Psoriasis in the Golden Years

From treatment challenges to a personalised approach in older adults

Elke ter Haar

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Psoriasis in the Golden Years
From treatment challenges to a personalised approach in older adults

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Chapter 1

General introduction, aims and thesis outline

Introduction

Ageing of the world population is accompanied by emerging challenges, especially in health care. In clinical practice, dermatologists and other caregivers will increasingly be confronted with the growing group of older adults with skin disease, leading to a strain on health care capacity and resources. Psoriasis, a common chronic skin disease, significantly impacts patients' quality of life, and is prevalent in all age groups, including older adults. Currently, evidence-based guidance regarding the treatment of older adults with psoriasis is sparse, resulting in a knowledge-gap and potentially leaving the way open for undertreatment of this growing population. Comorbidity, polypharmacy, frailty, and functional impairment are regularly present in older patients, often influencing and complicating treatment decision-making. The aim of this thesis was to contribute to the evidence-based guidance regarding the management of the growing group of older adults with psoriasis.

Older adults

Ageing

The world population is ageing at high speed, which presents unprecedented implications for health and social care. According to the United Nations, one in six people in the world will be aged 65 years or over in 2050, compared to one in eleven in 2019.[1] The amount of people aged 80 years or older is expected to triple between 2020 and 2050.[2] In the Netherlands, 20.2% of the total population is currently aged 65 years or over, compared to 12.8% in 1990. Furthermore, 4.9% of the total Dutch population is currently 80 years or older.[3] Since older adults generally need more care compared to younger people, the strain on health care capacity and resources is expected to increase. Ageing, the process of growing old, is a multifactorial process of genetic and environmental factors. Various transformations in the body occur, for example: immunosenescence see 1.1.2), organ impairment, endocrine system operation alterations, and changes in pharmacokinetics and -dynamics take place.[4-6] A summarized overview of the physiological changes in organ systems related to ageing is depicted in Figure 1. These changes are closely attributed to the accumulation of molecular and cellular damage over time, leading to a gradual decline in physical and cognitive capacity.[2]

Age typically is further stratified into chronological or biological age. Chronological age is defined as the amount of time that has passed from birth to the given date, which is the primarily used way to define age. Biological age is defined as the age of a person's cells and organs based on physiological functioning and appearance at a

certain time point. Biological age is also referred to as physiological or functional age.[6] Since the population of older adults is very heterogenous, chronological age often does not concur with the physiological and functional status of older adults. Therefore, it is suggested to not solely rely on chronological age, but instead, focus on biological age and integrate frailty assessment into medical decision-making. This is thought to provide a more accurate reflection of a patients real physiological and functional status.[6]

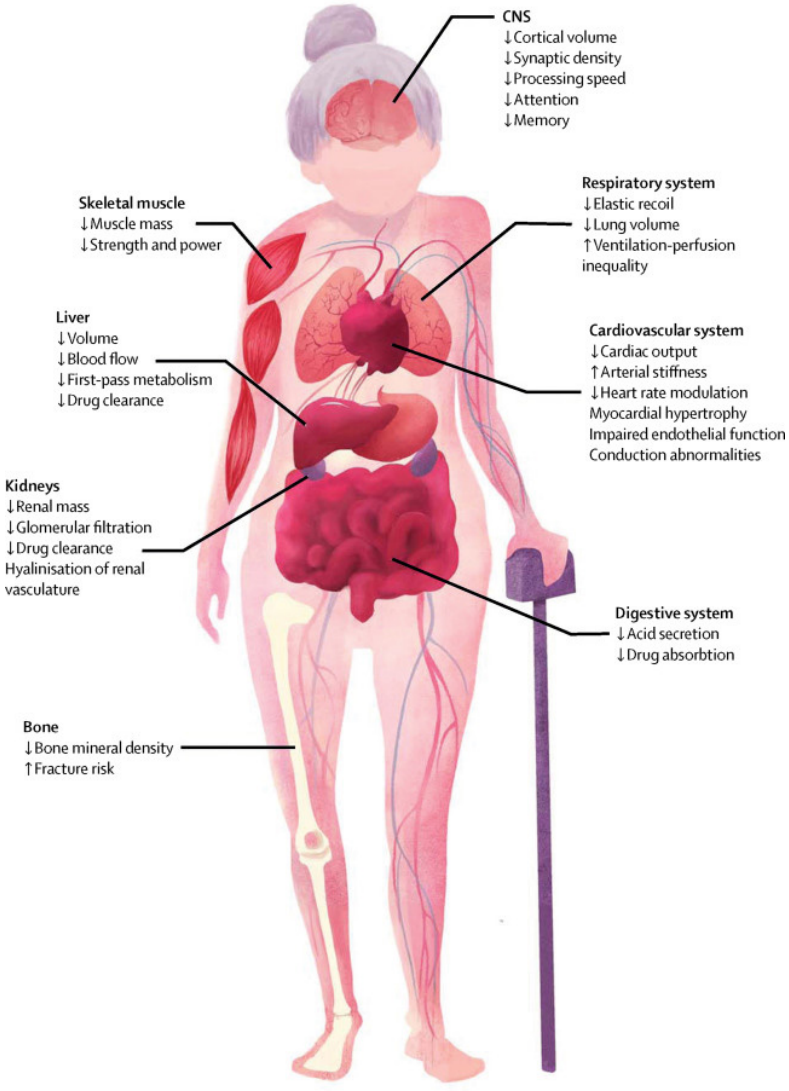

Figure 1. Illustration of physiological changes in organ systems as a result of ageing.[6]

Immunosenescence

Ageing of the immune system is commonly referred to as immunosenescence. This is an age-associated process of immune system alterations, leading to a higher risk to develop infections, autoimmune disease, and malignant tumours in older adults.[7] Inflammaging also known as chronic low-grade inflammation, is characterized by excretion of pro-inflammatory markers, linked to immunosenescence and considered a major risk factor for developing age-related diseases.[8] Regarding skin disease, immunosenescence is thought to play a role in the increased susceptibility of older adults into developing skin disorders, such as certain infections, autoimmunity and cutaneous malignancies .[8-11] Alterations in both the innate and adaptive immune system have been observed, e.g. a decline in B- and T-cell production/functioning and a reduction of antigen-presenting Langerhans cells.[12,13] As psoriasis is an immune-mediated inflammatory disease it is inevitable that there may be an influence of immunosenescence.[14] Previous research has reported a milder disease severity among psoriasis patients with a late disease or elderly-onset compared to patients with an early disease onset[15-17], possibly related to disruption of the inflammatory balance associated with immunosenescence. However, on the contrary higher proportions of senescent T-cells were observed in psoriasis patients, suggesting premature immunosenescence and probably resulting in prolonged inflammation.[18] As the body of evidence is scarce and conflicting, the interplay of immunosenescence and psoriasis is not yet understood.

Frailty and functional dependency

Frailty is a clinical syndrome, which can be defined by a diminished functional reserve leading to a decline in organ function, dependency, and a deterioration in psychosocial abilities. So, frail patients exhibit reduced tolerance to various stressors when compared to non-frail patients (Figure 2).[19,20] Following medical interventions, frail patients are at risk of adverse health outcomes (e.g. functional dependency, falls, delirium, hospitalisation, and mortality).[4,21] Although frailty is closely related to ageing, it is considered a separate entity. This is important because even though the incidence of frailty increases with age, not all older adults are frail. In fact, some individuals at the age of 85 exhibit greater independence, fitness, and overall health than certain 55-year-olds.[19] To understand and incorporate frailty in research and clinical practice, it is important to recognize the heterogeneity of the older adult population and the relation between ageing and frailty. Distinction of frail patients from those who are not frail, plays an essential role in the process of deciding upon starting a possibly harmful treatment in any medical field.[4]

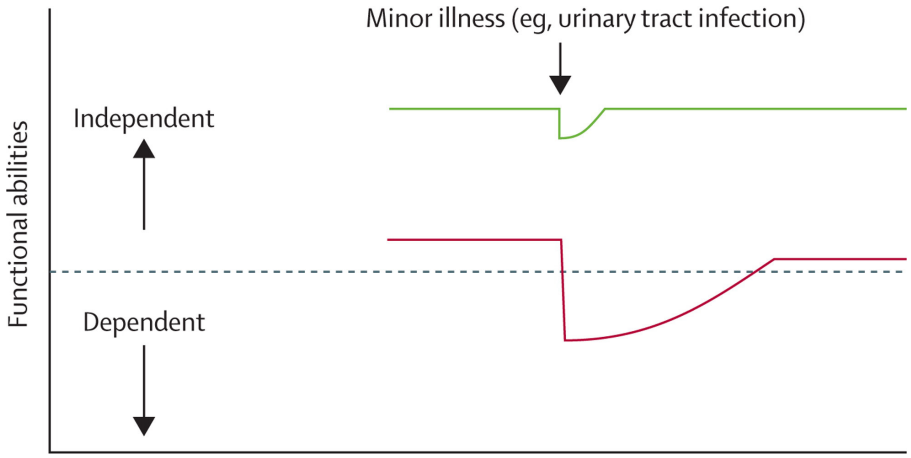

Figure 2. Vulnerability of frail elderly people to a sudden change in health status after a minor illness.[4] The green line represents a fit elderly individual who, after a minor stressor event such as an infection, has a small deterioration in function and then returns to homoeostasis. The red line represents a frail elderly individual who, after a similar stressor event, undergoes a larger deterioration, which may manifest as functional dependency, and who does not return to baseline homoeostasis. The horizontal dashed line represents the cut-off between dependent and independent.

To determine whether older adults are at risk for adverse health outcomes, multiple screening tools regarding frailty are used in clinical practice.[6] A comprehensive geriatric assessment (CGA) is the established gold standard to identify frailty in older adults.[4] It involves specialized care provided by a multidisciplinary team to systematically evaluate an individual's somatic, functional and psychological abilities. The goal of a CGA is to formulate a treatment and follow-up plan.[22] A CGA is often performed by or under supervision of a geriatrician. Even though the CGA is the golden standard, it is not always used to assess frailty in clinical practice or research since a certain expertise is required, it is time consuming, and the experts needed (geriatricians/CGA-teams) are not always available.[4] Furthermore, there is lack of agreement on the specific elements that should be incorporated into a CGA. The following components are commonly included: cognitive function, emotional state, nutritional state, comorbidity, polypharmacy, mobility/fall and, functional dependency.[20] Next to the CGA, several more concise, less time-consuming screening tools exist to identify patients at risk for frailty. The Geriatric-Eight (G8), Groningen Frailty Indicator (GFI), and Clinical Frailty Scale (CFS) are commonly used examples of these screening tools, all with their own advantages and disadvantages.[23-30] These screening tools can be used in various clinical settings, are capable of detecting potential frailty in approximately 5-15 minutes, and can be administered without the need for a geriatrician's involvement.

Functional dependency can be defined by the necessity for assistance and/or the inability to autonomously perform one or more activities of daily living, essential for independent living.[31] It is commonly considered as an advanced manifestation of frailty.[32,33] Functional dependency can be assessed by using the Activities of Daily Living questionnaire (ADL; bathing, dressing, transferring, toileting, continence, and eating) and Instrumental Activities of Daily Living questionnaire (IADL; telephoning, grocery shopping, preparing meals, housekeeping, laundering, using transportation, taking medication, and managing finances), also known as the Katz and Brody-Lawton indices respectively.[34,35]

Little is known about frailty and functional dependency in skin diseases, especially for patients with psoriasis. For the management of psoriasis in older adults, distinction of frailty and functional dependency might be of significance in aiding the treatment decision-making process. For instance, applying topical therapy might be challenging due to physical limitations, and the use of systemic medication for psoriasis in frail patients might result in a higher risk of adverse events.

Psoriasis

Psoriasis is a common and chronic immune-mediated inflammatory skin disease with a relapsing nature. It is estimated that 1-3% of the European population are affected by psoriasis.[36] All age groups can be affected by psoriasis, but peak incidences are reported around the age of 30-39 years and 50-59 years.[37] Currently, no cure is available for psoriasis, and the treatment predominantly revolves around addressing symptoms. Psoriasis can have a significant influence on quality of life, exerting a substantial impact on a patients physical, psychological, and social well-being.[38-40] In 2014, psoriasis was recognized as a serious non-communicable disease by the World Health Organisation, urging collaborative initiatives worldwide to promote research, awareness, and combat stigma's related to this skin disease.[41] Even though, the growing group of older adults with psoriasis constitute a large part of the total psoriasis population, this patient group is still underexposed. Limited research has been conducted and minimal specific guidelines for the treatment of older adults with psoriasis is available, leading to a significant knowledge gap. Therefore, in this thesis, the focus lies on providing evidence-based guidance regarding the management of older adults (≥65 years) with psoriasis.

Clinical features

Psoriasis is characterized by clinical symptoms such as erythematous, dry and scaly skin patches, causing itch, pain and bleeding. The clinical presentation can exhibit considerable variation, depending on distinct phenotypes. Plaque psoriasis is the

most common type of psoriasis and is present in 90% of patients.[42] Plaque psoriasis is identified by well demarcated erythematosquamous plaques, mainly located on the extensor sides of the elbows and knees, and often in symmetrical pattern (Figure 3). Other phenotypes are psoriasis capitis, inverse psoriasis, genital psoriasis, guttate psoriasis, palmoplantar psoriasis, pustular psoriasis, and erythrodermic psoriasis. Disease severity and clinical course can fluctuate overtime from a few affected skin patches to complete body coverage. Due to the relapsing nature of psoriasis, periods of remission and exacerbation are not unusual.

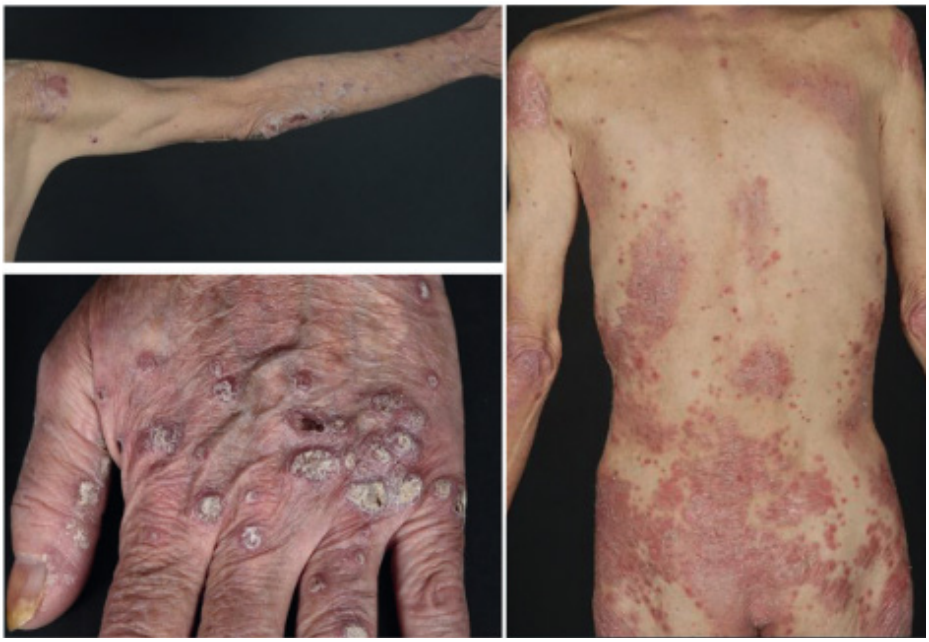

Figure 3. Psoriasis in older adults (≥65 years old).

Various factors can provoke a psoriasis exacerbation, including skin trauma (Koebner phenomenon), stress, infection (in particular streptococcal), and medications (e.g. beta-blockers, ACE-inhibitors, lithium carbonate, chloroquine, nonsteroidal anti-inflammatory drugs).[43,44] Some of these disease triggers are more commonly observed in older patients compared to younger patients such as usage of the mentioned medications and a fragile skin resulting in more frequent skin trauma. Because of the distinctive characteristics of psoriasis, a diagnosis based on physical examination is usually made. Even though psoriasis is common among older adults, limited research regarding this population is available. The exact prevalence of psoriasis in older adults is indefinite, but rates of 1-19% are

reported depending on variations in clinical settings and study populations.[36,37,45] A comparable disease severity between older and younger patients has been reported.[46,47] Regarding type of psoriasis, the plaque type is most common among older adults, which is similar to what is observed in younger patients. Some studies reported a higher prevalence of erythrodermic psoriasis in older adults compared to younger patients.[46,47] Psoriasis can negatively affect the quality of life (QoL) of patients due to the clinical symptoms (e.g. itching, scaling, pain), but also due to societal stigma related to the visibility of the disease, and treatment burden. While there is limited research regarding the influence of psoriasis on QoL in older adults, it appears that the impact on QoL can be significant in this group and should therefore be taken into account when treating older adults.[48]

Pathogenesis

The pathogenesis of psoriasis involves both genetic and environmental factors. Similarly, components of the innate and adaptive immune system are involved.[43,49,50] Genetic predisposition is a main risk factor for psoriasis development. The occurrence of continuous inflammation in psoriasis is thought to be the result of an interplay between the innate (e.g., dendritic cells, neutrophils and macrophages) and adaptive immune system activated by gene-environment interaction. The following pro-inflammatory cytokines as interleukin-12 (IL-12), IL-23, IL-17 and tumor necrosis factor (TNF)-alpha are important for the psoriatic disease manifestation (keratinocyt proliferation, skin thickening erythema, vasodilation, angiogenesis) (Figure 4). No disparity in gene expression related to psoriasis development is known between age groups.[51] As previously mentioned, immunosenescence or ageing of the immune system influences occurrence of certain infections, cancer, and inflammatory skin diseases.

Associated comorbidities

As psoriasis is a systemic inflammatory disease, it not solely affects the skin. Patients with psoriasis can have significant associated comorbidities. Psoriatic arthritis (PsA) is a common comorbidity associated with psoriasis. One in four patients with psoriasis are likely to develop PsA, with higher occurrence in patients with severe psoriasis.[52,53] PsA is a seronegative spondyloarthropathy, characterized by peripheral arthritis, dactylitis, and/or enthesitis. If not adequately treated, PsA can result in irreversible joint damage. Apart from PsA, psoriasis is associated with other impactful comorbidities such as cardiovascular disease, metabolic syndrome (including obesity, hypertension, hyperlipidaemia, diabetes mellitus), Crohn's disease, malignancies, hepatic disease, renal disease, and depression.[54-57] Patients with psoriasis have an increased risk of some specific comorbidities in comparison

to patients without psoriasis. Additionally, in older adults with psoriasis an increased incidence of psoriasis associated comorbidities has been specifically reported.[48,58] Furthermore, due to the aging process, older adults have a higher risk of developing comorbidities over the years in general. It can be difficult to unravel the direction and size of the causal relationship of these comorbidities with either the separate disease entity psoriasis and higher cumulative psoriasis disease years, consequences of (long) psoriasis treatment, the aging process, or a combination of the mentioned options.

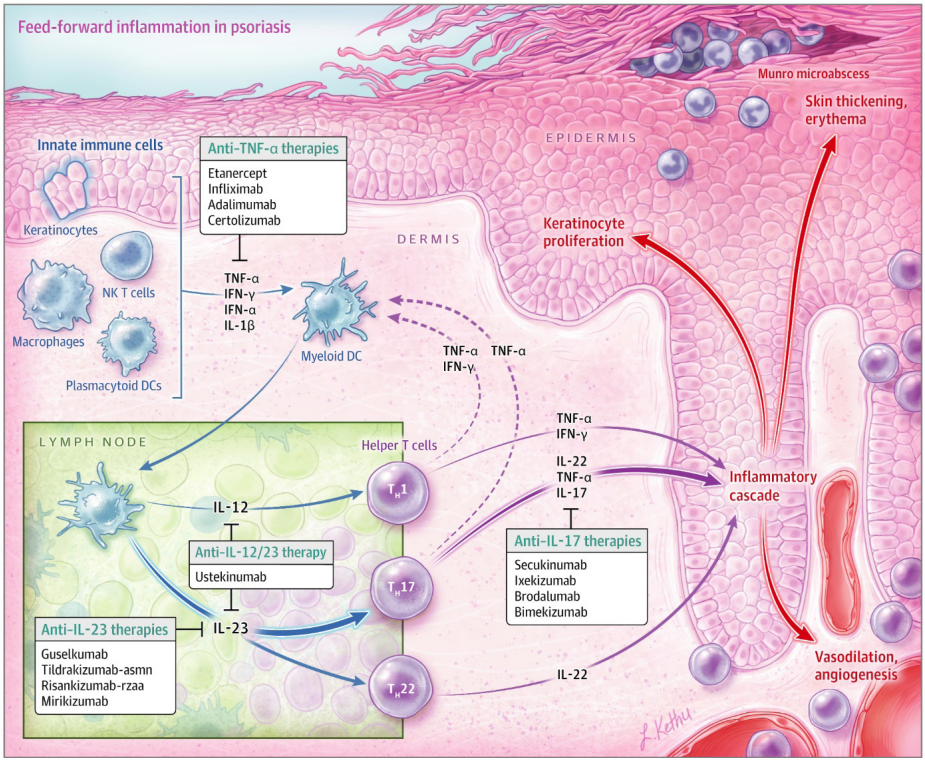

Figure 4. Pathophysiology of psoriasis including biologics and their respective targets.[50]

The pathophysiology of psoriasis involves excessive feed-forward activation of the adaptive immune system. Activated myeloid dendritic cells secrete excess IL-12 and IL-23. IL-12 induces differentiation of naive T cells to T-helper cells type 1 (TH1). IL-23 is central to the survival and proliferation of TH17 and TH22 cells. TH17 cells (and a multitude of other inflammatory cells) secrete IL-17; TH1 cells secrete tumor necrosis factor α (TNF-α); and TH22 cells secrete IL-22. These secreted cytokines activate intracellular signal transduction in keratinocytes to bring about gene transcription of cytokines and chemokines. This results in an inflammatory cascade that leads to psoriatic disease manifestations. DC indicates dendritic cell; IFN, interferon; NK, natural killer. Reproduced with permission from JAMA. 2020;323(19):1945-1960. Copyright©(2020) American Medical Association. All rights reserved.

Treatment options

The treatment options for patients with psoriasis include topical therapy (e.g., corticosteroids, coal tar, vitamin D analogues, dithranol, calcineurin inhibitors), phototherapy (narrowband ultraviolet B (UVB), ultraviolet A combined with psoralens (PUVA), conventional systemic therapies, and modern systemic therapies (biologics and small- molecule inhibitors (SMIs)). In the dermatology outpatient setting most patients with mild psoriasis use topical therapy and patients with moderate to severe psoriasis often use a combination of topical therapy with phototherapy or systemic therapy. Conventional systemic therapies (methotrexate, acitretin, ciclosporin, dimethyl fumaric acid) are used as psoriasis treatment for decades. Biologics and SMIs are targeted therapies blocking relevant cytokines and/or receptors involved in the psoriasis pathogenesis. Since the introduction of biologics starting in 2005, psoriasis care has improved significantly. They demonstrate increased effectiveness compared to conventional systemic agents. Currently four biological groups (TNF-α inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, IL-23 inhibitors) and apremilast (SMI) are available in clinical practice. The development of new biologics and SMIs is ongoing. Recently, deucravacitinib, a new oral drug that affects the JAK/STAT pathway by inhibiting tyrosine kinas 2 (TYK2) has been approved for mild to severe psoriasis.

