control studies; retrospective cohort study
Sotiriou - JEADV - 2019	3	Case-control studies; retrospective cohort study
Sotiriou - JEADV - 2022	3	Case-control studies; retrospective cohort study
Sruamsiri	3	Case-control studies; retrospective cohort study
Sullivan	3	Case-control studies; retrospective cohort study
Tada - Dermatol Ther	3	Case-control studies; retrospective cohort study
Tada - J Dermatol	3	Case-control studies; retrospective cohort study
Thein	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Torres - Am J Clin Derm - 2021	3	Case-control studies; retrospective cohort study
Torres - Am J Clin Derm - 2022	3	Case-control studies; retrospective cohort study
Torres - J Am Acad Dermatol	3	Case-control studies; retrospective cohort study
van den Reek	2	Well-designed controlled trial without randomization; prospective comparative cohort trial

Table S5 Continued

Author	Quality Rating Scheme for Studies and Other Evidence	
van Muijen	2	Well-designed controlled trial without randomization; prospective comparative cohort trial
Wang - Dermatol Ther	3	Case-control studies; retrospective cohort study
Wang - J Dermatol Treat	3	Case-control studies; retrospective cohort study
Yanase	3	Case-control studies; retrospective cohort study
Yiu	2	Well-designed controlled trial without randomization; prospective comparative cohort trial

Table S6 Summary drug survival estimates with 95% confidence intervals and drug survival estimates of sensitivity analysis using extrapolation

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
EHR/registry patient data						
Overall drug survival						
Studies included	29	17	NA	17	NA	NA
Patients included	9720	3864	NA	3678	NA	NA
Heterogeneity, I^2 (%)	71.5	56.9	NA	44.9	NA	NA
Year 1	0.82 [0.78-0.87]	0.81 [0.76-0.87]	NA	0.88 [0.85-0.92]	NA	NA
Year 2	0.67 [0.61-0.75]	0.69 [0.63-0.77]	NA	0.82 [0.77-0.86]	NA	NA
Year 3	0.54 [0.46-0.62]	0.63 [0.56-0.71]	NA	0.79 [0.74-0.83]	NA	NA
Year 5	0.37 [0.28-0.49]	0.56 [0.48-0.66]	NA	0.76 [0.72-0.81]	NA	NA
Pharmacy/claims data						
Studies included	11	9	3	NA	NA	NA
Patients included	12820	7564	552	NA	NA	NA
Heterogeneity, I^2 (%)	92.6	92.7	0.0	NA	NA	NA
Year 1	0.70 [0.59-0.84]	0.77 [0.61-0.96]	0.72 [0.61-0.83]	NA	NA	NA
Year 2	0.53 [0.40-0.70]	0.65 [0.46-0.92]	0.61 [0.49-0.76]	NA	NA	NA
Year 3	0.45 [0.32-0.63]	0.52 [0.34-0.80]	0.56 [0.43-0.73]	NA	NA	NA

EHR; electronic health records

Table S7 Summary drug survival estimates (95% confidence intervals) for overall drug survival, sensitivity analysis excluding high risk of bias studies according to QUIPS

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Registry/EHR data						
Overall drug survival						
Studies included	6[2, 9, 20, 41, 59, 67]	3[9, 20, 67]	4[20, 44, 45, 67]	4[5, 20, 26, 67]	3[20, 40, 67]	2[62, 67]
Patients included	2480	1616	1383	1359	867	191
Heterogeneity, I^2 (%)	3.0	0.0	35.6	0.0	0.0	0.0
Year 1	0.78 (0.72-0.84)	0.84 (0.79-0.90)	0.83 (0.71-0.97)	0.86 (0.79-0.94)	0.94 (0.90-0.97)	0.83 (0.73-0.94)
Year 2	0.62 (0.52-0.74)	0.72 (0.64-0.81)	0.74 (0.60-0.92)	0.79 (0.67-0.92)	0.90 (0.84-0.96)	NA
Year 3	0.51 (0.39-0.67)	0.67 (0.57-0.79)	0.67 (0.53-0.87)	0.77 (0.66-0.90)	0.88 (0.80-0.97)	NA
Year 5	0.39 (0.25-0.63)	0.65 (0.55-0.76)	NA	0.75 (0.65-0.88)	NA	NA
Ineffectiveness related drug survival						
Studies included	2[2, 3]	1[3]	0	2[3, 5]	0	0
Patients included	2873	703	0	925	0	0
Heterogeneity, I^2 (%)	0.0	NA	NA	0.0	NA	NA
Year 1	0.83 (0.75-0.91)	0.86[a]	NA	0.93 (0.91-0.96)	NA	NA
Year 2	0.70 (0.59-0.83)	0.75[a]	NA	0.89 (0.84-0.95)	NA	NA
Year 3	NA	NA	NA	NA	NA	NA
Year 5	NA	NA	NA	NA	NA	NA
Adverse event related drug survival						
Studies included	2[2, 3]	1[3]	0	2[3, 5]	0	0
Patients included	2873	703	0	925	0	0
Heterogeneity, I^2 (%)	0.0	NA	NA	0.0	NA	NA
Year 1	0.92 (0.88-0.97)	0.92[a]	NA	0.95 (0.91-0.98)	NA	NA
Year 2	0.89 (0.83-0.94)	0.88[a]	NA	0.90 (0.84-0.96)	NA	NA

Table S7 Continued

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Drug survival split for biological naivety						
Studies included Biologic naïve patients	5[2, 7-9, 20]	4[7, 9, 20, 21]	2[7, 20]	3[7, 20, 26]	1[20]	0
Patients included	390	299	67	116	13	0
Heterogeneity, I^2 (%)	0.0	0.0	0.0	0.0	NA	NA
Year 1	0.85 (0.80-0.91)	0.82 (0.75-0.90)	0.77 (0.64-0.92)	0.82 (0.70-0.96)	1.00[a]	NA
Year 2	0.70 (0.64-0.77)	0.66 (0.55-0.79)	0.52 (0.37-0.73)	NA	NA	NA
Year 3	0.55 (0.47-0.64)	0.56 (0.44-0.72)	NA	NA	NA	NA
Studies included Biologic experienced patients	5[2, 7-9, 20]	4[7, 9, 20, 21]	2[7, 20]	4[7, 20, 21, 26]	1[20]	0
Patients included	756	477	127	280	48	0
Heterogeneity, I^2 (%)	0.0	0.0	0.0	0.0	NA	NA
Year 1	0.75 (0.69-0.81)	0.76 (0.68-0.84)	0.73 (0.64-0.85)	0.77 (0.72-0.84)	0.95[a]	NA
Year 2	0.54 (0.48-0.61)	0.57 (0.48-0.67)	0.61 (0.50-0.74)	0.63 (0.53-0.76)	NA	NA
Year 3	0.43 (0.37-0.50)	0.48 (0.36-0.63)	0.50 (0.39-0.64)	NA	NA	NA
	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab

Table S7 Continued

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Pharmacy/claims databases						
Overall drug survival						
Studies included	0	0	0	0	0	0
Patients included	0	0	0	0	0	0
Heterogeneity, I^2 (%)	NA	NA	NA	NA	NA	NA
Year 1	NA	NA	NA	NA	NA	NA
Year 2	NA	NA	NA	NA	NA	NA
Year 3	NA	NA	NA	NA	NA	NA
Drug survival split for biological naivety						
Studies included Biologic naïve patients	1[38]	1[38]	0	0	0	0
Patients included	353	149	0	0	0	0
Heterogeneity, I^2 (%)	NA	NA	NA	NA	NA	NA
Year 1	0.47[a]	0.47[a]	NA	NA	NA	NA
Year 2	NA	NA	NA	NA	NA	NA
Year 3	NA	NA	NA	NA	NA	NA
Studies included Biologic experienced patients	1[38]	1[38]	0	0	0	0
Patients included	317	555	0	0	0	0
Heterogeneity, I^2 (%)	4.6	79.8	NA	NA	NA	NA
Year 1	0.33[a]	0.38[a]	NA	NA	NA	NA
Year 2	NA	NA	NA	NA	NA	NA
Year 3	NA	NA	NA	NA	NA	NA

[a] Drug survival estimate instead of summary drug survival estimate

Table S8 Summary drug survival estimates (95% confidence intervals) for overall drug survival, sensitivity analysis excluding serious risk of bias studies according to ROBINS-I

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Registry/EHR data						
Overall drug survival						
Studies included	26[1, 2, 6, 9-14, 17-20, 41, 42, 47, 48, 52, 55, 57-59, 63, 65, 67, 68]	15[4, 9-13, 18, 20, 47, 49, 53, 54, 56, 63, 67]	8[10, 11, 20, 44, 45, 60, 63, 67]	14[5, 12, 18, 20, 23, 24, 26, 46, 47, 50, 54, 57, 61, 67]	5[20, 40, 43, 57, 67]	4[43, 57, 62, 67]
Patients included	6903	3101	1801	2641	1140	304
Heterogeneity, I^2 (%)	28.5	15.1	16.8	0.0	0.0	0.0
Year 1	0.81 (0.77-0.85)	0.79 (0.73-0.86)	0.81 (0.72-0.90)	0.87 (0.83-0.92)	0.91 (0.88-0.95)	0.80 (0.71-0.91)
Year 2	0.66 (0.61-0.72)	0.67 (0.60-0.75)	0.71 (0.60-0.83)	0.81 (0.75-0.86)	0.88 (0.83-0.93)	0.47 (0.24-0.94)
Year 3	0.53 (0.46-0.62)	0.61 (0.54-0.70)	0.62 (0.51-0.77)	0.77 (0.72-0.83)	0.86 (0.80-0.92)	NA
Year 5	0.38 (0.28-0.50)	0.55 (0.47-0.65)	NA	0.75 (0.69-0.81)	NA	NA
Ineffectiveness related drug survival						
Studies included	6[1-3, 48, 64, 66]	3[3, 4, 66]	1[66]	3[3, 5, 66]	1[66]	0
Patients included	4070	1660	116	1323	118	0
Heterogeneity, I^2 (%)	0.0	0.0	NA	0.0	NA	NA
Year 1	0.87 (0.83-0.92)	0.91 (0.86-0.96)	0.93[a]	0.93 (0.92-0.95)	0.96[a]	NA
Year 2	0.74 (0.70-0.79)	0.83 (0.75-0.93)	0.88[a]	0.90 (0.87-0.93)	NA	NA
Year 3	0.64 (0.58-0.70)	0.82 (0.73-0.90)	NA	0.89 (0.86-0.92)	NA	NA
Year 5	0.60 (0.53-0.69)	0.72 (0.64-0.81)	NA	0.87 (0.84-0.91)	NA	NA
Adverse event related drug survival						
Studies included	3[1-3]	2[3, 4]	0	2[3, 5]	0	0
Patients included	2995	1009	0	925	0	0

Table S8 Continued

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Heterogeneity, I^2 (%)	0.0	0.0	NA	0.0	NA	NA
Year 1	0.93 (0.90-0.96)	0.94 (0.90-0.98)	NA	0.95 (0.91-0.98)	NA	NA
Year 2	0.89 (0.85-0.93)	0.88 (0.85-0.91)	NA	0.90 (0.84-0.96)	NA	NA
Drug survival split for biological naivety						
Studies included Biologic naïve patients	13[2, 6, 7, 9-14, 17-20]	8[7, 9-13, 20, 21]	3[4, 11, 20]	6[7, 12, 20, 23, 24, 26]	1[20]	0
Patients included	1481	500	215	343	13	0
Heterogeneity, I^2 (%)	0.0	0.0	0.0	0.0	NA	NA
Year 1	0.85 (0.81-0.90)	0.83 (0.76-0.90)	0.84 (0.73-0.97)	0.84 (0.76-0.93)	1.00[a]	NA
Year 2	0.71 (0.66-0.77)	0.68 (0.60-0.77)	0.68 (0.50-0.92)	0.73 (0.63-0.84)	NA	NA
Year 3	0.56 (0.49-0.64)	0.57 (0.48-0.69)	NA	0.68 (0.57-0.81)	NA	NA
Studies included Biologic experienced patients	13[2, 6, 7, 9-14, 17-20]	8[7, 9-13, 20, 21]	4[4, 10, 11, 20]	7[7, 12, 20, 21, 23, 24, 26]	1[20]	0
Patients included	2388	745	289	547	48	0
Heterogeneity, I^2 (%)	0.0	0.0	0.0	0.0	NA	NA
Year 1	0.75 (0.69-0.81)	0.74 (0.67-0.82)	0.72 (0.66-0.80)	0.81 (0.74-0.89)	0.95[a]	NA
Year 2	0.57 (0.51-0.64)	0.58 (0.50-0.67)	0.62 (0.52-0.73)	0.72 (0.62-0.83)	NA	NA
Year 3	0.44 (0.37-0.52)	0.50 (0.40-0.63)	0.51 (0.41-0.63)	0.62 (0.52-0.74)	NA	NA
	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Pharmacy/claims databases						
Overall drug survival						
Studies included	0	0	0	0	0	0

Table S8 Continued

	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
Patients included	0	0	0	0	0	0
Heterogeneity, I^2 (%)	NA	NA	NA	NA	NA	NA
Year 1	NA	NA	NA	NA	NA	NA
Year 2	NA	NA	NA	NA	NA	NA
Year 3	NA	NA	NA	NA	NA	NA
Drug survival split for biological naivety						
Studies included Biologic naïve patients	0	0	0	0	0	0
Patients included	0	0	0	0	0	0
Heterogeneity, I^2 (%)	NA	NA	NA	NA	NA	NA
Year 1	NA	NA	NA	NA	NA	NA
Year 2	NA	NA	NA	NA	NA	NA
Year 3	NA	NA	NA	NA	NA	NA
Studies included Biologic experienced patients	0	0	0	0	0	0
Patients included	0	0	0	0	0	0
Heterogeneity, I^2 (%)	NA	NA	NA	NA	NA	NA
Year 1	NA	NA	NA	NA	NA	NA
Year 2	NA	NA	NA	NA	NA	NA
Year 3	NA	NA	NA	NA	NA	NA

[a] Drug survival estimate instead of summary drug survival estimate

Table S9 Comparison of summary drug survival estimates

Overall drug survival registry/EHR databases						
	Estimated difference	**Lower limit**	**Upper limit**	**Estimated difference**	**Lower limit**	**Upper limit**
		SEC - IXE			**SEC - BRO**	
Year 1	0.0187	-0.0746	0.1119	0.0046	-0.1139	0.1232
Year 2	-0.0118	-0.1517	0.1281	-0.0477	-0.2271	0.1318
Year 3	-0.0834	-0.2752	0.1085	-0.0979	-0.3436	0.1478
		SEC - TIL			**IXE - BRO**	
Year 1	0.0068	-0.1309	0.1445	-0.0140	-0.1486	0.1205
Year 2	0.1872	-0.5102	0.8846	-0.0358	-0.2307	0.1591
Year 3	NA	NA	NA	-0.0145	-0.2527	0.2237
		IXE - TIL			**BRO - GUS**	
Year 1	-0.0119	-0.1636	0.1398	-0.0682	-0.1863	0.0500
Year 2	0.1990	-0.5025	0.9006	-0.0984	-0.2724	0.0756
Year 3	NA	NA	NA	-0.1438	-0.3581	0.0704
		GUS - RIS			**GUS – TIL**	
Year 1	-0.0416	-0.1046	0.0214	0.0703	-0.0670	0.2077
Year 2	-0.0710	-0.1611	0.0192	0.3333	-0.3628	1.0000
Year 3	-0.0862	-0.1906	0.0181	NA	NA	NA
Ineffectiveness related drug survival						
	Estimated difference	**Lower limit**	**Upper limit**	**Estimated difference**	**Lower limit**	**Upper limit**
		SEC - IXE			**SEC - GUS**	
Year 1	-0.0355	-0.1120	0.0410	**-0.0618**	**-0.1154**	**-0.0082**
Year 2	-0.0950	-0.2191	0.0292	**-0.1569**	**-0.2280**	**-0.0857**
Year 3	**-0.1784**	**-0.3246**	**-0.0322**	**-0.2538**	**-0.3576**	**-0.1500**
Overall drug survival using extrapolation						
		SEC - IXE			**SEC - GUS**	
Year 1	0.0102	-0.0811	0.1016	-0.0611	-0.1299	0.0077
Year 2	-0.0204	-0.1634	0.1227	**-0.1444**	**-0.2606**	**-0.0282**
Year 3	-0.0914	-0.2804	0.0977	**-0.2467**	**-0.4077**	**-0.0857**

In bold print statistically significant differences. EHR; electronic health records, SEC; secukinumab, IXE; ixekizumab, BRO; brodalumab, GUS; guselkumab, RIS; risankizumab, TIL; tildrakizumab, NA; not available

	Estimated difference	Lower limit	Upper limit	Estimated difference	Lower limit	Upper limit
		SEC - GUS			**SEC - RIS**	
	-0.0635	-0.1310	0.0040	**-0.1051**	**-0.1689**	**-0.0414**
	-0.1461	**-0.2549**	**-0.0372**	**-0.2171**	**-0.3173**	**-0.1168**
	-0.2417	**-0.4029**	**-0.0805**	**-0.3279**	**-0.4872**	**-0.1687**
		IXE - GUS			**IXE - RIS**	
	-0.0822	-0.1750	0.0106	**-0.1238**	**-0.2139**	**-0.0337**
	-0.1342	**-0.2671**	**-0.0014**	**-0.2052**	**-0.3311**	**-0.0793**
	-0.1583	**-0.3078**	**-0.0088**	**-0.2446**	**-0.3920**	**-0.0971**
		BRO - RIS			**BRO - TIL**	
	-0.1098	-0.2258	0.0063	0.0022	-0.1663	0.1706
	-0.1694	**-0.3381**	**-0.0007**	0.2349	-0.4756	0.9453
	-0.2301	**-0.4429**	**-0.0173**	NA	NA	NA
		RIS – TIL				
	0.1119	-0.0236	0.2475			
	0.4043	-0.2905	1.0000			

	Estimated difference	Lower limit	Upper limit
		IXE - GUS	
	-0.0263	-0.0866	0.0341
	-0.0619	-0.1726	0.0488
	-0.0754	-0.1885	0.0377

		IXE - GUS	
	-0.0713	-0.1523	0.0097
	-0.1240	**-0.2380**	**-0.0100**
	-0.1553	**-0.2864**	**-0.0243**

For Supplementary Table 10, see online supplementary files

Appendix S1 Modified QUIPS tool

1. Study participation

a. Source of target population: the population of interest is adequately described for key characteristics (age, sex, biologic naivety, BMI/weight, PsA)
   i. Yes: description of all key characteristics for specific biologic. Partial: description of all key characteristics for the whole cohort. no: no description.

b. Method used to identify problem: the sampling frame and recruitment are adequately described, possibly including methods to identify the sample (retrospective/prospective, place of recruitment, period of recruitment).
   i. Yes: description of all of the above. Partial: description of one or two of the above. No: no description.

c. Inclusion and exclusion criteria: inclusion and exclusion criteria are adequately described
   i. Yes: general impression of clear inclusion and exclusion criteria / partial: not adequately described, but clear who is included/excluded / no: not clear who is in/excluded.

d. Adequate study participation: there is adequate participation in the study by eligible individuals
   i. small <50, moderate 50-200, large >200

2. Study attrition

a. Reasons and potential impact of subjects lost to follow up: reasons for censoring are described
   i. Low risk of bias: description in text and display in figure / moderate risk: display in figure / high risk: no description or clear display)

3. Prognostic factor measurement

   a. Definition of the PF: a clear definition or description of the prognostic factors is provided (the influence of the biological on the outcome, what is needed to reach the outcome)
   i. Yes: clear description of dosing regimen (existing guidelines) and concomitant therapies / partial: description of dosing or concomitant therapy / no: no description

b. Valid and reliable measurement of Outcome: the method of outcome measurement used is valid and reliable to limit misclassification bias (for example how do we know if a patient really discontinued treatment? In claims data this is more complex)

i. Low risk: administered in hospital or prospective registry / moderate risk: medical records or retrospective registry / high risk: claims database

c. Method and setting of Outcome Measurement: the method and setting of outcome measurement is the same for all study participants
   i. Yes: all data obtained in same manner / no: several ways of collecting data

4. Outcome measurement

a. Definition of the Outcome: a clear definition of the Outcome is provided (definition of an event)
   i. Yes: clear definition of event / no: no definition
b. Valid and reliable measurement of Outcome: the method of outcome measurement used is valid and reliable to limit misclassification bias (for example how do we know if a patient really discontinued treatment? In claims data this is more complex): low risk: administered in hospital or prospective registry / moderate risk: medical records or retrospective registry / high risk: claims database
c. Method and setting of Outcome Measurement: the method and setting of outcome measurement is the same for all study participants
   i. Yes: all data obtained in same manner / no: several ways of collecting data

5. Study confounding: not applicable

6. Statistical Analysis and Reporting

a. Presentation of analytical strategy: there is sufficient presentation of data to assess the adequacy of the analysis
   i. Yes: description of Kaplan Meier analysis somewhere / partial: description of survival functions in text/table/figure / no: no clear description
b. Reporting of results: there is a description of the association of the prognostic factor and the outcome, including information about the statistical significance (focus on right way of drug survival, enough patients at risk)
   i. Yes: display of number of patients below graph and adequate data cut-off / partial: adequate data cut-off in graph / no: clearly <10 patients in graph

Appendix S2 – List of full citations included articles

1. Caldarola G, Mariani M, Pirro F, et al. Comparison of short- and long-term effectiveness of ixekizumab and secukinumab in real-world practice. Expert Opin Biol Ther. 2021 Feb;21(2):279-86 https://doi.org/10.1080/14712598.2021.1849133
2. van den Reek J, van Vugt LJ, van Doorn MBA, et al. Initial Results of Secukinumab Drug Survival in Patients with Psoriasis: A Multicentre Daily Practice Cohort Study. Acta Derm Venereol. 2018 Jul 11;98(7):648-54 https://doi.org/10.2340/00015555-2900
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69. Pina Vegas L, Penso L, Claudepierre P, Sbidian E. Long-term Persistence of First-line Biologics for Patients with Psoriasis and Psoriatic Arthritis in the French Health Insurance Database. JAMA Dermatology. 2022 https://doi.org/https://dx.doi.org/10.1001/jamadermatol.2022.0364

Appendix S3 List of excluded articles based on full-text screening for eligibilty

1. Alabas OA, Mason KJ, Yiu ZZN, et al. The association of age at psoriasis onset and HLA-C*06:02 with biologic survival in patients with moderate-to-severe psoriasis: a cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). Br J Dermatol. 2023 Dec 5.
   Exclusion reason: specific subpopulation

2. Akdogan N, Dogan S, Bostan E, et al. Age and psoriatic arthritis are important predictors of biologic agent switch in psoriasis. Expert Rev Clin Pharmacol. 2021 Sep 23:1-7.
   Exclusion reason: only patients who switched to another biologic were included for analysis

3. Armstrong A, Xia Q, John AR, et al. Treatment Patterns for Targeted Therapies, Non-Targeted Therapies, and Drug Holidays in Patients with Psoriasis. Dermatol Ther (Heidelb). 2022 Sep;12(9):2087-103.
   Exclusion reason: biologics of interest were not separately analyzed.

4. Armstrong AW, Patel M, Li C, et al. Real-world switching patterns and associated characteristics in patients with psoriasis treated with biologics in the United States. J Dermatolog Treat. 2023 Dec;34(1):2200870.
   Exclusion reason: Kaplan-Meier survival analysis was used to estimate the proportion of patients remaining on index biologic to assess switching patterns and not to analyze drug survival.

5. Assan F, Tubach F, Arlegui H, et al. First-Line Biologic Therapy and Obesity in Moderate-to-Severe Psoriasis: Results from the Prospective Multicenter Cohort Psobioteq. Dermatology. 2021;237(3):338-46.
   Exclusion reason: only Kaplan-Meier curves split for obese versus non-obese patients available

6. Bayaraa B, Imafuku S. Sustainability and switching of biologics for psoriasis and psoriatic arthritis at Fukuoka University Psoriasis Registry. J Dermatol. 2019 May;46(5):389-98.
   Exclusion reason: number of patients per biologic unclear

7. Banerjee P, Preissner S, Preissner R. Using real-world evidence data and digital monitoring to analyze the hepatotoxic profiles of biologics across more than two million patients. Sci Rep. 2023 Jul 5;13(1):10878.
   Exclusion reason: no drug survival analysis

8. Bissonnette R, Luger T, Thaçi D, et al. Secukinumab demonstrates high sustained efficacy and a favourable safety profile in patients with moderate-to-severe psoriasis through 5 years of treatment (SCULPTURE Extension Study). J Eur Acad Dermatol Venereol. 2018 Sep;32(9):1507-14.
   Exclusion reason: no drug survival (Kaplan-Meier) analysis

9. Blauvelt A, Shi N, Burge R, et al. Comparison of real-world treatment patterns among patients with psoriasis prescribed ixekizumab or secukinumab. J Am Acad Dermatol. 2020 Apr;82(4):927-35.
   Exclusion reason: overlapping patient population

10. Blauvelt A, Shi N, Murage M, et al. Long-Term Treatment Patterns Among Patients With Psoriasis Treated With Ixekizumab or Adalimumab: A Real-World Study. J Drugs Dermatol. 2022 Apr 1;21(4):399-407.
    Exclusion reason: overlapping patient population

11. Blauvelt A, Shi N, Somani N, et al. Comparison of two-year treatment adherence, persistence, discontinuation, reinitiation, and switching between psoriasis patients treated with ixekizumab or secukinumab in real-world settings. Journal of the American Academy of Dermatology. 2022;86(3):581-9.

Exclusion reason: overlapping patient population

12. Blauvelt A, Burge R, Gallo G, et al. A Retrospective Cohort Analysis of Treatment Patterns Over 1 Year in Patients with Psoriasis Treated with Ixekizumab or Guselkumab. Dermatol Ther (Heidelb). 2022 Mar;12(3):701-14.

Exclusion reason: overlapping patient population

13. Cariti C, Dapavo P, Mastorino L, et al. Comparison of Secukinumab and Ixekizumab in psoriasis: a real-life cohort study on the efficacy and drug survival of 445 patients. J Eur Acad Dermatol Venereol. 2022 Mar;36(3):e233-e5.