Deciding upon the most optimal treatment for psoriasis can depend on several factors such as disease severity, side effect profile, comedication use, comorbidity, and patient preferences and needs. Preferably shared-decision making is employed when choosing the most optimal psoriasis treatment. In older adults with psoriasis, factors such as comorbidity and polypharmacy are more prevalent. Physical impairments can complicate applying topical therapy or receiving phototherapy. Additionally, the use of systemic therapies might be challenging due to altered pharmacokinetics and -dynamics in this population. Despite the availability of numerous studies on systemic therapy in psoriasis, a knowledge-gap is present, as older adults are poorly represented in randomized controlled trials (RCTs) and observational studies.[59] A recent systematic review on the effectiveness and safety of systemic therapies among older adults with psoriasis confirms the absence of available data for older adults using systemic agents in psoriasis.[60] Furthermore, the authors report that older age is significantly associated with renal function decline in patients using ciclosporin, and lymphopenia in patients using dimethyl fumaric acid. For biologics in older adults, infections were the most common side effects, but no significant relation with age was found. The authors conclude, age alone should not be a limiting factor in treatment decision-making in older adults with psoriasis as safety results were scarce but limited to a higher chance of laboratory

deviations and infections in older adults. Furthermore the need for more real-world evidence was expressed.[60] This lack of evidence-based guidance may lead to reluctance among healthcare providers to prescribe certain systemic treatments in older adults, which might result in suboptimal psoriasis management.

Real-world evidence

RCTs are considered to be the gold standard to evaluate efficacy of drugs or interventions in medical research. Because of their study design, potential biases can be adequately addressed in RCTs. Randomization, allocation concealment, and the use of blinding can minimize bias and confounding.[61,62] For psoriasis, the efficacy and safety of systemic agents are investigated in RCTs, and psoriasis guidelines are primarily based on RCT findings. Even though RCTs are considered the golden standard, extrapolation of RCT results to the real-world situation is not always possible due to the strict in- and exclusion criteria used, and a relatively short observation time. In psoriasis research, 33.3% of RCTs used an upper age limit as exclusion criterium (ranging from 55-85 years) and 90.6% of RCTs used indirect exclusion criteria disproportionally affecting older adults (e.g. comorbidities and comedication use).[59] Thus, the RCT population is often not representative of the real-world population[59,63], resulting in a limited generalizability of RCT results in psoriasis research to older adults with psoriasis. Real-world evidence (RWE) is clinical evidence on safety and efficacy of a drug or intervention, collected using real-world data in daily clinical practice.[64] Currently, RWE is becoming more accepted to provide insights into safety and efficacy of drugs in psoriasis, alongside RCTs.[65]

Thesis aims and outline

The main objective of this thesis is to contribute to the optimization and personalization of psoriasis management in older adults by providing evidence-based guidance.

Improving personalised care for older adults with psoriasis requires gaining a comprehensive understanding of psoriasis and its consequences within this specific patient population. In **chapter 2.1**, we explored patient, disease- and treatment-characteristics of older adults with psoriasis including comorbidity, concomitant medication use, type of psoriasis, disease severity, current and past treatments, side effects, and needing help with applying or receiving psoriasis treatment. In this nationwide self-administered patient survey, age groups (<65 years old and ≥65 years old) were compared.

In **chapter 2.2**, the differences in burden of disease, patient preferences, and treatment goals between older adults and younger patients were assessed. Additionally, the impact of psoriasis on the quality of life was examined.

Older adults with psoriasis are often excluded from RCTs, resulting in lack of evidence-based guidance and limited external validity/generalizability of available RCT findings. Therefore, we quantified the extent of this issue in **chapter 2.3,** by conducting a multicentre retrospective daily practice cohort study. In this study we compared the comorbid disease status of older adults with psoriasis to the general population, as comorbidities often serve as exclusion criteria. Furthermore, we assessed the impact of RCT exclusion criteria on the generalizability of research findings to a real-world geriatric psoriasis cohort.

Despite comparable disease severity among older and younger psoriasis patients have been reported, older adults tend to receive less systemic therapy than younger patients. Besides a higher prevalence of contraindications (comorbidity, comedication use) among this population, treatment reluctance of health-care providers has also been mentioned as a probable explanation. This can possibly be linked to sparse evidence-based guidance and limited experience of healthcare providers with this specific patient group. In **chapter 2.4**, we conducted a mixed-methods study comprising of a nationwide survey and semi-structured interviews among dermatologists and dermatology residents. With this study we aimed to gain insights in prescribing patterns, comfort levels, barriers, and needs when applying systemic therapies in older adults with psoriasis.

Prior research in other medical fields has shown that frailty-related characteristics are associated with adverse treatment outcomes and mortality. Moreover, integrating frailty and functional dependency has been proven valuable in treatment decision-making in other medical conditions. Frailty and functional dependency have not been previously assessed in older adults with psoriasis. To further aid in personalised decision-making in geriatric psoriasis, a multicenter cohort study was performed in older adults with psoriasis. The aim of this study was to identify the prevalence and extent of frailty and functional dependency in older adults with psoriasis and their implications for psoriasis management, presented in **chapter 2.5**.

Selecting the most optimal systemic therapy for older adults with psoriasis can be challenging due to the above mentioned limited evidence-based guidance and reports of conflicting results regarding safety risks in small older adult populations. Therefore, in **chapter 3.1**, a multicentre retrospective daily practice cohort study was described, in which we aimed to gain an increased understanding of treatment safety in older adults with psoriasis using systemic therapy in a real-world cohort.

Biologics, one of the most recent additions to psoriasis therapeutic options have been proven to be an effective treatment for psoriasis. Since the representation of older adults in clinical trials is low, a knowledge gap exists regarding the safety and efficacy of biological treatment in this growing group of older adults. With the in **chapter 3.2** presented prospective observational study on biologics for psoriasis, we aimed to provide insight into the drug survival, safety, and effectiveness of biologics in older patients, comparing outcomes with a younger population.

For tildrakizumab (IL-23 inhibitor), one of the newest biologics, there is almost no evidence-based guidance available specifically for older adults with psoriasis. This could trigger treatment reluctance to prescribe tildrakizumab in older adults with psoriasis in fear of lower efficacy or tolerability. Therefore, in **chapter 3.3** a post hoc analysis of 2 phase III trials is demonstrated. The aim of this study was to compare efficacy and safety of tildrakizumab among younger and older patients with psoriasis.

The results described in this thesis are summarized and discussed in **chapter 4**, as well as possible clinical implications and future perspectives. A Dutch summary of this thesis is provided in **chapter 5**.

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Chapter 2

Personalised management of psoriasis in older adults

Chapter 2.1

Disease and treatment characteristics in geriatric psoriasis: a patient survey comparing age groups

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Abstract

Little is known about psoriasis in geriatric patients, whereas treating this growing population can be challenging due to comorbidities, comedication and physical impairments. To compare disease and treatment characteristics of psoriasis patients ≥ 65 years old with patients < 65 years old, a self-assessment survey was sent to all members of the Dutch Psoriasis Association (n = 3,310). In total, 985 (29.7%) patients returned the survey, 414 (43.6%) respondents were ≥ 65 years old. Patients ≥ 65 years old had experienced erythrodermic psoriasis significantly more frequently than patients < 65 years old, other disease characteristics were highly comparable. Despite a significantly higher prevalence of comorbidities and comedication use in patients ≥ 65 years old, no difference was seen between the age groups regarding systemic antipsoriatic treatment (38.3% in ≥ 65 years old vs 42.3% in < 65 years old; p = 0.219). Remarkably, treatment-related side-effects were reported more frequently by patients < 65 years old. In conclusion, age alone should not be a limiting factor in psoriasis management, and proper attention must be paid to additional patient-related factors.

Significance

Little is known about geriatric psoriasis, although health problems and medication can complicate the management of psoriasis. To compare characteristics of patients ≥ 65 years old with those < 65 years old, a survey was sent to all members (3,310) of the Dutch Psoriasis Association. In total, 985 (29.7%) patients returned the survey, 414 (43.6%) respondents were ≥ 65 years old. Despite more comorbidities and medication use in ≥ 65 years old, no difference was seen between age groups regarding systemic antipsoriatic treatment (38.3% vs 42.3%). Side-effects were reported more frequently by patients < 65 years old. Thus, age alone should not limit psoriasis treatment, and proper attention must be paid to patient-related factors.

Introduction

Psoriasis is an immune-mediated inflammatory disease which is frequently seen in older adults. As the ageing world population continues to expand, dermatologists will increasingly be confronted with patients aged 65 years and older. Although the exact prevalence of psoriasis in older adults is unknown, it is estimated to range from 1% to 19%.[1-3] Balancing the possible risks of antipsoriatic therapies in older adults and optimal psoriasis treatment can be challenging, due to factors such as comorbidities, concomitant medication, physical impairments and changing pharmacokinetics and pharmacodynamics.[4,5]

Little research has been conducted concerning disease and treatment characteristics in older psoriasis patients, or "geriatric psoriasis" **(Figure S1)**. The few available studies show similar disease severity compared with younger patients, although prescribed therapies appear to differ.[6,7] Moreover, data concerning the use of systemic treatment in geriatric psoriasis are scarce, since older adults are frequently excluded from clinical trials.[8,9] Therefore, it is currently unclear what risks are associated with antipsoriatic treatment in this growing population and whether geriatric patients with psoriasis are treated optimally.

To improve patient-centred clinical care in geriatric psoriasis, more knowledge needs to be acquired in this particular patient group. The objective of this study was therefore to provide more insight into the disease and treatment characteristics in older adults with psoriasis compared with younger patients.

Materials and methods

Study design and participants

A nationwide cross-sectional study was conducted to assess the clinical characteristics of older adult patients with psoriasis, as well as current and previous treatments. A self-assessing multimodality survey was sent to all members of the Dutch Psoriasis Association (n = 3,310), along with study information and a prepaid envelope. In addition to this paper-based version, a hyperlink to the online web-based survey (Qualtrics, Provo, UT, USA) was provided and printed repeatedly in the Dutch Psoriasis Association Magazine. Returning the survey was construed as informed consent. Approval from the Research Ethics Committee of Radboud University Medical Centre was obtained before starting the study. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[10]

Survey

A survey was developed based on an extensive review of the literature, patient interviews, and multiple meetings with a multidisciplinary focus group consisting of physicians in dermatology and rheumatology, (specialized) nurses, clinical researchers, and a dermato-psychologist. The survey included multiple sections enquiring about sociodemographic aspects, psoriasis characteristics and associated therapy using multiple choice questions, Likert scales, and visual analogue scales. Furthermore, open-ended questions were added to each section to further evaluate relevant items not captured by the questions included in the survey, answers were categorized for further analyses. Disease severity was measured using the Self-Administered Psoriasis Area Severity Index (SAPASI), a validated patient-assessed instrument based on the frequently used Psoriasis Area Severity Index.[11] The SAPASI ranges from 0 to 72 and can be classified into 4 categories: in remission (SAPASI = 0), mild ($> 0 \leq 3$), moderate ($> 3 \leq 15$) and severe (> 15).[12] Prescribed therapies were categorized into 4 different groups: topical therapy, phototherapy, conventional systemic therapy, and modern systemic therapy (biologics and small-molecule inhibitors). Body mass index (BMI) was calculated based on reported weight and height. Polypharmacy was defined as the simultaneous use of 5 or more medications.[13] A pilot study was performed in 10 geriatric patients with psoriasis prior to distribution of the survey to improve its quality, and assess the relevance and comprehensibility of the questions, instructions and response options.

Data processing and analysis

Data were processed anonymously using the automatic form identification software Remark Office Optical Mark Recognition, version 9.5 (Gravic, Inc. Malvern, PA, USA) and Castor Electronic Data Capture, a web-based data management system in compliance with Good Clinical Practice (GCP) standards (Castor Research Inc., Hoboken, NJ, USA). To ensure correct data entry, 10% of the data entry was checked manually by an independent researcher who was not involved in data entry. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 25.0 (IBM, Armonk, NY, USA). Descriptive statistics were used to summarize categorical data as frequencies and percentages and continuous variables as mean ± standard deviation (SD) or median (range), as appropriate according to the distribution of the data. Missing values were excluded from analyses. Patients were categorized into 2 age groups; patients ≥ 65 years old and patients < 65 years old. Comparisons were made using Student's t-test or Mann–Whitney U test for continuous variables, and the $\chi 2$ or Fisher's exact test for categorical variables. Subgroup analyses were performed comparing outcome measures of patients ≥ 80 years old with patients < 80 years old, and comparing patients with early disease

onset (onset of symptoms before the age of 40 years) and patients with late disease onset (onset of symptoms after the age of 40 years).[14] Logistic regression was used to correct for confounding variables and to determine odds ratios (ORs). Age and sex distribution of the respondent population were compared with the target population to test for non-response bias, using available current data on the members of the Dutch Psoriasis Association and previous research in this population.[15]

Results

Study participants

Between 11 December 2018 and 4 September 2019, 3,310 patients with psoriasis were approached for participation. In total, 985 (29.7%) surveys were returned. Due to missing age values, 27 respondents were excluded from analyses. Eight more respondents were excluded from analyses due an insufficient number of answered items (e.g. responses to age and sex only). The remaining 950 respondents were suitable for analysis. The mean ± SD age was 61.1 ± 13.7 years, range 7–95, and 414 (43.6%) of the respondents were ≥ 65 years old. Of these, 58 (14.0%) respondents were ≥ 80 years old. A full overview of responder characteristics is given in **Table 1**. Although a significant difference in sex was seen between patients ≥ 65 years old vs those < 65 years old, results after stratification for sex did not differ from the main analysis (data not shown).

Non-response bias was assessed by comparing age and sex distribution of the study respondents with the target population; no significant differences were found **(Table S1)**. Since 95.5% (n = 879) of the surveys were returned in the winter, an additional analysis on seasonal difference was performed; no significant impact on outcome measures was seen. There were no significant differences in outcome measures between paper-based and web-based responses (data not shown).

Comorbidities and medical history

Except for depression, all reported comorbidities were significantly more common in patients ≥ 65 years old, as is illustrated in **Table 1**. A cardiovascular risk profile (e.g. obesity, hypertension, hypercholesterolaemia, diabetes mellitus, myocardial infarction, heart failure and cerebral vascular accident) was more prevalent in patients ≥ 65 years old compared with patients < 65 years old. Moreover, patients ≥ 65 years old had a significantly higher BMI (median 26.2 (range 17.7–65.9 kg/m2) in ≥ 65 years old vs 25.4 (14.3–56.1 kg/m2) in < 65 years old; p = 0.006). A (history of) malignancy was significantly more often reported by patients ≥ 65 years old compared with

patients < 65 years old (n = 94 (23.2%) vs 44 (8.3%) respectively; p < 0.001). Of all patients reporting a (history of) malignancy, 71 (43.3%) reported skin cancers (35.2% non-melanoma skin cancer, 22.5% melanoma, 42.3% unknown type of skin cancer).

Table 1. Responder characteristics of geriatric psoriasis patients (≥65 years old) compared with patients <65 years old.

	<65 years old (n=536)	**≥65 years old (n=414)**	**p-value**
Sex, n (%)			
Male	247 (46.2)	246 (59.6)	<0.001
Female	288 (53.8)	167 (40.4)	
Age (years), median (range)	56 (7-64)	71 (65-95)	NA*
Mean ± SD	52.4 ± 11.4	72.4 ± 5.9	
Age at onset, n (%)			NA*
Early onset[a]	459 (85.6)	305 (73.7)	
Late onset[b]	74 (13.8)	108 (26.1)	
Unknown	2 (0.4)	0 (0.0)	
Family history of psoriasis, n (%)			0.719
Positive[c]	333 (62.2)	266 (64.6)	
Negative	118 (22.1)	88 (21.4)	
Unknown	84 (15.7)	58 (14.1)	
Medical history, n (%)			
Overweight (BMI >25)	285 (53.7)	250 (62.3)	0.008
Hypertension	108 (20.5)	197 (49.0)	<0.001
Hypercholesterolaemia	68 (12.9)	149 (37.3)	<0.001
Myocardial infarction	10 (1.9)	35 (8.8)	<0.001
Heart failure	21 (4.0)	66 (16.6)	<0.001
Cerebral vascular accident	9 (1.7)	22 (5.5)	0.002
Diabetes Mellitus	25 (4.7)	64 (15.9)	<0.001
Cancer[d]	44 (8.3)	94 (23.2)	<0.001
Depression	99 (18.9)	69 (17.3)	0.530
Use of comedication[e], n (%)	236 (44.7)	306 (75.6)	<0.001

Values might not add up due to missing values.

[a] Defined as onset of symptoms before and

[b] after the age of 40 years[14]

[c] Including all family members affected by psoriasis. Separate analyses were done only including first-degree family members; 233 (43.6%) patients <65 years old reported 1 or more affected first-degree family members, compared with 206 (50.0%) patients ≥65 years old (p=0.142).

[d] Excluding non-melanoma skin cancer (n=25). In uncertain cases (e.g., 30 patients reported "skin cancer"), patients were included in the analysis.

[e] Other than psoriasis medication.

NA: not applicable, since the categorization of patients in separate age groups automatically leads to differences in age-related variables; BMI: body mass index; SD: standard deviation.

The use of concomitant medication was reported by 306 (75.6%) patients ≥ 65 years old, vs 236 (44.7%) patients < 65 years old (p < 0.001). The most frequently used types of concomitant medication were cardiovascular drugs (n = 211 (69.0%)

≥ 65 years old vs n = 104 (44.1%) < 65 years old; p < 0.001) and antidiabetic drugs (n = 42 (13.7%) ≥ 65 years old vs n = 21 (8.9%) < 65 years old; p = 0.004). Moreover, polypharmacy was significantly more prevalent in patients ≥ 65 years old (n = 103 (30.7%) ≥ 65 years old vs n = 47 (13.9%) < 65 years old; p < 0.001).

Disease characteristics

As shown in **Table 2**, plaque psoriasis and psoriasis capitis were the most frequently reported clinical psoriasis types currently present in both patient groups (cumulative prevalence: 67.2% and 70.6%, respectively). Patients ≥ 65 years old had experienced erythrodermic psoriasis significantly more frequently than patients < 65 years old (n = 70 (17.1%) ≥ 65 years old vs n = 31 (5.8%) < 65 years old; p < 0.001). Comparable rates of psoriatic arthritis were reported in both age groups (n = 158 (38.5%) ≥ 65 years old vs n = 193 (36.2%) < 65 years old; p = 0.464). Guttate and genital psoriasis were significantly more frequently reported by patients < 65 years old. In both groups, patients experienced their first symptoms of psoriasis most frequently before the age of 18 years (n = 136 (32.9%) ≥ 65 years old vs n = 219 (40.9%) < 65 years old). Of all patients ≥ 65 years old, 65 (15.7%) reported disease onset after the age of 50 years, 14 (3.4%) respondents reported disease onset after the age of 65 years, as is illustrated in **Figure S2**.

A subgroup analysis was performed to compare disease characteristics in patients ≥ 65 years old with early disease onset with those with late disease onset. Erythrodermic psoriasis was significantly more frequently reported by patients with early disease onset (n = 63 (20.8%) vs n = 7 (6.5%); p = 0.001), as well as psoriasis unguium (n = 160 (52.8%) vs n = 42 (39.3%); p = 0.016). Other disease characteristics did not differ between the onset groups. The majority of all patients had never experienced a period of total skin clearance (n = 228 (55.6%) ≥ 65 years old vs n = 302 (56.7%) < 65 years old; n = 0.774). Only 82 (8.7%) patients in the total study population experienced a period of total skin clearance longer than 3 years in a row. Although patients ≥ 65 years old reported a slightly lower current SAPASI score compared with patients < 65 years old (median 5.24 (0–20.2) in ≥ 65 years old vs 5.72 (0–35.5) in < 65 years old; p = 0.016), disease severity was considerably high in both groups, as most patients currently received antipsoriatic treatment. When comparing the age groups according to categorized SAPASI scores, no significant difference was seen in disease severity; a current moderate disease activity was reported by 266 (68.9%) patients ≥ 65 years old, severe psoriasis was reported by 17 (4.4%) patients ≥ 65 years old, whereas 371 (71.1%) patients < 65 years old reported a moderate disease activity and 33 (6.3%) a severe disease activity (p = 0.260).

Table 2. Disease and treatment characteristics of geriatric psoriasis patients (≥65 years old) compared with patients <65 years old.

	<65 years old (n=536)	**≥65 years old (n=414)**	**p-value**
Type of psoriasis*, n (%)			
Plaque psoriasis	371 (69.6)	263 (64.1)	0.077
Guttate psoriasis	306 (57.4)	179 (43.7)	<0.001
Pustular psoriasis	24 (4.5)	20 (4.9)	0.787
Psoriasis capitis	378 (70.9)	288 (70.2)	0.821
Erythrodermic psoriasis	31 (5.8)	70 (17.1)	<0.001
Psoriatic arthritis	193 (36.2)	158 (38.5)	0.464
Inverse psoriasis	136 (25.5)	79 (19.3)	0.023
Genital psoriasis	166 (31.1)	69 (16.8)	<0.001
Psoriasis unguium	265 (49.7)	202 (49.3)	0.891
Self-Administered PASI, median, range	5.72 (0 - 35.5)	5.24 (0 - 20.2)	0.016
Current treatment*, n (%)			
Topicals[a]	353 (66.6)	268 (65.4)	0.691
UV therapy	26 (4.9)	20 (4.9)	0.984
Systemic	224 (42.3)	157 (38.3)	0.219
Conventional systemic[b]	140 (26.4)	107 (26.1)	0.913
Methotrexate	65 (12.3)	50 (12.2)	0.974
Ciclosporin	1 (0.2)	3 (0.7)	0.323
Acitretin	2 (0.4)	6 (1.5)	0.085
Fumaric acid	78 (14.7)	52 (12.7)	0.370
Modern systemic[c]	100 (18.9)	63 (15.4)	0.160
Apremilast	3 (0.6)	3 (0.7)	1.000
Etanercept	15 (2.8)	11 (2.7)	0.891
Adalimumab	38 (7.2)	23 (5.6)	0.336
Infliximab	1 (0.2)	2 (0.5)	0.583
Ustekinumab	31 (5.8)	16 (3.9)	0.174
Secukinumab	5 (0.9)	4 (1.0)	1.000
Ixekizumab	0 (0.0)	3 (0.7)	0.083
Brodalumab	4 (0.8)	0 (0.0)	0.136
Guselkumab	1 (0.2)	1 (0.2)	1.000
Certolizumab pegol	2 (0.4)	0 (0.0)	0.508
No prescribed therapies[d]	87 (16.4)	68 (16.6)	0.944
Side effects, n (%)	127 (25.9)	72 (19.8)	0.015[e]

Percentages are presented in relation to all study respondents, values might not add up due to missing values and combination therapies.

* Patients could select more than 1 answer option.

[a] Including keratolytic agents, corticosteroids, vitamin D derivatives, calcineurin inhibiting agents, coal tar, combination therapies, dithranol (anthralin).

[b] Including methotrexate, ciclosporin, acitretin and fumaric acid.

[c] Including apremilast, etanercept, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, certolizumab pegol.

[d] Defined as no prescribed therapies and non-prescription therapies, usage of emollients only, homeopathic treatment, over-the-counter products, and dietary or lifestyle adjustments.

[e] After correcting for type of treatment (only topical therapy, UV therapy with or without topical therapy, conventional systemic therapy with or without topical therapy, modern systemic with or without topical therapy and combined systemic therapies with or without topical therapy).