Exclusion reason: overlapping patient population

14. Castro-Ayarza JR, Barbosa-Rengifo M, Franco-Franco M, et al. Biological therapy optimization in patients with psoriasis by reducing the dose or increasing the time interval, in a specialized centre in Colombia. Revista Colombiana de Reumatología. 2023 2023/07/01/;30:S65-S9.

Exclusion reason: No drug survival analysis

15. Choi S, Oh S, Yoon HS. Association Between Short-Term PASI90 Achievement and Drug Survival of Biologics in Patients with Psoriasis. Ann Dermatol. 2022 Jun;34(3):173-81.

Exclusion reason: only Kaplan-Meier curves split for responders versus non-responders available

16. Cozzani E, Wei Y, Burlando M, et al. Serial biologic therapies in psoriasis patients: A 12-year, single-center, retrospective observational study. J Am Acad Dermatol. 2020 Jan;82(1):37-44.

Exclusion reason: overlapping patient population

17. Egeberg A, Bryld LE, Skov L. Drug survival of secukinumab and ixekizumab for moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2019 Jul;81(1):173-8.

Exclusion reason: overlapping patient population

18. Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol. 2018 Feb;178(2):509-19.

Exclusion reason: overlapping patient population

19. Elberdín L, Fernández-Torres RM, Paradela S, et al. Biologic Therapy for Moderate to Severe Psoriasis. Real-World Follow-up of Patients Who Initiated Biologic Therapy at Least 10 Years Ago. Dermatol Ther (Heidelb). 2022 Mar;12(3):761-70.

Exclusion reason: <10 patients per biologic

20. Feldman SR, Zhang J, Martinez DJ, et al. Real-world biologic and apremilast treatment patterns and healthcare costs in moderate-to-severe plaque psoriasis. Dermatol Online J. 2021 Jan 15;27(1).

Exclusion reason: overlapping patient population

21. Ferreira P, Mendes-Bastos P. Secukinumab: A complete approach to psoriatic patients-Real-world evidence study. Dermatol Ther. 2021 Mar;34(2):e14815.

Exclusion reason: overlapping patient population

22. Georgakopoulos JR, Yeung J. Rate of Patient-Driven Biologic Treatment Discontinuation During the COVID-19 Pandemic in 2 Academic Hospital Clinics at the University of Toronto. J Cutan Med Surg. 2020 Jul/Aug;24(4):424-5.

Exclusion reason: no drug survival (Kaplan-Meier) analysis

23. Gkanti V, Dalamaga M, Papadavid E. Drug survival of brodalumab is greater in patients with psoriasis and psoriatic arthritis in a real-world setting. Int J Dermatol. 2023 Jan;62(1):e31-e4.

Exclusion reason: specific subpopulation

24. Jung SW, Lim SH, Jeon JJ, et al. Comparison of the Efficacy and Safety of Biologics (Secukinumab, Ustekinumab, and Guselkumab) for the Treatment of Moderate-to-Severe Psoriasis: Real-World Data from a Single Korean Center. Biomedicines. 2022 May 3;10(5).

Exclusion reason: no censoring performed in Kaplan-Meier curves, although there were patients lost to follow-up

25. Kishimoto M, Komine M, Kamiya K, et al. Drug Survival of Tumor Necrosis Factor-Alpha Inhibitors and Switched Subsequent Biologic Agents in Patients with Psoriasis: A Retrospective Study. Dermatol Ther (Heidelb). 2023 Jun;13(6):1347-60.

Exclusion reason: biologics were not separately analyzed

26. Kojanova M, Fialova J, Cetkovska P, et al. Demographic data, comorbidities, quality of life, and survival probability of biologic therapy associated with sex-specific differences in psoriasis in the Czech Republic. Dermatol Ther. 2021 Mar;34(2):e14849.

Exclusion reason: no drug survival or Kaplan-Meier results split for different biologics

27. Krantz Å, Carrero JJ, Yang Y, et al. Psoriasis/Psoriatic Arthritis Patients' Long-term Treatment Patterns and Adherence to Systemic Treatments Monitoring Recommendations. Acta Derm Venereol. 2023 Jun 15;103:adv6505.

Exclusion reason: biologics were not separately analyzed

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Exclusion reason: overlapping patient population

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Exclusion reason: only Kaplan-Meier curves split for age group available

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Exclusion reason: censoring and events seem to be interchanged in the Kaplan-Meier curve

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Exclusion reason: nu drug survival (Kaplan-Meier) analysis

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Exclusion reason: overlapping patient population

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Exclusion reason: <10 patients per biologic

2.4 Switching to IL-23 inhibitors after ineffectiveness of ustekinumab: evaluating real-world outcomes in psoriasis treatment

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Dear Editor,

The interleukin (IL)-12/23 inhibitor ustekinumab has proven to be very efficacious for psoriasis. [1, 2] In the case of ineffectiveness to ustekinumab, switching to one of the selective IL-23 inhibitors (IL-23i) is a possibility, but little is known about their effectiveness after ustekinumab failure. The objective of this study was to investigate the drug survival (DS) and effectiveness of IL-23i after ustekinumab discontinuation due to ineffectiveness in patients with psoriasis, and to compare those with IL-23i outcomes in ustekinumab-naive patients.

A multicenter, real-world, post-hoc study was performed using prospectively collected BioCAPTURE registry data (www.biocapture.nl). Adult patients with psoriasis treated with the IL-23i guselkumab, risankizumab, or tildrakizumab were included and were divided into two groups: (1) patients who previously discontinued ustekinumab due to ineffectiveness, and (2) patients with no previous ustekinumab use.

Kaplan-Meier DS curves were constructed to demonstrate IL-23i DS. In the overall DS, discontinuation due to ineffectiveness, adverse events, or other reasons were considered as an event. In the DS curve pertaining to ineffectiveness, only discontinuation due to ineffectiveness was counted as an event. All other reasons for discontinuation were censored. Active users or patients lost-to-follow up were censored at their last visit. IL-23i DS was compared between patients who previously discontinued ustekinumab for ineffectiveness and ustekinumab-naive patients. In the Cox-regression model, correction for confounders (number of previously used biologics and apremilast, sex, body weight, and psoriatic arthritis) was applied. First-year Psoriasis Area and Severity Index (PASI) scores of patients with and without previous ustekinumab treatment were calculated. Linear regression, applying confounder correction, was used to compare PASI scores at 6 and 12 months of treatment between groups. Proportions of patients with an absolute PASI = 0, PASI ≤ 2 and PASI ≤ 5 and relative PASI75 and PASI90 were calculated quarterly for the first year of treatment. For an extensive description of methods: see the supplementary content.

We included 159 IL-23i patients, of whom 68 experienced previous ineffectiveness to ustekinumab and 91 had not previously used ustekinumab (Figure S1, Tables S1-2). The uncorrected, overall DS after 2 years was 54.9% in patients with previous ustekinumab ineffectiveness compared with 77.4% in patients with no ustekinumab treatment history. Uncorrected ineffectiveness related DS was 66.5% versus 92.7%

in patients with versus without previous ustekinumab ineffectiveness (Figure 1). However, after confounder correction using Cox-regression analysis, no statistically significant differences were observed between patients with previous ustekinumab ineffectiveness versus ustekinumab-naive patients for overall and ineffectiveness-related DS (hazard ratios [HR] 1,25, 95% confidence interval [CI] 0.48-3.25, p = 0.648 and HR 2.27 95% CI 0.59-8.75, p = 0.232, respectively). Guselkumab and risankizumab demonstrated similar DS when compared with each other after ustekinumab ineffectiveness (Figure S2).

Median baseline PASI scores of patients treated with IL-23i after ustekinumab ineffectiveness compared with ustekinumab-naive patients were 6.1 (interquartile range [IQR] 4.5) versus 8.1 (IQR 9.4). During 1-year follow-up, uncorrected PASI scores of patients who had previously used ustekinumab were less favorable than those of ustekinumab-naive patients (Fig. 2). After confounder correction, a statistically significant difference between these groups at 6 months (2.3-point lower PASI in ustekinumab-naive patients), but not at 12 months, was observed. This confounder-corrected analysis was repeated, omitting ustekinumab in the number of previous biologics, resulting in a 2.0-point lower PASI score at 12 months (p = 0.021) [Online Resource Table 3]. Proportions of patients achieving absolute (e.g., PASI < 5) and relative (e.g., PASI90) PASI scores are depicted in Online Resource Fig. 3 and Online Resource Table 4. Although it can be seen that ustekinumab-naive patients achieve better results, 80% of patients who discontinued ustekinumab due to ineffectiveness still achieved a PASI score of <5 and maintained this during the first year of IL-23i treatment.

The confounder-corrected analyses showed no difference between DS and absolute PASI at 12 months between IL-23i patients with or without previous ustekinumab use, but uncorrected analyses did show clear differences between the groups in favor of ustekinumab-naive patients. Note that the dataset's sample size remains relatively small, and some variables had missing values, which might hinder the detection of statistically significant differences after confounder-correction. Therefore, it is important to replicate these analyses in larger cohorts for robust validation. The mechanisms of action of ustekinumab and specific IL-23i partially overlap. However, targeting IL-12 may reduce the effectiveness of ustekinumab compared with IL-23i. [3, 4] Differential binding affinities exist among various IL-23i. Risankizumab and guselkumab demonstrated higher affinities than tildrakizumab and ustekinumab, which may also contribute to their heightened effectiveness. [3, 5] Our research demonstrated that IL-23i were still effective following ustekinumab ineffectiveness in a significant proportion of patients.

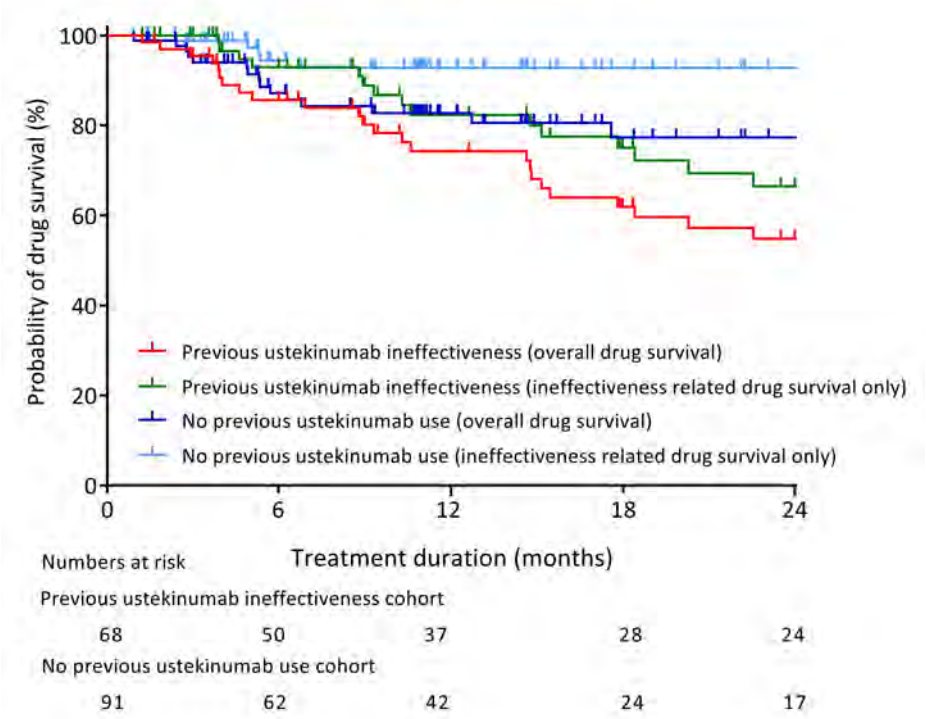

Figure 1 Drug survival of IL-23 inhibitors

Kaplan-Meier drug survival graphs of overall drug survival and ineffectiveness related drug survival of IL-23i, split for previous ustekinumab use; IL, interleukine; i, inhibitor

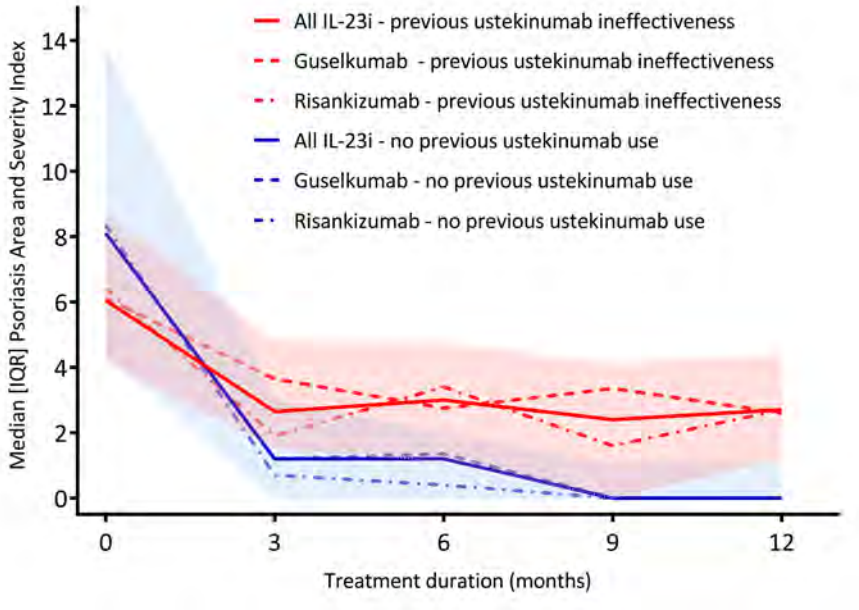

Figure 2 PASI course of IL-23 inhibitors

First-year median PASI course, split for previous ustekinumab use. As observed analysis. a) All IL-23 inhibitors; b) Guselkumab; c) Risankizumab; IL, interleukine; IQR, interquartile range

In conclusion, PASI outcomes at specific timepoints were better in ustekinumab-naive patients, but confounder-corrected DS was not influenced. Because a large proportion responded well to IL-23i after ustekinumab failure, IL-23i is a viable option after ustekinumab failure.

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Supplementary content

Supplementary Methods

Data were extracted from the prospective, multicenter, Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE-registry, www.biocapture.nl). The BioCAPTURE registry contains data from adult patients with psoriasis using biologics. Patients are included from 23 participating Dutch hospitals, of which 4 are academic and 19 are regional hospitals (2005-2023). Extraction of the data from the registry database was performed on April 25th, 2023. Ethical approval was not necessary due to the non-interventional nature of the study, however written informed consent was obtained from every included patient before inclusion in the BioCAPTURE registry.

Inclusion and exclusion criteria

Data were collected from adult (≥18 years old) psoriasis patients who received treatment with IL-23i. The included IL-23i cohort consisted of two groups: the first with patients who previously discontinued ustekinumab due to ineffectiveness, the second with no history of ustekinumab treatment. Ineffectiveness was determined by the treating physician and not limited to a certain PASI value. The usage of ustekinumab could have taken place before or during inclusion into BioCAPTURE, the IL-23i usage was always registered after inclusion in BioCAPTURE and prospectively collected.

Exclusion criteria were patients who used ustekinumab but stopped due to other reasons than ineffectiveness, for example solely adverse events or lost-to-follow-up. In case patients used multiple IL-23i, only the data of the first IL-23i treatment episode was used for the analyses.

Treatment characteristics

At baseline, the following characteristics were collected and measured: sex, age, disease duration, family history of psoriasis, psoriatic arthritis, duration of ustekinumab treatment, and the number and type of different previously used biologics and apremilast (PDE4 inhibitor). Body weight and body mass index (BMI) were collected as close to the start of the IL-23i as possible.

Drug survival analysis

Drug survival (Kaplan-Meier) curves were constructed to demonstrate the drug survival related to all discontinuation reasons and to ineffectiveness for patients using IL-23i. In the overall drug survival curve discontinuation due to

ineffectiveness, adverse events, or other reasons were considered as an event, while in the drug survival curve pertaining to ineffectiveness, only discontinuation due to ineffectiveness was counted as an event. All other reasons for discontinuation were censored, e.g. pregnancy wish. Active users or patients lost-to-follow up were censored at the time of their last visit. A treatment episode (TE) was defined as the time in which the patient actively used the IL-23i. When the IL-23i was interrupted for more than 90 days after the treatment should have been administered according to label, the TE ended.

IL-23i drug survival was compared between patients that previously stopped ustekinumab for ineffectiveness and ustekinumab naïve patients. Cox-regression analysis was used to correct for the influence of confounders. Confounding variables (the number of previously used biologics and apremilast, sex, body weight, and psoriatic arthritis) were selected based on previous literature on psoriasis drug survival studies.

Drug survival curves of separate IL-23i were constructed for biologics with more than twenty patients per group.

Psoriasis Area and Severity Index (PASI) analysis

First-year PASI-scores of patients with and without previous ustekinumab treatment were calculated. Linear regression was used to compare PASI-scores at 6 months and 12 months of treatment between patients with and without ustekinumab treatment history. Confounder-correction was applied, with confounders being selected based on clinical relevance. Additionally, linear regression analyses were repeated including the baseline PASI.

Additionally, proportions of patients with an absolute PASI=0, PASI≤2 and PASI≤5 and relative PASI75 and PASI90 were calculated at quarterly intervals during the first year of treatment, and displayed for the total IL-23 cohort as well as for the separate IL-23i.

Statistical Analysis

The data were presented as number and proportion of patients (categorical variables), or as mean ± SD and median [range] (continuous variables). All analyses were performed using IBM SPSS Statistics Version 27.0.1.0. A p-value <0.05 was considered statistically significant. In the confounder-corrected analyses, as a sensitivity analysis, the number of previously used biologics and apremilast was added once with, and once without prior ustekinumab taken into account.

Table S1 Baseline and treatment characteristics of patients with psoriasis, treated with IL-23 inhibitors

	IL-23i withprior ustekinumab ineffectiveness (n=68)	**IL-23i with no ustekinumab treatment history (n=91)**
Male sex, n (%)*	39 (57.4%)	63 (70.8%)
IL-23 inhibitors, n (%)		
Guselkumab	43 (63.2%)	43 (47.5%)
Risankizumab	22 (32.4%)	39 (42.9%)
Tildrakizumab	3 (4.4%)	9 (9.9%)
Age at time of start IL-23i (years)		
Median [range]	52.1 [25.1 - 86.5]	52.9 [23.8 - 75.9]
Disease duration at start IL-23i (years)		
Median [range]	21.6 [6.1 - 63.7]	21.2 [2.2 - 64.9]
Family history of psoriasis, n (%)	36 (59.0%)	53 (67.9%)
Psoriatic arthritis		
yes, confirmed (%)	18 (30.5%)	14 (18.7%)
no	39 (66.1%)	58 (77.3%)
mild/doubt about diagnosis	2 (3.4%)	3 (4.0%)
Body weight (kg)		
Median [range]	88.0 [63.7 - 146.2]	92.0 [55.8 - 150.0]
Body Mass Index (BMI)		
Median [range]	28.6 [21.8 - 45.6]	28.3 [19.1 - 44.1]
Baseline PASI		
Median [range]	6.1 [0.0-25.9]	8.1 [0.0-34.5]
Biologic naivety, n (%)		
yes	0 (0.0%)	30 (33.3%)
no	68 (100.0%)	61 (67.0%)
Previously used biologics and apremilast		
Median [range]	3.0 [1.0-10.0]	1.0 [0.0-5.0]
Duration of IL-23i treatment (months)		
Median [range]	14.8 [1.2 - 55.7]	11.1 [0.0-54.6]
Systemic psoriasis comedication, n (%)		
Methotrexate	3 (4.4%)	2 (2.2%)
Retinoids	1 (1.5%)	1 (1.1%)

*missing values: sex 2, disease duration at start 14, family history of psoriasis 20, psoriatic arthritis 31, body weight 23, BMI 27

Values might not add up because of missing values

IL, interleukine; i, inhibitor; n, number; kg, kilogram; PASI, Psoriasis Area and Severity Index

Table S2 Baseline characteristics of patients treated with specific IL-23 inhibitors, previously treated with ustekinumab

	Guselkumab (n=43)	**Risankizumab (n=22)**	**Tildrakizumab (n=3)**	**Total (n=68)**
Male sex (%)	26 (60.5%)	11 (50.0%)	2 (66.7%)	39 (57.4%)
Age start IL-23 inhibitor (years)				
Mean ± SD	50.8 ± 14.5	55.5 ± 14.2	53.9 ± 7.3	52.4 ± 14.2
Disease duration at start IL-23 inhibitor (years)				
Median [range]	20.7 [6.1 - 63.7]	24.8 [7.1 - 51.3]	27.6 [16.0 - 39.3]	21.6 [6.1 - 63.7]
Family history of psoriasis, n (%)	19 (51.4%)	15 (68.2%)	2 (66.7%)	36 (52.9%)
Psoriatic arthritis				
yes, confirmed (%)	13 (35.1%)	5 (23.8%)	0 (0.0%)	18 (30.5%)
no	23 (62.2%)	15 (71.4%)	1 (100.0%)	39 (66.1%)
mild/doubt about diagnosis	1 (2.7%)	1 (4.8%)	0 (0.0%)	2 (3.4%)
Body weight (kg)				
Median [range]	89.2 [63.7 - 146.2]	85.6 [21.8 - 43.5]	110.0 [107.0 - 112.9]	88.0 [63.7 - 146.2]
Body Mass Index (BMI)				
Median [range]	27.7 [23.6 - 45.6]	30.4 [21.8 - 43.5]	37.7 [34.9 - 40.5]	28.6 [21.8 - 45.6]
Duration of ustekinumab treatment (months)				
Median [range]	13.6 [2.6 - 121.4]	15.0 [3.7 - 106.7]	8.4 [8.3 - 66.9]	13.3 [2.6 - 121.4]
Duration of IL-23 inhibitor treatment (months)				
Median [range]	18.0 [1.22 - 55.7]	8.9 [1.22 - 38.6]	15.1 [1.6 - 18.3]	14.8 [1.2 - 55.7]
Systemic psoriasis comedication, n (%)				
Methotrexate	2 (4.7%)	1 (4.5%)	0 (0.0%)	3 (4.4%)
Retinoids	1 (2.3%)	0 (0.0%)	0 (0.0%)	1 (1.5%)

Table S3 Estimated PASI differences by linear regression model

Variables entered	Estimated PASI difference in ustekinumab naïve patients compared to previous ustekinumab users at 6 months of treatment	Estimated PASI difference in ustekinumab naïve patients compared to previous ustekinumab users at 12 months of treatment
Number of previous biologics (including ustekinumab), sex, psoriatic arthritis, body weight	-2.3 point, p-value 0.008	-1.8 point, p-value 0.081
Number of previous biologics (excluding ustekinumab), sex, psoriatic arthritis, body weight	-2.3 point, p-value 0.003	-2.0 point, p-value 0.021
Number of previous biologics (including ustekinumab), sex, psoriatic arthritis, body weight, baseline PASI	-2.0 point, p-value 0.024	-1.7 point, p-value 0.113
Number of previous biologics (excluding ustekinumab), sex, psoriatic arthritis, body weight, baseline PASI	-2.1 point, p-value 0.007	-1.9 point, p-value 0.032

Table S4 Percentage of patients that achieved PASI outcomes

Month	PASI 0	PASI ≤ 2	PASI ≤ 5	PASI75	PASI90
IL-23 inhibitors with history of ustekinumab ineffectiveness					
0	1.8	7.1	37.5		
3	14.7	35.3	79.4	30	16.7
6	14.7	38.2	82.4	43.3	16.7
9	26.1	47.8	82.6	42.1	26.3
12	15.8	31.6	78.9	38.9	22.2
IL-23 inhibitors with no history of ustekinumab usage					
0	4.5	11.9	28.4		
3	26.8	65.9	90.2	61.3	38.7
6	39.3	85.7	96.4	59.1	40.9
9	57.1	90.5	100	88.2	76.5
12	57.1	81	100	85	65
Guselkumab with history of ustekinumab ineffectiveness					
0	2.9	8.6	42.9		
3	15	20	75	27.8	16.7
6	15.4	38.5	84.6	45.8	16.7
9	18.8	37.5	75	33.3	16.7
12	21.4	35.7	71.4	35.7	28.6
Risankizumab with history of ustekinumab ineffectiveness					
0	0	5.6	27.8		
3	14.3	57.1	85.7	33.3	16.7
6	12.5	37.5	75	33.3	16.7
9	42.9	71.4	100	57.1	42.9
12	0	20	100	50	0

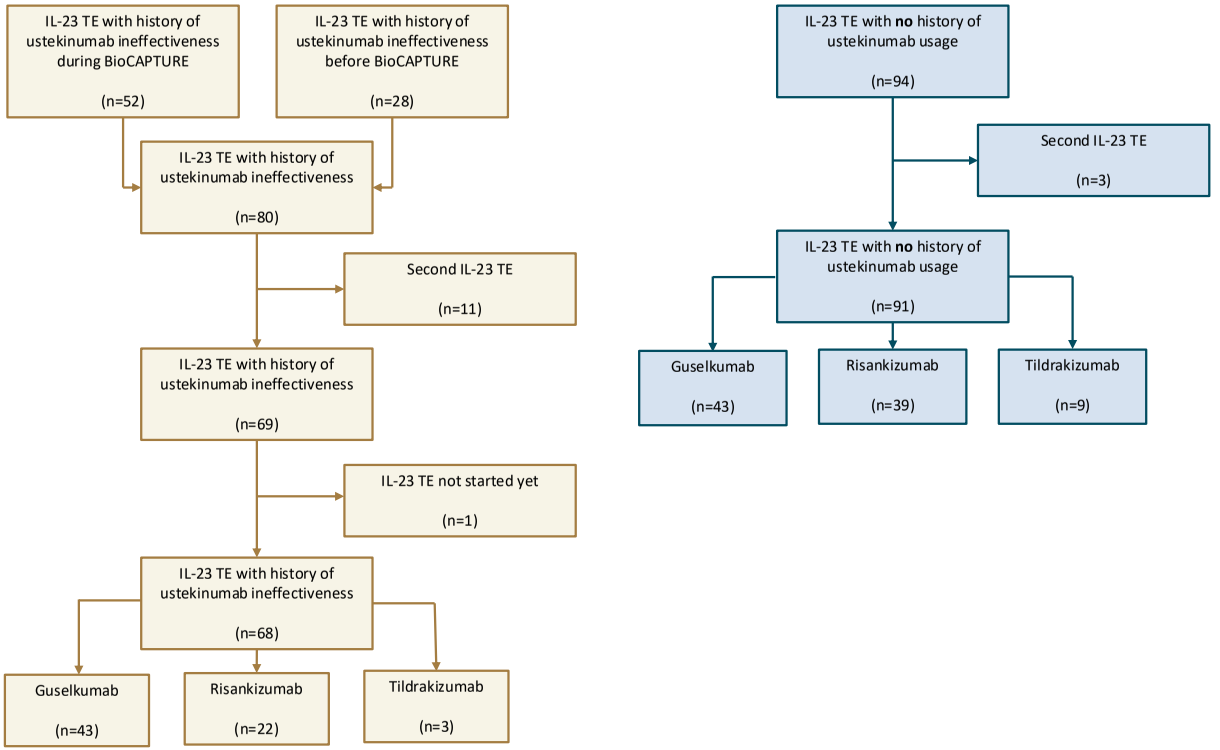


Figure S1 Flow diagram of included patients

IL: interleukine, i: inhibitor, TE: treatment episode, n: number

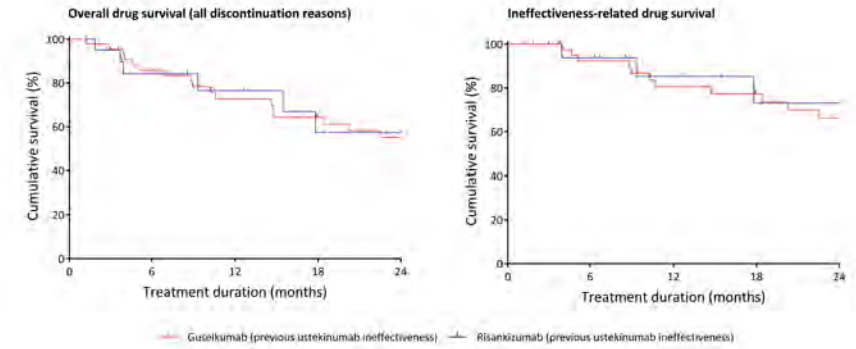


Figure S2 Drug survival of guselkumab and risankizumab after ustekinumab ineffectiveness

Kaplan-Meier drug survival graphs of overall drug survival and ineffectiveness related drug survival of guselkumab and risankizumab; IL, interleukine; i, inhibitor. DS curves of separate IL-23i were constructed for biologics with >20 patients per group.

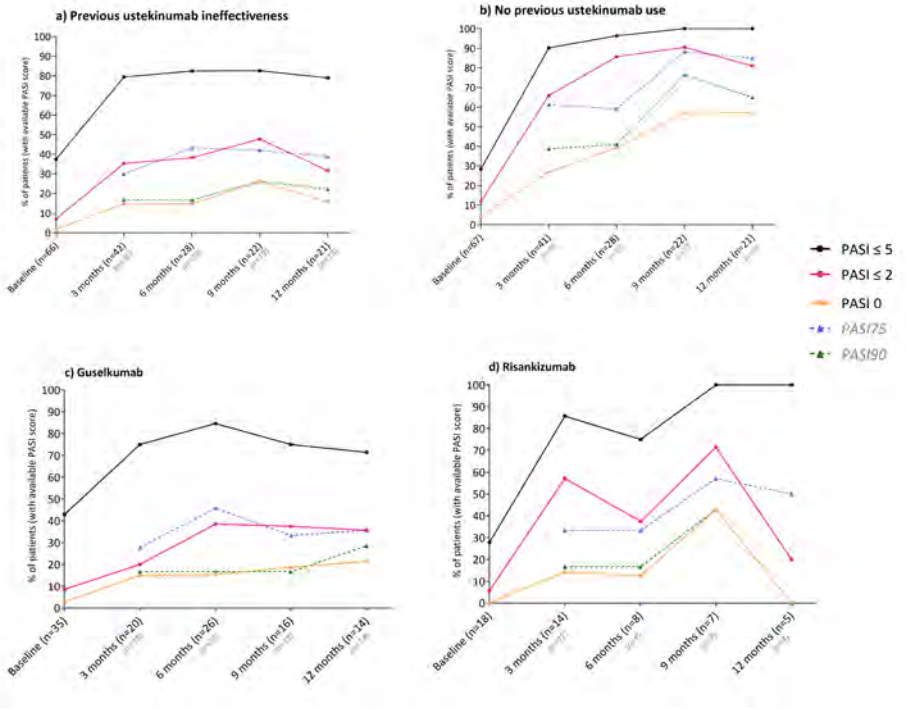
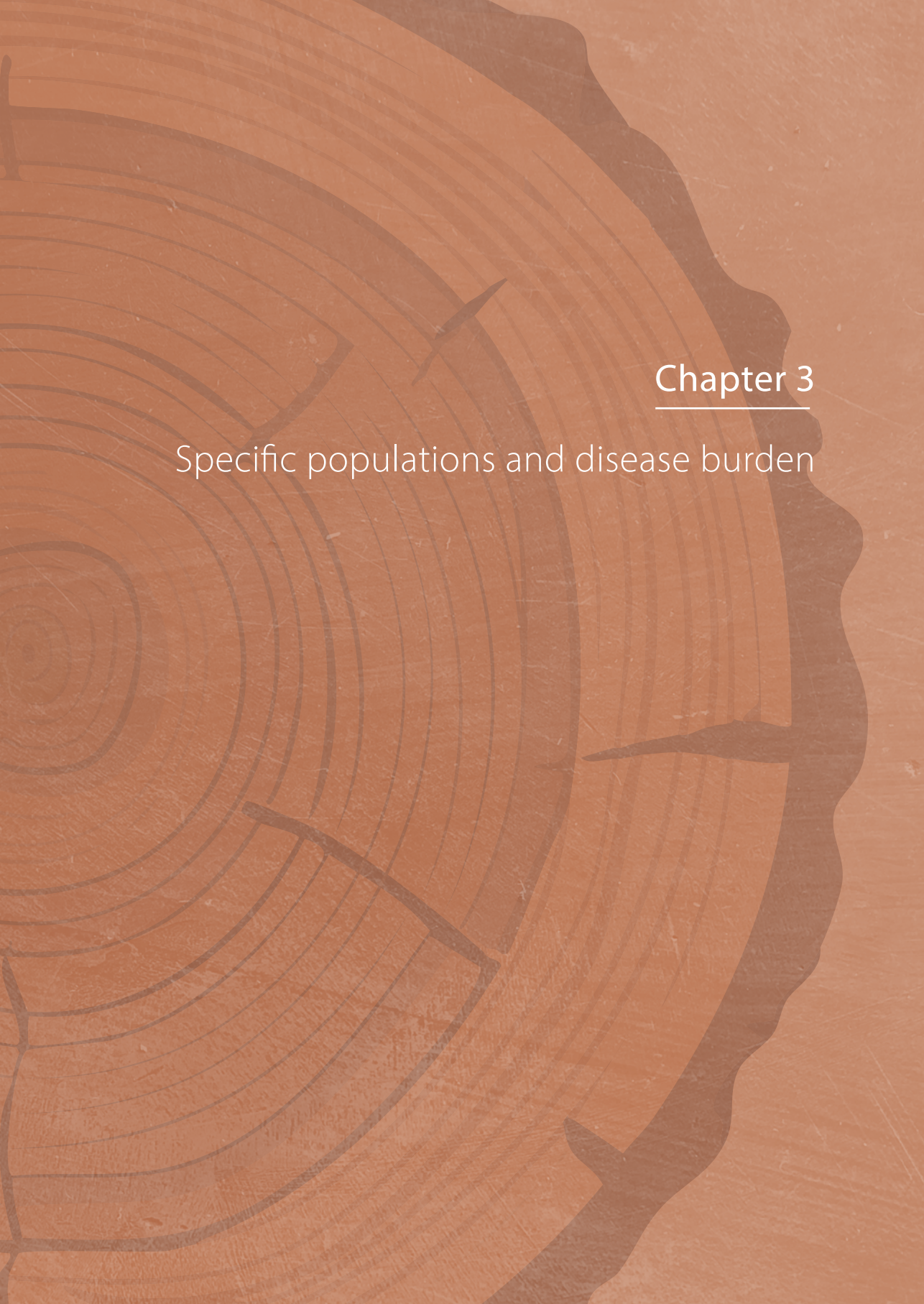


Figure S3 Absolute and relative PASI outcomes

Percentage of patients achieving absolute and relative PASI outcomes during the first year of treatment, as observed analysis. a) All IL-23 inhibitors after previous ustekinumab ineffectiveness; b) All-23 inhibitors without previous ustekinumab use; c) Guselkumab after ustekinumab ineffectiveness; d) Risankizumab after ustekinumab ineffectiveness; PASI, Psoriasis Area and Severity Index, n: number



Chapter 3

Specific populations and disease burden

3.1 Unveiling the impact of itch, pain, fatigue, and disease severity in paediatric patients with psoriasis and the influence of methotrexate and biologics

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Abstract

Background

Many paediatric patients with psoriasis suffer from itch, fatigue, pain, and severity of their disease. The extent of this burden, and the effect of treatment on these complaints has hardly been studied.

Objectives

To investigate the itch, pain, fatigue, and self-assessed disease severity in paediatric psoriasis patients at baseline and during one-year treatment with methotrexate (MTX) or biologics. Outcomes were related to Psoriasis Area and Severity Index (PASI).

Methods

Data were extracted from the prospective Child-CAPTURE registry. Visual Analogue Scales (VAS; 0-100) for itch, pain, fatigue, and disease severity were recorded quarterly and analysed using linear mixed models.

Results

We included 166 patients with 142 MTX and 76 biologic treatments. Median [IQR] VAS itch, pain, fatigue, and severity, were 64.0 [34], 16.0 [53], 22.0 [60], and 69.0 [23], respectively at start of MTX and 54.5 [52], 23.0 [64], 36.0 [62], and 73.0 [39] at start of biologic treatment. After three months, VAS-itch and VAS-severity showed the greatest decline in both groups. VAS-pain and VAS-fatigue also improved, except for VAS-fatigue in the MTX group. Median [IQR] PASI-scores at baseline and month 12 were 8.3 [5.8] and 2.4 [3.0] for MTX and 8.0 [6.4] and 1.5 [2.4] for biologics, respectively.

Conclusions

Itch and the severity of disease are a bigger burden for paediatric patients with psoriasis than pain and fatigue. Whereas itch, pain, and self-assessed severity decrease during both MTX- and biologic treatment, fatigue is not responsive to treatment, despite an objective decrease in PASI. PASI-scores at three months showed a greater decline in the biologic group compared to MTX group, especially in MTX-naïve patients. This study shows that attention for the burden of psoriasis, especially of itch and perceived severity, is important in daily clinical practice care for paediatric patients.

Introduction

Paediatric psoriasis can have a negative impact on children's quality of life and overall well-being.[1-8] While effective treatments exist, challenges persist in customizing treatment and reducing the burden of disease. One of the challenges in managing paediatric psoriasis is accurately assessing and treating the subjective symptoms itch, pain, fatigue, and self-reported disease severity. The Visual Analogue Scale (VAS) is a tool that can be easily understood by children. Children are asked to report their burden (e.g., itch) on a visual analogue scale ranging from "no itch at all" to "worst itch you can imagine". The VAS is a continuous scale, allowing for detailed measurement of symptoms and the ability to detect small changes over time.

Only few studies have reported separate VAS for paediatric patients with psoriasis.[6, 9, 10] To our knowledge, no extensive analysis incorporating itch, pain, fatigue, and self-assessed severity by VAS has been performed in paediatric psoriasis patients to date. The objective of our study was to assess the extent of burden, and to investigate the influence of methotrexate and biologics on VAS itch, pain, fatigue, and self-assessed disease severity. We aimed to relate these subjective scores to the objective Psoriasis Area and Severity Index (PASI) score of the two treatment groups in the first year of treatment.

Methods

We used data from the prospective observational daily practice cohort Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). All children (<18 years at first visit) treated with methotrexate or biologics who attended the outpatient clinic of the Department of Dermatology at the RadboudUMC in Nijmegen, the Netherlands, between September 2008 and January 2023 (data-lock), were included. In each patient, only the first treatment episode in Child-CAPTURE of methotrexate and/or the first biologic treatment episode was implemented in the analyses. This study was approved by the local ethical committee (Arnhem-Nijmegen) in compliance with the Declaration of Helsinki 2008, and local regulations. Written informed consent was obtained from the parents or guardians and/or from the participating paediatric patients according to applicable rules.

Patient and treatment characteristics, including VAS scales for itch, pain, fatigue, and disease severity as well as PASI were collected at baseline and every follow-up visit. The median [interquartile ranges, IQR] first-year VAS-scores per treatment

cohort (methotrexate/biologics) were calculated at baseline and at 3, 6, 9, and 12 months, using an as treated approach. Furthermore, a linear mixed model (LMM) analysis per separate treatment cohort and per VAS scale was performed, as this can handle multiple measurements occurring in one patient, as well as missing data.[11] Because many patients in the biologic cohort previously used methotrexate, and therefore were present in both the biologic and methotrexate cohort, no statistical comparisons were made between groups, but the influence of prior methotrexate use was tested in the biologic group by implementing the interaction term of prior methotrexate use and time in the LMM.

The influence of methotrexate and biologic treatment on PASI was analysed by as treated analyses. In the analysis of the PASI-course in the biologic cohort, PASI-scores were additionally split for methotrexate naivety.

Results

We included 166 patients (<18 years at start of treatment) with 142 methotrexate and 76 biologic treatments. Baseline characteristics are presented in **Table 1**. Methotrexate and biologic treatments were administered sequentially and not prescribed simultaneously. Baseline median VAS-itch, VAS-pain, VAS-fatigue, and VAS-severity were 64.0 [34], 16.0 [53], 22.0 [60], and 69.0 [23], respectively for MTX and 54.5 [52], 23.0 [64], 36.0 [62], and 73.0 [39] for biologic treatment. VAS-itch and VAS-severity showed a rapid decrease in the first 3 months of both MTX and biologic treatment (**Figure 1**). VAS-pain showed a more gradual decline in both treatment groups, whereas VAS-fatigue slightly increased in MTX-treated patients. After an initial decrease, an increase of VAS-fatigue was also found in biologic treated patients (**Figure 1**).

In the LMM analyses, these VAS score patterns were further investigated up to 1 year follow-up. Due to a clear slope difference in VAS-scores before and after three months, the VAS-course was divided into two parts. This resulted in fixed effects estimates of the LMM during the first 3 months, and from 3 months until 12 months. All fixed effects estimates can be found in **Tables S1** and **S2**. In both methotrexate and biologic treatments, all VAS decreased significantly during the first three months, except for VAS-fatigue in the methotrexate cohort. During the 3–12-month period, there were significant further reductions in both VAS-severity and VAS-fatigue in the methotrexate group, although these decreases were only slight. There was no significant decrease/increase in VAS-itch and VAS-pain in the methotrexate cohort.

In biologic treatments during the 3–12-month period no significant decrease or increase in VAS could be observed, except for VAS-fatigue, which significantly re-increased with 1.5 [0.2-2.7] points per month. Previous treatment with methotrexate had no significant effect on the VAS-courses in the biologic cohort.

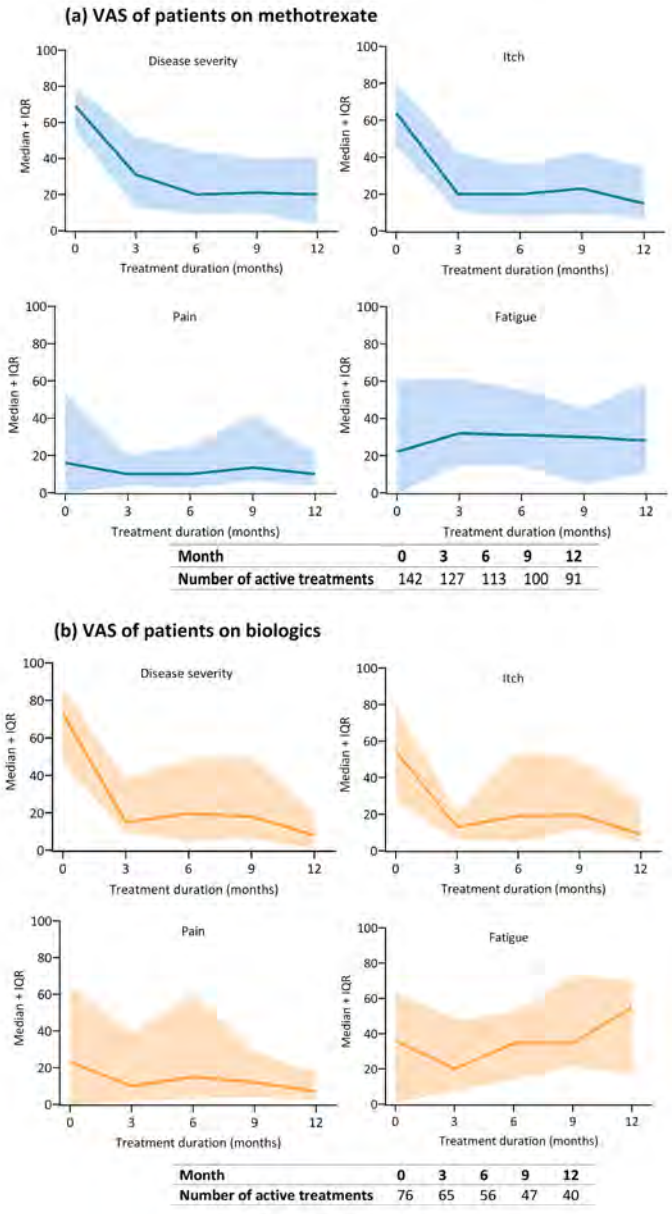

Figure 1 Median course of the Visual Analogue Scales (VAS) for itch, pain, fatigue, and disease severity for methotrexate (a) and biologics (b). IQR: interquartile range.

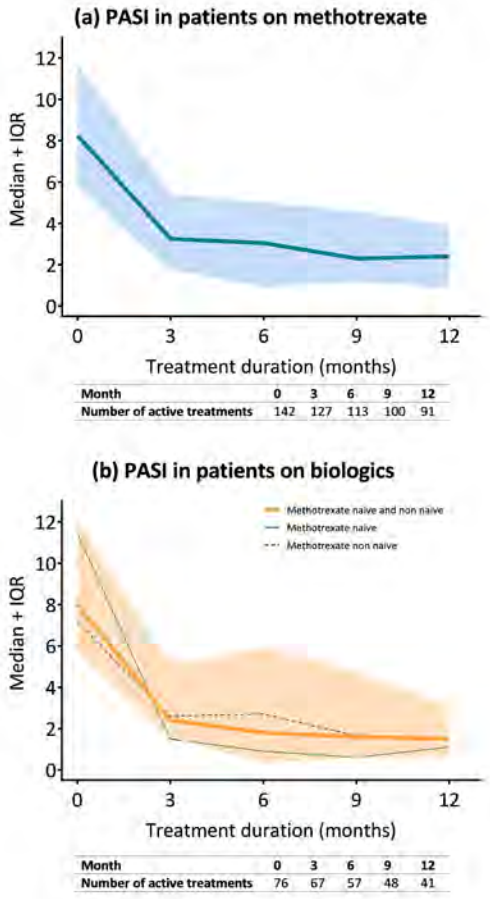

Figure 2 Median course of the Psoriasis Area and Severity Index (PASI) for methotrexate (a) and biologics (b). IQR; interquartile range.

In both treatment groups, a decrease in PASI was observed (**Figure 2**), with a lower median PASI for the biologics than for MTX after 3 months (2.4 [3.4] versus 3.3 [3.7]). After 12 months, median PASI-scores were 2.4 [3.0] for MTX and 1.5 [2.4] for biologics. In the biologic cohort, MTX-naive patients started with a higher median PASI (11.5 [15.7]) than MTX non-naïve patients (7.2 [6.0]) and achieved a lower PASI-score at three months (1.5 [3.7]) than MTX non-naive patients (2.6 [4.7]). The lower baseline PASI in MTX non-naïve patients is probably due to the fact that 50.0% of these patients ceased their MTX treatment due to side effects, and not due to a loss of efficacy (**Table 1**).

Table 1 Baseline characteristics

	Methotrexate cohort (142 patients)	**Biologic cohort (76 patients)**
Sex (male), n (%)	58 (40.8)	35 (46.1)
Age at start, mean ± SD	13.8 ± 3.1	14.5 ± 2.9
Methotrexate non-naïve, n (%)	12 (8.5)	52 (68.4)[a]
Prior MTX discontinuation due to:		
AE	*	*26 (50.0)*
Ineffectiveness	*	*24 (46.2)*
Biologic naive, n (%)	142 (100)	74 (97.4)
Treatment duration (months)		
Mean ± SD	20.0 ± 18.0	19.8 ± 23.5
Median [range]	16.0 [0.0-93.0]	12.5 [0.0-140.0]
Baseline VAS itch		
Mean ± SD	61.0 ± 26.2	52.0 ± 31.8
Median [range]	64.0 [0-100]	54.5 [0-100]
Baseline VAS pain		
Mean ± SD	27.9 ± 28.9	31.6 ± 23.0
Median [range]	16.0 [0-100]	23.0 [0-93]
Baseline VAS fatigue		
Mean ± SD	32.4 ± 31.9	37.3 ± 32.1
Median [range]	22.0 [0-100]	36.0 [0-100]
Baseline VAS severity		
Mean ± SD	65.7 ± 19.1	66.1 ± 26.9
Median [range]	69.0 [3-100]	73.0 [0-100]
Baseline PASI, median [range]	8.3 [0.3-42.1]	8.0 [2.4-37.8]
Baseline BSA, median [range]	9.8 [0.2-76.0]	8.5 [0.3-72.0]
Baseline CDLQI, median [range]	10.0 [1.0-24.0]	9.0 [0.0-24.0]

[a]52 patients of the biologic cohort were also present in the methotrexate cohort.
Missing values: methotrexate: baseline PASI 6; VAS psoriasis 35; VAS itch 29; VAS pain 29; VAS fatigue 29; BSA 6, CDLQI 10.
Biologics: baseline PASI: 2; VAS psoriasis 15, VAS itch 12; VAS pain 12, VAS fatigue 13, BSA 3, CDLQI 6.
*Not available due to treatment before inclusion Child-CAPTURE

Discussion

To our knowledge, this is the first study providing an extensive overview of the subjective symptoms paediatric patients with psoriasis experience in daily clinical practice. Longitudinal series of Visual analogue scale (VAS) scores of 218 methotrexate and biologic treatment episodes were analysed using data from the prospective real-world Child-CAPTURE registry. The highest VAS at baseline were reported for itch and disease severity, which were also most responsive to treatment. VAS-fatigue and VAS-pain were lower at baseline and VAS-pain was subject to minimal change during the first year of treatment. VAS-fatigue even showed a re-increase during biologic treatment, despite an adequate decrease in PASI.

This study underscores the fact that psoriasis severity is not the only symptom paediatric patients suffer from. Itch is also an important symptom, which formerly has been underacknowledged.[12] More recent studies do include itch as an important outcome measure for effectiveness of treatment.[10] The fact that paediatric patients in our cohort reported a steep decline in the self-assessed VAS-severity complements the objective clinical decline in PASI-scores during the first 3 months. Patients on biologics achieved lower absolute PASI-scores at three months than patients on methotrexate, which corresponds with the recently published findings in adult patients of Alabas et al.[13] However, it is important to highlight that also in patients undergoing methotrexate treatment, low PASI scores were attained, indicating well-controlled disease. For VAS-pain, a small decrease could be observed for both methotrexate and biologic treatment during the first 3 months. In our cohort, one-third of patients reported pain (VAS-pain > 0) in the first year of treatment, which is consistent with the findings of a large French survey among adults.[14] With respect to VAS-fatigue however, treatment with methotrexate and biologics did not seem to benefit the feeling of tiredness in paediatric patients, as VAS-fatigue was subject to minimal change (and even an increase in the biologic cohort) during the first year of treatment, despite significant improvement of severity. These data suggest that the burden of fatigue may not be (solely) related to psoriasis. Although self-perceived fatigue is often related to (chronic) illnesses, it is noteworthy that even among healthy adolescents fatigue prevalence is high.[15] Previous studies involving school-attending healthy adolescents have even reported that >25% experienced self-perceived fatigue at least once a week.[16] Thus, although it is important to assess fatigue, the interpretation of its origin is difficult, as many factors might play a role.

Our biologic cohort mainly consisted of patients prior treated with methotrexate, therefore we were able to assess the influence of previous methotrexate-use on the decline of VAS in biologic treated patients. This showed that all VAS, except for VAS-fatigue, in our biologic cohort still decreased significantly regardless of prior MTX use. Due to the large overlap between both groups, direct comparisons were not made. Our study is limited by some missing values for the VAS scales due to more remote visits during the COVID-19 pandemic, as VAS scales were only completed at outpatient visits. Nevertheless, the use of linear mixed models minimized the impact of these missing values on analyses. The relatively small number of included biologic treatments prohibited separate analyses for individual biologics.

This study has provided a deeper insight into the burden of paediatric psoriasis with respect to itch, pain, fatigue, and self-assessed disease severity. Patients especially suffered from itch and the self-assessed severity and to a lesser extent from pain and fatigue. After 3 months of treatment, itch, pain, and disease severity had decreased significantly in both MTX- and biologic-treated patients. Fatigue, however, was not responsive to treatment, despite an objective decrease in PASI scores. This study shows that attention for the burden of psoriasis, especially of itch and perceived severity, is important in daily clinical practice care for paediatric patients.

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Supplementary content

Table S1 Fixed effects **methotrexate** treatments

	Fixed effect	Lower	Upper	P
VAS itch				
First 3 months	-13.3	-15.2	-11.4	<.0001
3-12 months	-0.2	-0.9	0.5	0.5299
VAS pain				
First 3 months	-6.9	-8.7	-5.0	<.0001
3-12 months	0.2	-0.2	0.7	0.3358
VAS fatigue				
First 3 months	-1.5	-3.3	0.4	0.1249
3-12 months	-0.7	-1.3	-0.1	0.0199
VAS severity				
First 3 months	-11.8	-13.4	-10.1	<.0001
3-12 months	-0.7	-1.4	-0.0	0.0410

Table S2 Fixed effects **biologic** treatments

	Fixed effect	Lower	Upper	P
VAS itch				
First 3 months	-11.7	-14.5	-9.0	<.0001
3-12 months	0.8	-0.2	1.8	0.0973
VAS pain				
First 3 months	-6.1	-9.2	-3.1	0.0002
3-12 months	-0.2	-0.9	0.5	0.5281
VAS fatigue				
First 3 months	-5.1	-8.1	-2.1	0.0012
3-12 months	1.5	0.2	2.7	0.0250
VAS severity				
First 3 months	-14.2	-16.8	-11.6	<.0001
3-12 months	0.15	-0.9	1.2	0.7816

3.2 Drug survival, safety and effectiveness of biologics in older patients with psoriasis, a comparison with younger patients: a BioCAPTURE registry study

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Abstract

Background

Psoriasis is a common inflammatory disease in any age group, but also in older patients (≥65 years of age). Since older patients are often excluded from clinical trials, limited data specifically on this growing population are available, e.g. regarding the safety and performance of biological treatment.