PASI: Psoriasis Area and Severity Index; SAPASI: Self-Administered Psoriasis Area and Severity Index; UV: ultraviolet

Antipsoriatic treatment

As shown in **Table 2**, there were no significant differences in currently used therapies by patients ≥ 65 years old compared with patients < 65 years old. No significant difference was seen between the age groups regarding the use of conventional systemic therapies (n = 107 (26.1%) ≥ 65 years old vs n = 140 (26.4%) < 65 years old; p = 0.913), nor in the use of modern systemic therapies (n = 63 (15.4%) ≥ 65 years old vs n = 100 (18.9%) < 65 years old; p = 0.160). A combination of systemic agents was used by 17 (4.1%) patients ≥ 65 years old and 22 (4.2%) patients < 65 years old (p = 0.997). When comparing the specific systemic agents between the age groups, no significant differences were seen. As is shown in **Figure S3**, most frequently used systemic agents were fumaric acid, methotrexate and adalimumab in both age groups (cumulative respectively 34.1%, 30.2% and 16.0%). No significant differences between the age groups were seen in previously used therapies.

A separate analysis comparing patients ≥80 years old (n = 58) with patients p = 0.759). Modern systemic therapies were used in 6 (10.5%) patients ≥ 80 years old, compared with 157 (17.8%) patients p = 0.161). A significant higher number of patients ≥ 80 years old were currently treated with phototherapy, although the sample size was quite small (n = 8 (14.0%) vs n = 38 (4.3%); p = 0.001), as is summarized in **Table S3**.

Adverse events were reported significantly more frequently by patients < 65 years old compared with patients ≥ 65 years old, even after correction for type of treatment (only topical therapy, UV therapy with or without topical therapy, conventional systemic therapy with or without topical or UV therapy, modern systemic with or without topical or UV therapy and combined systemic therapies with or without topical therapy, OR: 1.57; 95% CI: 1.09–2.25; p = 0.015).

Patients ≥ 65 years old were significantly more often dependent on assistance with treatment or skin care compared with patients < 65 years old (n = 56 (14.9%) ≥ 65 years old vs n = 46 (9.0%) < 65 years old; p = 0.007); 47 (83.9%) were helped by a partner or family member, and 9 (16.1%) relied on medical caretakers or others. Of all patients ≥80 years old, 11 (20.8%) were dependent on others, 6 (54.5%) were assisted by a partner or family member, and 5 (45.5%) by medical caretakers. No difference was seen among the age groups in the daily amount of time patients spent on their treatment or skin care. Most patients spent less than 30 min per day on psoriasis management (n = 352 (92.9%) ≥ 65 years old vs n = 481 (94.3%) < 65 years old; p = 0.635).

Discussion

Managing psoriasis in older adults can be a clinical challenge, due to factors such as comorbidity, concomitant medication, ageing-related organ impairment and functional deterioration. Limited data are available to guide clinicians in treating this growing patient group. The aim of this study was to evaluate disease and treatment characteristics in geriatric psoriasis patients and to identify differences compared with a younger population.

In this large cross-sectional study, plaque psoriasis and psoriasis capitis were the most frequently reported types of psoriasis in both groups. Erythrodermic psoriasis was significantly more often reported by patients ≥ 65 years old, in line with previous research.[6,7,21] A possible explanation for this difference could be that patients ≥ 65 years old have been treated with less potent therapies in the past during prolonged periods of time, increasing the potential of developing more severe and extensive psoriasis. Furthermore, since the question was posed whether patients had ever experienced an episode of erythrodermic psoriasis in the past, the a priori chance is higher in older patients due to the higher number of cumulative disease years. This too explains the fact that erythrodermic psoriasis was reported more frequently by patients with early disease onset, as has also been stated previously.[14] Other types of psoriasis have been studied to a lesser extent; Phan et al. reported a higher prevalence of guttate psoriasis in patients ≥70 years old compared with patients < 70 years old.[21] In other studies, including the current study, this difference was not seen.[6,7]

In this study, the majority of patients ≥ 65 years old reported a moderate current disease activity, although median SAPASI scores were slightly higher in patients < 65 years old. Previous studies are in line with these results, showing comparable disease severity in both age groups.[6,7] Strikingly, the majority of the respondents in both groups reported never having achieved total skin clearance, while total clearance of psoriasis is frequently mentioned as one of the most important treatment goals to improve quality of life in patients with psoriasis.[22,23] It seems that psoriasis treatment in both age groups could be further improved, tailored to individualized treatment goals. Currently, little research is available assessing treatment goals and quality of life in geriatric psoriasis patients specifically, to evaluate whether patients consider themselves optimally treated.

Patients ≥ 65 years old reported significantly more comorbidities and concomitant medication in comparison with patients < 65 years old, in line with previous

research.[7,21] Comorbidities and concomitant medication should be acknowledged when considering management options, especially with regard to contra-indications of antipsoriatic therapies. Despite a significant higher prevalence of (relative) contra-indications for several antipsoriatic systemic therapies reported by patients ≥ 65 years old, no significant differences were found between the age groups when comparing the individual systemic agents. Even in a subgroup analysis of patients ≥80 years old, systemic therapies did not differ significantly from in younger patients, although the number of patients ≥80 years old using modern systemic therapies was small. This is in contrast with previous studies stating that (modern) systemic therapies are less often prescribed in older patients.[7,21,24,25] Some studies suggest that prescription of systemic therapies increases over time, due to the fact that physicians have gained more experience with these therapies and are therefore more comfortable with prescribing systemic therapies, explaining the difference between the present study results and those found in previous studies.[7,24] Another explanation could be that the treatment goals and preferences of patients ≥ 65 years old have changed over time, although available literature in this field is scarce.[23] Significantly more patients ≥ 65 years old required assistance with treatment or skin care, it is therefore important to consider this aspect in choosing antipsoriatic treatment.

In order to minimize the risks of potential drug interactions, as well as treatment-related adverse events, managing psoriasis in patients with comorbidities and concomitant medication requires extra attention. In this study, significantly fewer adverse events were reported by patients ≥ 65 years old, even when corrected for the type of treatment. It should be noted that this involves only self-reported side-effects and probably does not include asymptomatic treatment-related laboratory changes. Moreover, the reasons for ceasing previous therapies were not evaluated, which could be related to adverse events experienced in the past. Available research varies widely concerning the rates of adverse events and tolerability profiles in older adults, frequently stating adverse event rates do not differ between age gro ups.[6,7,25-27] More real-life data is needed to provide clarity and guidance in this field.

Limitations

This study has certain limitations due to the study design. Firstly, any survey is associated with a risk of recall bias and misinterpretation of the questions, although this risk was minimized by pre-testing the survey in a pilot study. Since all participants were members of a patient association, a risk of selection bias exists. A higher level of education was seen in the study population compared with the Dutch overall population[17], which might be associated with membership

of a patient association altogether **(Table S3)**. Moreover, members of a patient association might be older[16,18-20] and have more severe psoriasis than the overall psoriasis population.[20] Since this study aimed to study a population representative of daily dermatological care, it was assumed that the Dutch Psoriasis Association closely resembles the target population. A relatively large cohort of patients ≥ 65 years old responded compared with the composition of the Dutch population. The survey was introduced explaining the nature of the study; to study differences in psoriasis management and characteristics among different patient age groups. Therefore, patients ≥ 65 years old may have been stimulated to respond, whereas patients in middle-age felt less urge to respond (sampling bias). However, age and sex distribution of the respondent population were shown to be representative for the target population. In addition, response rates were similar to previous studies with comparable study designs.[15,28] Moreover, the current study comprised one of the largest geriatric psoriasis populations described so far.

Conclusion

Treating geriatric patients with psoriasis requires extra attention to comorbidities and the use of concomitant medication, since these were significantly more frequently seen in patients ≥ 65 years old than in patients < 65 years old. Despite these obvious differences in patient-related characteristics, a better tolerability profile was reported by patients ≥ 65 years old. Based on the results of this study, chronological age alone should not be a limiting factor in choosing antipsoriatic therapy, although patient-related characteristics must be considered; physical impairments, availability and necessity of help, and possible drug-interactions can complicate treatment decisions. In order to provide personalized medicine, more research on treatment goals and patient preferences in geriatric psoriasis patients is needed to further guide clinicians in optimally treating this growing patient group.

Acknowledgements

The authors would like to thank all respondents who completed the survey, and the Dutch Psoriasis Association for their efforts regarding this study. Moreover, the authors would like to thank the focus group members for their input, especially J. van den Reek, M. Kooijmans-Otero, S. Spillekom van Koulil, M. Eilander, M. Teunissen, A. van der Wielen-Willems.

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Supplemental material

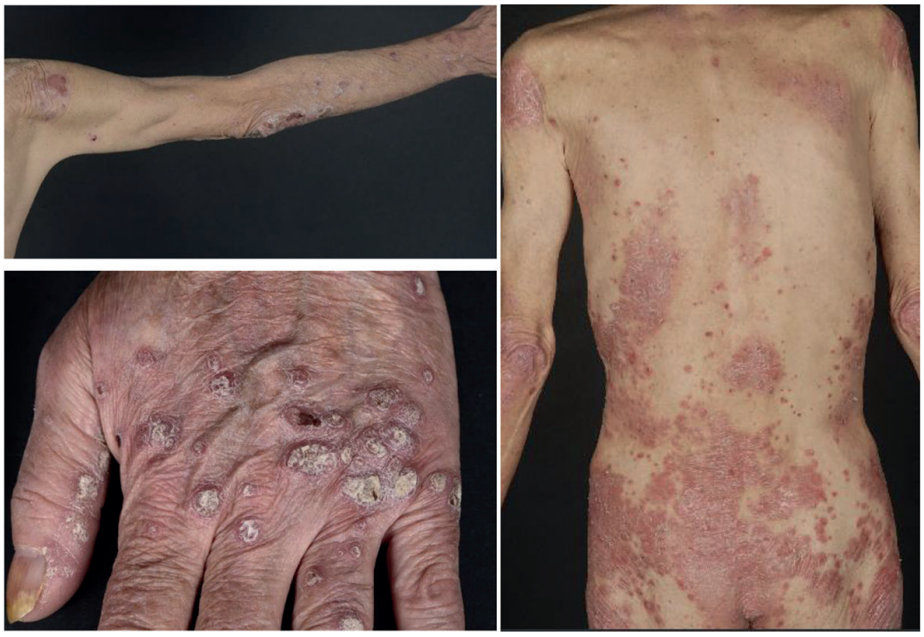

Figure S1. Psoriasis in geriatric patients (≥65 years old).

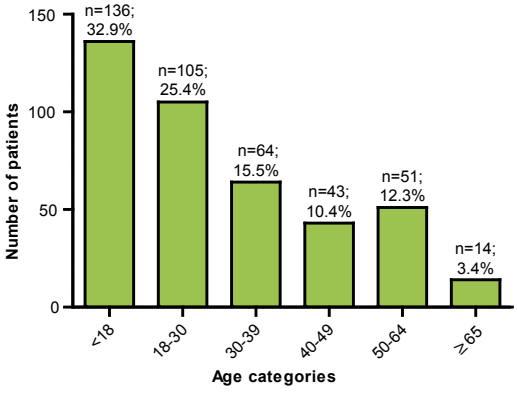

Figure S2. Age of onset in geriatric patients with psoriasis (≥65 years old, n=413).

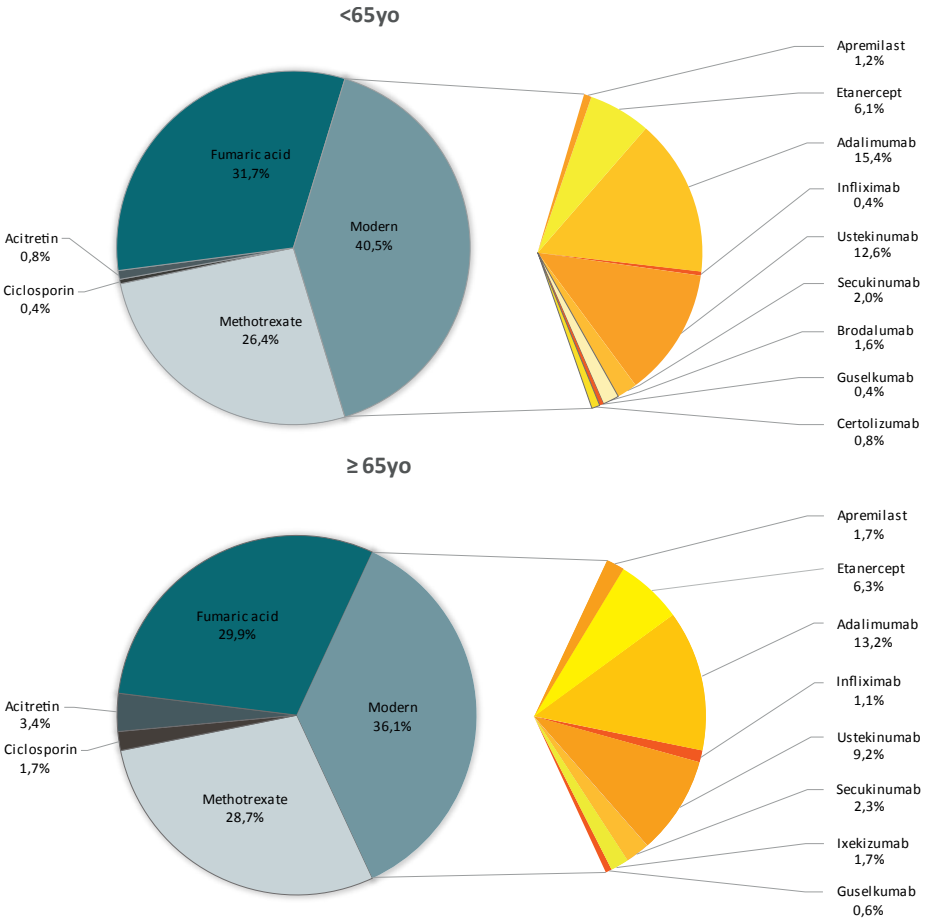

Figure S3. Current systemic therapies used in patients aged <65 years old and patients ≥65 years old.

Percentages are presented in relation to the percentage systemic therapies used. In case of combined systemic therapies (as were used by 22 <65 years old and 17 ≥65 years old), both categories were scored.

Table S1. Study respondent characteristics compared with the overall target population.

	Study respondent population,%	**Dutch Psoriasis Association[a],%**	**Klaassen et al., 2013[15],%**
Age			
<65 years	56.4%	59.0%	NR
≥65years	43.6%	41.0%[ns]	NR
Sex, male	52.0%	50.7%[ns]	48.3%[ns]
Education level			
Primary school, high school or vocational training	55.9%	unknown	NR
Higher education[b]	40.7%	unknown	NR
Other/unknown	3.4%	unknown	NR

Due to anonymity of the respondents, a formal non-responder analysis was not possible. Therefore, characteristics of respondents were compared with characteristics of the overall target population, if available.

[a] Age and sex distribution of the current members of the Dutch Psoriasis Association are represented here. Additional data on the overall population were provided by the Dutch Psoriasis Association upon request.

[b] Defined as universities of applied sciences (Dutch: *hogescholen or hoger beroepsonderwijs* (HBO)) and (research) universities.

NR: not reported; ns: not significant compared with the current study population.

Table S2. Treatment characteristics of geriatric patients with psoriasis (≥80 years old) compared with patients <80 years old.

	<80 years old (n=892), n (%)	**≥80 years old (n=58), n (%)**	**p-value**
Current treatment*, n (%)			
Topicals[a]	584 (66.1)	37 (64.9%)	0.850
UV therapy	38 (4.3)	8 (14.0)	0.001
Systemic	359 (40.7)	22 (38.6)	0.759
Conventional systemic[b], n (%)	230 (26.0)	17 (29.8)	0.530
Methotrexate	109 (12.3)	6 (10.5)	0.685
Ciclosporin	2 (0.2)	2 (3.5)	0.020
Acitretin	7 (1.4)	1 (1.8)	0.395
Fumaric acid	122 (13.8)	8 (14.0)	0.963
Modern systemic[c]	157 (17.8)	6 (10.5)	0.161
Apremilast	6 (0.7)	0 (0.0)	1.000
Etanercept	23 (2.6)	3 (5.3)	0.205
Adalimumab	59 (6.7)	2 (3.5)	0.575
Infliximab	3 (0.3)	0 (0.0)	1.000
Ustekinumab	46 (5.2)	1 (1.8)	0.355
Secukinumab	9 (1.0)	0 (0.0)	1.000
Ixekizumab	3 (0.3)	0 (0.0)	1.000
Brodalumab	4 (0.5)	0 (0.0)	1.000
Guselkumab	2 (0.2)	0 (0.0)	1.000
Certolizumab pegol	2 (0.2)	0 (0.0)	1.000
No prescribed therapies[d]	144 (16.3)	11 (19.3)	0.555
Requiring assistance with treatment or skin care, n (%)			
Yes	91 (10.9)	11 (20.8)	0.030
No	742 (89.1)	42 (79.2)	

Values might not add up due to missing values.

* Patients could select more than 1 answer option.

[a] Including keratolytic agents, corticosteroids, vitamin D derivatives, calcineurin inhibiting agents, coal tar, combination therapies, dithranol (anthralin).

[b] Including methotrexate, ciclosporin, acitretin and fumaric acid.

[c] Including apremilast, etanercept, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab,guselkumab, certolizumab pegol.

[d] Defined as no prescribed therapies and non-prescription therapies, usage of emollients only, homeopathic treatment, over-the-counter products, and dietary or lifestyle adjustments.

UV: ultraviolet.

Table S3. Representativeness of the study respondents compared with overall psoriasis populations.

	Study respondent population	**Dowlatshahi et al., 2017[20]**	**Egeberg et al., 2019[18]**	**Chiesa Fuxench et al., 2016[19]**	**Overall Dutch population, 2018[16,17]**
Age, years, mean ± SD	61.1 ± 13.7	48.2 ± 18.5*	51.1 ± 18.6*	46.4 ± 17.2*	41.8 ± NR
Sex, male	52.0%	49%[ns]	46.7%*	48.3%*	49.6%[ns]
Education level		NR		NR	
Primary school, high school or vocational training	55.9%		75.6%		68.3%
Higher education[a]	40.7%		18.1%		30.3%
Other/unknown	3.4%		6.3%*		1.4%*

* Statistically significant compared with the current study population.

[a] Defined as universities of applied sciences (Dutch: *hogescholen or hoger beroepsonderwijs* (HBO)) and (research) universities.

SD: standard deviation; NR: not reported; ns: not significant compared with the current study population.

Chapter 2.2

Quality of life, treatment goals, preferences and satisfaction in geriatric psoriasis: a patient survey comparing age groups

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Abstract

Background

To enhance personalized management in older adults with psoriasis, identifying the unmet needs in this rapidly growing population is of utmost importance to improve patient-centred care.

Objectives

To study disease burden, quality of life, treatment goals, preferences and satisfaction in geriatric psoriasis patients.

Methods

A self-administered survey was distributed among all members of the Dutch Psoriasis Association (n=3310). Patients were stratified into two age groups: respondents aged ≥65 years old (≥65yo) and respondents <65 years old (<65yo).

Results

A response rate of 29.7% (n=985) was achieved, 414 (43.6%) of the valid respondents were ≥65yo. The most bothersome aspects of psoriasis were itch, scaling and visibility in both groups, which were also rated as the most relevant treatment goals. Although the median Dermatology Life Quality Index (DLQI)-score was significantly higher in patients <65yo, the DLQI-Relevant, correcting for not relevant responses (NRRs), was not significantly different between the groups. Significantly more NRRs were marked by patients ≥65yo vs. patients <65yo (mean 1.91±2.43 vs. 0.79±1.77, $p<0.001$). Patients ≥65yo valued reduction of topical treatment, subcutaneously administered treatment, hospital visits and laboratory assessments as significantly more important than patients <65yo.

Conclusions

To evaluate QoL impairment, the DLQI-R is more appropriate in older psoriasis patients than the original DLQI. Patient preferences were significantly different in older adults compared to younger patients; in particular the reduction of medication use and hospital visits. The heterogeneity of the psoriasis population requires the identification of individual patient preferences and treatment goals to further facilitate shared decision-making in psoriasis management.

Introduction

Psoriasis is a chronic inflammatory disease frequently seen in older adults, which can be associated with a significant psychosocial burden.[1-3] Despite of increasingly available antipsoriatic therapies, evidence guiding psoriasis treatment in older adults is relatively limited.[4,5] Furthermore, previous studies show prescribed (systemic) therapies in older adults frequently differ from those prescribed to younger patients, although comparable disease severity was seen.[6-8] Next to a higher prevalence of specific contraindications (e.g. certain comorbidities or comedication), the reported differences are not yet fully understood and might be (partially) explained by differences in quality of life impairment, treatment goals, patient preferences and treatment satisfaction. Unfortunately, less is known regarding these essential topics in older adults with psoriasis. Although recognition of quality of life (QoL) impairment and disease burden increased over the past years, some studies suggest that currently available QoL assessment tools do not always appropriate reflect true QoL impairment in the rapidly expanding geriatric population.[9] To understand existing treatment patterns and improve patient-centred care for older psoriasis patients, the purpose of this study was to gain more insight on adequate QoL-assessment in older adults with the use of a patient-oriented survey. Also, we aimed to identify patient preferences and treatment goals in older psoriasis patients and compared these with preferences and goals of younger patients.

Methods

Study design and participants

A nationwide self-administered survey was distributed among all members of the Dutch Psoriasis Association in order to evaluate quality of life, treatment goals, preferences and treatment satisfaction in patients with psoriasis (n=3310). Both patients aged 65 years and over as well as younger patients were included, in order to compare outcomes among the age groups. The methodology of this study was more extensively described in a previous publication.[10] The Research Ethics Committee of the Radboud University Medical Centre passed a positive judgement on the study before execution of the study had started.

Survey

The survey was developed based on literature research, patient interviews and focus group meetings with a multidisciplinary team consisting of physicians,

(specialized) nurses, a medical psychologist and researchers studying psoriasis. The survey consisted of several sections enquiring about burden of the disease and QoL impact, treatment satisfaction, treatment goals and patient preferences using multiple choice questions and 5-point Likert scales. Open-ended questions were used to further evaluate which disease aspects were most bothersome for patients and to enquire about items not covered by the questions included in the survey. Answers to open questions were stratified into relevant categories for further analyses. The survey was pretested on 10 geriatric patients to assess the relevance and comprehensibility of the questions. The impact on health-related QoL was measured primarily using the Dermatology Life Quality Index (DLQI), a validated and frequently used questionnaire consisting of 10 items concerning domains possibly influenced by skin diseases.[11] Each item is scored with a 4-point Likert scale, and 8 items provide a not relevant response (NRR) option. A total score was calculated for each patient, yielding sum scores ranging from 0 to 30; a higher DLQI score representing a more severely impaired QoL. In addition, the DLQI-Relevant (DLQI-R) score was calculated, a scoring formula adjusting for the effects of NRRs.[12] A maximum of 3 NRRs per patient was maintained according to the suggestion of previous research.[12]

Data processing and analysis

Survey responses were processed anonymously with the aid of the automatic form identification software Remark Office Optical Mark Recognition, version 9.5 (Gravic, Inc. Malvern, PA, U.S.A.) and CASTOR Electronic Data Capture, a web-based data management system in compliance with Good Clinical Practice (GCP) standards (Castor Research Inc., Hoboken, NJ, U.S.A.). Ten percent of the data was checked by an independent researcher to ensure proper data processing. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 25.0 (IBM, Armonk, NY, U.S.A.). Patients were categorised into two groups: those aged 65 years and over (≥65yo) and those younger than 65 years of age (<65yo). To improve comprehensibility of the outcomes, all continuous variables were expressed as means (±SD), and categorical variables were presented as frequencies and percentages. A Mann-Whitney U-test was used to compare continuous variables in both age groups and a Kruskal-Wallis Test to compare continuous variables in more than two groups. Chi-square or Fisher's exact test were used for categorical variables. Missing values were not included in the analyses.