Aims

We aimed to give insight into this specific population by comparing the drug survival and safety of biologics in older patients with that in younger patients.

Methods

In this real-world observational study, data from 3 academic and 15 non-academic centres in The Netherlands were extracted from the prospective BioCAPTURE registry. Biologics included in this study were tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-12/23, and IL-23 inhibitors. Patients were divided into two age groups: ≥ 65 years and < 65 years. The Charlson Comorbidity Index (CCI) was used to measure comorbid disease status, and all adverse events (AEs) that led to treatment discontinuation were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. All AEs that led to treatment discontinuation were studied to check whether they could be classified as serious AEs (SAEs). Kaplan–Meier survival curves for overall 5-year drug survival and split according to reasons of discontinuation (ineffectiveness or AEs) were constructed. Cox regression models were used to correct for possible confounders and to investigate associations with drug survival in both age groups separately. Psoriasis Area and Severity Index (PASI) scores during the first 2 years of treatment and at the time of treatment discontinuation were assessed and compared between age groups.

Results

A total of 890 patients were included, of whom 102 (11.4%) were aged ≥ 65 years. Body mass index, sex, and distribution of biologic classes (e.g. TNFα, IL-12/23) were not significantly different between the two age groups. A significantly higher CCI score was found in older patients, indicative of more comorbidity ($p < 0.001$). The 5-year ineffectiveness-related drug survival was lower for older patients (44.5% vs. 60.5%; $p = 0.006$), and the 5-year overall (≥ 65 years: 32.4% vs. < 65 years: 42.1%; $p = 0.144$) and AE-related (≥ 65 years: 82.1% vs. < 65 years: 79.5%; $p = 0.913$) drug survival was comparable between age groups. Of all AEs (n = 155) that led to discontinuation, 16 (10.3%) were reported as SAEs but these only occurred in

younger patients. After correcting for confounders, the same trends were observed in the drug survival outcomes. Linear regression analyses on PASI scores showed no statistical differences at 6, 12, 18, and 24 months of treatment between age groups.

Conclusions

This study in a substantial, well-defined, prospective cohort provides further support that the use of biologics in older patients seems well-tolerated and effective. Biologic discontinuation due to AEs did not occur more frequently in older patients. Older patients discontinued biologic treatment more often due to ineffectiveness, although no clear difference in PASI scores was observed. More real-world studies on physician- and patient-related factors in older patients are warranted.

Key points

- In this real-world observational study regarding biologic treatment for psoriasis, drug survival, effectiveness and safety were mainly comparable between age groups (<65 and ≥65).
- Treatment of older patients with biologics appears a safe and effective therapeutic option.

Introduction

Psoriasis is a chronic immune-mediated disease associated with not only a physical but also a psychological burden. It affects 2-4% of the world's population and can occur at any age[1]. The combination of an aging world population and the chronic course of psoriasis results in an increase in the prevalence of older patients with psoriasis. [1, 2] As older patients are often excluded from clinical trials, only limited literature for this specific population is available regarding the effectiveness and safety of systemic anti-psoriatic treatments. [3-5]

Biologics are the most recent addition to the arsenal of therapeutic options for psoriasis and appear to be more effective than conventional systemic therapies in older patients. [3] However, choosing the optimal type of treatment can be challenging in older patients, not only due to limited evidence on safety and effectiveness, but also due to possibly complicating patient characteristics such as comorbidities, concomitant medication use, polypharmacy, functional status, and frailty. Therefore, it is possible that physicians are reluctant to prescribe certain systemic therapies such as biologics in older patients, which could lead to undertreatment of this patient group[6].

With this prospective observational real-world study in patients using biologics for psoriasis, we aimed to provide insight into the drug survival, safety and effectiveness of biologics in older patients and compare outcomes with a younger population.

Materials and methods

The BioCAPTURE database

In this real-world cohort study, data were extracted from the prospective, multicentre, Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE registry; www.biocapture.nl). We used data on psoriasis patients treated with biologic therapy from 3 academic and 15 non-academic centres in the Netherlands (2005-2021). The biologics included in this study were tumor necrosis factor (TNF)-α-, interleukin (IL-)17-, IL-12/23-, and IL-23-inhibitors (see **Table 1**). According to the regional Medical Ethics Committee, ethical approval was not necessary for this non-interventional study. Nevertheless, written informed consent is obtained from every included patient.

Data collection

Data were collected from adult patients treated with biologics. Two age groups were compared; patients ≥65 years and <65 years of age at the start of biological treatment. The 65 years of age threshold was chosen because it is widely used in psoriasis literature.[3, 7, 8] In this study, the first biologic treatment episode (TE) per patient in BioCAPTURE was included. A TE represents a continuous period of time in which a patient was treated with a certain biologic. If treatment was interrupted ≥90 days, the TE ended. The maximum follow-up duration was set at 5 years. Baseline patient characteristics were collected and calculated for every TE. To measure comorbid disease status, the International Classification of Diseases, Tenth Revision (ICD-10) version of the Charlson Comorbidity Index (CCI) was used.[9, 10] In addition to the CCI, depression and hypertension were added as these were regarded relevant comorbidities in the context of psoriasis. To assess the possibility that this cohort was comprised of relatively healthy older patients due to pre-selection on comorbidity in the context of biologic therapy initiation, a comparison of CCI scores with another Dutch psoriasis cohort including older adults (≥65 years) using all types of antipsoriatic therapy (n = 230) was performed (data available upon request). This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[11]

Drug survival analysis

Drug survival up to 5 years of treatment was visualized using Kaplan-Meier survival curves. For the overall drug survival curve, discontinuation due to ineffectiveness, adverse events (AEs), ineffectiveness and AEs combined, other reasons, and death were considered an event. Additionally, we assessed drug survival according to reason for discontinuation (separately for ineffectiveness and AEs). Patients were censored when lost to follow-up, when still 'on drug' at the moment of data lock (with a maximum follow-up of 5 years), or when a patient reached the age of 65 years during treatment. For the analyses based on discontinuation reasons, patients were censored when they discontinued their biologic for a reason other than the reason of interest. Log-rank tests were performed to compare Kaplan-Meier curves between patient groups.

Correcting for confounders

Baseline characteristics were compared between the two age groups; if baseline variables were different between groups, they were considered as confounders and were incorporated into the Cox regression model. Multiple imputation was used in the case of large amounts of missing data (>15%). Imputed variables were created and pooled in the model 10 times, and were incorporated in the confounder-

corrected model if the variable differed significantly between treatment groups or had a >10% effect on model outcomes.

Variables associated with drug survival

Additionally, Cox regression analyses with baseline variables were performed with a selection of patients < 65 years of age, and ≥ 65 years of age separately, to investigate associations with drug survival. Baseline variables were tested univariately and incorporated in the multivariable Cox regression model if their association with drug survival was considered clinically meaningful and the p-value was <0.1. Backward selection was used to identify relevant variables for the final model.

Adverse events leading to treatment discontinuation

All AEs that led to discontinuation of the biologic were collected and classified into categories according to the Medical Dictionary for Regulatory Activities (MedDRA). Patients could have more than one AE simultaneously leading to treatment discontinuation and these were counted as separate AEs in this study. Additionally, all AEs leading to discontinuation were studied to check if they could be classified as serious AEs (SAEs) according to the International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice Guidelines.[12]

Psoriasis Area and Severity Index (PASI) analysis

To be able to visualize treatment effectiveness in both age groups, the Psoriasis Area and Severity Index (PASI) scores were analysed. In the PASI analysis, only TEs with a baseline PASI and at least one follow-up PASI within the first year of treatment were included. Since scheduling visits at the exact time points is not feasible in a clinical setting, linear interpolation was used to estimate PASIs at the following time points: weeks 6, 12, 26, 39 and 52, and months 18 and 24. Interpolated PASI scores were used to calculate 1-year PASI ≤ 1 and ≤ 5 proportions. Additionally, PASI scores at the time of treatment discontinuation due to ineffectiveness were assessed. Linear regression analyses were performed, with age group as the independent outcome and PASI as the dependent outcome, at 6, 12, 18 and 24 months of treatment. Correction for possible confounders was applied in linear regression analyses.

In patients who discontinued treatment due to ineffectiveness and/or AEs, PASI scores at discontinuation were carried forward using the last observation carried forward (LOCF) method. With this method, PASI scores in the case of early discontinuation are carried forward, which ensures a more conservative approach.[13]

Statistical analysis

Analyses were performed in SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). A p value < 0.05 was considered significant. Baseline patient and treatment characteristics for the first TE per patient and per biologic were displayed using descriptive statistics [mean ± standard deviation (SD), median (range), N (%)]. Continuous variables were compared between patient groups using one-way analysis of variance (ANOVA) for parametric distributions and Mann–Whitney U tests for non-parametric distributions, respectively. Pearson's Chi-square test was used for comparison of categorical variables.

Results

Patient characteristics

We included a total of 890 patients, of whom 102 (11.5%) were 65 years of age or older at the start of biologic therapy compared with 788 (88.5%) patients aged under 65 years. In total, 2013 patient-years were observed: 206 years in patients ≥ 65 years of age and 1807 in patients < 65 years of age. The median follow-up duration was 19 months in patients ≥ 65 years of age versus 22 months in patients < 65 years of age. The median age at the start of biologic treatment was 48.3 years (19.1–82.5). Body mass index (BMI), sex, and the distribution of biologic classes prescribed (e.g. TNF, IL-12/23) were not significantly different between the two groups (**Table 1**). The most frequently reported comorbidities in older patients were hypertension (n = 45, 44.1%) and diabetes mellitus (n = 31, 30.4%) [see **Table 2**]. The frequencies of other comorbidities were considerably lower. A significantly higher median CCI score was found in older versus younger patients (1 [0–7] vs. 0 [0–6]; p < 0.001). The median CCI scores of this older population and those of another Dutch psoriasis cohort including older patients were highly comparable (1 [0–7] vs. 1 [0–7]; p = 0.380) [data not shown].

Drug survival

During the first 5 years of treatment, 220 (24.7%) patients discontinued treatment due to ineffectiveness, 90 (10.1%) due to AEs, and 60 (6.7%) for other reasons (mostly due to pregnancy [wish], patient's own initiative, or unknown reasons). Among those patients who discontinued treatment due to 'other reasons', three (0.3%) patients discontinued treatment due to the coronavirus disease 2019 (COVID-19) pandemic, all aged < 65 years. Crude drug survival rates are visualized using Kaplan–Meier curves (**Figure 1**). The crude overall 5-year drug survival in older patients was 32.4% versus 42.1% in younger patients (log-rank test, p = 0.144). Specifically for ineffectiveness, the 5-year drug survival was lower for older patients

than for younger patients (44.5% vs. 60.5%; p = 0.006), while the 5-year drug survival with regard to AEs was 82.1% in older patients versus 79.5% in younger patients (p = 0.913). An overview of the reasons for treatment discontinuation and drug survival per age group is given in **Table 3**.

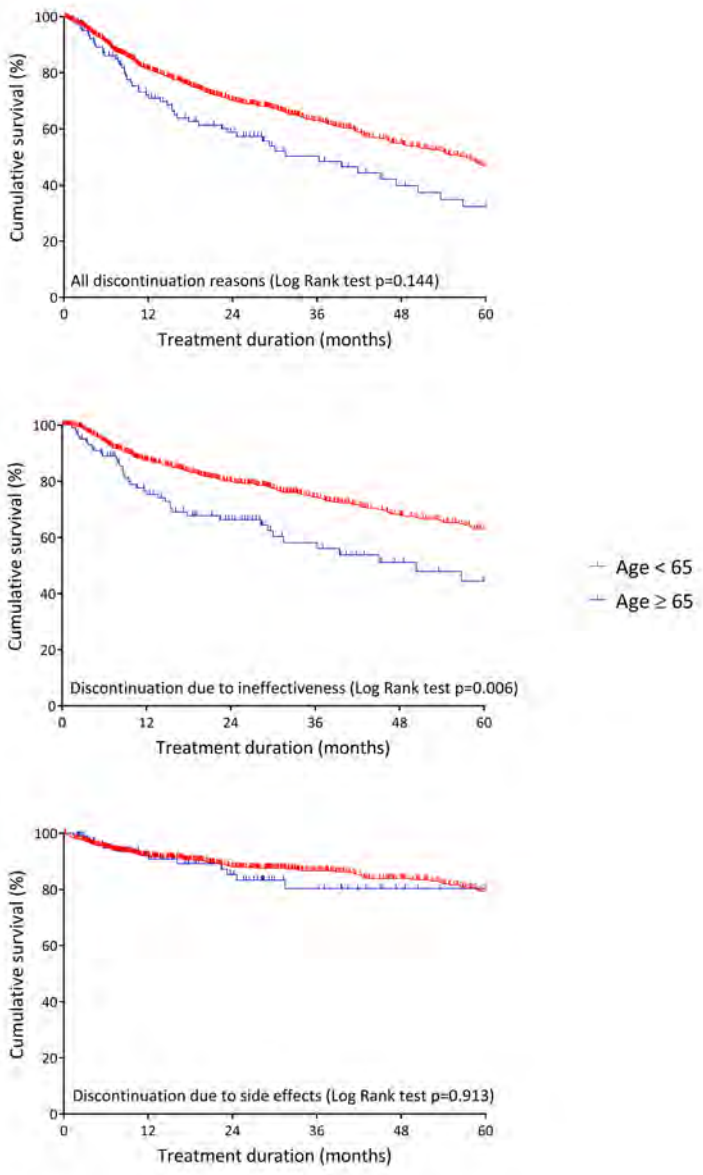

Figure 1 Five-year drug survival of older patients compared to younger patients using biologics treatment, split for discontinuation reasons

Table 1 Patient and treatment characteristics of older patients compared with younger patients using biologic treatment

	<65 years old (n = 788)	**≥65 years old (n = 102)**	**All patients (n = 890)**	**p-value[a]**
Age at start of biologic treatment, years				NA
mean ± SD	45.4 ± 11.1	70.3 ± 4.1	48.2 ± 13.2	
median, range	45.9 (19.1 – 64.8)	69.9 (65.1 – 82.5)	48.3 (19.1 – 82.5)	
Sex, *n (%)*[c]				0.515
male	487 (62.6)	60 (58.8)	547 (62.2)	
female	291 (37.4)	42 (41.2)	333 (37.8)	
Hospital type, *n (%)*				0.437
academic	526 (66.8)	64 (62.7)	590 (66.3)	
non-academic	262 (33.2)	38 (37.3)	300 (33.7)	
Body mass index (kg/m^2)[c]				0.930
mean ± SD	28.9 ± 6.1	28.5 ± 4.3	28.9 ± 5.9	
median, range	27.9 (16.4- 69.9)	27.3 (21.4 – 42.6)	27.9 (16.4 – 69.9)	
Age at onset of psoriasis,years[c]	24.8 ± 12.3	41.9 ± 18.8		NA
mean ± SD	22.0 (0 -59)	47.0 (2- 76)	26.7 ± 14.2	
median, range			23.0 (0 – 76)	
Duration of psoriasis until start biologic, years[b,c]	20.0 ± 11.9	26.5 ± 18.5		0.001
mean ± SD	18.2 (0.6-57.2)	17.4 (1.7-72.0)	20.7 ± 12.9	
median, range			18.2 (0.6-72.0)	
Biologic naive, *n (%)*	510 (64.7)	65 (63.7)		0.827
yes	278 (35.3)	37 (36.3)	575 (64.6)	
no			315 (35.4)	
Family history of psoriasis, *n (%)*[c]	472 (66.9)	50 (59.5)		0.311
yes	234 (33.1)	33 (40.5)	522 (66.1)	
no			268 (33.9)	
Psoriatic arthritis, *n (%)*[c]	211 (32.0)	22 (27.2)		0.447
yes	448 (68.0)	59 (72.8)	233 (31.5)	
no			507 (68.5)	
Baseline PASI score[c]				0.421
mean ± SD	13.2 ± 7.7	12.3 ± 6.8	13.1 ± 7.6	
median, range	11.8 (0 - 45.2)	11.0 (0 – 36.2)	11.4 (0 – 45.2)	
Biologic treatment, *n (%)*				0.291
TNF-α	515 (65.4)	74 (72.5)	589 (66.2)	
adalimumab	*268 (34.0)*	*49 (48.0)*	*317 (35.6)*	
certolizumab	*4 (0.5)*	*0 (0.0)*	*4 (0.4)*	
etanercept	*234 (29.7)*	*25 (24.5)*	*259 (29.1)*	
infliximab	*9 (1.1)*	*0 (0.0)*	*9 (1.0)*	
IL-12-23 (*ustekinumab*)	182 (23.1)	21 (20.6)	203 (22.8)	
IL-17	60 (7.6)	3 (2.9)	63 (7.1)	
brodalumab	*3 (0.4)*	*1 (1.0)*	*4 (0.4)*	
ixekizumab	*23 (2.9)*	*1 (1.0)*	*24 (2.7)*	
secukinumab	*34 (4.3)*	*1 (1.0)*	*35 (3.9)*	
IL-23	31 (3.9)	4 (3.9)	35 (3.9)	
guselkumab	*21 (2.7)*	*1 (1.0)*	*22 (2.5)*	
risankizumab	*9 (1.1)*	*3 (2.9)*	*12 (1.3)*	
tildrakizumab	*1 (0.1)*	*0 (0.0)*	*1 (0.1)*	

Table 1 Continued

	<65 years old (n = 788)	≥65 years old (n = 102)	All patients (n = 890)	p-value[a]
Number of previously used biologics				0.737
0	510 (64.7)	65 (63.7)	575 (64.6)	
1	159 (20.2)	18 (17.6)	177 (19.9)	
2	59 (7.5)	11 (10.8)	70 (7.9)	
3	30 (3.8)	5 (4.9)	35 (3.9)	
4	18 (2.3)	3 (2.9)	21 (2.4)	
≥5	12 (1.5)	0 (0.0)	12 (1.3)	
Number of previously used conventional systemics				0.070
0	4 (0.5)	1 (1.0)	5 (0.6)	
1	204 (25.9)	35 (34.3)	239 (26.9)	
2	301 (38.2)	35 (34.3)	336 (37.8)	
3	209 (26.5)	26 (25.5)	235 (26.4)	
4	70 (8.9)	5 (4.9)	75 (8.4)	
Type of prior conventional systemic				NA
Cyclosporin	303 (38.5)	22 (21.6)	325 (36.5)	0.001
Fumaric acid	442 (56.1)	45 (44.1)	487 (54.7)	0.026
Methotrexate	697 (88.5)	93 (91.2)	790 (88.8)	0.506
Systemic retinoid	242 (30.7)	40 (39.2)	282 (31.7)	0.090

Values might not add up due to missing values

SD standard deviation, NA not applicable, since the categorization of patients in the two age groups automatically leads to differences in age-related variables, ANOVA analysis of variance, PASI Psoriasis Area and Severity Index

[a]Pearson's Chi-square test was used for categorical outcomes, one-way ANOVA was used for continuous parametric distribution, and the Mann– Whitney U test was used for continuous non-parametric distribution

[b]Selection of biologic-naïve patients

[c]Missing sex: 10; missing body mass index: 117; missing age at onset: 76; missing duration until start of biologic: 76; missing family history of psoriasis: 100; missing psoriatic arthritis: 150; missing baseline PASI: 107

Correcting for confounders

No extensive confounder correction was performed as age groups had no statistical differences except for the CCI score and hypertension. When corrected for CCI score and hypertension, the hazard ratio (HR) for the variable 'age group' was not statistically significant for drug survival due to all discontinuation reasons and drug survival due to AEs. For drug survival due to ineffectiveness, the confounder-corrected HR for age group was 1.497 (95% confidence interval [CI] 1.053–2.129), indicating that older patients had more risk of discontinuing their biologic therapy due to ineffectiveness compared with younger patients.

Variables associated with drug survival

When analysing univariable HRs in the two different age groups separately, sex, BMI, and treatment class were associated with discontinuation due to ineffectiveness, AEs, and 'all reasons' in the younger patient group; however, there were no statistically significant associations with discontinuation in older patients. The results of separate univariable and multivariable Cox regression analyses are presented in **Tables S1** and **S2.**

When implementing imputed data in univariable Cox regression analyses, HRs were pointing in the same direction, showing robustness of the results.

Table 2 Overview of comorbidities/medical history in older and younger patients using biologics

	<65 years old (n = 788)	**≥65 years old (n = 102)**	**All patients (n=890)**
Comorbidity/medical history			
Myocardial infarction[c]	30 (3.8)	11 (10.8)	41 (4.6)
Cardiac failure[c]	4 (0.5)	2 (2.0)	6 (0.7)
Peripheral vascular disease[c]	3 (0.4)	8 (7.8)	11 (1.2)
Cerebral vascular disease[c]	17 (2.1)	11 (10.8)	28 (3.1)
Diabetes mellitus[c]	69 (8.7)	31 (30.4)	100 (11.2)
Chronic pulmonary disease[c]	45 (5.7)	11 (10.8)	56 (6.3)
Connective tissue disorder[c]	9 (1.1)	1 (1.0)	10 (1.1)
Cancer[ac]	15 (1.9)	14 (13.7)	29 (3.2)
Metastatic[c]	1 (0.1)	0 (0.0)	1 (0.1)
Chronic kidney disease[c]	9 (1.1)	0 (0.0)	9 (1.0)
Peptic ulcer[c]	13 (1.6)	6 (5.9)	19 (2.1)
Liver disease[c]	83 (10.5)	16 (15.7)	99 (11.1)
Dementia[c]	2 (0.2)	3 (2.9)	5 (0.6)
Paraplegia[c]	0 (0.0)	0 (0.0)	0 (0.0)
HIV[c]	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	157 (19.9)	45 (44.1)	202 (22.7)
Depression	66 (8.4)	7 (6.9)	73 (8.2)
CCI[b], median, range	0 (0 - 6)	1 (0 - 7)	0 (0 - 7)[d]
0	598 (75.9)	42 (41.2)	640 (71.9)
1	140 (17.8)	32 (31.4)	172 (19.3)
2	31 (3.9)	13 (12.7)	44 (4.9)
≥3	19 (2.4)	15 (14.7)	34 (3.8)

Data are expressed as n (%) unless otherwise specified

CCI Charlson Comorbidity Index, *SD* standard deviation, *ICD-10* International Classification of Diseases, Tenth Revision

[a]Included all types of cancer other than non-melanoma skin cancer

[b]The CCI consists of 17 comorbidities and each comorbidity is given a separate weight

[c]Comorbidities scored in the CCI. In a few cases, specific comorbidities were not scored in the CCI calculation but are depicted here. For specific CCI definitions, see the ICD-10 codes reported by Sundararajan et al. [10]

[d]A significantly higher CCI was seen in older adults compared with younger patients ($p < 0.001$)

Table 3 Reasons for treatment discontinuation and drug survival in older patients compared to younger patients

	All patients (n=890)	<65 years old (n=788)	≥65 years old (n=102)	p-value[a]
Reasons for treatment discontinuation (n (%))				
Ineffectiveness	220 (24.7)	185 (23.5)	35 (34.3)	
Adverse events	90 (10.1)	82 (10.4)	8 (7.8)	
Ineffectiveness and adverse events	25 (2.8)	21 (2.7)	4 (3.9)	
Other	60 (6.7)	57 (7.2)	3 (2.9)	
Lost to follow-up	46 (5.2)	42 (5.3)	4 (3.9)	
Survival functions (Kaplan-Meier analyses)[b]				
1-year (%)				
All reasons	75.5%	75.9%	72.0%	0.475
Ineffectiveness	84.0%	85.0%	76.5%	0.036
Adverse events	91.0%	90.2%	92.2%	0.613
5-year (%)				
All reasons	41.1%	42.1%	32.4%	0.144
Ineffectiveness	58.7%	60.5%	44.5%	0.006
Adverse events	79.7%	79.5%	82.1%	0.913

[a]Log-rank tests were performed to compare Kaplan-Meier curves of <65 and ≥65 year old patients.
[b]The percentage of patients calculated with Kaplan-Meier analysis that are still on drug after one or five years of treatment, split for discontinuation reason.

Adverse events leading to treatment discontinuation

Overall, 115 (12.9%) patients discontinued biologic treatment due to AEs, or AEs and ineffectiveness combined, with a maximum follow-up of years. In older patients, 12 (11.8%) patients discontinued biologic therapy due to AEs compared with 103 (13.1%) younger patients. In total, 155 AEs leading to treatment discontinuation were reported—16 AEs in older patients and 139 AEs in younger patients (see **Table 4**). Of all AEs, 16 were reported as serious, and these only occurred in younger patients. In both age groups, treatment discontinuation due to AEs was most frequently attributed to infectious causes (5/102 [4.9%] ≥ 65 years and 25/788 [3.2%] < 65 years). Upper respiratory infections/flu-like symptoms were the most frequently reported infections in both age groups.

Table 4 Adverse events leading to treatment discontinuation of biologic therapy in older patients compared to younger patients

Adverse events (MedDRA classification)	<65 years old (n=103)	≥65 years old (n=12)	All patients (n=115)
All AEs	139	16	155
Cardiac disorders	5 (3.6)	0 (0.0)	5 (3.2)
Endocrine disorders	1 (0.7)	0 (0.0)	1 (0.6)
Eye disorders	2 (1.4)	0 (0.0)	2 (1.3)
Gastrointestinal disorders	5 (3.6)	0 (0.0)	5 (3.2)
General disorders and administration site conditions	18 (12.9)	1 (6.3)	19 (12.3)
Fatigue	6 (4.3)	1 (6.3)	7 (4.5)
Fever	4 (2.9)	0 (0.0)	4 (2.6)
Oedema	3 (2.2	0 (0.0)	3 (1.9)
Malaise	2 (1.4)	0 (0.0)	2 (1.3)
Other[a]	3 (2.2)	0 (0.0)	3 (1.9)
Immune system disorders	10 (7.2)	2 (12.5)	12 (7.7)
Infections and infestations	25 (18.0)	5 (31.3)	29 (18.7)
Upper respiratory infections/flue-like symptoms	9 (52.0)	2 (12.5)	11 (7.1)
Pneumonia	4 (2.9)	1 (6.3)	4 (2.6)
Skin infections[b]	3 (2.2)	1 (6.3)	4 (2.6)
Urinary tract infections	2 (1.4)	0 (0.0)	2 (1.3)
Sepsis	1 (0.7)	0 (0.0)	1 (0.6)
Other[c]	6 (4.3)	1 (6.3)	7 (4.5)
Investigations	4 (2.9)	0 (0.0)	4 (2.6)
Musculoskeletal and connective tissue disorders	12 (8.6)	1 (6.3)	13 (8.4)
Neoplasms benign, malignant and unspecified	8 (5.8)	1 (6.3)	9 (5.8)
Nervous system disorders	13 (9.4)	1 (6.3)	14 (9.0)
Psychiatric disorders	6 (4.3)	1 (6.3)	7 (4.5)
Renal and urinary disorders	1 (0.7)	0 (0.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	8 (5.8)	1 (6.3)	9 (5.8)
Skin and subcutaneous tissue disorders	12 (8.6)	1 (6.3)	14 (9.0)
Surgical and medical procedures	4 (2.9)	1 (6.3)	5 (3.2)
Vascular disorders	2 (1.4)	0 (0.0)	2 (1.3)
Unknown	3 (2.2)	1 (6.3)	4 (2.6)

Data are expressed as *n (%)*

Percentages are calculated using the total amount of AEs in the age groups

Twenty-seven patients (24 younger patients and 3 older patients) had more than one AE simultaneously, leading to treatment discontinuation

For the MedDRA classification categories blood and lymphatic system disorders; ear and labyrinth disorders; hepatobiliary disorders; injury, poisoning and procedural complications; metabolism and nutrition disorders; reproductive system; and breast disorders, no AEs that led to treatment discontinuation were reported

AEs adverse events, *MedDRA* Medical Dictionary for Regulatory Activities

[a]Included throat complaints, cough, and pain on the chest after biologic injection

[b]Included wound infections, infection of eczema, condylomata

[c]Included latent tuberculosis infection, recurrent infections, toe infection, oral candidiasis, ear infection, gingivitis, fungal infection

PASI analysis

The mean 2-year PASI course split according to age group is shown in **Figure 2**. The median baseline PASI was 11.0 (0.0–36.2) in older patients and 11.8 (0.0–45.2) in younger patients. After 1 year of treatment, the median PASI in older and younger patients was 2.8 (0.0–11.5) and 2.6 (0.0–21.7), respectively. The proportion of patients ≥ 65 years of age who reached a PASI score of < 1 after 1 year of treatment was 20.0%, versus 24.6% in patients aged < 65 years. Furthermore, a PASI score of < 5 after 1 year of treatment was reached in 77.1% of patients aged ≥ 65 years, versus 75.4% in patients aged < 65 years. Linear regression analyses on PASI scores showed no statistical differences at 6, 12, 18, and 24 months of treatment, nor after confounder correction for CCI score and hypertension. After applying the LOCF method, similar PASI results were seen (see supplementary text).

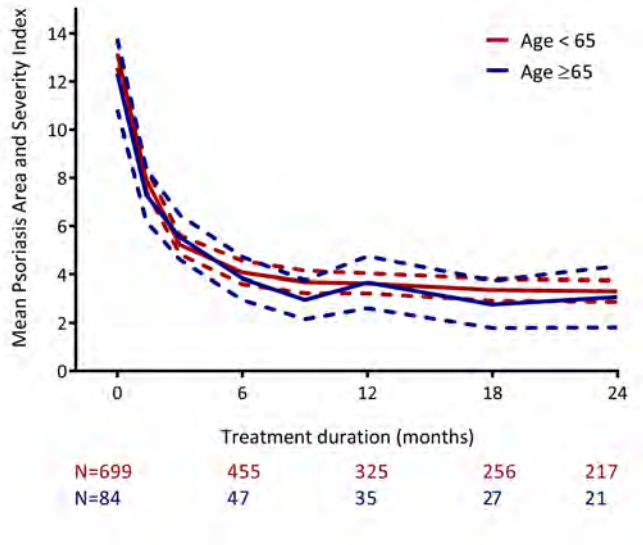

Figure 2 Mean two year PASI course + 95% confidence intervals of patients using biologics, comparing age groups

In cases where patients discontinued treatment due to ineffectiveness, PASI scores at discontinuation were collected. In patients ≥ 65 years of age, the median PASI at discontinuation was 7.8 (2.6–14.8), compared with 9.6 (0.0–34.4) in patients < 65 years of age. This difference was not statistically significant (p = 0.347).

Discussion

In this prospective real-world psoriasis cohort study, we provide insights into the drug survival, safety, and effectiveness of biologics in older patients with psoriasis, and compare outcomes in younger patients. We set out to reduce the current knowledge gap and improve personalized care for older patients with psoriasis. In total, data of 890 patients were analysed, of whom 102 were aged ≥ 65 years (11.5%). Overall, the two age groups (< 65 years and ≥ 65 years) were highly comparable regarding patient and disease characteristics. Comorbidities were more common in older patients at the start of biologic treatment, as expected and in line with previous research. [14-16] The overall 5-year drug survival of biologic treatment, including all reasons for treatment discontinuation, was comparable between age groups (≥ 65 years, 32.4%; < 65 years, 42.1%). A significant difference in 5-year drug survival was found only for ineffectiveness as the reason for treatment discontinuation; older patients had a lower ineffectiveness-related drug survival (44.5%) compared with younger patients (60.5%). Furthermore, no difference in 5-year AE-related drug survival between age groups was found (82.1% in older patients vs. 79.5% in younger patients). The number of reported AEs leading to treatment discontinuation in the first 5 years of treatment was low in both groups (≥ 65 years, 11.8%; < 65 years, 13.1%). The PASI course during the first 2 years of treatment was comparable between age groups.

Drug survival is a widely used measure that combines several aspects of treatment modalities (e.g., effectiveness and safety) [17-19]; however, literature on drug survival in older patients with psoriasis is sparse. We found a comparable overall drug survival between the age groups, before and after correction for confounding factors, as also reported for a period of 2 years by Osuna et al. [20] The crude and confounder-corrected drug survival with regard to ineffectiveness was lower for patients aged ≥65 years. Remarkably, PASI scores at discontinuation were slightly lower in older patients, although this was not statistically significant (≥ 65 years, 7.8 [2.6–14.8] versus < 65 years, 9.6 [0.0–34.4]; p = 0.347). A possible explanation for the more frequent treatment discontinuation due to ineffectiveness in older patients is the difference in needs or treatment burden between these age groups. Treatment effectiveness in research is often based on disease severity outcome, however, individual treatment goals, needs and preferences can play a significant role in treatment decision making. Although limited literature is available on the needs and treatment goals of older psoriasis patients, some distinct differences have been reported compared with those of younger patients. [21, 22] Older patients found it more important to be free of scaling and redness and to have complete clearance of psoriasis lesions than their

younger counterparts. Furthermore, minimization of different treatment modalities such as the use of topical treatment, injections, and tablets or capsules, as well as reducing hospital visits and laboratory assessments were valued significantly higher by older patients. [21] This may indicate that the treatment burden is experienced as higher, possibly due to aging-related factors such as comorbidity, polypharmacy, functional impairment, and low confidence in psoriasis therapy due to more extensive treatment history. [22-25] Another possible influential factor on drug survival differences is treatment adherence; however, evidence regarding the influence of age on treatment adherence in psoriasis is scarce. [26] One study described a modest relation between older age and higher levels of treatment adherence in patients using traditional systemic and biologic treatment. [27]

In general, older patients are more at risk of AEs using systemic medication due to comorbidity, polypharmacy, and drug metabolism alterations. [28] We found no difference in 5-year drug survival with regard to AEs between age groups and no SAEs were reported as the reason for treatment discontinuation in older patients. Infections are the most frequently reported AEs in older patients using biologics[14, 29-31]; however, a recent systematic review on systemic therapies in older patients with psoriasis described no significant association with infection occurrence and age. [3] In our study, infections were the most frequently reported AEs that led to treatment discontinuation in both age groups. Nevertheless, absolute numbers were comparable and low. Conflicting evidence has been reported regarding the occurrence of neoplasms in older patients using biologics[32]; we only report one neoplasm leading to treatment discontinuation. Note that we focused only on neoplasms as the reason for discontinuation and not on absolute rates of neoplasms during therapy in both groups.

The PASI course in this study was highly comparable between age groups, implicating a comparable treatment response. This trend has previously been described for adalimumab and etanercept regarding PASI outcomes and older age. [33-35] A recent systematic review concluded that effectiveness in older patients is in line with that of younger patients. [3] Studies evaluating the effectiveness of IL-17 and IL-23-inhibitors in older patients are scarce and would be of added value in the future.

Studies regarding older patients using biologics often have limited sample sizes and focused mainly on separate biologics. Furthermore, studies describing drug survival in this population are lacking. Our study is an addition to the current scarce body of evidence in older patients; however, more evidence regarding older patients

with psoriasis is being published.[20, 36-38] A strength of this study is its high external validity, due to its real-world practice nature, multicentre, and prospective design. When evaluating eligibility for biologic treatment, there is a chance that patients with high comorbid disease status are more often excluded. Therefore, the chance of selection bias regarding comorbidity was assessed. The CCI-score of our older population was compared with that of another Dutch psoriasis cohort, showing no significant difference, and implicating a limited influence of pre-selection. A limitation of this study is the smaller number of older patients. Furthermore, the 65-year age threshold is arbitrary, as chronological age does not always reflect health status. However, to be able to make a comparison between age groups this cut-off value was chosen in accordance with existing psoriasis literature.[3, 21, 36, 39]

To conclude, in this real-world observational study on biologic treatment in older (≥65 years of age) and younger (<65 years of age) patients, drug survival regarding discontinuation for all reasons and adverse events was high and comparable in older and younger patients. Older patients discontinued biologic treatment more often due to ineffectiveness. This may indicate a difference in needs or treatment burden between age groups, possibly related to aging factors such as extensive comorbid disease status, polypharmacy, or functional impairments. Biologic discontinuation due to AEs did not occur more frequently in older patients and no SAEs leading to treatment discontinuation in older patients were reported. Therefore, treatment of older patients with biologics appears a well-tolerated and effective therapeutic option.

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Supplementary content

Table S1 Associations with drug survival in patients aged < 65 years

Variables	**Discontinuation for all reasons** *Event = ineffectiveness, AE, ineffectiveness + AE, other reasons, death* *HR [95% CI]*	
	Univariate	*Multivariable*
Age at start of biologic	0.994 [0.982-1.004] p-value 0.235	
Age at onset of psoriasis	1.000 [0.991-1.010] p-value 0.993	
Female sex	**1.452 [1.172-1.798]** **p-value 0.001**	**1.474 [1.178-1.845]** **p-value 0.001**
Body mass index	**1.026 [1.009-1.044]** **p-value 0.003**	**1.022 [1.004-1.040]** **p-value 0.015**
Psoriatic arthritis	1.212 [0.958-1.534] p-value 0.109	
Biologic naivety	0.884 [0.712-1.098] p-value 0.266	
Family history of psoriasis	0.896 [0.711-1.130] p-value 0.355	
First-degree family history	0.937 [0.750-1.169] p-value 0.562	
Baseline PASI	1.004 [0.990-1.018] p-value 0.579	
CCI-score	**1.142 [1.013-1.288]** **p-value 0.030**	**1.168 [1.036-1.316]** **p-value 0.011**
Treatment class[1]		
• IL-12/23	**0.513 [0.383-0.686]** **p-value <0.001**	**0.516 [0.382-0.697]** **p-value <0.001**
• IL-17	1.148 [0.766-1.722] p-value 0.504	1.292 [0.847-1.973] p-value 0.235
• IL-23	0.693 [0.342-1.405] p-value 0.309	0.388 [0.144-1.045] p-value 0.062

Abbreviations: AE, Adverse Events; HR, Hazard Ratio; CI, confidence interval; PASI, Psoriasis Area and Severity Index; CCI, Charlson Comorbidity Index; IL, Interleukin.
A p-value of <0.05 was considered significant. In bold statistically significant HRs. [1] Reference category: TNF-α inhibitors.

Discontinuation due to ineffectiveness *Event = ineffectiveness, ineffectiveness + AE* *HR [95% CI]*		**Discontinuation due to adverse events** *Event = AE, ineffectiveness + AE*	*HR [95% CI]*
Univariate	*Multivariable*	*Univariate*	*Multivariable*
1.000 [0.987-1.013] p-value 0.989		1.014 [0.995-1.033] p-value 0.147	
0.999 [0.987-1.011] p-value 0.861		1.010 [0.993-1.026] p-value 0.240	
1.418 [1.074-1.872] **p-value 0.014**	**1.374 [1.008-1.874]** **p-value 0.044**	**1.687 [1.146-2.485]** **p-value 0.008**	**1.824 [1.226-2.714]** **p-value 0.003**
1.032 [1.010-1.055] **p-value 0.005**	**1.043 [1.021-1.065]** **p-value <0.001**	**1.032 [1.002-1.063]** **p-value 0.039**	
1.362 [1.010-1.837] **p-value 0.043**		1.193 [0780-1.824] p-value 0.416	
0.815 [0.616-1.078] p-value 0.151		0.770 [0.520-1.141] p-value 0.193	
0.837 [0.622-1.125] p-value 0.238		0.808 [0.538-1.215] p-value 0.306	
0.803 [0.602-1.071] p-value 0.135		1.018 [0.687-1.510] p-value 0.928	
1.019 [1.002-1.037] p-value 0.031		0.995 [0.969-1.022] p-value 0.715	
1.137 [0.971-1.331] p-value 0.110		**1.394 [1.181-1.646]** **p-value <0.001**	**1.404 [1.178-1.673]** **p-value <0.001**
0.432 [0.289-0.645] **p-value <0.001**	**0.414 [0.265-0.646]** **p-value <0.001**	**0.407 [0.227-0.732]** **p-value 0.003**	**0.378 [0.205-0.698]** **p-value 0.002**
1.244 [0.752-2.057] p-value 0.395	1.404 [0.817-2.412] p-value 0.220	1.210 [0.65-2.418] p-value 0.590	1.447 [0.722-2.902] p-value 0.298
0.578 [0.213-1.563] p-value 0.280	0.381 [0.093-1.554] p-value 0.179	0.258 [0.036-1.856] p-value 0.178	0.302 [0.042-2.184] p-value 0.236

Table S2 Associations with drug survival in patients aged ≥65

Variables	**Discontinuation for all reasons** *Event = ineffectiveness, AE, ineffectiveness + AE, other reasons, death*	**Discontinuation due to ineffectiveness** *Event = ineffectiveness, ineffectiveness + AE*	**Discontinuation due to adverse events** *Event = AE, ineffectiveness + AE*
	HR [95% CI]	*HR [95% CI]*	*HR [95% CI]*
Age at start of biologic	0.983 [0.910-1.062] p-value 0.656	0.950 [0.867-1.041] p-value 0.274	1.022 [.881-1.185] p-value 0.771
Age at onset of psoriasis	1.007 [0.991-1.023] p-value 0.392	0.999 [0.982-1.017] p-value 0.937	1.019 [0.985-1.053] p-value 0.272
Female sex	1.015 [0.578-1.783] p-value 0.958	1.089 [0.577-2.054] p-value 0.793	2.890 [0.870-9.601] p-value 0.083
Body mass index	0.986 [0.924-1.053] p-value 0.679	0.958 [0.886-1.037] p-value 0.291	1.086 [0.967-1.220] p-value 0.163
Psoriatic arthritis	0.939 [0.469-1.881] p-value 0.859	1.024 [0.471-2.226] p-value 0.952	0.639 [0.136-3.008] p-value 0.571
Biologic naivety	0.790 [0.450-1.388] p-value 0.412	0.917 [0.476-1.766] p-value 0.795	0.755 [0.240-2.380] p-value 0.631
Family history of psoriasis	0.740 [0.412-1.329] p-value 0.314	1.100 [0.546-2.217] p-value 0.789	0.305 [0.092-1.013] p-value 0.053
First-degree family history	0.719 [0.42-1.286] p-value 0.266	0.936 [0.481-1.825] p-value 0.847	0.414 [0.125-1.377] p-value 0.151
Baseline PASI	1.019 [0.972-1.068] p-value 0.427	1.027 [0.975-1.082] p-value 0.320	1.032 [0.947-1.124] p-value 0.470
CCI-score	1.019 [0.853-1.217] p-value 0.833	0.924 [0.734-1.163] p-value 0.501	1.029 [0.732-1.447] p-value 0.870
Treatment class[1]			
• IL-12/23	0.819 [0.419-1.600] p-value 0.558	0.648 [0.285-1.474] p-value 0.301	1.464 [0.441-4.868] p-value 0.534
• IL-17	0.741 [0.101-5.412] p-value 0.768	0.889 [0.121-6.537] p-value 0.908	NA
• IL-23	NA	NA	NA

Abbreviations: AE, Adverse Events; HR, Hazard ratio; CI, confidence interval; PASI, Psoriasis Area and Severity Index; CCI, Charlson Comorbidity Index; IL, Interleukin.

A p-value of <0.05 was considered significant. In bold statistically significant HRs.

NA: not applicable, cannot be computed due to the low numbers in this age group.

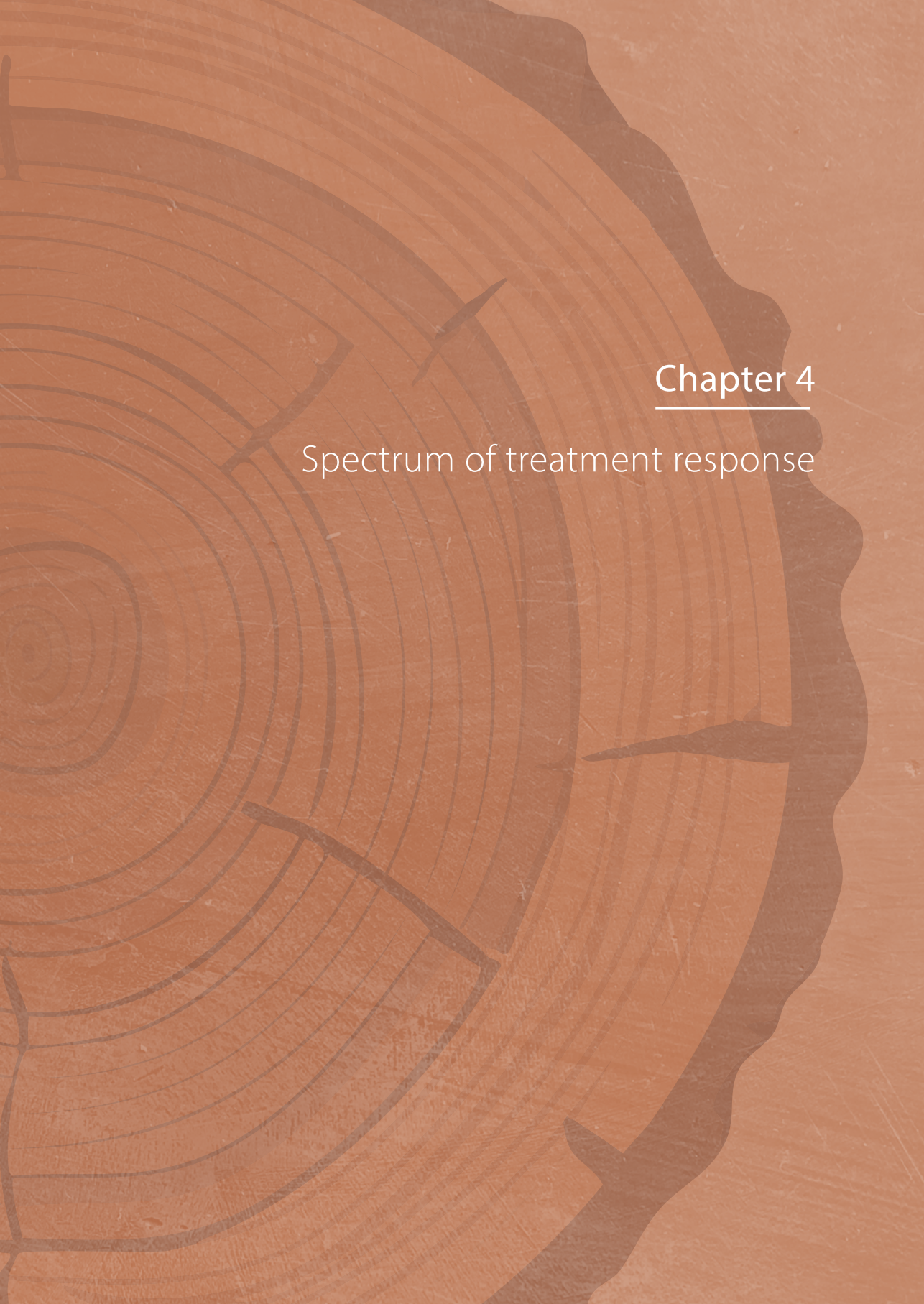
[1] Reference category: TNF-α inhibitors.

Supplement LOCF

In patients who discontinued treatment due to ineffectiveness and/or adverse events, PASI-scores at discontinuation were carried forward using the last observation carried forward method (LOCF). With this method, PASI-scores in the case of early-determination are carried forward, which ensures a more conservative approach.

Using LOCF data, linear regression analyses showed no difference in PASI-outcomes on month 6, 12, 18, and 24.

Absolute and relative PASI outcomes were more conservative after applying the LOCF-method compared to the raw data. After one year of treatment, the median [range] PASI in older patients was 4.5 [12.0] versus 3.6 [35.4] in younger patients. The proportion of patients ≥65 who reached a PASI-score <1 after one year of treatment was 12.3% vs. 18.9% in patients <65. A PASI-score <5 after one year of treatment was reached in 65.5% of patients ≥65 vs. 64.9% in patients <65.



Chapter 4

Spectrum of treatment response

4.1 How to define a 'super-responder' to biologics in psoriasis studies?

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Dear editor,

The field of biologic treatment for patients with psoriasis has witnessed rapid advances over the last two decades, leading to the development of highly effective therapeutic options. Recently, there has been an increase of publications on 'super-responders' to biologic therapy. However, to date, there has been no consensus on the definition of a super-responder in literature. Classifying the super-responders in a similar manner can play a pivotal role in identifying biomarkers or predictors for super-response and could therefore help in selecting the most appropriate therapy for individuals. In this study, we aimed to contribute to this growing area of research by (i) synthesizing the different definitions of super-responders currently being used in the psoriasis literature; and (ii) evaluating the impact of these different definitions on the composition of the super-responder group.

To achieve this, PubMed was searched with several synonyms for the words 'super-responder', 'psoriasis' and all biologics currently used in the treatment of psoriasis (etanercept, infliximab, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, risankizumab and tildrakizumab). This search, executed in March 2023, yielded 10 studies that used 8 different definitions of super-response. An overview of these eight currently used super-responder definitions is presented in **Table 1**. The primary aspect that all super-responder studies have in common is the use of the Psoriasis Area and Severity Index (PASI) to classify patients into different responder groups. The studies used absolute or relative PASI outcomes, with varying cut-off values [e.g. absolute PASI≤1, relative ≥ 90% improvement in PASI (PASI 90)]. Other notable distinctions in the current literature included the timepoint chosen to define a super-responder as well as the duration of maintenance of the super-response status. Most studies used a relatively short period (<6 months) for defining the super-responder status[1-5], although some studies applied a long-term super-responder status with a maintenance of 2-5 years[6-8]. The studies also used different data sources: post hoc analyses using trial data[1, 4], and analyses using real-world data. Lastly, six studies analysed super-response for only one biologic, whereas two studies analysed two treatment classes: tumour necrosis factor-α inhibitors and ustekinumab[6], and interleukin (IL)-17 and IL-23 inhibitors[5].

To assess how much the chosen definition of a super-responder can influence the percentage of super-responders found, we applied three different super-responder definitions from the current literature to a fixed cohort of patients. Using data from the prospective real-world BioCAPTURE registry, which contains data for

all currently available biologics (www.biocapture.nl; data-lock November 2022), we applied the following divergent definitions of super-response as used in the aforementioned studies: (i) absolute PASI 0 at weeks 12 and 24[3], (ii) absolute PASI ≤1 at week 12/16[2], and (iii) relative PASI≥90 at week 28[4]. PASI scores of 891 biologic treatments during the first 6 months of treatment were available for analyses. Definition (i) resulted in 32 (3.6%) super-responders, definition (ii) in 103 (11.6%) super-responders, and definition (iii) in 210 (23.6%) super-responders. This demonstrates that the chosen definition of a super-responder greatly influences results, because the proportion of super-responders significantly differed among the used definitions. When analysing these results while stratifying by individual biologics, we observed a consistent pattern of differences (data not shown). As these results are often used in subsequent analyses that explore the association between super-responder status and baseline characteristics or biomarkers, such analyses are inevitably affected by the choice of definition of super-responders.

Table 1 Different definitions for super-responder status in current literature

Author	First published	Biologic	Definition of super-responder used
Talamonti et al.	May 2019	Ustekinumab	Maintained PASI100 for 2 years
Morelli et al.	December 2021	Secukinumab	Maintaining PASI100 up to weeks 88 and 100
Feldman et al.	March 2022	Tildrakizumab	PASI 90 at week 28
Loft et al.	April 2022	TNF-a and IL-12/23	Super-responders were patients treated with their first biologic for a minimum of 5 years without an absolute PASI >3 between 6 months and 5 years
Reich et al.	August 2022	Guselkumab	PASI 100 response at week 20 and 28
Ruiz-Villaverde et al.	September 2022	Guselkumab	PASI 0 at week 12 and week 24
Rompoti et al.	January 2023	Brodalumab	PASI ≤1 at week 12/16
Mastorino et al.	December 2022	IL-17 and IL-23 inhibitors	Bio-naïve patients with PASI 100 at week 16 and maintained at week 28

IL, interleukin; PASI, Psoriasis Area and Severity Index; PASI 90, ≥90% improvement in PASI; PASI 100, 100% improvement in PASI; TNF; tumour necrosis factor.