Results

Study participants

The patients demographics, as well as disease and treatment characteristics are presented in the previous publication of Van Winden et al.[10] A total of 3310 psoriasis patients were approached for participation, 985 (29.7%) returned the survey thereby consenting for participation. Data was collected between December 11, 2018 to September 4, 2019. Data of 950 respondents was included in the analysis; 27 respondents were excluded from analyses due to missing values in age, eight more respondents were excluded due to missing data on too many other relevant questions (e.g. responses to age and gender only). The mean age of the 414 (43.6%) patients ≥65yo was 72.4±5.9 years (median 71, range 65-95), compared with 52.4±11.4 years in patients <65yo (median 56, range 7-64). Comparable disease severity was seen in both age groups, and no significant differences were found in currently used therapies (e.g. systemic medication usage in n=157 [38.3%] ≥65yo, vs. n=224 [42.3%] <65yo; p=0.219).[10]

Disease burden and quality of life

Disease burden

Both patients ≥65yo and patients <65yo reported pruritus as the most bothersome aspect of their psoriasis (n=127 [35.0%] ≥65yo vs. n=200 [39.8%] <65yo, p=0.146), followed by flaking (n=72 [19.8%] ≥65yo vs. n=122 [24.3%] <65yo, p=0.120) and visibility (n=58 [16.0%] ≥65yo vs. n=107 [21.3%] <65yo, p=0.049). Social factors were significantly less often reported by patients ≥65yo, whereas these were regularly mentioned by patients <65yo: psychological problems due to psoriasis were mentioned by 13 (3.6%) patients ≥65yo compared with 35 (7.0%) patients <65yo (p=0.032), and stigmatization by 5 (1.4%) patients ≥65yo and 20 (4.0%) patients <65yo (p=0.024). A summary of the most frequently reported bothersome aspects is shown in **Figure 1.**

Dermatology Life Quality Index (DLQI)

The overall DLQI was significantly lower in patients ≥65yo compared with patients <65yo (mean 2.98±3.5 vs. 3.89±4.55 respectively, p=0.006). A current DLQI >5 was seen in 63 (16.1%) ≥65yo vs. 122 (23.7%) <65yo (p=0.005). As illustrated by **Figure 2**, significantly more NRRs were reported by patients ≥65yo in comparison with patients <65yo (mean 1.91±2.43 vs. 0.79±1.77, p<0.001). At least one NRR was reported by 238 (60.7%) patients ≥65yo, compared with 161 (31.3%) patients <65yo (p<0.001). The least applicable items according to patients ≥65yo were item 7

(work; n=191 [49.2%]) and item 6 (sports; n=117 [30.3%]). The distribution of the DLQI outcomes and NRRs per DLQI item in both age groups is illustrated in **Figure 3**.

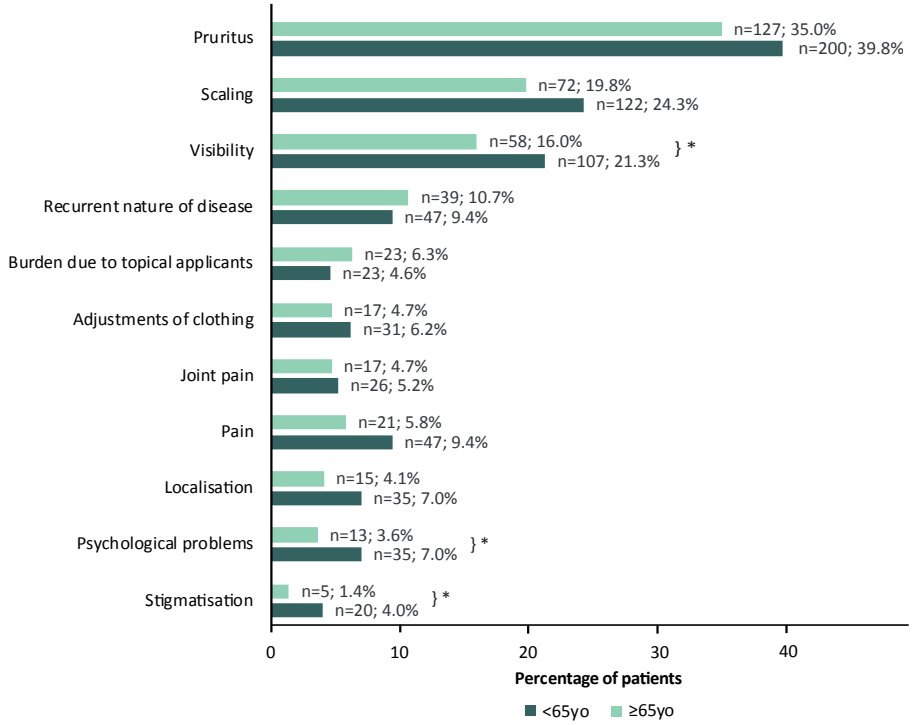

Figure 1. Self-reported most bothersome aspects of psoriasis in patients ≥65 years oldcompared with patients <65 years old.

* indicating a significant difference between patients ≥65yo and patients <65yo was found.
yo, years old.

Dermatology Life Quality Index-Relevant (DLQI-R)

The mean DLQI-R was 3.42±4.00 in patients ≥65yo, vs. 4.13±4.76 in patients <65yo (p=0.076). In patients ≥65yo, the mean increase between the DLQI and the DLQI-R score was 0.44±0.84 vs. 0.24±0.62 in patients <65yo (p<0.001). Significantly less patients ≥65yo reported that the DLQI lacked assessment of important QoL-related aspects (n=90 [24.4%] ≥65yo vs. n=160 [32.9%] <65yo, p=0.009). Most frequently mentioned items were the lack of specific attention for joint pain (overall n=35 [14.0%]), followed by lifestyle adjustments such as dietary alterations (n=17 [6.8%]), e.g. alcohol consumption.

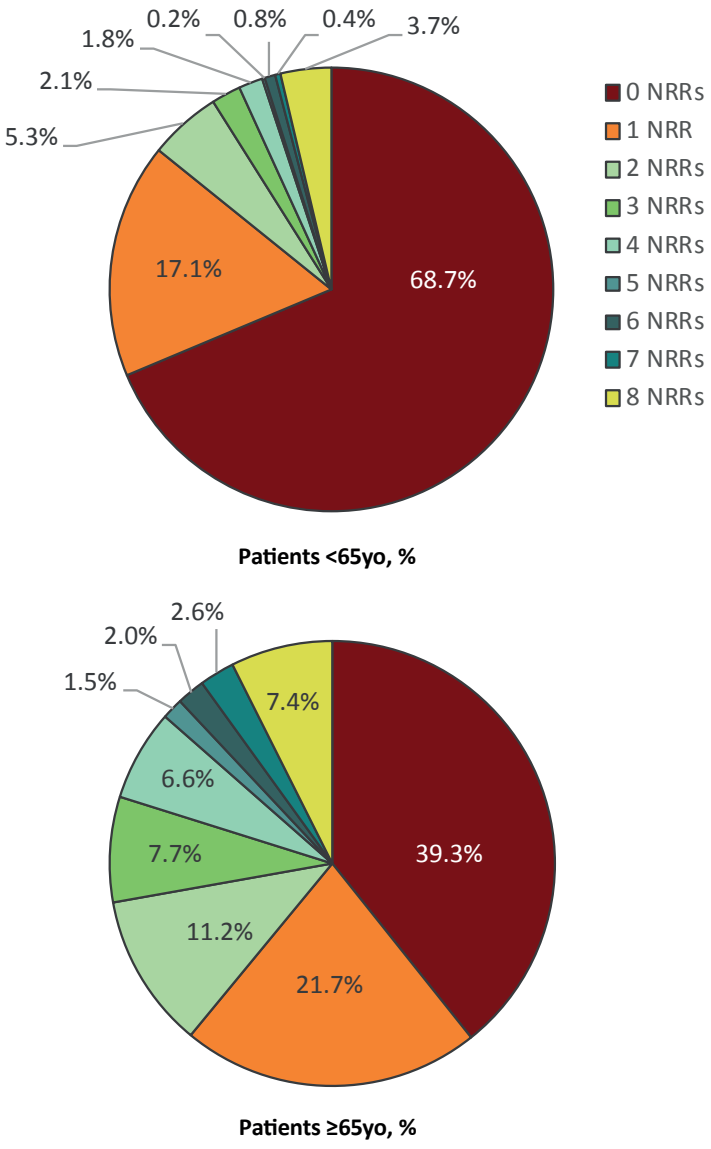

Figure 2. The frequency of not relevant responses (NRRs) Dermatology Quality of Life In- dex (DLQI) as used by both patients aged <65 years old and those aged 65 years or over.

yo, years old

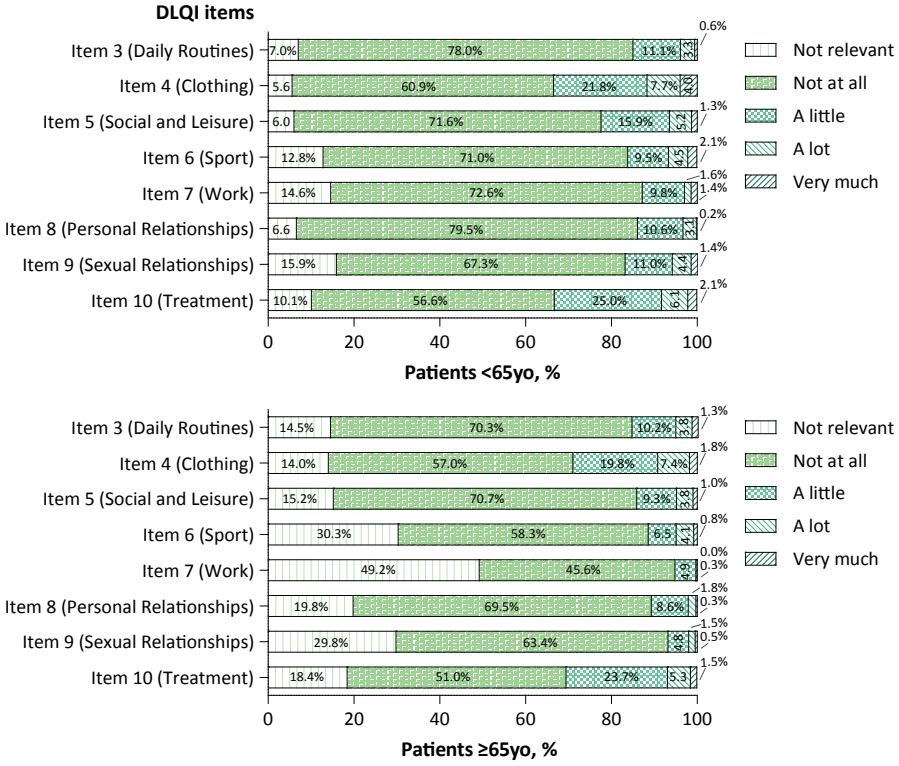

Figure 3. Responses to Dermatology Life Quality Index (DLQI) items offering a not- relevant response in patients <65 years old (<65yo) and patients ≥65 years old (≥65yo).

Respondents were instructed to answer to what extend their skin problem had affected their lives in the past 7 days. A not relevant response (NRR) option was offered in eight out of ten items (as presented here; e.g. patient does not work or study), as well as categorical responses to allow respondents to grade the influence (e.g. the skin problem had affected work or study: very much, a lot, a little, not at all).

Treatment goals, preferences and satisfaction

Treatment goals

To be free of pruritus and scaling, as well as visible lesions were most frequently reported as relevant in both groups (NRR in n=39 [4.1%], n=6 [0.6%] and n=9 [0.9%] respectively) and were also valued as important treatment goals (overall mean respectively 4.56, 4.37 and 4.15). Pain and sleeping disturbances were marked not relevant by respectively 181 (19.1%) and 371 (39.1%) patients. However, the remaining patients highly valued these treatment goals (overall respectively mean 4.44 and 4.35). Patients ≥65yo valued to be free of scaling, complete clearance of all skin lesions, and to be free of redness as significantly more important than patients <65yo (mean 4.43 in ≥65yo vs. 4.32 in <65yo, p=0.003, 4.16 in ≥65yo vs. 4.00 in <65yo, p=0.009 and 4.11 vs. 3.94, p=0.006). An overview of the treatment goals as scored by both patients groups is presented in **Table 1**.

Patient preferences

Minimalization of adverse events associated with antipsoriatic therapies was valued as the most important patient preference in both age groups (overall mean 4.63). To have confidence in the therapy and to be able to apply or use therapies without help from others scored an overall mean of respectively 4.61 and 4.56. Minimizing the use of topical treatment, injections and pills or capsules were valued significantly more important by patients ≥65yo vs. patients <65yo, as can be seen in **Table 1**. Patients ≥65yo valued the minimalization of topical treatment and injections more important than not having to use pills or capsules (mean 4.13, 4.13 and 3.84, respectively). Moreover, the reduction of hospital visits was valued significantly more important by patients ≥65yo vs. patients <65yo.

Treatment satisfaction

Overall, patients in both groups were satisfied with their current treatment (overall mean 3.73). However, 102 (11.5%) patients were dissatisfied or very dissatisfied (Likert-score<3). Patients ≥65yo using a combination of systemic therapies (e.g. methotrexate combined with adalimumab) were most satisfied (mean treatment satisfaction 4.47 vs. 3.98 [modern systemic therapies], vs. 4.14 [conventional systemic therapies] vs. 3.43 [topical treatment only], vs. 3.11 [UV therapy], p<0.001). Patients ≥65yo reporting adverse events due to their therapies, scored the burden of the adverse events equally low as patients <65yo (mean adverse event burden was 2.56 in in ≥65yo vs. 2.51 in <65yo, p=0.806).

Table 1. An overview of treatment goals, treatment satisfaction and patient preferences inpatients ≥65yo with psoriasis compared to patients <65yo.

	<65 years	≥65 years	NRR, n (%)	p-value*
Treatment goals				
To be free of pruritus (mean±SD)	4.52±0.7	4.61±0.6	39 (4.1)	0.059
To be free of pain (mean±SD)	4.41±0.7	4.47±0.7	181 (19.1)	0.517
To be free of scaling (mean±SD)	4.32±0.7	4.43±0.8	6 (0.6)	0.003
To be free of sleep disturbances (mean±SD)	4.31±0.9	4.39±0.8	371 (39.1)	0.374
To be free of negative impact on daily activities (mean±SD)	4.28±0.8	4.23±0.9	192 (20.2)	0.713
To be free of visible lesions (mean±SD)	4.09±1.0	4.23±0.9	9 (0.9)	0.050
Complete clearance of psoriasis lesions (mean±SD)	4.00±1.0	4.16±0.9	2 (0.2)	0.009
To be free of redness (mean±SD)	3.94±0.9	4.11±0.9	19 (2.0)	0.006
Treatment satisfaction				
Ease of current treatment (mean±SD)	3.90±1.0	3.96±0.9	-	0.433
Overall treatment satisfaction (mean±SD)	3.71±1.0	3.75±1.0	-	0.763
Satisfaction regarding treatment frequency (mean±SD)	3.58±1.1	3.69±1.0	-	0.165
Burden of side effects (mean±SD)	2.51±0.9	2.56±0.9	-	0.806
Patient preferences				
Minimize the adverse effects of therapy (mean±SD)	4.64±0.5	4.61±0.7	-	0.875
To have confidence in therapy (mean±SD)	4.64±0.5	4.57±0.6	-	0.170
To apply/use therapy without help from others (mean±SD)	4.56±0.7	4.56±0.7	-	0.891
Minimize the use of topical treatment (mean±SD)	3.94±1.1	4.13±1.0	-	0.004
No usage of injections/syringes/intravenous treatment (mean±SD)	3.74±1.4	4.13±1.2	-	<0.001
Minimize the amount of hospital visits (mean±SD)	3.77±1.2	4.04±1.1	-	<0.001
No usage of pills/capsules (mean±SD)	3.40±1.4	3.84±1.3	-	<0.001
To apply/use therapy without laboratory assessment (mean±SD)	2.89±1.4	3.34±1.4	-	<0.001

Treatment goals and patient preferences were measured using a 5-point Likert scale, 5 indicating highly important, 1 indicating not important at all. Treatment satisfaction was measured using a 5-point Likert scale, 5 indicating highly satisfied and 1 indicating least satisfied. The burden of side effects was measured using a 5-point Likert scale, 5 indicating a high burden, 1 indicating no burden at all.

* All results were calculated using a Mann-Whitney U test; means were presented to improve comprehensibility of the outcomes.

NRR: not relevant response; SD: standard deviation.

Discussion

Psoriasis management in patients ≥65yo can be complex due to age- and frailty-related characteristics and the limited available data on treating this specific patient group.[5] Since disease severity in patients ≥65yo with psoriasis is often mentioned to be comparable to patients <65yo,[3,7,8,10] a difference in treatment choices might be due to differences in comorbidities and concomitant medication, or due to disease perception by geriatric patients.[6,7,13] As the array of therapeutic options continues to expand, it is crucial to further specify the unmet needs of this frequently vulnerable population. This might help to understand existing treatment patterns and improve patient-centred care for older psoriasis patients. Therefore, the aim of this study was to gain insight in quality of life, treatment goals, preferences and satisfaction in geriatric psoriasis patients.

In this study, QoL impact measured by the DLQI-R did not significantly differ between patients ≥65yo and patients <65yo. However, the original DLQI score did show differences between the groups, due to varying rates of NRR between age groups. For patients ≥65yo, significantly more DLQI items were not relevant, and a significant higher increase between DLQI and DLQI-R was seen compared with patients <65yo. These results are in accordance with previous studies stating that DLQI responses are affected by age and that older patients more frequently mark NRRs.[9] This suggests an underestimation of the actual quality of life impairment, as NRRs are currently scored as "0", equivalent to not at all. Moreover, previous studies have shown that patients using NRRs had more severe disease than patients using a not at all response.[14,15] Thus, in line with previous research,[13,15,16] this study emphasizes that using original DLQI scoring system in patients ≥65yo results in a disproportional underestimation of true QoL-impact.

Several studies criticize the frequently used DLQI, as medical decision-making currently quite heavily relies on the DLQI score despite its psychometric shortcomings in heterogeneous populations.[9,16-18] An insufficient reflection of QoL-impairment and undertreatment could be a consequence, since reimbursement criteria in several countries are based on a minimum DLQI score for certain treatment options.[14,16] Moreover, in other QoL-instruments as the Short Form Survey (SF-36) and Skindex-29 no NRR option is offered at all. Moreover, neither of the tools assess symptoms related to psoriatic arthritis (PsA); which was most frequently mentioned by respondents of this study as currently lacking in the DLQI. Using the DLQI-R would not solve the lack of PsA assessment, but could possibly reflect QoL-impairment better than the already widely used original DLQI.

Moreover, although patients ≥65yo more frequently marked NRRs than patients <65yo, significantly less patients ≥65yo reported to miss certain items in the DLQI. Therefore, the relevant items included in the DLQI might be adequate for a group of patients ≥65yo, whereas using the original scoring system might not adequately represent the true QoL-impact in many patients. Especially in case of clinical decisions depending on QoL-impact (e.g. reimbursement criteria for biologic therapies) or studies comparing QoL between age groups, calculation of the DLQI-R should be considered. Specific attention to PsA assessment and other personal bothersome aspects not captured by the DLQI-R, could further improve personalized psoriasis-care.

In line with previous research,[19-21] this study showed that itch, scaling and visibility were reported as most bothersome aspects of psoriasis in both age groups and were consequently the top-cited treatment goals. Although small differences were seen in treatment goals and satisfaction, no clinically relevant differences were found between the age groups. Whereas visible lesions were less frequently experienced as bothersome by patients ≥65yo than those <65yo, it was still considered as one of the most bothersome aspects in both age groups. Moreover, visibility-related treatment goals as complete clearance and to be free of redness were valued as more important treatment goals by patients ≥65yo. Also, treatment goals related to pain and sleep disturbances were highly valued in those patients for whom applicable. These differences further accentuate the heterogeneity of the psoriasis population, pleading for an individualized patient-centred approach assessing relevant treatment goals, reaching further than age alone.

Patient preferences regarding the reduction of different treatment modalities were valued significantly more important by patients ≥65yo when compared with patients <65yo. More specifically, patients ≥65yo valued a reduction of topical treatment and subcutaneous treatment as significantly more important compared with patients <65yo. Dependency on others could be an explanation for this outcome, since functional impairments in this patient group can cause difficulty in reaching those areas of the body affected by psoriasis.[10] The treatment burden of topical therapies and subcutaneously administrated therapies can therefore be higher in patients ≥65yo. Moreover, patients ≥65yo use concomitant medication more often than patients <65yo,10 which is a well-known factor associated with the patient preference to reduce medication use altogether.[22] Furthermore, patients ≥65yo valued the reduction of laboratory tests and hospital visits as more important than patients <65yo. This is consistent with previous research by Maul et al, and can be explained by the longer duration of the disease leading to subsequent higher

number of hospital visits in the past.[23] Dependency on others and the necessity of hospital visits for other health issues could attribute to this preference. The extent to which patients ≥65yo are burdened by these aspects, depends on many more factors (e.g. somatic, psychosocial and functional factors) which should be individually assessed.

Naturally, certain limitations need to be addressed. Any survey is associated with factors as recall bias and a possibility of misinterpretation of the questions. However, a pilot study was performed in advance of the study to reduce these risks. Although this study gained insight in important aspects of one of the largest geriatric psoriasis populations assessing disease burden so far, members of a patient association are frequently older and show higher disease severity, possibly resulting in selection bias.[10] The results of this study might therefore not be generalizable to all psoriasis patients. Lastly, the results of this study should be interpreted with caution since this study did not evaluate changes in outcome measures over time or changes due to therapies, which could limit representativity of the results in other circumstances. Future studies evaluating disease burden and management considerations in older adults are needed to evaluate temporal changes in disease course.

In conclusion, the use of the DLQI-R in patients ≥65yo should be preferred over DLQI assessment, since it appears NRRs frequently lead to an underestimation of the true QoL impact in patients ≥65yo. Overall treatment goals, bothersome disease aspects and treatment satisfaction were comparable between the age groups, although the heterogeneity in these outcomes accentuate the need of individualized management decisions and specific attention for individual patient goals and preferences. It should be taken into account that patient preferences in patients ≥65yo differ from those of patients <65yo (in particular the reduction of medication use and hospital visits), possibly depending on functional deterioration, dependency on others, comorbidities and comedication.