Several factors contribute to the differences observed between the definitions. Firstly, the timing of defining and/or maintaining super-response has a significant impact. Applying definition (i) - absolute PASI 0 at weeks 12 and 24 - in our cohort yielded 32 (3.6%) super-responders. However, applying PASI 0 only at week 24 (omitting PASI 0 at week 12) resulted in 140 (15.7%) super-responders. Another

factor that could influence the proportion of super-responders is whether absolute or relative PASI-scores are used. Using relative PASI-scores in the definition of a super-responder could exclude patients from super-responder status in real-world evidence (RWE) studies, as baseline PASI-scores are generally lower in RWE studies than in randomized controlled trials. Therefore, we suggest using a combined measure, including both a relative measure (e.g. PASI 90) and an absolute threshold (e.g. PASI < 2). In addition, maintenance of therapy with a high response could be considered. As there is no established definition for super-response, future studies testing the robustness of different thresholds and timepoints of super-response (i.e. sensitivity analyses) could be considered, as well as the use of advanced statistical models, in order to analyse longitudinal data on super-responders.

The number of super-responders is expected to increase in the coming years due to the availability of more potent biologic treatments. Hence, we believe awareness of the different super-responder definitions used is of importance, and consensus could be reached using a Delphi approach.

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4.2 Multi-treatment resistance to biological treatment in patients with psoriasis: definitions and implications

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Dear Editor,

Although many psoriasis patients respond well to biologics, a subgroup remains for whom treatment with multiple subsequent biologics is unsuccessful. A standardized classification for this difficult-to-treat group designated as patients with 'multi-treatment resistance' (MTR) is not yet defined, but it is important for better understanding of underlying factors and improving patient care.

To identify classifications for MTR utilized in literature, we conducted a PubMed search, merging synonyms for 'multi-treatment resistance', combined with keywords for psoriasis and biologics. The implications of these different definitions on the point-prevalence of MTR were analysed using data from BioCAPTURE, a prospective, multicentre registry on biologics for psoriasis (www.biocapture.nl). Each centre prescribed a wide variety of biologics, mostly with the absence of access limitations, which enabled providing insight into the implications of using different MTR definitions in a general psoriasis population. The impact of various thresholds for numbers of discontinued biologics (≥2 to ≥9) and biologic classes (≥2, ≥3 or 4) was tested, per reason of discontinuation (**Table 2**).

The literature search (28 November, 2023) yielded four articles with a definition for MTR for biologics in psoriasis.[1-4] These definitions all differed and were proposed by the authors of the publications, with three of them exclusively focusing on ineffectiveness (**Table 1**).

For testing the impact of various MTR definitions on the psoriasis cohort, 1266 patients were eligible. Applying the MTR definitions found in the literature resulted in a wide variation of MTR point-prevalences ranging from 3.2% to 29.5% (**Table 1**). Additionally, with the analysis of various thresholds for the minimum required number of discontinued biologics, which could potentially be incorporated in the MTR definition, a reduction in the corresponding point-prevalence was seen with increasing numbers of previously discontinued biologics and biologic classes (**Table 2**). The most common reason for treatment discontinuation in BioCAPTURE was ineffectiveness, followed by adverse events; this distribution remained present with increasing numbers of discontinued biologics and biologic classes. Adding failure to different biologic classes to the definition exerted a significant impact on MTR prevalence, for example, 17.1% discontinued ≥2 biologics due to ineffectiveness versus 12.6% discontinued ≥2 biologics due to ineffectiveness from ≥2 classes. Of note, it should be realized that absolute point-prevalences of MTR in the analyses were based on real-world data, which may differ when using other

sources like prescription databases. However, it is expected that differences in used definition will affect the change in MTR prevalence to a similar extent.

Future studies should take the implications associated with different definitions for MTR into account, as we here illustrated that these differences exert substantial changes in the corresponding point-prevalences of MTR. Various factors could be considered for incorporation into the definition of MTR. For instance, the requirement to solely include patients who discontinued biologics from different classes in defining MTR should be discussed, as previous research demonstrated the success of intra-class switching.[5, 6] Additionally, besides defining MTR based on treatment ineffectiveness, failure based on adverse events related to biologics use could also be implemented.[7, 8] Furthermore, incorporating a time component and disease activity measures upon discontinuation is possible. Additionally, strategies like dose adjustments and concomitant systemic treatment may influence the risk of discontinuation. However, adding more factors contributes to more complexity in the definition of MTR as it requires detailed information. It is important to reach a well-balanced definition for MTR that should contain enough information and be convenient to use in practice. Through a Delphi approach, including national and international psoriasis societies, consensus on the MTR definition can be obtained. This study may facilitate reaching consensus on the MTR definition, paving the way for more insight into, and improvement of, treatment for this difficult-to-treat group of patients.

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Table 1 Definitions of multi-treatment resistance (MTR) in current literature, and implications of the definitions on the prevalence of MTR using data from the BioCAPTURE cohort

Author	Date published	Study type	Number of included MTR patients (n)	Definition of MTR	Method used for defining MTR	Proportion of the BioCAPTURE registry
Mastorino et al.[1]	Aug 2022	Retrospective observational cohort study	10	Patients not responding to at least four biologics	Literature search with definition based on opinion of the authors	3.2%
Loft. et al.[2]	Aug 2022	Prospective observational cohort study	214	Patients with treatment failure (due to lack of /loss of effectiveness) to at least three different biologics in at least two different biologic classes	Definition based on opinion of the authors	6.6%
Jin et al.[3]	Nov 2023	Prospective observational cohort study	65	Patients who discontinued ≥2 biologics of different classes, each used for ≥90 days, due to inadequate efficacy	Definition based on opinion of the authors	12.6% (the duration of ≥90 days of use was not accounted for in our analyses)
Hadeler et al.[4]	Jan 2023	Cross-sectional study	51	Patients with the use of three or more biologics	Definition based on opinion of the authors	29.5% (definition not conclusive and therefore interpreted as discontinuation of ≥2 biologics including all reasons of discontinuation)

Table 2 Point prevalence of multi-treatment resistance (MTR) using different thresholds for number of previously discontinued biologics or biologic classes, split for reasons of discontinuation

	Discontinuation of ≥ 2 biologics	Discontinuation of ≥ 3 biologics	Discontinuation of ≥ 4 biologics	Discontinuation of ≥ 5 biologics	Discontinuation of ≥ 6 biologics	Discontinuation of ≥ 7 biologics
All reasons for discontinuation n (%)[a]	373 (29.5%)	186 (14.7%)	101 (8.0%)	51 (4.0%)	23 (1.8%)	7 (0.6%)
Discontinuation due to ineffectiveness n (%)[b]	217 (17.1%)	88 (7.0%)	40 (3.2%)	16 (1.3%)	5 (0.4%)	n.a.
Discontinuation due to adverse events n (%)[b]	62 (4.9%)	20 (1.6%)	7 (0.6%)	2 (0.2%)	2 (0.2%)	1 (0.08%)
Discontinuation due to other reasons n (%)[c]	2 (0.2%)	n.a.	n.a.	n.a.	n.a.	n.a.
Discontinuation due to unknown causes n (%)	45 (3.6%)	12 (0.9%)	2 (0.2%)	n.a.	n.a.	n.a.

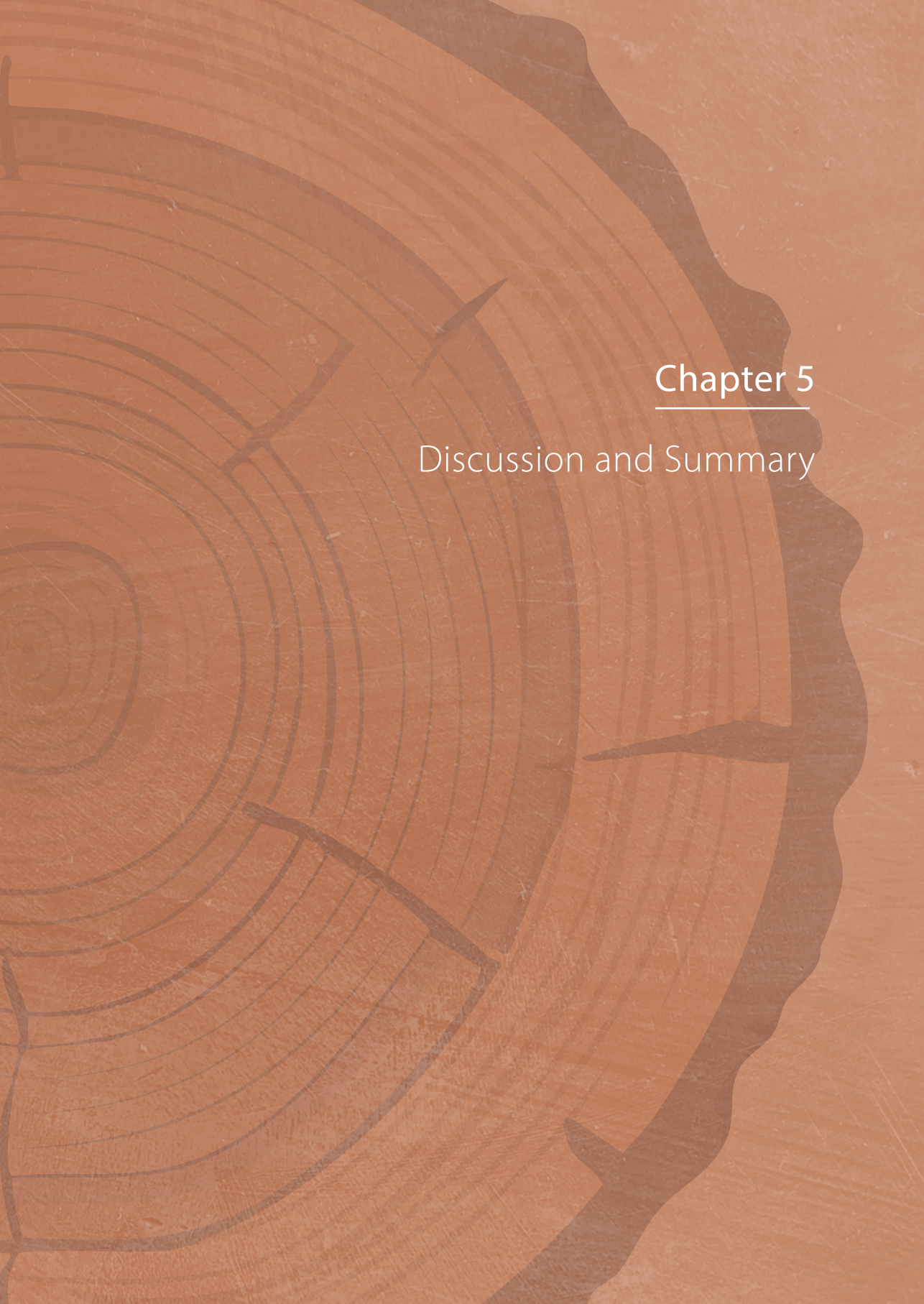
	Discontinuation of ≥ 8 biologics	Discontinuation of ≥ 9 biologics	Discontinuation of ≥ 2 biologic classes	Discontinuation of ≥ 3 biologic classes	Discontinuation of ≥ 4 biologic classes
All reasons for discontinuation n (%)[a]	3 (0.2%)	2 (0.2%)	273 (21.6%)	123 (9.7%)	28 (2.2%)
Discontinuation due to ineffectiveness n (%)[b]	n.a.	n.a.	160 (12.6%)	53 (4.2%)	11 (0.9%)
Discontinuation due to adverse events n (%)[b]	n.a.	n.a.	52 (4.1%)	12 (0.9%)	2 (0.2%)
Discontinuation due to other reasons n (%)[c]	n.a.	n.a.	2 (0.2%)	n.a.	n.a.
Discontinuation due to unknown causes n (%)	n.a.	n.a.	29 (2.3%)	1 (0.08%)	n.a.

Note: Data from the BioCAPTURE registry (n = 1266). 497 patients were still treated with their first biologic, and 769 patients discontinued ≥1 biologic including all reasons for discontinuation. The four different biologic classes include TNF-α inhibitors, IL-12/23 antagonist, IL-17 antagonists and IL-23 antagonists. Analysis was limited to currently registered biologics for the treatment of psoriasis. Treatment episodes discontinued due to loss of follow-up or death were excluded. Solely the last treatment episodes per individual biologic per patient were included, as previous discontinuation(s) were per definition temporary.

[a] All reasons for discontinuation included ineffectiveness, adverse events, other causes and unknown causes.

[b] Treatment episodes with the reason of treatment discontinuation including both ineffectiveness and adverse events were incorporated in both treatment discontinuation due to effectiveness as well as treatment discontinuation due to adverse events.

[c] Other reasons included one patient who discontinued treatment due to remission.



Chapter 5

Discussion and Summary

This thesis aimed to generate scientific evidence on the effectiveness, safety, and patient satisfaction of biologic treatments for psoriasis. The primary data source was the BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics) registry. As treatment options continue to expand, psoriasis management in daily clinical practice is evolving. The findings of this thesis are intended to inform clinical decision-making in psoriasis treatment and provide context for certain research methodologies in the field. In this chapter, the main findings are summarized and discussed according to the following overarching aims as stated in the introduction:

- To explore and compare real-world drug survival and effectiveness of biologics for psoriasis
- To generate real-world evidence of treatment with biologics in children and older adults with psoriasis
- To study the influence of current definitions for super-response and multi-treatment failure on psoriasis studies

Aim I: to explore and compare real-world drug survival and effectiveness of biologics for psoriasis

At the time of drafting **Chapter 2.1**, real-world evidence (RWE) comparing the effectiveness of interleukin (IL)-17-inhibitors, IL-23-inhibitors, tumour necrosis factor alpha (TNF-α)-inhibitors, and an IL-12/23-inhibitor in treating psoriasis was limited. In **Chapter 2.1**, we aimed to directly compare the effectiveness of these biologic therapies for psoriasis over the first year of treatment, while accounting for potential confounders. Utilizing BioCAPTURE data, 1,080 treatment episodes involving 700 psoriasis patients were included. We assessed the mean absolute Psoriasis Area and Severity Index (PASI) scores and the proportion of patients achieving PASI90/PASI75 using linear mixed models and mixed logistic regression models, respectively, while adjusting for baseline PASI, biologic naivety, and body weight. Patients receiving adalimumab, ustekinumab, secukinumab, ixekizumab, or guselkumab exhibited significantly lower mean PASI scores after 12 months compared to those on etanercept. Additionally, they had significantly higher odds of achieving PASI90 compared to etanercept-treated patients. Specifically, patients treated with ixekizumab or guselkumab demonstrated higher probabilities of achieving PASI90 compared to those on adalimumab, ustekinumab, or secukinumab. Notably, the proportions of patients reaching PASI90/75 were substantially lower in this real-world study compared to randomized controlled trials (RCTs).

As outlined in the introduction, another way to study the real-world effectiveness of drugs is by using drug survival analysis. Drug survival refers to the duration a particular medication is used, often termed "time on drug." This is analyzed using the Kaplan-Meier methodology. The length of time until discontinuation of a drug is influenced by various factors, including effectiveness, side effects, and tolerability, making drug survival a comprehensive measure. In **Chapter 2.2,** the drug survival of guselkumab, the first IL-23 inhibitor for the treatment of psoriasis, was subject of investigation. The aim of this observational multicentre study was to evaluate the 1- and 2-year drug survival of guselkumab in psoriasis patients and to elucidate predictors of drug survival. Data from the BioCAPTURE registry was combined with data from 4 other centres in the Netherlands. Drug survival was analysed using Kaplan-Meier survival curves, split for reason of discontinuation. We included 195 patients on guselkumab treatment, of which 29.7% were biologic naive. Overall 1- and 2-year drug survival rates were 85.5% and 77.8%, respectively. In multivariable Cox regression analyses, diabetes mellitus type 2 and psoriatic arthritis were associated with shorter drug survival due to ineffectiveness or adverse events, respectively. When separately assessing ineffectiveness-related and adverse event-related discontinuation, high survival rates were seen for both groups (2-year survival rates 88.7% and 92.1%, respectively).

In addition to investigating drug survival within the BioCAPTURE cohort, we aimed to study the drug survival of the 'newer' biologic classes, the IL-17 and IL-23 inhibitors, by conducting a systematic review and meta-analysis (**Chapter 2.3**). We systematically searched four databases up to December 27, 2023. Inclusion criteria encompassed cohort studies involving patients aged ≥ 18 years with plaque psoriasis, evaluating drug survival of at least one IL-17 or IL-23 inhibitor. Survival probabilities from Kaplan-Meier curves were extracted using a semi-automated tool. Non-parametric random-effects models pooled the data to construct distribution-free summary survival curves, categorized by discontinuation reasons and biologic naivety. Results were segregated for registry/electronic health records (EHR) and pharmacy/claims data. The review incorporated 69 studies encompassing 48,704 patients receiving secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, or tildrakizumab. Summary drug survival estimates from registry/EHR studies revealed high rates for overall drug survival, encompassing all different reasons for discontinuation. When we analysed discontinuation due to ineffectiveness and discontinuation due to adverse events separately, high summary drug survival estimates were observed as well (all point estimates ≥ 0.8 at year 1). Guselkumab and risankizumab demonstrated the highest summary drug survival estimates for all outcomes, reflecting that the chance that patients stay on

these drugs is higher in the case of guselkumab and risankizumab. Notably, the source of data used made a difference; estimates from pharmacy/claims databases were lower than those from registry/EHR data.

In the last chapter **(Chapter 2.4)** of the first aim, the performance of treatment with an IL-23 inhibitor was studied in patients that were previously treated with the IL-12/23 inhibitor ustekinumab but experienced insufficient therapeutic effect. In general, when ustekinumab (IL-12/23-inhibitor) proves ineffective, transitioning to the newer generation IL-23-inhibitors is a potential alternative, yet there is limited understanding of their effectiveness following unsuccessful ustekinumab treatment. Since ustekinumab and IL-23 inhibitors partially share their mechanism of action through the IL-23/IL-17 axis, it can be hypothesized that treating patients with IL-23 inhibitors after IL-12/23 treatment may not be the most effective option. In this study, we aimed to investigate this hypothesis. Conducted as a prospective, multicentre, real-world investigation utilizing data from the BioCAPTURE registry, we enrolled adult psoriasis patients undergoing treatment with the IL-23 inhibitors guselkumab, risankizumab, or tildrakizumab. A total of 159 patients with an IL-23 inhibitor treatment episode were included, 68 of whom had previously experienced ineffectiveness with ustekinumab, while 91 had not used ustekinumab previously. Drug survival analyses were performed to evaluate and contrast two-year drug survival rates. Effectiveness was assessed by analysing first-year PASI-scores. Results were juxtaposed with those of patients receiving IL-23 inhibitors without prior ustekinumab therapy, with confounder correction applied. Patients with a history of ustekinumab ineffectiveness showed a tendency towards lower drug survival rates on IL-23 inhibitors and higher PASI-scores compared to those without prior ustekinumab exposure. However, after confounder correction, the difference in drug survival disappeared. For PASI, the difference remained statistically significant at 6 months, but it was not consistently observed at 12 months. Given that a substantial proportion of patients responded adequately to IL-23 inhibitors following ustekinumab failure, we concluded that IL-23 inhibitors emerged as a viable treatment option subsequent to ustekinumab failure.

An essential, overarching lesson drawn from the initial chapters of this thesis is the critical role of investigating separate reasons for discontinuation in drug survival analyses. In **Chapter 2.2,** the importance of analysing discontinuation reasons separately was highlighted when we identified a small group of patients who discontinued guselkumab due to remission. If these discontinuations had been classified as regular cessations, the estimated drug survival rates would have appeared poorer, and valuable information would have been lost. Discontinuation

due to remission is in fact a positive reason for drug discontinuation and should be depicted and handled as such. [1] In general, the most frequent reason for discontinuing biologics in psoriasis treatment has been ineffectiveness. [2-4] However, when analysing our data on guselkumab drug survival, we observed that very few patients discontinued guselkumab due to ineffectiveness, as well as due to adverse events, resulting in a very high drug survival. The nearly equal drug survival outcomes for drug survival specifically for ineffectiveness and specifically for adverse events observed in our study contrasts with earlier research findings on different biologics. Other real-world studies on the drug survival of guselkumab report promising results as well, as shown in our meta-analysis (**Chapter 2.3**). [5-18] Lastly, analysing discontinuation due to side effects separately allowed us to identify that patients with PsA were more likely to discontinue their biologic therapy earlier in our cohort. The association between discontinuation due to side effects and PsA was primarily attributed to patients with a pre-existing PsA diagnosis who experienced an increase in musculoskeletal complaints as a side effect. This finding was unexpected, given that guselkumab is an approved treatment for PsA. [19] Furthermore, a meta-analysis pooling data of almost 25,000 patients on the association between PsA and drug survival, observed that PsA was associated with an improved drug survival. [2] The improved drug survival was hypothesized to be linked to an increased motivation and awareness of the importance of treatment in case of concomitant arthritis.

The matter of analysing reasons for discontinuation of treatment separately was further evident when examining the drug survival outcomes of the 69 included studies in our systematic review and meta-analysis in **Chapter 2.3**. Drug survival studies have become increasingly prevalent in the field of dermatology in recent years. However, most studies included in our review reported combined drug survival rates for all discontinuation reasons without transparency regarding which reasons were included in their analyses. For example, for secukinumab, the 'oldest' biologic included in our review, 36 studies reported on overall drug survival, opposed to 6 studies on drug survival related to ineffectiveness, and to only 3 studies on drug survival related to adverse events. This lack of specificity makes it more challenging to interpret the combined results. In daily clinical practice, several factors can influence drug survival outcomes that should not be considered as treatment-related discontinuation reasons, such as family planning or, relevant during the research period of **Chapter 2.2**, fear of COVID-19 due to the pandemic. [15, 20] By encouraging more researchers to analyse drug survival split for specific discontinuation reasons, the results would become more comparable

between studies and more precise, facilitating subsequent research and ultimately improving clinical decision-making.

In line with this argument, we encountered another challenge in analysing drug survival data. During our review, we identified multiple studies based on pharmacy or claims databases. These databases, which compile information on doctors' appointments, insurance, and prescriptions, typically encompass larger populations than patient registries or cohorts based on medical records.[21] However, since access to patients medical records is not available for pharmacy/claims databases, these databases often lack critical data, particularly regarding reasons for treatment discontinuation. Consequently, in our review, we observed consistently lower drug survival rates in studies utilizing pharmacy or claims databases, probably due to the fact that these studies report on overall drug survival without distinguishing between different discontinuation reasons and capture dispensing data of medication but not the actual use. It is important to consider that various reasons for discontinuation, such as the desire for pregnancy or financial constraints, may not be directly related to the drug's performance. Insurance coverage and reimbursement policies can significantly influence drug survival rates. Restrictions imposed by insurance companies, such as prior authorization requirements or limited formulary options, may create barriers to accessing certain medications. Patients who face difficulties in obtaining insurance coverage for a prescribed medication are more likely to discontinue treatment. Financial reasons should be registered separately to prevent them from skewing drug survival rates related to ineffectiveness and adverse events. All of these nuanced aspects are not accurately reflected in data from pharmacy/claims databases. In future studies, we strongly encourage reporting drug survival separately for different discontinuation reasons and factors influencing drug survival, rather than only combining all reasons into an overall drug survival rate. For now, it is crucial to consider the differences between these data sources when interpreting the results of these studies.

As described in the introduction of this thesis (**Chapter 1**) RCTs and RWE complement each other and the combination of both types of research can help our understanding of the drugs under investigation. The fact that our real-world results are less favourable than those from RCTs is not surprising. RCTs take place in a more controlled setting, often including a specific and less heterogeneous population.[22] The difference between RCTs and RWE results in relation to the PASI score became more evident in **Chapter 2.1** and **2.4**. In RCTs, patients typically have a higher baseline PASI than in RWE. In real-world settings, patients possibly have lower baseline PASIs scores due to lingering effects of previous treatments. Achieving a

relative PASI outcome, such as 90% reduction in PASI (PASI90), is typically easier with higher initial PASI scores, as reported in RCTs. When comparing our data from **Chapter 2.1** to RCTs, the gap between absolute outcomes in real-world and RCT data appears to be smaller for absolute outcome measures, particularly in achieving a PASI ≤5. For instance, in the 52-week follow-up data on ixekizumab from the IXORA-S trial, 88.2% of patients reached an absolute PASI ≤5, which is similar to the 85.7% observed in our cohort. However, the proportions achieving a relative PASI90 differed significantly, with 76.5% in the IXORA-S trial compared to 21.4% in our cohort. [23] Higher baseline PASIs are not only reported in RCTs, but there are also differences between RWE cohorts thereby influencing outcomes. When comparing the relative PASI90 scores of patients switching from ustekinumab to guselkumab (**Chapter 2.4**) with those from other cohorts, we observed notably larger differences (28.6% in our cohort versus 71%-77% in other cohorts[24, 25]) than when comparing the absolute PASI ≤5 scores (71% in our cohort versus 81% in another cohort[26]). Hence, when comparing effectiveness between cohorts, as well as outcomes from RCTs, we would advocate for additional reporting of absolute PASI outcomes on top of relative PASI outcomes, as the absolute outcomes are not influenced by baseline PASI.

Another key conclusion from the initial chapters of this thesis is that IL-23 inhibitors consistently perform as good as, or even better than other biologics. Guselkumab, the first available IL-23 inhibitor, demonstrated superior effect on PASI scores compared to the other biologics in **Chapters 2.1** and **2.4**, and, along with risankizumab (another IL-23 inhibitor), showed the highest drug survival rates in **Chapters 2.2** and **2.3**. The high drug survival and effectiveness of IL-23 inhibitors could be attributed to their upstream effect on the IL-23/IL-17 cytokine pathway. [27] As detailed in **Chapter 1**, IL-23 is crucial for the development and activation of Th17 cells and other cytokines. Neutralizing IL-23 not only reduces the expression of IL-17A but also other cytokines such as IL-17F, IL-21, and IL-22, which also contribute to the pathogenesis of psoriasis but to a lesser extent. [28, 29] In **Chapter 2.4**, we examined the effectiveness of IL-23 inhibitors in patients who had previously failed ustekinumab, an IL-12/23 inhibitor. It was reassuring to observe that IL-23 inhibitors remained a viable treatment option for these patients. In literature, it is further hypothesized that inhibiting IL-12 alongside IL-23 (with ustekinumab, an IL-12/23 inhibitor) is not beneficial in psoriasis. [30, 31] Due to the limited availability of treatments as a result of their more recent introduction, a comprehensive comparison between separate IL-23 inhibitors was not yet feasible in this thesis. Future research is needed to determine the precise positioning of this treatment class within the full spectrum of psoriasis therapies.

Aim II: to generate real-world evidence of treatment with biologics in in children and older adults with psoriasis

The second aim of this thesis focused on two age groups at the extremes of the age spectrum, which are often understudied. **Chapter 3.1** specifically concentrated on patients under 18 years of age. Psoriasis in paediatric patients often brings about symptoms like itch, pain, and fatigue, but the extent of this burden and the impact of treatment on these complaints remain largely unexplored. This study aimed to investigate the levels of itch, pain, fatigue, and self-assessed disease severity in paediatric psoriasis patients both at baseline and during one-year treatment with either methotrexate or biologics, and to connect these outcomes with the Psoriasis Area and Severity Index (PASI). Data were extracted from the prospective Child-CAPTURE registry. Visual Analogue Scales (VAS; ranging from 0 to 100) for itch, pain, fatigue, and disease severity were recorded quarterly and analysed using linear mixed models. The study included 166 paediatric patients with psoriasis, with 142 methotrexate and 76 biologic treatment episodes. Itch and disease severity posed a more significant burden on children with psoriasis than pain and fatigue. While itch, pain, and self-assessed disease severity decreased during both methotrexate and biologic treatment, fatigue remained unresponsive to treatment, despite an objective decrease in PASI. Notably, PASI scores at three months demonstrated a greater reduction in the biologic treated group, particularly in methotrexate-naïve patients.

As psoriasis is a prevalent inflammatory condition affecting individuals of all ages, older adults are also affected (**Chapter 3.2**). However, older patients are frequently excluded from clinical trials, resulting in limited data on this subpopulation, particularly concerning the safety and efficacy/effectiveness of biologic treatments. This study aimed to address this gap by comparing the drug survival and safety of biologics in older adults with psoriasis to that of younger patients. Patients treated with tumour necrosis factor (TNF)-α, interleukin (IL)-17, IL-12/23, and IL-23 inhibitors in the BioCAPTURE registry were included and categorized into two age groups: ≥65 years and <65 years. The Charlson Comorbidity Index (CCI) assessed comorbidity status, while adverse events (AEs) leading to treatment discontinuation were classified according to the Medical Dictionary for Regulatory Activities (MedDRA). Kaplan–Meier survival curves were constructed for overall 5-year drug survival and split by reasons for discontinuation. Cox regression models were used to correct for confounders and examined associations with drug survival in both age groups. PASI scores during the first 2 years of treatment were compared between age groups. The study included 890 patients, with 102 (11.4%) aged ≥65 years. Older

adults with psoriasis exhibited a higher CCI score, indicating more comorbidity ($p < 0.001$). While overall 5-year drug survival rates were comparable between age groups (≥65 years: 32.4%; <65 years: 42.1%), a significant difference was noted in 5-year ineffectiveness-related drug survival, with older adults with psoriasis experiencing lower rates (44.5% vs. 60.5%). However, AE-related drug survival rates at 5 years of treatment did not differ between age groups (≥65 years: 82.1%; <65 years: 79.5%). The incidence of AEs leading to treatment discontinuation was low in both groups (≥65 years: 11.8%; <65 years: 13.1%). PASI scores over the first 2 years of treatment were similar across age groups. Overall, biologic treatment appeared well-tolerated and effective in older adults with psoriasis, with no increased incidence of AEs leading to treatment discontinuation. While older adults with psoriasis discontinued treatment more frequently due to ineffectiveness, no discernible difference in PASI scores was observed.

As described in **Chapter 1**, psoriasis can occur at any age. Most children with psoriasis have a mild form of psoriasis, responsive to topical treatment. [32] For the more severe cases, methotrexate is the most commonly used conventional systemic agent. Currently, five biologics have also been approved by the EMA for the treatment of psoriasis in children and RCTs on other biologics for children are ongoing. [33, 34] RCTs are considered the gold standard for evaluating the efficacy and safety of new treatments. However, their internal validity often comes at the cost of generalizability, as the criteria for studies in paediatric psoriasis might be overly restrictive. Many children with psoriasis are excluded from RCTs due to previous or concurrent psoriasis treatments or significant comorbidities. [35] Additionally, the baseline requirement for minimal psoriasis severity (e.g., PASI ≥ 12) and stringent compliance monitoring in RCTs can result in greater improvements in relative psoriasis severity scores compared to real-world studies. Thus, we aimed to contribute to the limited body of evidence regarding the treatment of psoriasis in children. Conversely, another age group that is frequently understudied is elderly patients. The combination of an aging global population and the chronic nature of psoriasis has led to an increase in the prevalence of older patients with the condition. [36, 37] However, similar to children, elderly patients are often excluded from clinical trials, resulting in limited literature on the effectiveness and safety of systemic anti-psoriatic treatments for this specific population. [38-40] **Chapter 3.2** was established to investigate various aspects of psoriasis treatment with biologics in this demographic patient group as well.

In **Chapter 3.1**, we aimed to gain deeper insight into the subjective experiences of children undergoing treatment for psoriasis with methotrexate and biologics.

Our findings revealed that at the onset of both treatments, children were most troubled by itch and disease severity, with pain and fatigue being less prominent concerns. Encouragingly, both treatment cohorts exhibited a reduction in itch and disease severity within the first year of treatment with methotrexate or biologics. The significant decrease in self-assessed VAS-severity reported by paediatric patients in our cohort aligns with the objective reduction in PASI scores observed during the first three months. Additionally, patients on biologics attained lower absolute PASI scores at three months compared to those on methotrexate, consistent with the recent findings in adult patients by Alabas et al. [41] Furthermore, our study underscored that psoriasis severity is not the only significant symptom experienced by paediatric patients; itch is also a major, previously underacknowledged, symptom. [42] It is known that itch can significantly influence quality of life. [43] Historically, psoriasis has been considered nonpruritic compared to atopic dermatitis. [42] However, a meta-analysis from 2017 compiling data from 22 clinical trials revealed no significant difference in baseline itch between atopic dermatitis and psoriasis. [44] In atopic dermatitis, itch is a diagnostic criterion and clinical endpoint in studies. Recently, studies on psoriasis have begun to include itch as a crucial outcome measure for evaluating treatment effectiveness. [45] Our study underscores the importance of considering burdens such as itch in children. The impact of psoriasis symptoms can significantly affect development and self-confidence during childhood and early adolescence. [46] The International Psoriasis Council is currently conducting a comprehensive literature review on the global burden of paediatric psoriasis, compiling all available evidence on the subject. [47]

Given the profound effects of psoriasis on children, it is crucial to continuously evaluate the best treatment options. A recent cross-sectional survey-study documented that for patients not on a biologic, although their psoriasis condition did warrant the use of a biologic according to their physician, most common reasons for not using a biologic were: concerns regarding safety, guardians not wanting patients to take a biologic, and guardians not wanting to administer biologics. [48] However, overall, the use of biologics has become more prevalent in addition to the well-established therapy for the treatment of moderate to severe psoriasis, i.e. methotrexate, which has a long history of use. The high effectiveness and favourable safety profile of biologics are increasingly well-documented. [49-52] An update of the German guideline already positions adalimumab as first-line systemic therapy for the treatment of moderate to severe paediatric psoriasis instead of methotrexate. [53] Collectively, as our experience with biologics grows and we further understand the impact of psoriasis, we will be better equipped in the coming years to choose the most appropriate treatment at the right time.

In older adults with psoriasis, biologics appear to be an effective addition to the conventional systemic therapies.[40] However, choosing the optimal treatment for older patients is challenging due to the limited evidence on safety and effectiveness and complicating patient characteristics such as comorbidities, concomitant medication use, polypharmacy, functional status, and frailty. Consequently, physicians may be reluctant to prescribe certain systemic therapies, such as biologics, to older adults with psoriasis, potentially leading to the undertreatment of this patient group.[54] The results of the drug survival analyses and PASI scores of **Chapter 3.2**, reassured us that the hesitancy to prescribe biologics in older adults with psoriasis was unfounded in our cohort. Again, it was challenging to compare our drug survival results split by reasons for discontinuation with other cohorts, as these cohorts typically report overall drug survival. When we compared the overall drug survival, we found a similar two-year drug survival rate as reported in the study by Osuna et al.[55]

Our study reported a lower drug survival regarding ineffectiveness in patients aged ≥65 years compared to patients aged <65 years. Interestingly, PASI scores at discontinuation were slightly lower in older adults with psoriasis, indicating less severe psoriasis than in younger patients. A possible explanation for the higher frequency of treatment discontinuation due to ineffectiveness in older adults with psoriasis could be the difference in needs or treatment burden between these age groups. While treatment effectiveness in research is often measured by disease severity outcomes, individual treatment goals, needs, and preferences can significantly influence treatment decisions. Although limited literature is available on the needs and treatment goals of older adults with psoriasis, some distinct differences have been reported compared to younger patients.[56, 57] In a recent survey study, it was found that older adults with psoriasis placed greater importance on being completely free of psoriasis and free of redness compared to younger adults. Additionally, older adults showed a stronger preference for minimizing the use of topical treatments than their younger counterparts.[57] Furthermore, it can be hypothesized that dry skin and itching can also contribute to quicker discontinuation of treatment due to ineffectiveness, as these symptoms can be hard to distinguish from psoriasis itself.

When contextualizing the results of **Chapter 3.2** within the existing literature in a broader scope than drug survival only, several studies have also reported that biologics are safe and effective for treating psoriasis in older adults, even in the presence of comorbidities and prior treatment failures.[55, 58-61] Consistent with the findings of **Chapter 3.2,** infections are the most commonly reported adverse

events among older adults using biologics.[62-65] However, a recent systematic review found no significant association between infection rates and age.[40] This review underscored the importance of not considering age alone as a limiting factor in psoriasis management and emphasized that older adults can also benefit from biologic treatment. Increased awareness of the aging population and a growing body of publications on this topic have fortunately set important developments in motion. The International Psoriasis Council has introduced two items focused on psoriasis in older adults in 2024.[66, 67] These initiatives highlight specific considerations, such as the potential for reduced adherence to therapies and challenges in applying topical treatments. Additionally, it was highlighted that the selection of systemic agents should be approached with greater caution in older than in younger adult patients, due to the higher prevalence of concurrent chronic diseases and the increased likelihood of drug interactions. Further investigation into physician- and patient-related factors in older psoriasis patients is warranted to optimize care in this population.

Aim III: to study the influence of current definitions for super-response and multi-treatment failure on psoriasis studies

To address the last aim, the focus was on the definitions for specific subgroups regarding treatment response, used within the psoriasis literature. While biologic treatments are highly effective for most patients, there is a subgroup that requires multiple consecutive biologics, often referred to as "multi-treatment resistant". Conversely, there is a subgroup that responds exceptionally well to biologics, known as "super-responders". Currently, no clear definitions exist for these subgroups in psoriasis literature, resulting in the use of varying definitions across studies – and consequently – limiting comparability of study results.

In **Chapter 4.1**, we aimed to contribute to this area by (i) synthesizing various definitions of super-responders in psoriasis literature, and (ii) assessing the impact of these definitions on the composition of the super-responder group. A search of PubMed was conducted, resulting in the identification of 10 studies that utilized 8 different definitions of super-response. These definitions primarily relied on the PASI to categorize patients into responder groups, with variations in absolute or relative PASI outcomes and cut-off values. Differences were also noted in the timing and duration of defining super-response and the data sources used. Applying these varied definitions to a fixed patient cohort from the BioCAPTURE registry

demonstrated significant differences in the proportion of super-responders identified (ranging from 3.6% to 23.6%, depending on definition). Several factors contributed to the observed differences in definitions, including the timing of defining and maintaining super-response, the use of absolute versus relative PASI scores, and the duration of therapy maintenance.

As stated, a standardized classification for the difficult-to-treat group on the other end of the spectrum, designated as patients with 'multi-treatment resistance' is not yet defined, but important for better understanding of underlying factors and improving patient care. **Chapter 4.2** was set up to identify classifications for MTR utilized in literature.

We conducted a PubMed search, merging synonyms for 'multi-treatment resistance', combined with keywords for psoriasis and biologics. The implications of these different definitions on the point-prevalence of multi-treatment resistance were analysed using data from BioCAPTURE. The literature search yielded four articles with a definition for multi-treatment resistance for biologics in psoriasis. These definitions all differed and were proposed by the authors of the publications, with three of them exclusively focusing on ineffectiveness. Applying the multi-treatment resistance definitions found in literature to the BioCAPTURE cohort resulted in a wide variation of multi-treatment resistance point-prevalences ranging from 3.2%-29.5%.

One of the key strengths of reporting research results from various patient registries and medical records is the ability to detect long-term signals of a treatment. Originally, the establishment of registries aimed to monitor safety of treatments without relying on spontaneous reporting and randomized controlled trials (RCTs), thereby reflecting the real world effects of therapy in a heterogeneous group of patients. [68, 69] However, besides safety, most patient registries also track the effectiveness of treatments. A recent study on patient registries in dermatology examined the number and variety of registries, highlighting in their future directions the potential benefits of a federation focused on standardized datasets, reusable blueprints, and harmonized definitions across registries. [70] This approach with harmonized definitions would be particularly valuable in the context of "super-responders" and "multi-treatment resistant" patients, given the significant variability demonstrated in definitions currently used in the literature. The variation in definitions is particularly significant in research that relies on these group classifications. For instance, several studies categorize groups based on super-response and then examine the presence of one or more biomarkers. [71-73]

A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention'.[74] It is evident that using a very strict definition to classify super-responders can yield different biomarker results compared to using a more lenient definition, which results in a different patient group composition. A related publication by Ramessur et al. on behalf of the BIOMAP consortium discussed multiple approaches to measuring disease severity. The study made several recommendations: instead of relying on a single measure, multiple measures should be considered since one measure alone cannot capture all aspects of disease severity. Both the physician's and the patient's perspectives on disease severity should be taken into account. Additionally, it is important to consider disease severity at a single point in time as well as over a period of time.[75]

The studies included in our research on super-response employed subgroup analyses to determine if certain baseline characteristics were more prevalent among super-responders. Notable baseline characteristics that appeared more frequently in the super-responder subgroup included lower weight, fewer comorbidities, and younger age. Some studies exclusively used a relative PASI measure, requiring a certain percentage reduction from the baseline PASI, which could make achieving super-responder status more challenging. Another influential factor is the timing of defining and/or maintaining super-response. When a PASI score must be maintained over several years, it significantly affects the group that will meet the definition. Considering these and previously described factors, it is advisable to reach a consensus on the definition of super-response among a group of experts using, for example a Delphi consensus procedure.

The group of multi-treatment resistant patients presents other unique challenges, further complicated by the evolving perspective on these patients over time. In a historical cohort such as BioCAPTURE, patients deemed 'treatment-refractory' a decade ago faced limited options due to the lack of new biologics. However even now, with the current abundance of biologic options, there are patients with psoriasis that used all available biologics and are in need for new therapies. Fortunately, as mentioned in the introduction of this dissertation, there are ongoing developments in the creation of new medications for psoriasis, such as the emergence of new oral small peptides that exert their working mechanism by blocking the receptor for certain cytokines such as IL-23. Despite these changes over the last decades and the changes yet to come, it remains crucial to focus our efforts on the unmet need of this patient group today. An important step in our research is to ensure that these definitions are consistent so that we can conduct

follow-up studies with a clearly defined group. Several components could be considered, including how we define multi-treatment resistance. Specifically, it could be considered whether a patient should be classified as multi-treatment resistant if they switch from one biologic to another regardless of the class, or if we should distinguish between intra-class switching (within the same class) and inter-class switching (between different classes). Additionally, it could be helpful to consider the duration of use of the same biologic before switching. A patient who uses the same biologic for an extended period before switching is in a different situation than one who uses a biologic for a short duration before switching. It can also be important to examine the disease activity at the time of discontinuation, as this could provide insights into the differences in the goals and preferences between patients and healthcare providers. These considerations form a complex but necessary evaluation, especially since our findings in **Chapter 4.2** indicated a significant population of multi-treatment resistant patients (e.g., 15% of the BioCAPTURE cohort discontinued 3 or more biologics).

Main findings

Aim I: to explore and compare real-world drug survival and effectiveness of biologics for psoriasis

- In daily practice, ixekizumab and guselkumab demonstrated higher effectiveness compared to etanercept, adalimumab, ustekinumab, and secukinumab.
- Etanercept appears to be less effective in daily practice than adalimumab, ustekinumab, secukinumab, ixekizumab, and guselkumab.
- The proportion of patients achieving PASI90 in real-world settings was relatively low for all biologics compared to what has been reported in randomized controlled trials (RCTs), in contrast to absolute PASI scores which were more comparable between cohorts.
- We advocate reporting absolute PASI outcomes in addition to relative PASI outcomes, to facilitate comparisons between studies, and between real-world evidence (RWE) and RCT data.
- Guselkumab showed high drug survival at both 1- and 2-year follow-up.
- Summary drug survival estimates of 69 different studies revealed high drug survival rates for all IL-17 and IL-23 inhibitors at 1 year of treatment (all point estimates ≥0.8), with the highest estimates for guselkumab and risankizumab.
- Summary drug survival estimates of data from pharmacy/claims database studies were lower than those from registry/electronic health record data, probably due to crucial missing information on discontinuation reasons.

- Patients treated with IL-23 inhibitors, who had a history of ineffectiveness with ustekinumab, showed a tendency towards lower drug survival rates and higher PASI scores compared to those without prior ustekinumab exposure.
- The majority of patients on IL-23 inhibitors who discontinued ustekinumab due to ineffectiveness still responded well to IL-23 inhibition.

Aim II: to generate real-world evidence of treatment with biologics in in children and older adults with psoriasis

- Itch and disease severity posed a more significant burden than pain and fatigue in children undergoing methotrexate and biologic treatments, and were both responsive to treatment.
- In children, in the biologic group, PASI scores at three months of treatment demonstrated a greater reduction compared to the methotrexate group, especially in methotrexate-naïve patients.
- Overall drug survival and adverse event-related drug survival did not differ significantly between patients aged <65 years and those aged ≥65 years.
- The incidence of adverse events leading to treatment discontinuation was low and comparable between patients aged <65 years and those aged ≥65 years.

Aim III: to study the influence of current definitions for super-response and multi-treatment failure on psoriasis studies

- Applying the varied definitions for super-response found in the literature to a fixed patient cohort from the BioCAPTURE registry demonstrated significant differences in the proportion of identified super-responders. Depending on the definition used, the percentage of super-responders ranged from 3.6% to 23.6%.
- Applying the varied definitions of multi-treatment resistance from the literature to the BioCAPTURE cohort resulted in a wide variation of multi-treatment resistance point-prevalences. Depending on the definition used, the prevalence of multi-treatment resistant patients ranged from 3.2% to 29.5%.
- To conduct reliable follow-up research, attention must be given to achieving a consensus on the definitions of the groups being studied.

Future directions

Over the past twenty years, the treatment of psoriasis has undergone a significant transformation with the introduction of biologics. These therapies have established a new high standard of care, where the majority of patients can expect a substantial reduction in psoriasis plaques. There are now multiple options available within

the biologics category (inhibition of TNF-α, IL-12/23, IL-17, and IL-23) and two oral small molecule inhibitors (inhibition of PDE4 and TYK2). However, there remains a subset of patients with multi-treatment resistance who require new therapies, as they do not respond adequately to current treatments. Additionally, some patients experience initial effectiveness, but lack of therapeutic benefit in the long run. Fortunately, as described in **Chapter 1**, the landscape continues to evolve. Upcoming developments are expected to focus on oral treatments, specifically small molecule inhibitors.[76] Small molecules can cross cell membranes and directly block intracellular pathways. These agents are easier to synthesize compared to biologics, less expensive to produce, and can be administered orally or topically, potentially improving patient convenience and quality of life.[77, 78] As new oral therapies are introduced into the psoriasis treatment landscape, long-term trials and comparative studies with existing oral and biologic agents are necessary to better understand their position in the current treatment algorithm. Given that many patients already achieve satisfactory results with current biologics, there may be little incentive for them to switch to newer treatments. Consequently, registries for new small molecule inhibitors (but also for new biologics) are likely to require more time to collect sufficient data to generate real-world evidence. Thus, collaborations between various registries will become increasingly important.

Fortunately, recent years have seen an increase in initiatives to consolidate efforts, address research questions collaboratively, and share data. On an international level, this is supported by the Horizon Europe program of the European Union.[79] On a national level, there is the promising NGID (Next Generation Immunodermatology) project, funded by the NWO (Nederlandse Organisatie voor Wetenschappelijk Onderzoek). This project will investigate six different inflammatory skin diseases including psoriasis in ultra-high detail. It involves collaboration among various groups, including patients, dermatologists, biologists, bioinformaticians, statisticians, behavioural scientists, and communication researchers. Bringing together these diverse experts, along with their knowledge and data, is expected to advance our understanding of biomarkers significantly in the coming years. Ideally, biomarkers could help in deciding which therapy to choose and/or predict whether a therapy is suitable for a patient. Currently, selecting a therapy often remains a matter of trial and error.

One of the challenges in coming years, caused by an increasing number of expensive therapies for psoriasis, is to manage the costs associated with this growing group. Ongoing research into how to achieve this will be essential if we are to make significant progress. One of the most effective ways to reduce costs will

be dose reduction in patients with low disease activity. There is extensive evidence that dose reduction for the "older" biologics is not inferior to standard therapy.[80] Upcoming study results for the "newer" biologics will determine if this approach is also feasible for those therapies. Promisingly, a cost-utility analysis of the older biologics (adalimumab, etanercept, and ustekinumab) showed that the average annual cost saving was €3,820 per patient compared with standard psoriasis care.[81] In the coming years, it will be crucial to explore how dose reduction can be applied and implemented on a larger scale. Previous studies have indicated that the primary reasons for not yet applying dose reduction are lack of awareness, knowledge, and time.[82] However, it is highly likely that investing time will ultimately pay off due to the significant cost savings associated with dose reduction. Currently, a chapter on dose reduction is being developed for the national psoriasis guideline. Another development, still in an early stage, is the use of biologics as needed/on demand, meaning that patients self-administer biologics when they deem it necessary, guided by specific protocols or guidelines. Studies conducted so far on this topic have shown that interval extension is possible.[8, 83, 84] Since this has only been investigated on a small scale, it presents an interesting angle for future research.

In addition to large-scale epidemiological research, advancements in understanding the pathogenesis of psoriasis on a more detailed level may yield valuable insights in the coming years. It has been observed that following the onset of psoriasis, a small number of tissue-resident memory T-cells (TRMs) remain in the skin, gradually accumulating over time.[85, 86] This expansion of TRMs is believed to drive the progression of the disease into a chronic state. Additionally, TRMs may trigger disease recurrence in response to various stimuli. Early intervention with biologics in psoriasis has been suggested to significantly impact TRMs, potentially halting the recruitment of IL-17 producing cells. This could lead to long-term drug-free remission and consequently reduce the costs associated with the chronic use of biologics. A small-scale substudy[87] (n = 20) from the multicentre ECLIPSE trial[88] demonstrated that guselkumab (an IL-23 inhibitor) decreased the proportion of TRMs in healed psoriatic skin six months after treatment initiation. Further analyses from an ongoing trial[89] are expected to provide more detailed insights into the relationship between TRMs and clinical response. Ideally, early intervention with biologics could lead to the complete resolution of psoriasis. However, this goal is not yet within reach. Therefore, it remains essential to continue evaluating and researching the cost-effectiveness of early intervention strategies.

Another promising development and a key area for research in controlling the costs in the coming years, is the utilization of biosimilars. As described in the introduction

of this thesis, when the patent of an originator biologic expires, biosimilars can enter the market. Due to the use of living cells in the manufacturing process, it is impossible to create exact copies of biologics. [90] Currently, several biosimilars are available for infliximab, etanercept, and adalimumab. Additionally, the first biosimilar of ustekinumab has been approved by the EMA and is expected to enter the market soon. [91] A recent systematic review compiled the available evidence on the use of biosimilars in psoriasis and compared the results with originator biologics (or bio-originators). [92] The review concluded that there were no clinically or statistically significant differences in efficacy and safety between the biosimilars and originators. However, high-quality evidence from real-world patient registries or medical records was lacking according to this review. Longer-term studies will likely provide us with more comprehensive insights into the advantages and disadvantages of these agents.

Developments in telemedicine and remote care can also contribute to cost control. During the COVID-19 pandemic, clinicians experienced a unique situation where the standard protocol for patient monitoring was modified. Various forms of telemedicine, including calls, video calls, apps, and emails, became viable options. Particularly for the chronically ill population under investigation in this thesis, it is essential to assess whether telemedicine is as effective as in-person visits. Ideally, the frequency of online or in-person visits can be customized to meet the patient's needs. A 2022 economic modelling study indicated that implementing telemedicine on a national scale in the US could reduce healthcare costs by $1.5 billion. Additionally, it estimated significant work-related savings in time and costs due to decreased absenteeism and reduced travel for employees. [93] Promisingly, a recent Dutch survey on remote care reported high overall patient satisfaction with remote consultations. [94] Future studies should also investigate whether clinical disease severity measures change when transitioning from in-person visits to telemedicine.

As described, current achievements of controlling psoriasis with biologics are impressive. However, several aspects still hold potential for further developments. The insights provided in this thesis can aid in advancing future research.