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Chapter 2.3

Exclusion by age, cardiovascular comorbidity and malignancies are the main factors that impact generalizability of evidence from trials to the real-world situation in older adults with psoriasis

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Dear Editor,

Psoriasis is prevalent in the growing group of older adults (≥65 years), resulting in an absolute increase in this population in dermatological practice. Optimal treatment selection in this population is often complicated by comorbidity, comedication use and limited evidence-based guidance.[1,2] The scarcity of available evidence for this population can be explained by the high (in)direct exclusion rates of older adults from randomized controlled trials (RCTs).[3] Therefore, the external validity or generalizability of RCT findings might be limited when applied to aged patients in practice.[4] This study aims to quantify the extent of this issue by (1) comparing comorbid disease status of older adults with psoriasis to the general population, as comorbidities often serve as exclusion criteria, and (2) determining the impact of RCT exclusion criteria on the generalizability of research findings to a real-world geriatric psoriasis cohort.

We conducted a multicentre retrospective daily practice cohort study, involving older adult patients (≥65 years) from six centres. The study setup was previously described.[5] To compare the comorbid disease status of study participants to the general Dutch population, standardized prevalence ratios (SPR) were calculated: the number of observed cases was divided by expected cases based on general population data sources **(Table 1)**, stratified for age. To determine the impact of RCT exclusion criteria on this cohort of older adults with psoriasis, an 'impact statistic' (ranging from 0 to 100) was calculated by multiplying the occurrence of exclusion criteria of RCTs with the actual comorbidity prevalence in this cohort, divided by 100. If an exclusion criterium (comorbidity) is uncommon but the prevalence of the comorbidity is high, it results in a relatively high impact statistic indicating that there can still be a substantial impact in the generalizability of RCT data to the older population with psoriasis. Vice versa, if an exclusion criterium is often used in RCTs but the actual prevalence in practice is low, it results in a low-impact statistic and the impact of this criterium on the older population will likely be minimal. Baseline characteristics are described in **Table 1**. In this real-world cohort of older adults with psoriasis ($n = 230$), depression ($SPR = 2.84$; $p < 0.001$), skin cancer ($SPR = 2.69$; $p < 0.001$), obesity ($SPR = 1.98$; $p < 0.001$), hyperlipidaemia ($SPR = 1.37$; $p < 0.05$) and being overweight ($SPR = 1.28$; $p < 0.05$) were more prevalent compared to the general older Dutch population **(Table 1)**. The majority ($n = 185$; 82.6%) of patients had ≥1 comorbid condition classified as indirect exclusion criterium in RCTs. **Figure 1** shows the prevalence of (indirect) exclusion criteria in this cohort, in RCTs, and the resulting impact statistic deduced from these prevalences. The age limit of

65 years had the highest impact statistic (25.9), followed by cardiovascular disease (23.0), malignancy (11.2) and hepatic or renal impairment (10.3).

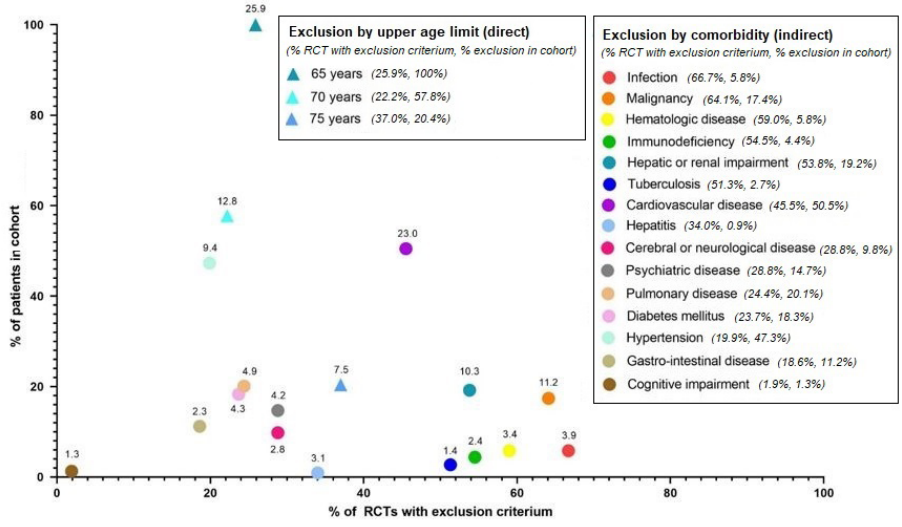

Figure 1. Visualization of the impact of RCT exclusion criteria on a real-world cohort of older adults with psoriasis, depicting impact statistics.

On the *x* axis, the occurrence of exclusion criteria among randomized controlled trials (RCTs) is presented, and data are retrieved from Schaap et al.[3] On the *y* axis the percentage of patients affected by the exclusion criteria within the study cohort is presented. The direct and indirect exclusion criteria used in clinical trials are depicted separately. The impact statistic, which is depicted in the number adjacent to the symbols in the graph, is calculated by multiplying the percentage of RCTs with a specific exclusion criterium by the percentage of patients in this real-world cohort affected by the exclusion criterium and divided by 100.

It is known that patients with psoriasis have a higher risk of developing comorbidities, compared to patients without psoriasis.[6, 7] Also, older adults with psoriasis seem to have more comorbidity than younger psoriasis patients.[8,9] It is however difficult to disentangle the specific roles of age versus psoriasis within this relation. The present study describes a more extensive comorbid disease burden in older patients with psoriasis compared to older patients without psoriasis. Therefore, besides age, psoriasis seems to further increase the comorbidity risk substantially in this specific group. This emphasizes the need for prevention and management of associated comorbidity in patients with psoriasis.[6,10] With regard to (in)direct exclusion criteria, age, cardiovascular disease and (history of) malignancy were identified as having the largest impact on generalizability of RCT data to

this real-world cohort of elderly patients. Therefore, more data (RCT, RWE) on older patients with psoriasis is needed to substantiate the scarce evidence-based guidance for this large population.

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We are grateful to all patients who participated in this study by providing an informed consent. We want to thank all the participating dermatologic practices for their efforts.

Table 1. Comparison of comorbidity in older patients with psoriasis to older adults in the general Dutch population.

	Study cohort	General population			
Comorbidity	**(≥65 yrs), *n* (%)**	**(≥65 yrs), %**	**SPR**	**95% CI**	***p*-value**
Age (yrs), mean ± SD	71 ± 4.9				
Sex, male	127 (55.2)				
Current treatment					
Topical monotherapy	74 (32.2)				
UV-therapy	56 (24.3)				
Conventional systemic[a]	67 (29.1)				
Biologic/apremilast[a]	39 (17.0)				
No treatment	1 (0.4)				
Overweight (BMI ≥ 25)	93 (76.9)	58.0	1.28	1.04–1.57	0.02
Obesity (BMI ≥ 30)	42 (34.7)	16.5	1.98	1.44–2.65	<0.001
Diabetes mellitus[b]	41 (18.3)	20.5	0.98	0.71–1.32	0.91
Cardiovascular disease[c]	67 (30.2)	35.0	1.05	0.82–1.32	0.69
Ischemic heart disease	20 (8.9)	8.4	1.25	0.78–1.89	0.32
Heart failure	7 (3.1)	6.1	0.85	0.37–1.68	0.70
Cerebral vascular accident	19 (8.5)	10.9	0.98	0.61–1.50	0.95
Hypertension[b]	106 (47.3)	50.8	1.02	0.84–1.23	0.82
Hyperlipidaemia[b]	75 (33.5)	24.6	1.37	1.08–1.71	<0.05
Cancer[d]	39 (17.4)	14.1	1.35	0.97–1.83	0.07
Skin cancer[e]	16 (7.1)	3.5	2.69	1.59–4.28	<0.001
Depression[f]	25 (11.2)	3.9	2.84	1.88–4.13	<0.001
Chronic kidney disease[g]	25 (11.2)	9.8	0.93	0.62–1.36	0.76

Data sources Dutch National Institute for Public Health and the Environment (RIVM), Statistics Netherlands (CBS) and Netherlands Cancer Registry (NCR).

[a] Seven patients used double treatment. Combinations with methotrexate; n = 2 biologic, n = 1 UVB-therapy. Combinations with dimethyl fumarate; n = 1 biologic, n = 1 UVB-therapy. Combination with acitretin; n = 2 biologic. Missings in study cohort: overweight and obesity (n = 109); cardiovascular disease (n = 8); other comorbidities (n = 6).

[b] In study cohort only counted when patients had a diagnosis and used medication.

[c] Includes MACEs (incident myocardial infarction, stroke, cardiovascular death), heart failure, coronary artery disease, coronary or peripheral revascularization, heart rhythm disorders, transient ischemic attack, valvular disease, disorders of the endocardium.

[d] All types of cancer excluding non-melanoma skin cancer.

[e] All types of skin cancer excluding basal cell carcinoma.

[f] Depression including dysthymia and bipolar disorder.

[g] Chronic kidney disease is defined as a GFR <60mL/min/1.73m2 for at least 3 months.

BMI: body mass index; CI: confidence interval; MACE: major adverse cardiovascular events; SPR: standardized prevalence ratio; yrs: years.

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Chapter 2.4

Age-based treatment differences in and reluctance to treating older adults with systemic antipsoriatic therapy: A mixed-method pilot study

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Abstract

Background

Evidence-based guidance in older adults (≥65 years) with psoriasis is sparse and undertreatment might be present.

Objectives

To assess prescribing patterns, comfort levels, barriers and needs of dermatologists when treating older adults with systemic antipsoriatic therapy.

Methods

A mixed-methods design was used including a survey among all Dutch dermatologists and residents, followed by semi-structured interviews.

Results

Most of the survey respondents applied systemic treatment to the same extent in older versus younger patients (n=49; 67.1%) and weren't reluctant prescribing systemic therapy (n=50; 68.5%) in older adults. However, 26% (n=19) of the respondents treated older adults less often with systemic therapy compared to younger patients and 68.1% (n=49) performed additional actions in older adults, e.g. intensified monitoring or dose reduction. Based on the survey and interviews (n=10), the main reasons for these age-based treatment differences were comorbidity, comedication, and fear of adverse events. More evidence-based guidance, education, and time to assess older adults were identified as most important needs, especially regarding frailty screening.

Conclusions

Age-based treatment differences in and reluctance to treating older adults with systemic antipsoriatic therapy were common. There is a need for more evidence-based guidance, education, and consultation time, to improve treatment in this growing population.

Introduction

Psoriasis is prevalent in older adults (≥65 years) and dermatologists will be increasingly confronted with this patient group due to an aging world population.[1-4] Selecting the most appropriate treatment might vary between age groups and depends on various factors such as patient preferences, quality of life, disease severity, comorbidity and comedication.[5-7]

Literature regarding this specific population is sparse, since older adults are repeatedly excluded from clinical trials.[8,9] Although a comparable disease severity between older adults and younger patients has been reported, older adults tend to receive less systemic therapy than younger patients.[10-13] Several possible explanations can be assumed for the apparent differences in treatment choices between age groups, such as a higher rate of comorbidities, comedication use, frailty, and differences in treatment goals.[6,13,14] Furthermore, a (disproportional) reluctance amongst physicians to prescribe systemic antipsoriatic therapy in older adults is suggested as a probable explanation, possibly caused by limited experience and sparse evidence-based guidance.[15] The objective of this study was to gain insights in the prescribing patterns, comfort levels, possible barriers, and needs of dermatologists when applying systemic therapies in older adults with psoriasis. These insights are expected to contribute to the optimization of care in this population.

Methods

Study design and recruitment of participants

A mixed-methods study was conducted, consisting of two consecutive sub studies. First, a nationwide survey was sent by email to all dermatologists and dermatology residents in the Netherlands through the Dutch Society for Dermatology and Venereology (n=714). A hyperlink to an online survey (Qualtrics, Provo, UT, USA) was provided and after five weeks a reminder was sent. Secondly, in-depth semi-structured interviews were performed with a subgroup of respondents. For the interviews, we attempted to include an equal number of participants who were (1) reluctant to prescribe systemic antipsoriatic therapy in older adults, (2) not reluctant, or (3) unknown (based on the individuals' response from the survey). This study is reported following the Standards for Reporting Qualitative Research (SRQR) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[16,17] The committee on Research Involving Human Subjects of the Radboud

University Medical Center reviewed the study proposal and waived further formal study approval (reference number: 2021-8107). All participants provided written informed consent for participation.

Survey, data collection and analysis

A survey concerning systemic therapy use in older adults with psoriasis was developed, based on a literature search and experiences from previous research.[6,13] To assess the comprehensiveness, clarity and relevance of the formulated questions, the survey was pre-tested by ten dermatologists and residents. Mostly multiple-choice questions were used to assess practitioners prescribing patterns, preferences and influential factors when treating older adults with psoriasis. To assess the comfort levels of respondents regarding prescription of systemic antipsoriatic therapy in older adults, a five-point Likert-scale was used with the options: very comfortable (5), comfortable (4), neither comfortable nor uncomfortable (3), uncomfortable (2), very uncomfortable (1). Furthermore, open-ended questions were added to further evaluate relevant items not captured by the multiple-choice questions and these answers were manually categorized for further analysis. The survey also enquired about socio-demographic practitioner information (e.g. age, sex, years of experience). Completing the survey was anonymous, but respondents could leave their contact details voluntary if they were willing to be contacted for any additional questions/interview. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM, Armonk, NY) and R (version 3.6.3).[18] To summarize continuous variables and categorical data descriptive statistics were used such as mean (± standard deviation (SD)) or median (range) and frequencies and percentages, respectively. To determine the comfort levels using Likert-scales, the overall mean score per treatment was calculated and differences among treatments were tested using a multilevel model with a random intercept for respondent followed by a correction for multiple testing using Bonferroni. Selection bias due to nonresponse was tested by comparing respondents' sex and age with the target population using a chi-square test and independent t-test. A p-value $<.05$ was considered significant.

Interviews, data collection and analysis

A semi-structured interview guide was developed after a literature review, assessing the survey data and discussion in the research group, including an expert on qualitative research (MT). The interviews were conducted in Dutch and audio recorded by EtH from March 2021 to July 2021 until data saturation was reached, defined as when no new concepts emerged. The interview-guide was adjusted throughout the interviewing process, when new subjects or questions emerged.

Data were analyzed using inductive thematic analysis. The codes and themes were derived directly from the data using Atlas.ti 8 software.[19] The interviews were transcribed verbatim by EtH and the transcripts were read several times resulting in a coding framework. In regular meetings the codes were discussed with the research team. The coding framework was used to define themes and subthemes which were discussed with SL and MT until consensus was achieved.

Results

Study participants

Between September 2020 and April 2021, a total of 89 responses were collected (response rate 12.5%). Due to an insufficient amount of answered items (e.g. baseline respondent characteristics only) 16 responses were excluded, leaving 73 responses suitable for further analyses. The median respondent age was 46 years (range: 27–64) and 30 respondents (41.1%) were male. Of the respondents 59 (80.8%) were dermatologists and 14 (19.2%) were residents. A comparison of age and sex between the survey respondents and the target population showed no significant differences, indicating representativeness on age and sex **(Supplemental Table 1)**. In total ten in-depth semi-structured interviews were conducted, resulting in data saturation. Half of the interviews were conducted in person, the other half using an online video connection. The mean duration of the interviews was 36 minutes (range: 24–49). A full overview of survey respondent characteristics and interview participants is given in **Table 1**.

Table 1. Survey respondent and interview participant characteristics.

	Respondents survey (n=73)	**Participants interview (n=10)**
Age[a] (years), median, range	46 (27 - 64)	38 (28 - 61)
Sex, n (%)		
Male	30 (41.1)	5 (50.0)
Female	43 (58.9)	5 (50.0)
Physician subgroup, n (%)		
Dermatologists	59 (80.8)	7 (70.0)
Dermatology resident	14 (19.2)	3 (30.0)
Type of medical center[b], n (%)		
Academic medical center	45 (60.8)	5 (45.4)
General hospital	25 (33.8)	5 (45.4)
Private practice	11 (14.9)	1 (9.1)
Experience with psoriasis treatment (years), median, range	15 (2-35)	13 (2 – 31)

Table 1. Continued

	Respondents survey (n=73)	**Participants interview (n=10)**
Number of patients (≥ 65 years) currently under treatment with systemic antipsoriatic therapy, median, range	15 (0 – 150)	15 (0- 150)
Prescribed systemic antipsoriatic therapy, despite of age, n (%)		
Methotrexate	73 (100)	10 (100)
Dimethyl fumarate	73 (100)	10 (100)
Acitretin	70 (95.9)	10 (100)
Ciclosporin	63 (86.3)	8 (80)
Ustekinumab	66 (90.4)	9 (90)
Adalimumab	64 (87.7)	7 (70)
Etanercept	58 (78.4)	7 (70)
Secukinumab	54 (74.0)	7 (70)
Ixekizumab	32 (43.8)	5 (50)
Guselkumab	27 (37.0)	3 (30)
Infliximab	25 (34.2)	5 (50)
Risankizumab	18 (24.7)	3 (30)
Certolizumab-pegol	16 (21.9)	5 (50)
Brodalumab	15 (20.5)	3 (30)
Tildrakizumab	7 (9.6)	1 (10)
Apremilast	45 (61.6)	5 (50)
No systemic treatment	0 (0.0)	0 (0.0)
Prescribed systemic antipsoriatic therapy in older adults, n (%)		
Methotrexate	70 (95.9)	9 (90)
Dimethyl fumarate	53 (72.6)	7 (70)
Acitretin	52 (71.2)	7 (70)
Ciclosporin	26 (35.6)	6 (60)
Ustekinumab	39 (53.4)	5 (50)
Adalimumab	47 (64.4)	5 (50)
Etanercept	28 (38.4)	6 (60)
Secukinumab	19 (26.0)	2 (20)
Ixekizumab	7 (9.6)	2 (20)
Guselkumab	9 (12.3)	2 (20)
Infliximab	9 (12.3)	3 (30)
Risankizumab	3 (4.1)	0 (0)
Certolizumab-pegol	3 (4.1)	1 (10)
Brodalumab	3 (4.1)	1 (10)
Tildrakizumab	2 (2.7)	1 (10)
Apremilast	14 (19.2)	3 (30)
No systemic treatment	1 (1.4)	1 (10)
Unknown	2 (2.7)	0 (0)
Other[c]	1 (1.4)	0 (0)

[a] Missing: n=1.

[b] Respondents could select more than one answer and one interviewee worked in two medical centers.

[c] Other; prednisone.

Quantitative results: survey

Systemic antipsoriatic therapy in older adults

Most respondents had experience with prescribing methotrexate, dimethyl fumarate, acitretin and adalimumab in older adults with psoriasis. The majority of respondents (n=49; 67.1%) indicated that they treated older and younger patients to the same extent with regard to systemic therapy. Twenty-six percent of the respondents (n=19) reported to treat older adults less often with systemic therapy compared to younger patients. Most reported reasons for this were (reporting of multiple reasons was possible): presence of comorbidity (n=19), comedication use (n=16), risk of adverse events (n=14), and treatment choices of the patient (n=10). Furthermore, most respondents (n=49; 68.1%) performed additional actions when using systemic antipsoriatic therapy in older adults compared to younger patients. The most frequently reported additional actions were: more intensive monitoring of comorbidity and comedication use (n=37), more frequent consultations with other specialists and/or general practitioners (n=24), prescribing a lower dosage compared to standard care (n=24), and performing laboratory tests more frequently (n=19). A full overview is given in **Table 2**.

Table 2. Survey respondent experiences when treating psoriasis in older adult patients with systemic therapy.

	Respondents (n=73)
The use of systemic antipsoriatic therapy in older adults, n (%)	
Older adults less	19 (26.0)
Comparable between older and younger patients	49 (67.1)
Older adults more	1 (1.4)
Unknown	4 (5.5)
Number of respondents performing additional actions when treating older adults with systemic antipsoriatic therapy when compared to younger patients[a], n (%)	
Yes	49 (68.1)
No	20 (27.8)
Unknown	3 (4.2)
Additional actions when treating older adults with systemic antipsoriatic therapy[b], n (%)	
Extra checks on comorbidity and/or comedication use	37 (75.5)
More frequent consultation with other specialist/GP	24 (49.0)
Prescribing a lower dose than usual	24 (49.0)
More frequent lab controls	19 (38.8)
Steering in the choice of certain medication	11 (22.4)
Start home care or supportive care	9 (18.4)
Extra control appointment in the clinic	5 (10.2)
Reduced prescription of certain systemic antipsoriatic therapy	6 (12.2)
Other[c]	5 (10.2)

Table 2. Continued

	Respondents (n=73)
Reasons to not perform additional actions when treating older adults with systemic antipsoriatic therapy[d], n (%)	
Following the Dutch guidelines is sufficient	7 (35.0)
Choosing antipsoriatic therapy is age independent and depends on the presence of comorbidity/comedication	8 (40.0)

[a] Missing: n=1.

[b] Reporting of multiple reasons was possible. Percentages calculated with only respondents that performed additional actions when treating older adults with systemic antipsoriatic therapy (n=49).

[c] Other included; less explanation needed (n=1), depending on patient's cognition involving family more easily (n=1), more consideration whether the therapy is not worse than the disease (n=1), additional explanation of a higher risk of infection (n=1), older patients respond better to Neotigason than younger people (n=1).

[d] Reporting of multiple reasons was possible. Percentages calculated with only respondents that did not perform additional actions when treating older adults with systemic antipsoriatic therapy (n=20).

GP: general practitioner.

Reluctance with prescribing systemic antipsoriatic therapy

Almost half of the respondents (n=33; 45.2%) indicated that their colleagues are (more) reluctant to use systemic therapy in older adults. However, when asked whether the respondents themselves were reluctant to prescribe these therapies in older adults, the majority reported that they were not (n=50; 68.5%). Respondents that reported to be reluctant (n=20; 27.4%) described several reasons for this, of which most reported reasons were (reporting of multiple reasons was possible): presence of comorbidity (n=19), use of comedication (n=17), and risk of adverse events (n=15). A full overview is provided in **Table 3**.

Table 3. Reluctance amongst survey respondents with systemic antipsoriatic therapy in older adults.

	Respondents (n=73)
Number of respondents thinking their colleagues are reluctant to use systemic antipsoriatic therapy in older adults, n (%)	
Yes	33 (45.2)
No	14 (19.2)
Unknown	26 (35.6)
Number of respondents reluctant with the use of systemic antipsoriatic therapy in older adults, n (%)	
Yes	20 (27.4)
No	50 (68.5)
Unknown	3 (4.1)

Table 3. Continued

	Respondents (n=73)
Number of reasons to be reluctant[a], n (%)	
Presence of comorbidity	19 (95.0)
Presence of comedication	17 (85.0)
Risk of adverse events	15 (75.0)
Treatment goals/preferences of the patient	9 (45.0)
Cognitive state of the patient	7 (35.0)
Inexperience with systemic antipsoriatic therapy in older patients	3 (15.0)
Degree of self-reliance (e.g. need of homecare)	2 (10.0)
Limited evidence available regarding treatment safety	2 (10.0)
Other[b]	5 (25.0)

[a] Reporting of multiple reasons was possible. Percentages calculated with only respondents that were reluctant with systemic antipsoriatic therapy in older adults (n=20).

[b] Other included; limited evidence available regarding treatment efficacy (n=1), increased risk of infections (n=1), (limiting) number of outpatient visits (n=1), mobility of the patient (n=1), social network/informal care (n=1).