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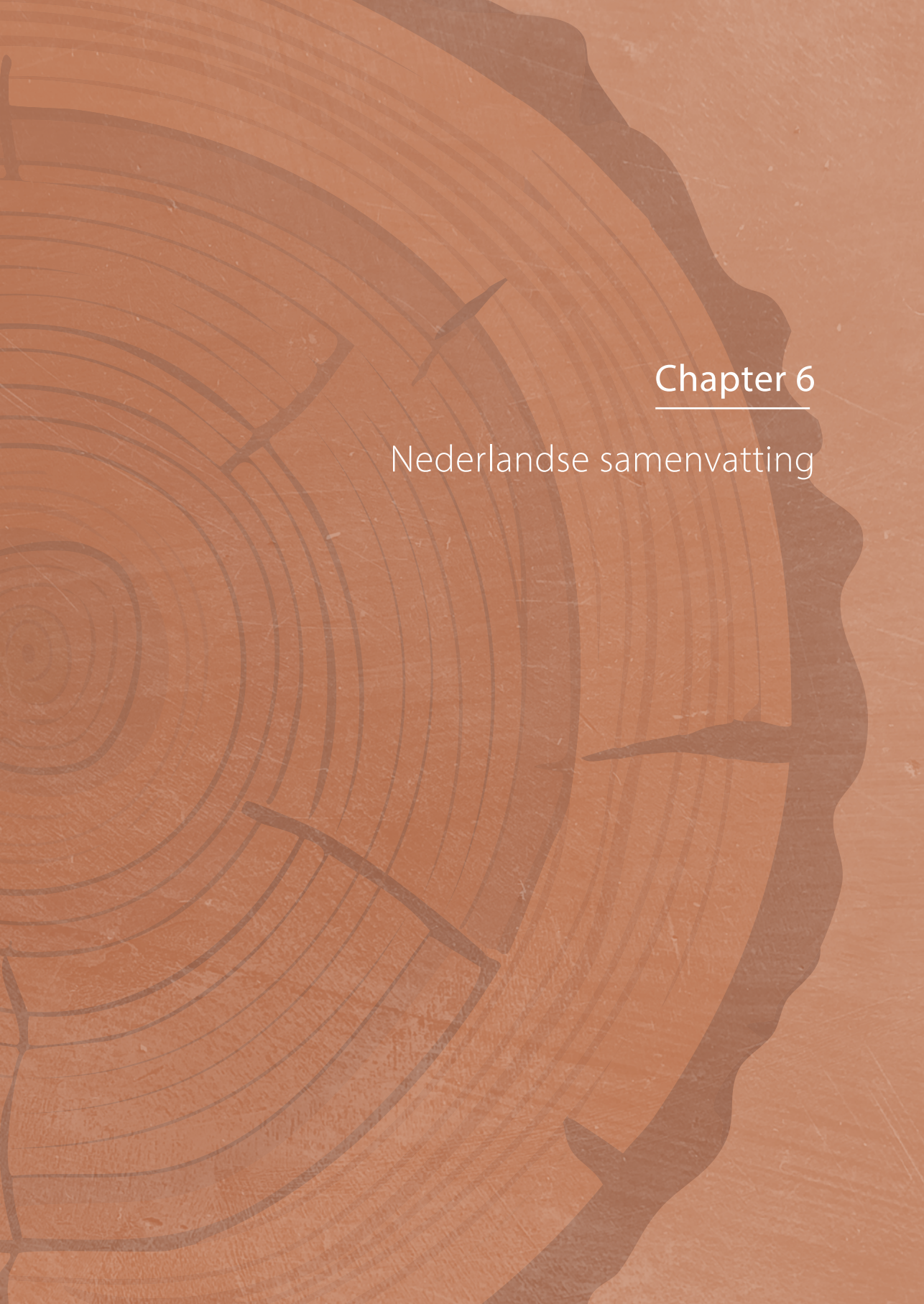

Chapter 6

Nederlandse samenvatting

Psoriasis is een chronische huidziekte die rode, schilderende plekken op het lichaam veroorzaakt. Deze aandoening is geassocieerd met verschillende comorbiditeiten en heeft grote individuele en maatschappelijke impact. Sinds 2005 zijn biologics geïntroduceerd voor de behandeling van patiënten met psoriasis. Biologics zijn zeer effectieve geneesmiddelen die het immuunsysteem moduleren en ontstekingsreacties remmen. Gezien het inmiddels brede scala aan beschikbare biologics voor patiënten met psoriasis is het essentieel om beter inzicht te krijgen in welke biologic het meest geschikt is voor welke patiënt. Dit is daarbij ook belangrijk om deze behandelingen zo effectief en verantwoord mogelijk in te zetten, om de kans op bijwerkingen zoveel mogelijk te beperken en omdat beandeling met deze middelen met hoge kosten gepaard kan gaan. In dit proefschrift onderzochten wij de effectiviteit en veiligheid van, en patiënttevredenheid over biologics bij de behandeling van patiënten met psoriasis. De primaire databron voor dit onderzoek is het prospectieve, multicentre, BioCAPTURE-register (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics). De bevindingen uit dit proefschrift zijn bedoeld ter ondersteuning van de klinische besluitvorming bij de behandeling van mensen met psoriasis en bieden tevens inzicht in specifieke onderzoeksmethoden binnen dit vakgebied. De belangrijkste bevindingen worden gestructureerd besproken aan de hand van de volgende hoofdstukken.

Hoofdstuk 2: Real-world evidence (RWE) over de effectiviteit en drug survival van biologics voor patiënten met psoriasis

In de laatste twee decennia is het aantal studies over de behandeling van psoriasis met biologics aanzienlijk toegenomen. In dit hoofdstuk richten we ons op het vergelijken van de resultaten tussen verschillende biologics.

In **hoofdstuk 2.1** werd de effectiviteit van zes veelgebruikte biologics voor psoriasis in het eerste jaar van behandeling vergeleken met behulp van BioCAPTURE-data. Hierbij werden 1080 behandelingen van 700 patiënten geanalyseerd. Patiënten behandeld met adalimumab, ustekinumab, secukinumab, ixekizumab of guselkumab, hadden significant lagere gemiddelde absolute Psoriasis Area and Severity Index (PASI) scores en hogere kansen om een relatieve PASI90 (90% afname van de PASI score ten opzichte van baseline) te bereiken vergeleken met patiënten behandeld met etanercept. De kans op het bereiken van PASI90 was het hoogst bij behandeling met ixekizumab of guselkumab. Het aantal patiënten dat een PASI90 behaalde was aanzienlijk lager in deze studie in vergelijking met cijfers

afkomstig uit 'randomized controlled trials (RCT's)'. Het rapporteren van de absolute PASI scores (bijvoorbeeld een PASI <2) naast relatieve PASI scores (afname van 90% ten opzichte van baseline) is van belang om de vergelijking tussen verschillende cohorten en RWE en RCT's gemakkelijker te maken.

In **hoofdstuk 2.2** onderzochten we de drug survival van guselkumab, de eerste IL-23-remmer beschikbaar voor de behandeling van psoriasis, met data uit meerdere centra naast het BioCAPTURE netwerk. Drug survival is de duur dat een middel gebruikt wordt en wordt geanalyseerd door middel van de Kaplan-Meier methode. Met behulp van de drug survival methode kunnen in een cohort patronen in relatie tot het stoppen van een medicijn worden geëvalueerd. De 1- en 2-jaar drug survival percentages van guselkumab in dit hoofdstuk waren hoog en respectievelijk 85,5% en 77,8%. Toen we de drug survival specifiek voor stoppen vanwege ineffectiviteit analyseerden, zagen we dat er zeer weinig patiënten stopten met guselkumab. Dit in tegenstelling tot andere biologics, waarbij ineffectiviteit vaak de grootste reden is tot stoppen. Het hebben van diabetes mellitus type 2 en artritis psoriatica waren geassocieerd met een kortere drug survival.

Om de drug survival van nieuwere biologics (IL-17 en IL-23-remmers) te vergelijken, werd in **hoofdstuk 2.3** een systematic review en meta-analyse uitgevoerd. De review omvatte 69 studies met data van 48.704 patiënten. De resultaten toonden hoge drug survival percentages (alle puntschattingen op jaar 1 ≥ 80%), waarbij guselkumab en risankizumab (beide IL-23 remmers) de hoogste percentages hadden. De drug survival percentages uit administratieve en/of apotheek databases waren opvallend lager dan die uit databases gebaseerd op patiënten registers of medische dossiers. Omdat cruciale informatie zoals de stopreden ontbrak in de data uit administratieve en/of apotheek databases, is voorzichtigheid geboden bij het interpreteren van de drug survival resultaten afkomstig van deze databases.

In **Hoofdstuk 2.4** werd het overschakelen naar selectieve IL-23-remmers na ineffectiviteit van ustekinumab (IL-12/23 remmer) onderzocht met data uit het BioCAPTURE register. Aangezien een aanzienlijk aandeel van de patiënten adequaat reageerde op behandeling met IL-23 remmers na het falen van ustekinumab, lijken IL-23 remmers een effectieve optie te zijn na het stoppen met ustekinumab.

Hoofdstuk 3: Het genereren van real-world evidence over de behandeling van kinderen en ouderen met biologics

De twee leeftijdsgroepen aan de uiteinden van het leeftijds-spectrum worden vaak uitgesloten van deelname aan klinische trials. In dit hoofdstuk beoogden we een bijdrage te leveren aan de bestaande kennis over het gebruik van biologics bij kinderen en ouderen in de dagelijkse praktijk.

In **hoofdstuk 3.1** onderzochten we, met behulp van de visueel analoge schaal (VAS), de mate van jeuk, vermoeidheid, pijn, en de ernst van de psoriasis bij kinderen met psoriasis met data afkomstig uit het prospectieve Child-CAPTURE register. Vervolgens werd de verandering in deze symptomen tijdens behandeling met methotrexaat en biologics geëvalueerd en gekoppeld aan de PASI-score. De kinderen hadden vooral veel last van jeuk en de ernst van de psoriasis zelf, en beide klachten verbeterden op behandeling. Vermoeidheid en pijn werd veel minder gerapporteerd. Onze studie bevestigde daarmee dat jeuk een belangrijk symptoom is voor kinderen. Jeuk als symptoom van psoriasis werd in het verleden onderschat. Daarnaast zagen we een grotere afname in de PASI score in de groep die een biologic gebruikte dan in de groep die methotrexaat gebruikte na 3 maanden. Het feit dat er een lagere PASI score bereikt werd met een biologic dan met methotrexaat, sluit aan bij recent onderzoek bij volwassenen.

In **hoofdstuk 3.2** onderzochten we de effectiviteit en veiligheid van biologics, door de drug survival, PASI-scores, comorbiditeit en bijwerkingen tussen oudere en jongere patiënten (< 65 versus ≥ 65 jaar oud) te vergelijken. Oudere patiënten hadden bij de start van de biologic meer comorbiditeit dan jongere patiënten. Desalniettemin zagen we dat het aantal oudere patiënten dat stopte met een biologic vanwege een bijwerking erg laag was en vergelijkbaar was met het aantal jongere patiënten dat stopte. Oudere patiënten stopten wel vaker met hun biologic vanwege ineffectiviteit. Er werd geen verschil in PASI scores gevonden tussen de groepen. De resultaten van onze studie bevestigden dat terughoudendheid bij het voorschrijven van biologics bij ouderen niet nodig is.

Hoofdstuk 4: De invloed van huidige definities voor 'super-response' en 'multi-treatment resistance' op psoriasis studies

Hoewel de meeste patiënten goed reageren op behandeling met biologics, is er ook een subgroep patiënten waarbij de behandeling met biologics onvoldoende werkt. In de literatuur wordt deze subgroep aangeduid met 'multi-treatment resistant'. Aan de andere kant van het spectrum is er een subgroep met patiënten die uitzonderlijk goed reageren op biologics, de zogenaamde 'super-responders'. In dit hoofdstuk onderzochten we de invloed die de gestelde definitie van super-response en multi-treatment resistance heeft op de samenstelling en grootte van de subgroep.

We zagen aan de hand van de literatuurstudie in **hoofdstuk 4.1** dat er veel verschillende definities zijn voor super-response. Toen we deze uiteenlopende definities toepasten op het BioCAPTURE cohort, bleek er aan aanzienlijke variatie te zijn in de groep die als super-responder werd geclassificeerd. Dit onderstreept het belang van een gestandaardiseerde definitie voor super-response, vastgesteld door een groep experts, om de samenhang en vergelijkbaarheid van toekomstig onderzoek te waarborgen.

Hetzelfde principe geldt voor de multi-treatment resistant patiënten, onderzocht in **hoofdstuk 4.2.** De definitie voor multi-treatment resistance is vaak gebaseerd op het aantal gestopte biologics. Echter, zowel het aantal als de specifieke klasse van deze biologics verschilde aanzienlijk tussen studies, wat resulteerde in grote variaties in het aantal patiënten dat als multi-treatment resistant wordt beschouwd. Ook voor deze groep patiënten is het van belang dat de definitie wordt geëvalueerd, zodat vervolgonderzoek vergelijkbaar blijft.

Appendices

List of publications

Research data management

PhD portfolio

Dankwoord

List of abbreviations

Curriculum Vitae

List of publications

Henckens NFT, **Thomas SE**, van den Reek JMPA, de Jong EMGJ; BioCAPTURE Network. Multi-treatment resistance to biological treatment in patients with psoriasis: Definitions and implications. J Eur Acad Dermatol Venereol. 2024 May 31. doi: 10.1111/jdv.20133. Epub ahead of print. PMID: 38818854.

Thomas SE, Seyger MMB, Mangnus JE, Otero ME, Gostynski AH, Njoo MD, Ossenkoppele PM, Haeck IM, Hendricksen-Roelofzen JHJ, Körver JEM, Dodemont SRP, Tupker RA, Berends MAM, Weppner-Parren LMJT, Keijsers RRMC, Oostveen AM, Peters B, Mommers R, van Doorn MBA, Tjioe M, Veldkamp WR, Kuijpers ALA, Kleinpenning MM, de Jong EMGJ, van den Reek JMPA. Switching to Interleukin-23 Inhibitors After Ineffectiveness of Ustekinumab: Evaluating Real-World Outcomes in Psoriasis Treatment. Am J Clin Dermatol. 2024 May 27. doi: 10.1007/s40257-024-00868-x. Epub ahead of print. PMID: 38802618.

Thomas SE, Barenbrug L, Hannink G, Seyger MMB, de Jong EMGJ, van den Reek JMPA. Drug Survival of IL-17 and IL-23 Inhibitors for Psoriasis: A Systematic Review and Meta-Analysis. Drugs. 2024 Apr 17. doi: 10.1007/s40265-024-02028-1. Epub ahead of print. PMID: 38630365.

Thomas SE, van den Reek JMPA, Bruins FM, Groenewoud HMM, de Jong EMGJ, Seyger MMB. Unveiling the impact of itch, pain, fatigue and disease severity in paediatric patients with psoriasis and the influence of methotrexate and biologics. J Eur Acad Dermatol Venereol. 2024 Mar 7. doi: 10.1111/jdv.19942. Epub ahead of print. PMID: 38450775.

Thomas SE, van den Reek JMPA, Seyger MMB, de Jong EMGJ. How to define a 'super-responder' to biologics in psoriasis studies. Br J Dermatol. 2023 Oct 25;189(5):621-622. doi: 10.1093/bjd/ljad280. PMID: 37595133.

Ter Haar ELM*, **Thomas SE***, van den Reek JMPA et al. Drug Survival, Safety, and Effectiveness of Biologics in Older Patients with Psoriasis: A Comparison with Younger Patients-A BioCAPTURE Registry Study. Drugs Aging. 2022 Sep;39(9):715-727.

Van Muijen ME, **Thomas SE**, Vellinga D, et al. Real-world Data Reveal Long Drug Survival for Guselkumab in Patients with Plaque Psoriasis. Acta Derm Venereol. 2022 Aug 11;102:adv00755.

Van Muijen ME*, **Thomas SE*,** Groenewoud HMM, et al. Direct Comparison of Real-world Effectiveness of Biologics for Psoriasis using Absolute and Relative Psoriasis Area and Severity Index Scores in a Prospective Multicentre Cohort. Acta Derm Venereol. 2022 May 16;102:adv00712.

*shared first authorship

Publications not related to this thesis

van den Reek JMPA, van der Leest RJT, **Thomas SE**, Prevoo R, Plantenga ME, de Jong EMGJ. Improved Quality of Life in Patients with Psoriasis Receiving Apremilast: Real-World Data from the Netherlands. Adv Ther. 2024 Feb 24. doi: 10.1007/s12325-023-02759-9. Epub ahead of print. PMID: 38402373.

Thomas SE, van den Reek JMPA. Should we prefer biologics over nonbiological agents in psoriasis? Br J Dermatol. 2023 Aug 24;189(3):258-259.

Research data management

Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants. Data for chapters 2.1, 2.2, 2.4, 3.2, 4.1, and 4.2 were sourced from the Dutch BioCAPTURE-registry. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands (CMO Regio Arnhem-Nijmegen) has declared that formal ethical approval was not necessary for this non-interventional registry. However, written informed consent is obtained from every patient included in the registry. As chapters 2.1, 2.2, 2.4, 3.2, 4.1, and 4.2 are based on data from the BioCAPTURE registry, additional informed consent for these separate studies was not required.

In chapter 2.2, prospective data from the BioCAPTURE was supplemented with retrospective data from 4 Dutch hospitals that were not part of the BioCAPTURE network. Patients provided written informed consent for inclusion in the BioCAPTURE registry, or written informed consent for retrospective data collection for this specific study (CMO Radboudumc, dossier 2020-6187). In one academic centre (University Medical Centre Groningen; UMCG), an opt-out approach was used: written informed consent was not required, as only retrospective pseudonymized data from regular care were collected, and the study was granted exemption from reviewing by the institutional review board from the UMCG.

Data for chapter 3.1 was sourced from the Dutch Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use) registry. Studies from this registry were exempted from formal ethical approval by the medical ethical review committee 'METC Oost-Nederland' (registration number: 2012/383). Still, written informed consent is obtained from all patients (and/or their guardians) that were enrolled in the Child-CAPTURE registry.

Data collection and storage

For chapters 2.1, 2.2, 2.4, 3.1, 3.2, 4.1, and 4.2, data was collected through electronic Case Report Forms (eCRF) using Castor EDC. From Castor EDC data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA) or SAS (SAS Institute Inc). Pseudonymized data were stored and analyzed in the Azure DRE, on the department server and in Castor EDC and are only accessible by project members working at the Radboudumc. Paper (hardcopy) data is stored in cabinets in the Radboudumc.

Availability of data

Whenever possible, studies were published open access. The data will be archived for 15 years after termination of the study. Reusing the data for future research is only possible after a renewed permission by the participants.

PhD portfolio of Sarah Elisabeth Thomas

Department: **Dermatology**

PhD period: **01/07/2021– 01/07/2024**

PhD Supervisor(s): **Prof. E.M.G.J. de Jong**

PhD Co-supervisor(s): **Dr. J.M.P.A. van den Reek and dr. M.M.B. Seyger**

Training activities	Hours
Courses	
• Radboudumc - Introduction day (2021)	6.00
• EndNote Workshop UMC (2021)	1.00
• Radboudumc - eBROK course (2021)	42.00
• RU - Mindfulness Based Stress Reduction (2021)	45.00
• RU - Writing Scientific Articles (2022)	96.00
• RIHS - Introduction course for PhD candidates (2022)	15.00
• Radboudumc - Scientific integrity (2023)	20.00
• Workshop 2 + 3 Project Supervision research project (2023)	14.00
• RU - The Art of Finishing Up (2023)	10.00
• RU - Presentation Skills (2023)	42.00
Seminars	
• Webinar 'Verder kijken dan de huid' (2021)	1.50
• Lunchsessie: 'Efficient scannen van medische literatuur' (2021)	1.00
• Lunchsessie: 'Regressie analyse' (2021)	1.00
• Research Integrity Round: The Dark Side of Science: Misconduct in Biomedical Research (2021)	1.50
• EADV Review 2021 (2021)	2.00
• Masterclass Dermatology (2021)	3.00
• Annual BioCAPTURE meeting (oral presentation) (2022)	2.00
• Research Integrity Round: Research Integrity in times of crisis: Juggling slow and fast science (2022)	1.50
• Let's talk: RWE in psoriasis (oral presentation) (2022)	5.00
• Research Integrity Round: Publication ethics: Promises, problems and perspectives (2022)	1.50 1.00
• RIHS Lecture: Sustainability in science (2022)	4.00
• Radboud Research Rounds (oral presentation) (2022)	2.00
• Annual BioCAPTURE meeting (oral presentation) (2023)	
• Research Integrity Round: Collegetour with Prof. Hedi Claahsen and Prof. Sandra Heskamp (2023)	1.50 7.00
• National Dermatology Science Conference (Landelijke dag) (2023)	78.00
• Journal club Dermatology (2023)	78.00
• Research presentations Dermatology (2023)	
• Research Intergrity Round: Research ethical issues in the physician/ researcher/patiënt/participant quadrangle (2023)	2.00
• Research Intergrity Round: Artificial Intelligence and Research Integrity: a good marriage? (2024)	1.50

Training activities	Hours
Conferences	
• European Academy of Dermatology and Venereology (EADV, poster presentation) (2021)	7.00
• Psoriasis Gene To Clinic – 9th International Congress (poster presentation) (2021)	28.00
• ZonMW Congres Goed Gebruik Geneesmiddelen (2022)	8.00
• PhD retreat (2022)	14.00
• Annual meeting Nederlandse Vereniging Experimentele Dermatologie (NVED) (oral presentation) (2022)	22.00
• European Academy of Dermatology and Venereology (2022)	24.00
• Masterclass Real-World Evidence (2023)	14.00
• Annual meeting Nederlandse Vereniging Experimentele Dermatologie (NVED) (oral presentation) (2023)	22.00
• Eilanddagen (oral presentation) (2023)	14.00
• European Academy of Dermatology and Venereology (poster presentation) (2023)	24.00
• Annual meeting Nederlandse Vereniging Experimentele Dermatologie (NVED) (oral presentation) (2024)	22.00
• Annual BioCAPTURE meeting (oral presentation) (2024)	2.00
Other	
• Radboudumc - General Radboudumc introduction for research personnel (2021)	9.00
• NVDV - Werkgroeplid richtlijnherziening Psoriasis (2021-2022) (2022)	20.00
Teaching activities	
Lecturing	
• Meet the PhD project bachelor biomedical sciences students (2022)	4.00
• Meet the PhD project bachelor biomedical sciences students (2023)	4.00
Supervision of internships / other	
• Supervision research internship master biomedical sciences student (2022)	16.00
• Supervision research internship master biomedical sciences student (2022)	30.00
• Supervision research internship master medical student (2022)	28.00
• Supervision research project 2nd year medical sciences (2023)	45.00
• Supervision research internship master medical student (2023)	40.00
Total	**883.00**

*

Dankwoord

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De leden van de manuscriptcommissie, **prof. dr. van der Horst-Bruinsma, prof. dr. Spuls, dr. de Jong, en andere opponenten** wil ik hartelijk bedanken voor het nemen van de tijd om mijn proefschrift te beoordelen en hun aanwezigheid.

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*

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*

List of abbreviations

AE	Adverse Event
AEoSI	Adverse Event of Special Interest
ADA	Adalimumab OR Anti Drug Antibody
ANOVA	Analysis of Variance
BioCAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry with Biologics
BMI	Body Mass Index
BRO	Brodalumab
BSA	Body Surface Area
CCL	Chemokine Ligand
CAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry
CCI	Charlson Comorbidity Index
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CMO	Commissie Mensgebonden Onderzoek
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CXCL	C-X-C motif chemokine
D	Day
DLQI	Dermatology Life Quality Index
DM	Diabetes Mellitus
DS	Drug survival
EHR	Electronic Health Record
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
ICD-10	International Classification of Diseases and Related Health Problems, tenth revision
ICH	International Council for Harmonisation
ID	Initiation Dose
IFN	Interferon
IFX OR INF	Infliximab
IgG	Immunoglobulin G
IMID	Immune Mediated Inflammatory Diseases
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
JPsA	Juvenile Psoriatic Arthritis
LMM	Linear Mixed Model
LOCF	Last Observation Carried Forward
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MLR	Mixed logistic regression model
MOOSE	Meta-analyses Of Observational Studies in Epidemiology
MTX	Methotrexate

MTR	Multi treatment resistance
N	Total number of individuals or observations
NA	Not applicable
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
PDE4	Phosphodiesterase-4
PGA	Physician Global Assessment
PsA	Psoriatic arthritis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient Reported Outcome
PY	Patient-Years
QoL	Quality of life
QUIPS	Quality in Prognostic Studies
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RIHS	Radboud Institute for Health Sciences
RIS	Risankizumab
RoB	Risk Of Bias
ROBINS	Risk Of Bias In Non-randomised Studies - of Interventions
RWE	Real world evidence
SAE	Serious Adverse Event
S.c.	Subcutaneous
SD	Standard Deviation
SEC	Secukinumab
SF-36	Short Form-36
SI	Serious Infection
SMI	Small molecule inhibitor
SPSS	Statistical Package for Social Sciences
SSE	Summary (drug) survival estimate
STAT	Signal Transducer and Activator of Transcription
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	Tuberculosis
TE	Treatment Episode
Th cell	T-helper cell
TIL	Tildrakizumab
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor Inhibitor
TRM	Tissue Resident Memory
TYK	Tyrosine Kinase
UMCG	Universitair Medisch Centrum Groningen
UST	Ustekinumab
UV	Ultraviolet
VAS	Visual Analogue Scale
WHO	World Health Organization
Wk	Week
Y	Year

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Curriculum Vitae

Sarah Elisabeth Thomas werd geboren op 19 december 1994 te Rotterdam en groeide op in Diepenveen. Na het afronden van het Gymnasium op het Etty Hillesum Lyceum in Deventer, startte zij in 2013 met de opleiding Geneeskunde aan de Radboud Universiteit te Nijmegen. In de wachttijd op de coschappen was zij actief in het bestuur van de Medische Studentenvereniging, de MFVN, waar zij gedurende een jaar Ab Actis was. In 2020 sloot zij haar studie af met een wetenschappelijke stage bij de afdeling Dermatologie in het Radboudumc. Vanwege de COVID-19 maatregelen werd haar keuzecoschap in Paramaribo, Suriname ingekort en de tijd bij de Dermatologie in het Radboudumc verlengd. Alhier werd haar interesse voor het uitvoeren van wetenschappelijk onderzoek gewekt.

Eind 2020 startte zij als arts-onderzoeker op dezelfde afdeling in het BioCAPTURE team. In juli 2021 zette zij haar onderzoek voort als promotie-traject onder begeleiding van Prof. dr. Elke de Jong, dr. Juul van den Reek en dr. Marieke Seyger. Het onderwerp van haar promotie-traject betrof de behandeling van psoriasis met biologics, met speciale aandacht voor de effectiviteit en het behandelen van speciale patiëntengroepen. Zij heeft hiervoor voornamelijk gebruik gemaakt van data uit het BioCAPTURE netwerk. Daarnaast werkte zij samen met meerdere ziekenhuizen in Nederland. Het onderzoek werd gecombineerd met het zien van onderzoekspatiënten op het gespecialiseerde biological spreekuur en het geven van onderwijs.

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