Comfort-levels in systemic antipsoriatic therapy

Respondents indicated they were most comfortable prescribing the following systemic antipsoriatic therapies in older adults (range 1-5; higher scores indicate respondents to be more comfortable): methotrexate (4.26 ± 0.6), acitretin (4.18 ± 0.6), ustekinumab (4.03 ± 0.7), and adalimumab (4.03 ± 0.7). For ciclosporin (2.82 ± 1.1, $p<.001$) and infliximab (3.12 ± 1.2, $p<.001$) a significant lower mean score was seen compared to methotrexate, indicating that respondents were most uncomfortable prescribing these therapies **(Table 4)**.

Qualitative results: interviews

The following themes were identified from the interviews: prescribing patterns, challenges and barriers when prescribing systemic antipsoriatic therapy in older adults, needs when treating older adults with psoriasis, and future recommendations for treating older adults with psoriasis. See **Table 5** for an overview of themes/subthemes. For illustrative quotes supporting the themes see **Supplemental Tables S2-S5**.

Table 4. Comparison of comfort levels of respondents when using systemic antipsoriatic therapy in older adults.

Systemic therapy, n(%)	Mean score[a] ± SD	Very comfortable	Comfortable	Neutral	Uncomfortable	Very uncomfortable	95% CI	p-value[b]
Methotrexate	4.26 ± 0.6	23 (32.9)	42 (60.0)	5 (7.1)	0 (0.0)	0 (0.0)	4.04 … 4.41	*Reference*
Ciclosporin	2.82 ± 1.1	4 (6.1)	15 (22.7)	17 (25.8)	25 (37.9)	5 (7.6)	-1.63 … -1.22	<0.001
Acitretin	4.18 ± 0.6	18 (27.7)	42 (64.6)	4 (6.2)	1 (1.5)	0 (0.0)	-0.31 … 0.09	1.000
Dimethyl fumarate	3.99 ± 0.7	14 (20.6)	41 (60.3)	11 (16.2)	2 (2.9)	0 (0.0)	-0.47 … -0.07	0.113
Etanercept	4.00 ± 0.8	14 (29.2)	22 (45.8)	10 (20.8)	2 (4.2)	0 (0.0)	-0.49 … -0.04	0.273
Adalimumab	4.03 ± 0.7	15 (25.4)	32 (54.2)	11 (18.6)	1 (1.7)	0 (0.0)	-0.39 … 0.02	1.000
Infliximab	3.12 ± 1.2	5 (15.2)	9 (27.3)	7 (21.2)	9 (27.3)	3 (9.1)	-1.34 … -0.83	<0.001
Ustekinumab	4.03 ± 0.7	14 (22.6)	38 (61.3)	8 (12.9)	2 (3.2)	0 (0.0)	-0.39 … 0.03	1.000
Secukinumab	3.98 ± 0.8	12 (25.0)	25 (52.1)	9 (18.8)	2 (4.2)	0 (0.0)	-0.46 … -0.02	0.508
Ixekizumab	3.85 ± 0.9	10 (29.4)	11 (32.4)	11 (32.4)	2 (5.9)	0 (0.0)	-0.66 … -0.15	0.024
Certolizumab-pegol	3.86 ± 1.1	8 (38.1)	4 (19.0)	7 (33.3)	2 (9.5)	0 (0.0)	-0.80 … -0.20	0.016
Brodalumab	3.78 ± 1.0	8 (34.8)	4 (17.4)	9 (39.1)	2 (8.7)	0 (0.0)	-0.79 … -0.21	0.010
Guselkumab	3.89 ± 0.9	11 (31.4)	11 (31.4)	11 (31.4)	2 (5.7)	0 (0.0)	-0.63 … -0.14	0.032
Tildrakizumab	3.79 ± 1.1	9 (37.5)	3 (12.5)	10 (41.7)	2 (8.3)	0 (0.0)	-0.77 … -0.20	0.014
Risankizumab	3.79 ± 1.0	9 (32.1)	6 (21.4)	11 (39.3)	2 (7.1)	0 (0.0)	-0.78 … -0.24	0.003
Apremilast	4.00 ± 0.8	11 (28.2)	17 (43.6)	11 (28.2)	0 (0.0)	0 (0.0)	-0.45 … 0.02	1.000

Values might not add up to missing values.

[a] Overall mean score per treatment. Comfort-levels were measured using a 5-point Likert scale, 5 indicating very comfortable, 1 indicating very uncomfortable.

[b] Corrected for multiple testing using Bonferroni.

SD: standard deviation; CI: confidence interval.

Table 5. Overview of the key themes, subthemes and codes, emerged from the interview analysis regarding systemic antipsoriatic therapy in older adults.

Key themes	Subthemes	Codes

Challenges and barriers when prescribing systemic therapy in older adults with psoriasis	• *Prescribing patterns; age-based treatment (in)equality*
	• *Frailty*
	• *Comorbidity/comedication*
	• *Other patient characteristics*
	• *Prescriber characteristics*
		• Age-based treatment (in)equality
		  ◦ *Equality*
		  – Equal treatment
		  – Following the Dutch guidelines; no extra lab controls
		  – Depending on disease severity
		  – Shared-decision making
		  – Elderly is not aged ≥65 years
		  ◦ *Inequality*
		  – More cautious not reluctant, higher threshold
		  – Fear of AEs specifically irreversible AEs
		  – Presence of under treatment; patient-related, prescriber-related
		  – Suspected difference in treatment goals
		  – Frailty; mobility, social support, cognitive state, medication errors
		  – Reluctance of patients' family members
		  – Actions: dose adjustments, more precise lab controls, more precise with supplying information, consultation of other specialists, actively checking patient understanding of treatment use
		• Frailty
		  – Cognitive state/ patient comprehensibility
		  – Mobility
		  – Social support/surroundings
		  – Comorbidity/comedication/polypharmacy
		• Comorbidity/comedication
		  – Reluctant due to comorbidity/comedication
		• Other patient characteristics
		  – Perceived reluctancy
		  – Perceived treatment goals
		  – Patient competency/resilience
		  – Therapy compliance

Table 5. Continued

Key themes	Subthemes	Codes
		• Prescriber characteristics – Feeling competent – Fear of occurrence of AEs – Fear of misjudging cognition – Experience/education of prescriber – Reluctance of colleagues, generation of physicians – Guidelines can be complex – Limited time clinical visits
Physicians' needs when treating older adults with psoriasis	• *Evidence-based guidance* • *Education* • *Health care system adjustments* • *No needs*	• Evidence-based guidance – Psoriasis guidelines; additional information regarding older adults, compact overview of treatments, if applicable other dosing regiments, specific contra-indications, influence of systemic antipsoriatic therapy on mobility, treatment related AEs or related due to age. – Large prospective studies on older adults with psoriasis • Education – More attention for older adults in residency – Education for all physicians on older adults • Health care system adjustments – More consultation time when needed – Information leaflets for older adults • No needs – No need for additional information on older adults in guidelines or education
Future recommendations when treating older adults with psoriasis	• *Patient centered care* • *Safety measures*	• Patient centered care – Information provision specially for older adults – Assessment of frailty and acting accordingly/therapy compliance: drug Baxter system, home UV-therapy, involving social support system • Safety measures – Support at the outpatient clinic e.g. deployment of nurse practitioners – Standard coordination/communication with social support system

AEs: adverse events.

Prescribing patterns

Regardless of a patient's age, most participants considered several factors when deciding upon a treatment type, e.g. disease severity, patient treatment goals, and (potential) contra-indications. For the treatment of older adult patients, participants mostly tended to follow the current psoriasis guideline recommendations, as they would in younger patients (age-based treatment equality).

> *'Older people are entitled to systemic therapy like all other age categories. It's just a safe and good way of treatment, provided that you do it lege artis' (P4)*

Often, the concept of shared-decision making is used as a tool for treatment selection.

> *'I always try to apply shared-decision making, so I will never present a patient with only one treatment option' (P2)*

However, in older adult patients the following factors related to aging receives more attention by participants in daily practice: comedication use, comorbidity, frailty, mobility, cognitive function, and social support system. Participants indicated that these factors can lead to a more cautious treatment approach and are likely to contribute to a reluctance for prescribing systemic therapy and perform additional actions in this population. Examples of the latter are: dose adjustments, more frequent lab controls, consulting other specialists and actively checking patients understanding of treatment use (age-based treatment inequality).

> *'I feel that I am slightly more reluctant with systemic antipsoriatic therapy in older adults than in the younger population' (P5)*

Challenges and barriers

The factors as described above, were also defined by the participants as barriers and challenges for the use of systemic antipsoriatic therapy in older adults. Especially in frail patients, participants are more cautious and sometimes reluctant to prescribe systemic antipsoriatic therapy. The difficulty of making a good estimate and prevent misjudgment of patients' vulnerabilities (e.g. cognitive function, patients comprehensibility, mobility, social support system), especially in the short amount of time given at an outpatient clinic was defined as a barrier. Other defined barriers are the often more extensive multimorbidity and comedication use in this population, which can complicate the prescription of certain antipsoriatic therapies.

'Especially the comorbidity and multi-drug use, I often find that difficult' (P9)

Other possible barriers for the use of systemic antipsoriatic therapy in older adults were: fear of adverse events, inexperience with the prescription of specific treatment options, the presence of patient-related treatment reluctancy, patients' dependency in activities of daily living (i.e. proper use of prescribed therapy), suboptimal compliance, and patient's outspokenness (i.e. will the patient ask for help when needed or will the patient indicate whether treatment regimens are unclear).

'I think there's that fear, that you're doing more harm than the condition you're treating' (P4)

'You can be well trained in systemic therapy, however, if you don't prescribe it often in clinical practice, you might become more reluctant to prescribe it' (P4)

'Patients' understanding of the antipsoriatic therapy, especially when older patients live alone, is the treatment going well? Patients ability to recognize adverse events and ask for help' (P2)

Unmet needs and future recommendations

Participants were asked whether they have unmet needs regarding the prescription of systemic antipsoriatic therapy in older adults. Most participants wished for more evidence-based guidance concerning older adults, such as a compact overview of safe treatments for older adults including dosing regimens, specific contra-indications, and especially treatment-related adverse events.

'I think that relatively few patients of this age are included in clinical trials due to contraindications and exclusion criteria. So I think it makes sense to specifically collect data from this patient population, to obtain more real life data' (P9)

Some others opted for more education regarding older adults with psoriasis during their residency but also for dermatologists. Also, specific measures were described such as; more consultation time and specific information leaflets for older adults.

'I think it is important to have more consultation time and to involve the social support system of the patient, this should be more standard in clinical practice' (P8)

Furthermore, some additional future recommendations were suggested: (1) more focus on personalized medicine in dermatology practice (e.g. assessment of frailty and acting accordingly), (2) specific safety measures (e.g. more support at the outpatient clinic by nurse practitioners), and (3) easier and more frequent contact with other caregivers (e.g. homecare facilities).

> *'It is desirable to have a nurse practitioner at the outpatient clinic who knows everything about our systemic antipsoriatic medication. Who can relieve the workload in terms of the time needed explaining the antipsoriatic treatments to patients and can also give patients much more insight into the medication they are about to get' (P5)*

Discussion

In this mixed-methods study the prescribing patterns, possible barriers, and needs of dermatologists and residents regarding systemic antipsoriatic therapy in older adults were explored. The most important findings were that most survey respondents applied systemic therapy to the same extent in older adults compared to younger patients (67.1%) and were not reluctant to prescribe systemic therapy in this population (68.5%). However, age-based treatment differences and systemic treatment reluctance in this population were also seen. A quarter of the respondents reported to treat older adults less often with systemic therapy compared to younger patients, and respondents often indicated that their colleagues are (more) reluctant to use systemic therapy in this population (45.2%). Furthermore, most respondents (68.1%) performed additional actions when treating older adults with systemic therapy, in particular more intensive monitoring of comorbidity and comedication, more frequent consultations with other specialist, and prescribing a lower dose of systemic antipsoriatic therapy than standard practice.

The main reasons for these age-based treatment differences and reluctance, as indicated by the survey respondents and the additional in-depth interviews, were the presence of comorbidity, comedication use, and the fear of adverse events in older adults. In addition, interviewees mentioned the sparse evidence-based guidance regarding efficacy and safety of these treatments in a geriatric population as another important reason for treatment reluctance. Fortunately, there seems to be more attention for this specific population in all medical fields nowadays. Recent studies regarding older adults with psoriasis report an acceptable safety profile in older adults and that age alone should not be a restrictive factor when

treating psoriasis.[14,20-22] Reluctance to prescribe certain medications in older adults is common amongst healthcare providers in other medical specialties and the mentioned reasons to be reluctant in the current study are generally in line with previous research regarding prescription of systemic antipsoriatic therapy in older adults with psoriasis.[23-26] A reluctance to use systemic antipsoriatic therapy might be rational and necessary, for instance when possible (relative) contra-indications are present. However, sometimes this reluctance might also be disproportional and potentially leads to undertreatment. This could for instance be due to a lack of knowledge or experience to treat older adults or the conceptions of ageist stereotypes and age-based assumptions without paying proper attention to the heterogeneity of the older adult population in terms of frailty and resilience.

Frailty is a factor physicians find especially hard to assess in older adults. Even though frailty screening tools are available and seem suitable for dermatology practice, there are no studies on this topic for older psoriasis patients.[27] These frailty tools might be useful for the management of older adult patients with psoriasis, future studies on frailty screening, and the consequences of frailty in this population would be beneficial to enhance further risk-stratification and optimize personalized medicine in the heterogenous population of older adults with psoriasis. Furthermore, the interviewees in the current study expressed the need for more education and time to assess older patients during their clinical visits. Since it is expected this will aid in assessing frailty and, as a result, may decrease reluctance to prescribe systemic antipsoriatic therapy.

Focusing on specific types of systemic antipsoriatic therapy, the results of the survey showed that respondents had most experience with prescribing conventional systemic antipsoriatic therapy (mainly methotrexate, dimethyl fumarate, and acitretin) in older adults with psoriasis. Respondents had less experience with prescribing biologics in this specific population, which is also seen in literature.[12,13] In addition, respondents were asked to indicate their level of comfortability with the different types of systemic antipsoriatic therapies. Methotrexate, acitretin, ustekinumab and adalimumab were rated as most comfortable to prescribe in older adults. Ciclosporin was rated as being most uncomfortable with when prescribing in older adults, which was correspondingly also the least prescribed conventional systemic antipsoriatic therapy for older adults in this study, which is in line with literature.[13] Obviously, it is not surprising to find this correlation between prescription behavior and the level of comfortability with the different types of systemic antipsoriatic therapies. Also, existing data on efficacy and safety seem to reflect these findings (e.g. the risk for adverse events of ciclosporin in older

adults probably reflecting in a low comfortability-score).[14] However, as mentioned before, a lack of knowledge or experience with specific treatment options might also result in a reluctance to prescribe these options in general or in this specific population, potentially leading to undertreatment. This highlights the mentioned needs for more evidence-based guidance and education. This mixed-method design is subjected to factors as recall bias and the possibility of misinterpretation. To mitigate these, the survey was pretested by several dermatologists and residents and the interview guide was reviewed by the research team. In regular meetings the interview codes and themes were discussed until consensus was reached. The results we found might not be generalizable to all dermatologists/residents due to the possibility of selection bias and limited number of respondents. However, a non-response analysis was conducted to check for selection bias and in the selection for interview participants we aimed to include balanced groups regarding sex and type of medical center.

In conclusion, this study highlights that age-based treatment differences and reluctance to treat older adults with systemic antipsoriatic therapy are common. Comorbidity, comedication, and fear for adverse events were mentioned as the most important reasons for this. More evidence-based guidance, education, consultation time, and the use of frailty screening were the most important needs, to improve treatment and prevent undertreatment in this growing population.

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Supplemental tables

Table S1. Study population characteristics compared with target population.

	Study population dermatologists (n=59)	National population dermatologists (n=480)	Study population-dermatology residents (n=14)	National population dermatology residents (n=185)
Age, mean ± SD	49.2 ± 9.9	48.6 ± 9.6 [ns]	30.5 ± 2.1	31.4 ± 3.1 [ns]
Sex, n (%)				
Male	26 (44.1)	244 (50.8) [ns]	4 (28.6)	46 (24.9) [ns]
Female	33 (55.9)	236 (49.2)	10 (71.4)	139 (75.1)

Ns: no significant difference was found compared to the current study population.

Table S2. Illustrative quotes of prescribing patterns.

Sub-themes	Illustrative quotes
Age-based equality	
Equal treatment	'*Basically, I think I treat them [older adults] like other patients*' (P1)
	*'I don't treat them [*older adults] *any differently than someone who is, let's say, 25 years old'* (P2)
	'Standard treatment ladder, same as for people not older than 65' (P4)
	*'I treat [*older adults] *the same way as I treat adults. I don't think we should start systemic therapy too late. Certainly not too early, but also not too late. And yes, for me personally being older is not a barrier to consider starting systemic therapy'* (P4)
	'In general, I have the idea, yes, that we can treat the elderly psoriasis patients well. There is always a solution. If light therapy does not work, then systemic therapy and if that does not work or whatever, yes, then biologicals also work great, so that is another option' (P7)
Following the Dutch guidelines	*'That is a step-by-step method, depending on the disease severity you start with topical therapy such as Dovobet or Enstilar. Is it more extensive than we offer them light therapy. When it is more extensive or when they quickly relapse after light therapy, we offer them systemic therapy'* (P6)
	*'I treat according to protocol and depending on the severity' (*P2)
	'Older people are entitled to systemic therapy like all other age categories. It's just a safe and good way of treatment, provided that you do it lege artis' (P4)
	'I just do my laboratory follow-up like I would with younger adults' (P10)
Depending on disease severity	*'I treat according to protocol and depending on how bad it is' (*P2)
	'Well, that depends a bit on how extensive the psoriasis is and the disease burden someone experiences' (P7)
	'I always look at what the possibilities are and what the wishes of the patients are. When it does not work with intensive topical therapy, or whether topical therapy is no longer desirable. Then I make the step to either light therapy or systemic therapy in older adults. To eventually get a better quality of life' (P9)

Table S2. Continued

Shared-decision making	*'I always try to apply shared-decision making, so I will never present a patient with only one treatment option'* (P2)
	'I explain of course what the different treatment options are and then we apply shared-decision making using either the decision aid formor the consultation card' (P9)
	'The most important factor is the shared decision making, to make the choice for a treatment together. What qualifies as good, is not really determined by me, but by the patient and if they think it's good enough, even though I know there are even better options' (P3)
Elderly is not aged ≥65years	*'For me being older is not exactly related to the age number. A person over 65 who comes to me without comedication and who looks very fit, I will indeed not treat them differently than someone of 40 years old with psoriasis'* (P1)
	'Naturally you have old and old, so you have people of 65 and they are still young, and you have people of 55 who are already old. Yes, there's nothing you can do about that' (P3)
	'Not every 85-year-old is old, one can be very fit, and you think, they can still get a lot out of life' (P10)
Age-based inequality	
Being cautious, higher threshold, not reluctant	*'If a more frail person presents himself to me, with a lot of medication, I notice that I am less eager to start methotrexate, especially in this period [COVID-19 situation] with regard to infection risk'* (P1)
	'With adults it [using systemic antipsoriatic therapy] usually goes well. In clinical practice you control the blood values, and everything is good, but especially with older people, you really have to be cautious and keep an eye on them. You really just have to pursue those strict controls' (P4)
	'I am a little more careful, I keep an eye on it [using systemic therapy in older adults] more and yes there are more factors to consider' (P8)
	'I feel that I am slightly more reluctant [with systemic antipsoriatic therapy in older adults] than in the younger population. The threshold may be a little higher, but I will almost always look for and overcome the threshold' (P5)
Fear of irreversible adverse events	*'I think there's that fear, that you're doing more harm than the condition you're treating [when using systemic antipsoriatic therapy in older adults]'* (P4)
	'You are scared a little sooner with a suddenly declining kidney function of someone aged 85 or 80 than you would be with someone aged 35 years old' (P5)
	'I think fear, fear of side effects, and that maybe one day something really goes wrong for which they [prescribers of antipsoriatic therapy in older adults] are responsible, or feel responsible for, yes I can relate to that' (P8)

Table S2. Continued

Undertreatment Prescriber- related	*'I think [undertreatment] certainly is present. Yes, maybe amongst the older dermatologists who might still feel a little less comfortable with systemic therapy or simply don't have the time for it. I don't know, but these [undertreated] patients will still be around somewhere yes. I hope there aren't too many of them'* (P8)
	'I certainly think so [that undertreatment is present]. Yes, I don't think it is only present in the elderly but in general… There are general practitioners who still think that there is nothing to be done about psoriasis. That it's a chronic disease, there's nothing you can do about it, but hey, those are two different things' (P9)
Undertreatment Patient- related	*'It is of course also the generation, patients who have been living with psoriasis for 40 years and where there used to be less effective treatments, they [older patients] have learned to live with that, while of course now we know much more and there are plenty of treatments available to try. This is perhaps less known among the older generation [of patients]'* (P10)
	'I'm afraid they [older patients] sometimes undertreat themselves. Because they think, well it doesn't bother me that much. I'm used to it' (P3)
Difference in treatment goals	*'Elderly patients may be more satisfied sooner, I don't know, but they get on well with that [with topical therapy only]'* (P3)
	'You notice that the younger category of patients is much more concerned with do I have visible spots, that don't bother me much, but others do see that. In the elderly patients they say well I don't wear short trousers anymore, I don't suffer from itching. Then why would I risk side effects? I think that's more the patient category itself, which doesn't care as much about those social aspects than I do as a doctor' (P1)
Reluctance of patients or family members	*'I don't think that older patients are reluctant about systemic therapy, rather the son or the daughter. Not necessarily the patient'* (P2)
	'At some point patients say well but if this is the next step, I am not willing to dare use that treatment at this stage of my life' (P1)
Differently done actions in older adults	*'If people are really old, you start a little lower in your dosage and yes I am also a bit more on top of those control appointments for example; that you keep the laboratory check-ups a bit stricter. In a younger patient you might be able to postpone a blood check for a few weeks. In an older person I would do that a little less quickly, so yes I am a bit more careful but not too careful I think'* (P8)
	'I also think providing good information is more necessary for older patients, because they cannot easily look something up on the internet, so you may need to inform them a bit better about the real pros and cons of the treatment and work with information leaflets to give to your patients and verify whether they use the treatment in the right way' (P10)
	'So, with the elderly, you have to keep a closer eye in terms of lab check-ups, side effects and not to dose too high too quickly. So, start with a lower dose, slowly increase and give a good explanation. That is very important, take your time for it, because with a younger person it all goes quite quickly. If they receive a brochure, they can read it and if they don't understand it, they will call you. But an older person may be ashamed that he has not understood the explanation or only heard half of it. They might not ask for help until things don't go well. Of course, this does not apply for every older patient, but as a doctor you have to play a more active role in that, such as getting people to come back more often and check whether the patient had understood everything' (P4)

Table S3. Illustrative quotes of the theme: challenges and barriers when prescribing systemic antipsoriatic therapy in older adults.

Sub-themes	Illustrative quotes
Frailty	
Cognitive statePatient comprehensibility	*'Patients' understanding of the antipsoriatic therapy, especially patients that live alone, is the treatment going well? Patients' ability to recognize adverse events and ask for help'* (P2)
	'The understanding, that I think they [older adults] understand or that I know they have someone to guide them. If I notice that they really don't get it; how and what, then I'm not going to prescribe it. I must have the confidence that the patient can follow my advice and knows how to follow it' (P4)
Patient mobility	*'What important is with elderly patients is whether they are mobile and how they live, it is necessary to ask about the living situation, does someone have home care, can someone apply topical therapy, can someone come to the hospital for light treatment?'* (P2)
	'Sometimes also the mobility, to what extent patients are able to actually come by, for example for light therapy, which can be a great burden' (P7)
Patients social support system/ surroundings	*'I think it is important for the doctor to know that there is someone in the patients' surrounding who can monitor [treatment intake] and that you know that the patient is not alone'* (P2)
	'When I start with topical therapy and when the psoriasis is located on the back, is there someone who can help with applying, or do they have a partner or should a neighbor be involved or something like that' (P10)
Comorbidity, comedication, polypharmacy	
Comorbidity	*'Especially the comorbidity and multi-drug use. I often find that difficult'* (P9)
Polypharmacy	*'Especially the polypharmacy, and also things like kidney function to consider'* (P1)
Comorbidity and/or comedication use	*'Regarding systemic therapy, the comorbidities and the comedication that these patients have'* (P7)
	'I think the biggest barrier for me is comedication use*. The older you get, the more comorbidity. But that's less of a threshold for me. It is mainly the comedication'* (P5)
Patient characteristics	
Treatment goals	*'That you try to achieve as little psoriasis as possible, so older adults often say well it is quite good, I'm used to it. That you still try to encourage them to use topical therapy, or to take oral medication'* (P3)
	*'At the outpatient clinic where we prescribe biologics there are patients who have very extensive psoriasis, and the older patients are often very satisfied with only PASI 50 improvement. And then they say no, I don't have to use topical therapy, I'm already satisfied. I know from the past how bad it can be' (*P10)
Perceived reluctancy	*'You sometimes hear that older patients are afraid to make the switch from topical and light therapy to systemic therapy'* (P9)
Competency/ resilience	*'Some elderly people find it complicated to use antipsoriatic therapy, so they need home care because they can't manage on their own anymore. They forget to apply topical therapy and then they are also not suitable for systemic therapy. I actually think that people either need to be helped by arranging extra care or that they should be able to oversee their treatment regimen otherwise I think that systemic therapy is too dangerous'* (P3)

Table S3. Continued

Sub-themes	Illustrative quotes
Outspokenness/being informed	*'This also has to do with cognitive functions. Whether someone asks for help when something is wrong'* (P8) *'They don't always ask for help, only when things really don't go well, not everyone of course'* (P4)
Therapy compliance	*'I also think therapy adherence. When it comes to topical therapy schedules or, for example, methotrexate use, that they only take it once a week. That they don't make dosing errors, I find that a challenge'* (P8)
Prescriber characteristics	
Fear of adverse events	*'That they [older adults] are more likely to have side effects. Yes, the sensitivity for infections'* (P8) *'The vulnerability. I think the same goes for children. That you would also be less likely to go towards systemic medication there. I think just that worry for side effects'* (P1)
Feeling competent	*'Follow your start-up protocol neatly and if you see deviating values that you are less skilled at as a dermatologist, you should ask for your help'* (P1)
Fear of misjudging cognition	*'I had that with a patient, she came in with her husband, and I started methotrexate and as they walked out the door, we both thought, I hope it goes well, you kind of felt like oh you don't know for sure whether it will work out at home and whether they understood what it was for and what it did'* (P2) *'Elderly people who are starting to have dementia, which may not be so clear in the beginning. So sometimes there can be a situation where you initially think that someone understands well and can follow your instructions. But, where you sometimes gradually find out, hey, something isn't quite right here. Looks like someone forgot or whatever. And that, yes, that is sometimes not immediately clear. And the risk is greater in the elderly than in the young'* (P7)
Experience with and education about antipsoriatic therapy	*'You can be well trained in using systemic therapy, however, if you don't prescribe it often in clinical practice, you might become more reluctant to prescribe it'* (P4) *'Unknown makes unloved, don't you think?'* (P1) *'Dermatologists who have graduated here feel comfortable with giving systemic medication. So they will use it often. For example, if you look at this [other] hospital. They use relatively little systemic therapy there. So they are less familiar with giving systemic therapy in general. Let alone use systemic therapy in the elderly, it is a matter of experience'* (P4)
Limited time clinical visits	*'I think it is very important that you get more time during your consultation, you can't explain this [systemic therapy] very quickly to someone like that [older patients]. You need enough time to explain it, time to consult with a pharmacist or a general practitioner. To make sure that you don't start too soon and that you do proper research to see if the therapy is possible'* (P2)
Reluctance of colleagues/ generation of physicians	*'When I look at my own team, I don't want to generalize, but especially among the younger dermatologists you see that they are less reluctant to use systemic therapy and that the older ones are still a bit more reluctant. Since the older dermatologists are mostly trained to use topical therapy'* (P8)

Table S4. Illustrative quotes of the theme: physicians' needs when treating older adults with psoriasis.

Sub-themes	Illustrative quotes
Evidence-based guidance	
Psoriasis guidelines	*'That you clearly list everything in the guideline regarding elderly, for example: from which kidney function do you have to do what? With which medicine? when should you consult with whom? And what are the real contraindications in the elderly? There is an idea about this in the global guidelines, but in practice it is actually more guess work'* (P5)
	'It [addition of a chapter regarding older adults] might be an idea to put in the psoriasis guideline, there is a chapter for children, but there is no chapter for the elderly in it, for example, maybe you should include a chapter or maybe you should indeed just make a specific part for each medication in the guideline and add a piece regarding the elderly like you have to pay extra attention to this, or this or, this or maybe you don't have to pay extra attention' (P8)
Data generation	*'It would be good if large studies were conducted on the elderly only. And for example, maybe you should apply dose adjustments for the elderly, I think that would maybe be an outcome of a big trial'* (P4)
	''There are only a few studies that have been specifically performed on older people, so it would be nice if there were more studies and that we could convince everyone that we can treat elderly safely. Or maybe that it is not safe at all, I don't know. Because most of the time, the elderly patients are excluded from studies, aren't they? So that would be nice if we had more studies' (P8)
	'I think that relatively few patients of this age are included in clinical trials due to contraindications and exclusion criteria. So, I think it makes sense to specifically collect data from this patient population, to obtain more real-life data' (P9)
Education	
In dermatologists and residents	*'I think that [training regarding older adults] could be better. No, I can't remember any training that specifically deals with older patients. So, I think it's good to pay attention to that'* (P9)
	*'I would really like to have a talk about what the evidence is in adults and what we should or should not worry about. More like an eye opener. Whether that should take place nationally in the curriculum is the question, I don't know. I actually think it's nice' (*P5)
	'I think that we need to get rid of the fear to treat elderly with systemic drugs. A refresher course or something from people who have a lot of experience with treating older adults would be preferable. So that you can learn from their experience' (P4)
Health care system adjustments	
Time management	*'I think it is important to have more consultation time and to involve the social support system of the patient, this should be more standard in clinical practice'* (P8)
	'To determine the mental capacity of the patient. That is something that you have to take into account with this patient category, especially because some are in such a dormant phase, in which the family themselves may not yet be completely sure how quickly a person is or not deteriorating or has deteriorated. That is something that you have to take into account and you can't always do that in ten minutes, so to speak' (P1)

Table S4. Continued

Sub-themes	Illustrative quotes
Information provision	*'I think that with more time in consultation and yes that we make standard procedure to involve patient's environment at consultation or afterwards call the daughter or children or well, whoever. Yes and good communication indeed, to keep everyone involved, or that you write a clinical letter? Perhaps you should not just send the message to the general practitioner, but also to a family member and to the nursing home doctor, just to name a few. I think we need time and communication'* (P8)
	'I think that the provision of information can improve, so that people are more comfortable at a given moment or that there is less undertreatment. It is very much about providing information and involving patients and yes properly instructing, explaining and that, that is not something you have to do once, but several times and perhaps involve people around those patients' (P9)
No needs	
No additional information/ education	*'I didn't have anything specifically about the elderly in my medical training. But I wonder if that's really a loss. Look, you just have to master systemic medication well and it is interwoven that we among other things, needs to be careful with the elderly'* (P4)
	'No, you are educated, you've seen and treated hundreds of patients, and when you get to work, it is really important to maintain your knowledge and skills. This applies for everyone, whether you are at the end or the start of your career, you need to maintain your knowledge and skills' (P6)

Table S5. Illustrative quotes of the theme: future recommendations when treating older adults with psoriasis.

Sub-themes	Illustrative quotes
Patient centered care	
Information provision	*'An extra information leaflet for the elderly. Where it is explained a little easier. As I said the methotrexate leaflet is eight pages long and I don't think every elderly person will read it entirely and pregnancy in this age group is irrelevant. Maybe the explanation for older adults can be simplified, using pictures or something like that"* (P2)
	'Surely that's the communication and the transfer of information, especially to the people around them. When you say we want to treat those characteristics optimally and yes, we want to prevent something from going wrong. Then I think we should communicate better with the social surroundings of the patient' (P8)
Adjusting for frailty/ therapy compliance	*'Yes, especially with regards to forgetfulness, although I think that with a blister from the pharmacy you can also get a lot of things done and that can be arranged. When someone is living alone without a support system, then you will of course sometimes have leftovers from the prescribed pills, because people do not want to be dependent on home care. So those are things you discuss. If you do not opt for tablets, then we will have to arrange something to apply the topical therapy'* (P1)
Safety measures	
Support in clinical practice	*'Yes, ideally you could say that when there is a nurse who gets extra training in this. Since you have relatively little time, they can give extra explanation to an older person. If possible'* (P2)
	'Whether or not to have a specialized nurse or assistant. Of course, it is a plus, isn't it? Who can give extra explanation and can take the time for it. This is not a possibility for every practice' (P4)
	'It is desirable to have a nurse practitioner at the outpatient clinic who knows everything about our systemic antipsoriatic medication. Who can relieve the workload in terms of the time needed explaining the antipsoriatic treatments to patients and can also give patients much more insight into the medication they are about to get' (P5)
Coordination with social support system	*'I think a lot it comes down to good communication and good contact with the network of those people, don't you? So with a partner or children or when someone is in a nursing home, yes, to communicate with the doctor there and with the nurses, and I think that sometimes, yes, that that happens too little. That we need to find out who's actually there in front of us, what kind of person is that? How does he/she function cognitively? What exactly is the comorbidity, comedication? How does someone live? The people who know the patient well can actually estimate much better whether that patient is going to take the medication correctly, so more time and more communication with the people close to the patients. Yes, I think you'll come a long way'* (P8)
	'Or if someone opts for light therapy, but is not able to come to the outpatient clinic themselves, we need to do this in consultation with the people supporting the patient, the first contact person' (P1)

Chapter 2.5

Frailty and functional dependency in a multicenter cohort of older adults with psoriasis: prevalence and extent of and implications for psoriasis management

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Abstract

Background
Little is known on frailty and functional dependency in older adults with psoriasis.

Objective
To assess the prevalence and extent of frailty and functional dependency in older adults with psoriasis and their implications for psoriasis management.

Methods
A cross-sectional analysis was performed in a multicenter cohort of older adults (≥65 years) with psoriasis. Prevalence and extent of frailty and functional dependency were assessed by Geriatric-eight (G8), Groningen Frailty Indicator (GFI), Clinical Frailty Scale (CFS), and (instrumental) Activities of Daily Living ((i)ADL) indices. Psoriasis management implications were also investigated.

Results
Of 102 included patients 42.2%, 26.0%, and 13.7% were frail according to G8, GFI, and CFS respectively. Furthermore, 14.3% of patients were ADL-dependent and 37.6% iADL-dependent. Needing treatment assistance was more common in frail versus non-frail patients (G8, CFS) (p=0.007; p=0.019), and in ADL-dependent compared to ADL-independent patients (p=0.021). Frail patients (CFS) were less satisfied with medication regarding 'global satisfaction' and 'side-effects' than non-frail patients (p=0.005, p=0.004). Likewise, frail (GFI) and ADL-dependent patients were less satisfied with 'side-effects', versus non-frail/ADL-independent patients (p=0.009, p=0.015).

Limitations
Small sample size.

Conclusion
Frailty and functional dependency are common in older adults with psoriasis, leading to increased need for treatment assistance and less treatment satisfaction.

Introduction

Psoriasis is a common, chronic skin disease presenting at any age.[1] This chronicity in combination with the aging world population leads to a growing group of older adults with psoriasis, and an increase in the need for effective and safe treatment.[2] Choosing the most optimal therapy in this population can be challenging since evidence-based guidance is scarce and comorbidity and comedication use are prevalent.[3-5] Furthermore, patient values and preferences, as well as logistical and functional (im)possibilities (e.g. number of hospital visits) should also be considered when selecting the most optimal treatment for an individual patient.[6,7] Research in various medical fields has shown that age alone is often insufficient to predict treatment feasibility, (adverse) treatment outcomes and treatment burden.[8-10] Incorporating assessment of frailty and functional dependency has been shown to assist in optimal treatment selection in various older patient populations, however less is known on these factors in older patients with psoriasis.[9,11] Frailty is an aging-related clinical syndrome, characterized by physiological decline and diminished resistance to stressors, resulting in a higher risk of (permanent) adverse health outcomes (e.g. functional dependency, hospitalization).[12] Functional dependency can be defined as needing help with and/or being unable to perform one or more activities of daily living independently. In this study, we aimed to assess the prevalence and extent of frailty and functional dependency in older adults with psoriasis and their implications for psoriasis management.

Methods

Study design and population

A multicenter cross-sectional cohort study was performed to assess frailty and functional dependency amongst older adults (≥65 years) with psoriasis. Patients from two hospitals in Nijmegen (one academic: Radboud university medical center; and one general: Canisius-Wilhelmina Hospital) were invited, excluding those unable to understand the questionnaires. Patients were allowed to receive help from proxies in completing the questionnaires. Approval from the medical ethic committee Arnhem-Nijmegen (reference number: 2020-6349) and written informed consent from each patient was obtained. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[13]

Outcome measures

Primary outcomes included prevalence and extent of frailty and functional dependency. To asses (potential) frailty the following screening tools were selected: Geriatric Eight (G8), the Groningen Frailty Index (GFI) and the Clinical Frailty Scale (CFS), based on psychometric properties and feasibility in daily clinical practice.[11,14-18] The G8 is administered by a healthcare provider and consists of eight items, scores can range from 0 (heavily impaired) to 17 points (not at all impaired). The cut-off point determining frailty lies at ≤14.[19] The GFI is filled in by the patient and consists of 15 questions, scores can range from 0 till 15. The cut-off point for frailty is reached at GFI ≥4.[20] The CFS is a 9-point scale ranging from very fit (1) to terminally ill (9), which is commonly used to determine frailty in clinical practice. It is not a questionnaire but a summary of the level of frailty after clinical evaluation by a healthcare provider.[21] Patients with a CFS ≥5 are considered frail. Functional dependency was measured using the Activities of Daily Living (ADL) and instrumental Activities of Daily Living (iADL) tools, which are commonly referred to as the Katz and Brody-Lawton indices.[22,23] Patients were considered ADL-dependent if unable to perform ≥1 ADL activity independently, iADL-dependent if unable to perform ≥1 iADL activity independently.[24] To further specify functional dependency regarding psoriasis management, additional questions were added following a literature review and a research group brainstorming session **(Table 2)**.

Secondary outcomes were implications of frailty and functional dependency for psoriasis management, including the need for treatment assistance, treatment satisfaction, and treatment burden. The need for treatment assistance was assessed using a multiple choice question (yes/no). Treatment satisfaction was evaluated using the Treatment Satisfaction Questionnaire for Medication (TSQM) version II.[25] The

TSQM consists of four domains: effectiveness, side effects, convenience, and global satisfaction. Scores range from 0 to 100, higher scores indicating greater satisfaction. An official threshold for TSQM-scores has not yet been established. Therefore, in consultation with the TSQM-developer (M. Atkinson), we chose a threshold of ≥65 ('satisfied') per domain which corresponds with being 'satisfied', 'very satisfied', and 'extremely satisfied', indicative of treatment satisfaction. To assess possible implications of frailty and functional dependency, the difference on TSQM domains for frail versus non-frail, and functional dependent versus functional independent patients was assessed. Only the TSQM domains 'global satisfaction', 'convenience', and 'side-effects' were used, as we did not expect effectiveness of psoriasis therapy to be influenced by frailty or functional dependency. To measure treatment burden, a patient-reported Visual Analogue Scale (VAS) was used ranging from 0-10. A higher score indicates a greater treatment burden as perceived by the patient.

Comorbid disease status was calculated using the Charlson Comorbidity Index (CCI).[26,27] Polypharmacy was defined as the simultaneous use of ≥5 medications.[28] Disease severity was measured using the Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), Patient Global Assessment (PGA), Investigator Global Assessment (IGA), and a VAS score for disease severity.[29]

Data collection

Patients were informed about the study and asked for informed consent by the research physician (EtH). During the study visit, patients were asked to fill in the patient-reported outcomes (GFI, ADL/iADL, VAS, PGA, DLQI, and TSQM) and the research physician (EtH) filled in the physician-reported outcomes (G8, CFS, PASI, and IGA). Data was pseudonymized and coded in CASTOR Electronic Data Capture, a secure web-based data management application (Castor Research Inc., Hoboken, NJ, USA) which is in compliance with Good Clinical Practice and relevant legislations.

Statistical analyses

Based on existing literature and daily practice experience combined with our study aim, inclusion of 50 patients per center (100 patients in total) was strived for. Data were summarized using descriptive statistics. Categorical data were presented as frequencies/percentages. Continuous variables were presented as mean with standard deviation (SD) or median with ranges, depending on the distribution. Comparisons with continuous variables were conducted using Mann-Whitney U-test and Kruskal-Wallis test. The chi-square or Fisher's exact test was used for comparing categorical variables. Missing values were not included in the analyses. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 27.0 (IBM, Armonk, NY, USA).

Results

A total of 102 patients was enrolled from July 2020-September 2022, with a mean age of 72.8±5.2 years. Polypharmacy (n=56;61.5%) and multimorbidity (mean CCI 2.08±2.15) were common. Disease severity based on PGA was mostly rated as mild (n=37;36.6%). Full results are shown in **Table 1**.

Table 1. Patient and disease characteristics of older adults with psoriasis.

	Patients (n=102)
Age (years), mean ± SD	72.8 ± 5.23
median, range	72.0 (65 – 86)
Sex, n (%), male	64 (62.7)
Type of medical center, n (%)	54 (52.9)
Academic medical center	48 (47.1)
General hospital	
Use of co-medication, n (%)	88 (86.3)
Polypharmacy[a]	56 (61.5)
Comorbidity/medical history, n (%)	96 (94.1)
None	43 (43.4)
Overweight (BMI ≥25), n (%)	28 (28.3)
Obesity (BMI ≥30), n (%)	51 (50.0)
Hypertension	40 (39.2)
Hyperlipidemia	15 (14.7)
Myocardial infarction	5 (4.9)
Heart failure	19 (18.6)
Cerebral vascular accident	23 (22.5)
Diabetes mellitus	27 (26.5)
Cancer[b]	3 (11.1)
Metastatic	22 (21.6)
Skin cancer[c]	21 (20.6)
Depression	
Charlson Comorbidity Index[d], mean ± SD	2.08 ± 2.15
median (range)	2 (0 – 14)
Current type(s) of psoriasis, n (%)	96 (94.1)
Plaque psoriasis	51 (50.0)
Psoriasis capitis	30 (29.4)
Genital/inverse psoriasis	5 (4.9)
Guttate psoriasis	14 (13.7)
Palmoplantar	36 (35.3)
Nail psoriasis	9 (8.8)
Psoriatic arthritis	
PASI, mean ± SD	3.24 ± 2.44
median (range)	2.80 (0 – 11.7)
PGA[e] (0-5), mean ± SD	1.96 ± 1.11
median (range)	2.00 (0 – 5)

Table 1. Continued

	Patients (n=102)
IGA[e] (0-5), mean ± SD median (range)	1.74 ± 0.92 2 (0 – 4)
VAS (0-10)[f] Disease severity, mean ± SD median (range)	2.83 ± 2.24 4 (0 – 10)
DLQI, mean ± SD median (range)	3.27 ± 3.72 2.00 (0 – 21)

Values might not add up due to missing values and combination of variables. Missings per variable: BMI: n=3, DLQI: n=1, PASI: n=1, PGA/IGA: n=1, VAS disease severity: n=1.

[a] Polypharmacy was defined as the simultaneous use of ≥5 medications.

[b] All types of cancer excluding keratinocyt carcinoma.

[c] All types of skin cancer.

[d] The CCI consists of 17 comorbidities. For each comorbidity a separate weight was assigned.[23,24]

[e] The PGA and IGA is a 6-point scale used to measure the severity of disease at the time of the evaluation: 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), 5 (very severe).

[f] This is a single-item measure assessing patients perceived disease severity on a scale of 0 to 10.

BMI:, Body Mass Index; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; SD: standard deviation. PGA: Patient Global Assessment, IGA: Investigator Global Assessment; VAS: Visual Analogue Scale.

Treatment assistance, treatment satisfaction and treatment burden

Topical monotherapy was mostly frequently used (n=48; 47.1%), followed by systemic treatment (n=47; 46.1%), and UV-therapy (n=6; 5.9%). Of all patients, 27/102 (27.0%) indicated that they need help with applying/using psoriasis treatment. TSQM scores including all treatments (topical, UV-therapy, and systemic therapy) indicated that patients were satisfied with treatment's effectiveness (median 67, range 0-100), convenience (median 67, range 17-100), global satisfaction (median 67, range 17-100), and side effects (median 100, range 33-100) domains. The VAS treatment burden showed a low and comparable (p=0.888) treatment burden for topical monotherapy (mean 1.87±2.89), UV-therapy (mean 1.67±2.66), and systemic therapy (mean 1.35±2.55). All results are shown in **Table 2**.

Table 2. Treatment characteristics of older adults with psoriasis.

	Patients (n=102)
Current treatment type(s)[a], *n (%)*	
Topical monotherapy	48 (47.1)
UV-therapy	6 (5.9)
Systemic	47 (46.1)
Conventional systemic	26 (25.5)
Methotrexate	13 (12.7)
Dimethyl fumarate	8 (7.8)
Acitretin	7 (6.9)
Biologic/apremilast	21 (20.6)
Biological	20 (19.6)
Apremilast	1 (1.0)
No treatment	1 (1.0)
Need help with psoriasis treatment, yes, *n (%)*	27 (27.0)
Need help with topical treatment, yes, *n (%)*	23 (23.2)
Need help with systemic treatment, yes, *n (%)*	4 (4.0)
Need help to come to the hospital, yes, *n (%)*	10 (9.9)
TSQM all treatment types (0-100)	
Global satisfaction, mean ± SD	64.43 ± 18.00
median (range)	66.66 (16.67 – 100)
Convenience, mean ± SD	69.85 ± 15.25
median (range)	66.66 (16.67 – 100)
Side effects, mean ± SD	92.28 ± 15.01
median (range)	100 (33.33 – 100)
Effectiveness, mean ± SD	62.2 ± 21.40
median (range)	66.66 (0 – 100)
TSQM systemic therapy (0-100)	
Global satisfaction, mean ± SD	69.29 ± 19.29
median (range)	70.83 (16.67 – 100)
Convenience, mean ± SD	73.09 ± 18.38
median (range)	72.22 (16.67 – 100)
Side effects, mean ± SD	89.86 ± 14.18
median (range)	100 (58.33 – 100)
Effectiveness, mean ± SD	68.86 ± 20.92
median (range)	66.66 (8.33 – 100)
VAS (0-10)[b]	
Treatment burden all treatment types, mean ± SD	1.62 ± 2.70
median (range)	0 (0 – 9.1)
Treatment burden topical monotherapy, mean ± SD	1.87 ± 2.89
median (range)	0 (0 – 9.0)
Treatment burden UV-therapy, mean ± SD	1.67 ± 2.66
median (range)	0 (0 – 6.0)
Treatment burden systemic therapy, mean ± SD	1.35 ± 2.55
median (range)	0 (0 – 9.1)

Values might not add up due to missing values and combination of variables.

Missings per variable: need help with psoriasis treatment: n=2, need help to come to the hospital: n=1, TSQM effectiveness: n=20, TSQM side effects: n=21. TSQM convenience: n=20, TSQM global satisfaction: n=20, VAS treatment burden: n=16.

[a] Patients could use different types of psoriasis treatment at the same time.

[b] This is a single-item measure assessing patients perceived treatment burden on a scale of 0 to 10.

TSQM: Treatment Satisfaction Questionnaire for Medication; SD: standard deviation; VAS: Visual Analogue Scale.

Frailty and functional dependency

Frailty assessment showed that 42.2% (n=43) and 26.0% (n=25) of patients were considered frail according to the G8 and the GFI respectively. According to the CFS, 20.6% (n=21) of patients were considered vulnerable and 13.7% (n=14) was considered mildly to severely frail. A total of 52 (51%) patients were classified as frail by at least one of three frailty tools. Only six patients were frail according to all frailty screening tools. **Supplemental Figure 1** provides an overview of the overlap in frailty classification by the screening tools used. Furthermore, 14.3% of patients were ADL-dependent and 37.6% iADL-dependent. Results in **Table 3** and **supplemental Table 1**.

Table 3. The prevalence and extent of frailty and functional dependency in older adults with psoriasis.

	Patients (n=102)
G8 (0-17), mean ± SD	14.6 ± 1.7
median (range)	15 (10 – 17)
frail (score ≤14), *n (%)*	43 (42.2)
not frail (score >14), *n (%)*	59 (57.8)
GFI (0-15), mean ± SD	2.59 ± 2.2
median (range)	2.00 (0 – 9)
frail (score ≥4), *n (%)*	26 (26.0)
not frail (score <4), *n (%)*	74 (74.0)
CFS (1-9)	14 (13.7)
frail (≥5), *n (%)*	88 (86.3)
not frail (<5), *n (%)*	6 (5.9)
Very fit, *n (%)*	40 (39.2)
Well, *n (%)*	21 (20.6)
Managing well, *n (%)*	21 (20.6)
Vulnerable, *n (%)*	11 (10.8)
Mild frail, *n (%)*	2 (2.0)
Moderately frail, *n (%)*	1 (1.0)
Severely frail, *n (%)*	0 (0)
Very severely frail, *n (%)*	0 (0)
Terminally ill, *n (%)*	
ADL dependent, *n (%)*	15 (14.9)
iADL dependent, *n (%)*	38 (37.6)

Values might not add up due to missing values and combination of variables. Missings per variable: GFI: n=2, (i)ADL: n=1.

G8: Geriatric 8; GFI: Groningen Frailty Index; CFS: Clinical Frailty Scale; (i)ADL: (instrumental) Activities of Daily Living; SD: standard deviation.

Implications of frailty and functional dependency for psoriasis management

Needing help with applying/using psoriasis treatment was more common in frail patients versus non-frail patients defined by the G8 (41.5% vs. 16.9%; p=0.007) and CFS (57.1% vs. 22.1%; p=0.019), but not in frail patients compared to non-frail patients defined by the GFI (40.0% vs. 21.9%; p=0.077) (**Table 4)**. In ADL-dependent patients, needing help with psoriasis treatment was more common versus ADL-independent patients (53.3% vs. 21.4%; p=0.021). No significant difference was observed regarding needing help with psoriasis treatment among iADL-dependent/independent patients **(Table 5)**.

Regarding treatment satisfaction, frail patients as classified by the CFS were less often satisfied on the TSQM domains 'global satisfaction' (20.0% vs. 68.1%; p=0.005) and 'side effects' (60.0%. vs. 95.8%; p=0.004) compared to non-frail patients. Likewise, patients considered frail according to the GFI were significantly less often satisfied with the 'side effects' domain, versus non-frail patients (GFI: 75.0% vs. 96.7%; p=0.009) **(Table 4)**. ADL-dependent patients were also less often satisfied with the 'side effects' domain of the TSQM, compared to ADL-independent patients (71.4% vs. 95.5%; p=0.015). No significant differences regarding treatment satisfaction amongst iADL-dependent/independent patients was seen **(Table 5)**. Comparison of frail/non-frail and functional dependent/functional independent patients showed no significant differences regarding perceived treatment burden **(Table 4 and Table 5)**.

Table 4. Implications of frailty for psoriasis management, including the need for treatment assistance, treatment satisfaction and treatment burden.

	G8 frail (n=43)	G8 not frail (n=59)	*p-value*	GFI frail (n=26)	GFI not frail (n=74)	*p-value*	CFS frail (n=14)	CFS not frail(n=88)	*p-value*
Patients needing help with psoriasis treatment									
Yes, *n (%)*	17/41 (41.5)	10/59 (16.9)	*0.007*	10/25 (40.0)	16/73 (21.9)	0.077	8/14 (57.1)	19/86 (22.1)	*0.019*
TSQM global satisfaction									
Median (range)	66.7 (33.3 – 100)	66.7 (16.7 –100)		66.7 (33.3 – 100)	66.7 (16.7 – 100)		58.3 (33.3 – 83.3)	66.7 (16.7 – 100)	
Mean ± SD	63.4 ± 17.4	65.1 ± 18.5		65.8 ± 14.5	64.0 ± 19.1		55.0 ± 14.3	65.7 ±18.2	
Satisfied, *n (%)*	18/33 (54.5)	33/49 (67.3)	0.241	12/20 (60.0)	39/62 (62.9)	0.816	2/10 (20.0)	49/72 (68.1)	*0.005*
TSQM convenience									
Median (range)	66.7 (40.0 – 100)	66.7 (16.7 –100)		66.7 (38.9 – 100)	66.7 (16.7 – 100)		69.4 (38.9 – 83.3)	66.7 (16.7 – 100)	
Mean ± SD	70.4 ± 14.3	69.5 ± 16.0		71.7 ± 12.2	69.3 ± 16.1		66.1 ± 15.4	70.4 ± 15.3	
Satisfied, *n (%)*	25/33 (75.8)	40/49 (81.6)	0.584	18/20 (90.0)	47/62 (75.8)	0.219	8/10 (80.0)	57/72 (79.2)	1.000
TSQM side effects									
Median (range)	100 (33.3 – 100)	100 (33.3 – 100)		100 (33.3 – 100)	100 (58.3 – 100)		91.7 (33.3 – 100)	100 (33.3 – 100)	
Mean ± SD	89.8 ± 17.4	93.9 ± 13.2		84.6 ± 22.8	94.8 ± 10.4		79.2 ± 24.6	94.1 ± 12.3	
Satisfied, *n (%)*	27/32 (84.4)	47/49 (95.9)	0.107	15/20 (75.0)	59/61 (96.7)	*0.009*	6/10 (60.0)	68/71 (95.8)	*0.004*
Treatment burden (VAS)									
Median (range)	0 (0 – 9.0)	0 (0 – 9.1)	0.688	0 (0 – 9.1)	0 (0- 8.0)	0.447	0 (0 – 9.1)	0 (0 – 9.0)	0.730
Mean ± SD	1.7 ± 3.0	1.5 ± 2.5		2.2 ± 3.5	1.5 ± 2.4		1.4 ± 3.0	1.7 ± 2.7	

Values might not add up due to missing and combinations of variables.

G8: Geriatric 8; GFI: Groningen Frailty Index; CFS: Clinical Frailty Scale; SD: standard deviation; TSQM: Treatment Satisfaction Questionnaire for Medication; VAS: Visual Analogue Scale.

Table 5. Implications of functional dependency for psoriasis management, including the need for treatment assistance, treatment satisfaction and treatment burden. Values might not add up due to missing and combinations of variables.

	ADL dependent (n=15)	**ADL independent (n=86)**	***p-value***	**iADL dependent (n=38)**	**iADL independent (n=63)**	***p-value***
Patients needing help with psoriasis treatment						
Yes, *n (%)*	8/15 (53.3)	18/84 (21.4)	*0.021*	10/38 (26.3)	16/61 (26.2)	0.992
TSQM Global satisfaction						
Median (range)	62.5 (25.0 – 83.3)	66.7 (16.7 – 100)		66.7 (25.0 – 100)	66.7 (16.7 – 100)	
Mean ± SD	56.5 ± 19.9	66.1 ± 17.3		67.2 ± 18.5	62.6 ± 17.6	
Satisfied, *n (%)*	7/14 (50.0)	44/68 (64.7)	0.301	20/33 (60.6)	31/49 (63.3)	0.821
TSQM Convenience						
Median (range)	66.7 (38.9 – 88.9)	66.7 (16.7 – 100)		72.2 (22.2 – 100)	66.7 (16.7 – 100)	
Mean ± SD	69.0 ± 11.9	70.0 ± 15.9		72.6 ± 15.6	68.0 ± 14.9	
Satisfied, *n (%)*	12/14 (85.7)	53/68 (77.9)	0.723	28/33 (84.8)	37/49 (75.5)	0.306
TSQM Side effects						
Median (range)	100 (58.3 – 100)	100 (33.3 – 100)		100 (58.3– 100)	100 (33.3 – 100)	
Mean ± SD	85.7 ± 18.9	93.7 ± 13.8		91.7 ±14.0	92.7 ± 15.8	
Satisfied, *n (%)*	10/14 (71.4)	64/67 (95.5)	*0.015*	29/33 (87.9)	45/48 (93.8)	0.435
Treatment burden (VAS)						
Median (range)	0.4 (0 – 6.0)	0.0 (0 – 9.1)	0.717	0 (0 – 8.0)	0 (0 – 9.1)	0.280
Mean ± SD	1.3 ± 2.2	1.7 ± 2.8		1.4 ± 2.7	1.8 ± 2.7	

SD: standard deviation;; (i)ADL: (instrumental) Activities of Daily Living; TSQM: Treatment Satisfaction Questionnaire for Medication; VAS: Visual Analogue Scale.

Discussion

Management of psoriasis in the growing group of older adults can be challenging due to comorbidity, comedication, and functional and physical deterioration. Sparse evidence-based guidance is available to assist clinicians in making treatment decisions in this patient group. Furthermore, age alone has been shown to be often insufficient to predict treatment feasibility and outcomes in other fields of medicine. The aim of this study was to assess the prevalence and extent of frailty and functional dependency in older adults with psoriasis and their implications for psoriasis management. In this study, frailty and functional dependency were common. Patients considered frail or functionally dependent require assistance with psoriasis treatment more often than non-frail/functional independent patients. Overall, lower treatment satisfaction scores were observed among frail and functional dependent patients.

In this real-world study on 102 patients ≥65 years, frailty was common, although important differences were found between the different frailty screening tools. Frailty was found in 42.2%, 26.0%, and 13.7% of patients according to the G8, GFI, and CFS, respectively. Even though the gold standard to detect frailty is a comprehensive geriatric assessment, multiple frailty screening tools have been developed as a less time-consuming alternative and more feasible work-up in daily clinical practice.[30] In this study three generally accepted and extensively studied frailty screening tools were selected based on psychometric properties and daily practice feasibility. Limited overlap in frailty classification was observed among the different screening tools, which is also seen in other studies.[31,32] This can be explained by variations in the construct to be measured and the intended objective for which the tools were designed. Besides frailty, functional dependency was also prevalent among older patients with psoriasis, with 14.3% requiring assistance with activities of daily living (ADL) and 37.6% needing assistance with instrumental activities of daily living (iADL).

Comparison of the prevalence of frailty and functional dependency with other studies is challenging due to discrepancies in definitions, methods and age-limits.[33] Population studies among community-dwelling older adults indicate that 13-32% of people aged >65 years are considered frail according to the GFI, which is comparable with the findings in this study. [11,34] Studies assessing frailty using the CFS show higher rates (28-54.3%) of frailty compared to our study results, but the investigated populations differed significantly (e.g. community-dwelling older adults (≥65 years) in receipt of home support, community-dwelling older adults

(≥65 years) including those living in supervised accommodation, and hospital admitted burn patients (≥50 years).[35-37] In addition, based on these CFS outcomes we hypothesise that older adults with psoriasis who visit a dermatologist might have a better health status and are less frail compared to patients who may not seek consultation by a dermatologist as their psoriasis holds a lower priority compared to other health issues and/or due to logistical (im)possibilities (e.g. the burden of a hospital visit). The G8 is primarily applied to assess frailty among cancer patients, making literature on this questionnaire less comparable to our study population.[32,38,39] Regarding functional dependency, studies focusing on community-dwelling older adults in western countries report a broad range of ADL-dependency (11.0-36.2.%) and iADL-dependency (11.0-44.0%) rates.[40-42] With regards to our study population, ADL and iADL-dependency rates align with the previously mentioned range.

Since the population of older adults can be highly heterogenous, treatment decision-making based on chronological age alone is often inadequate.[8,43,44] Research from other medical fields has shown that frailty increases the risk of adverse outcomes in patients undergoing medical interventions.[45] Encompassing frailty and functional dependency has been shown to support medical decision-making in various older patients populations.[9] In this study, the possible management implications of being frail and functionally dependent in a daily practice population of older adults with psoriasis were assessed. Approximately one fourth (27%) of the study population required help with applying or using psoriasis treatment, which is a higher amount than previously reported among older adults with psoriasis (n=56; 14.9%).[3] Importantly, patients classified as frail according to the G8 and CFS and/or patients who were ADL-dependent needed significantly more often help with their psoriasis therapy. Furthermore, frail patients were either overall less often satisfied with their psoriasis treatment (frail according to CFS) or less often satisfied about the side-effects related to their psoriasis treatment (frail according to GFI and CFS). In this study, the experienced treatment burden was low, and there were no significant differences in treatment burden between frail/non-frail and functional dependent/functional independent patients. In conclusion, the CFS shows promise to use in treatment decision-making, since it detected the most treatment implications in this study. Further research focusing on the consequences of daily practice implementation of the CFS (e.g. prediction of treatment-related outcomes) among older adults with psoriasis on a larger scale could be beneficial. The GFI, G8 and the functional dependency measures ((i)ADL)) seem less suitable to use in the treatment decision-making process, given the fact that fewer consequences in treatment implications were detected.

As previously mentioned, a limitation of this study is the relatively small sample size. Furthermore, since variations among the frailty screening tools used in this study were observed, comparisons with a comprehensive geriatric assessment as the established golden standard would have been of added value. Nonetheless, with this study we provided a first overview of the prevalence and extent of frailty and functional dependency in a geriatric psoriasis population in a multicenter setting.

Conclusion

To conclude, frailty and functional dependency in older adults (≥65 years) with psoriasis are common but vary depending on the tool used for identification. Needing help with psoriasis treatment and lower treatment satisfaction scores were more common among frail and functionally dependent patients. Of the included screening tools the CFS seems most promising for treatment decision-making and detection of patients where implications for management are expected. Future larger-scale research focusing on the consequence of daily practice implementation of the CFS is suggested.

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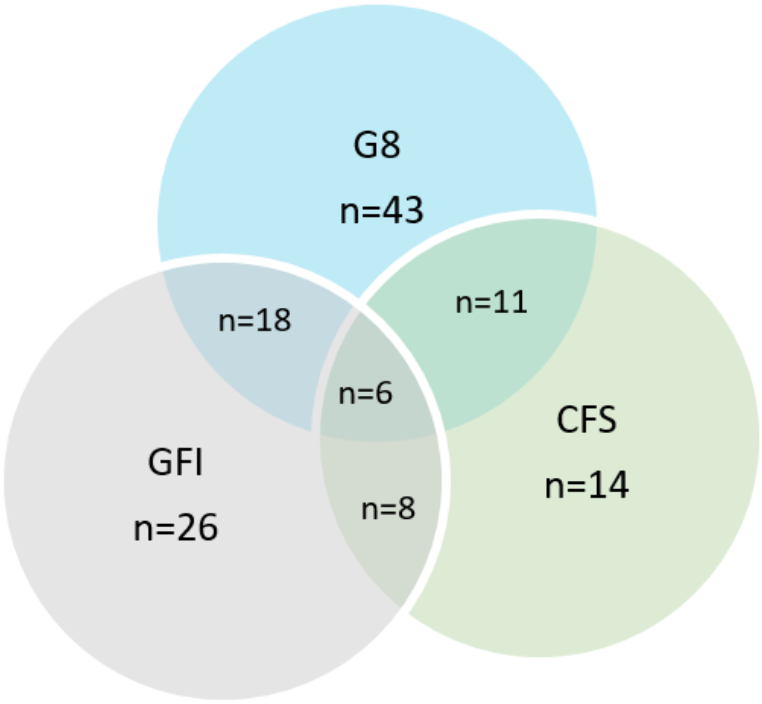
Supplemental figure and table



Supplemental Figure 1. Venn diagram showing the overlap of the classification of frailty, as scored by the three different frailty screening tools used in this study (G8, GFI, CFS), depicting a low overlap of the screening tools.

n= number of patients considered frail according to the frailty screening tool.
G8**:** Geriatric 8; GFI**:** Groningen Frailty Index; CFS**:** Clinical Frailty Scale.

Supplemental Table 1. Overview of frailty and functional dependency in older adults with psoriasis, including all sub-items of the different tools used.

	Patients (n=102)
G8 (0-17), mean ± SD	14.6 ± 1.69
median (range)	15 (10 – 17)
frail (score ≤14), *n (%)*	43 (42.2)
Not frail (score >14), *n (%)*	59 (57.8)
G8 categories, *n (%)*	
Food intake during the last three months	
Severe decrease in food intake	2 (2.0)
Moderate decrease in food intake	12 (11.8)
No decrease in food intake	88 (86.3)
Weight loss during the last three months	
>3 kg	8 (7.8)
1-3 kg	13 (12.7)
Does not know	1 (1.0)
No weight loss	80 (78.4)
Mobility	
Bed or chair bound	0 (0.0)
Does not go out/ is able to get out of bed/chair	3 (2.9)
Goes out	99 (97.1)
Neuropsychological	
Severe dementia or depression	0 (0.0)
Mild dementia or depression	20 (19.6)
No psychological problems	82 (80.4)
Body Mass Index BMI	
< 19	1 (1.0)
19 ≤ BMI < 21	2 (2.0)
21 ≤ BMI < 23	3 (2.9)
BMI ≥ 23	96 (94.1)
Medication use >3	
Yes	69 (67.6)
No	33 (32.4)
Health status in comparison to other people of same age	
Not as good	18 (17.6)
Does not know	10 (9.8)
As good	23 (22.5)
Better	51 (50.0)
Age	
0 = > 85	1 (1.0)
1 = 80 – 85	12 (11.8)
2 = < 80	89 (87.3)
Additional question not originally in G8	
Falling in last 6 months, *yes, n (%)*	20 (19.6)
GFI (0-15), mean ± SD	2.59 ± 2.16
median (range)	2.00 (0-9)
frail (score ≥4), *n (%)*	26 (26.0)
Not Frail (score <4), *n (%)*	74 (74.0)
GFI categories	
Mobility, yes, n (%)	
Grocery shopping	97 (96.0)
Walk outside house (around house or to neighbour)	100 (99.0)
Getting (un)dressed	101 (100)
Visiting restroom	100 (100)

Supplemental Table 1. Continued

	Patients (n=102)
Vision, yes, n (%)	
Problems in daily life because of impaired vision	9 (8.9)
Hearing, yes, n (%)	
Problems in daily life because of impaired hearing	20 (19.8)
Nutrition,yes, n (%)	
Unintentionally lost a lot of weight last 6 months	6 (5.9)
Comorbidity, yes, n (%)	
Use of =>4 different types of medication	58 (57.4)
Cognition, yes, n (%)/ sometimes, n (%)	
Do you experience memory loss	5 (5.0)/42 (41.6)
Psychosocial, yes, n (%)/ sometimes, n (%)	
Do you experience emptiness	6 (5.9)/ 19 (18.8)
Do you miss the presence of other people around	8 (8.0)/ 23 (23.0)
Do you feel left alone	0 (0.0)/ 16 (16.0)
Do you feel down or depressed	10 (10.0)/ 25 (25.0)
Do you feel nervous or anxious	9 (8.9)/ 18 (17.8)
Physical fitness score (0-10), mean ± SD	7.06 ± 1.59
median (range)	7.06 (2- 10)
Rate of physical fitness reduced (0-6), *n (%)*	32 (32.0)
Rate of physical fitness (7-10), *n (%)*	68 (68.0)
CFS (1-9)	
Frail (≥5), *n (%)*	14 (13.7)
Not frail (<5), *n (%)*	88 (86.3)
Very fit, *n (%)*	6 (5.9)
Well, *n (%)*	40 (39.2)
Managing well, *n (%)*	21 (20.6)
Vulnerable, *n (%)*	21 (20.6)
Mild frail, *n (%)*	11 (10.8)
Moderately frail, *n (%)*	2 (2.0)
Severely frail, *n (%)*	1 (1.0)
Very severely frail, *n (%)*	0 (0)
Terminally ill, *n (%)*	0 (0)
Needing help with applying topical treatment, yes, *n (%)*	23 (23.0)
Needing help with systemic treatment, yes, *n (%)*	4 (4.0)
Needing help to come to the hospital, yes, *n (%)*	10 (9.9)
ADL dependent, *n (%)*	15 (14.9)
Bathing	1 (1.0)
Dressing	1 (1.0)
Toileting	0 (0.0)
Transferring/ambulating	0 (0.0)
Continence	15 (14.9)
Feeding	1 (1.0)
iADL dependent, *n (%)*	38 (37.6)
Telephoning	0 (0.0)
Shopping	7 (6.9)
Food preparation	6 (6.0)
Housekeeping	1 (1.0)
Laundry	25 (24.8)
Transportation (own vehicle or public transportation)	2 (2.0)
Managing medications	9 (8.9)
Managing finances	9 (8.9)

Values might not add up due to missing values and combination of variables.

G8: Geriatric 8; GFI: Groningen Frailty Index; CFS: Clinical Frailty Scale; (i)ADL: (instrumental) Activities of Daily Living; BMI: Body Mass Index; SD: standard deviation.

Chapter 3

Safety and effectiveness of systemic treatment in older adults with psoriasis

Chapter 3.1

Safety assessment of conventional and biological systemic therapy in older adults with psoriasis, a real-world multicentre cohort study

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Abstract

Optimal selection of systemic therapy in older adults with psoriasis can be challenging, due to sparse evidence-based guidance. This multicentre retrospective study investigated the safety of systemic therapy with causality assessment in a real-world cohort of older adults (≥ 65 years) with psoriasis. Data from 6 hospitals on (serious) adverse events were collected, causality assessment performed and incidence rate ratios calculated. Potential predictors for adverse events-occurrence were studied using multivariable logistic regression analysis. In total, 117 patients with 176 treatment episodes and 390 patient-years were included, comprising 115 (65.3%) and 61 (34.7%) treatment episodes with conventional systemic therapy and biologics/apremilast, respectively. After causality assessment, 232 of 319 (72.7%) adverse events remained and were analysed further, including 12 serious adverse events. No significant differences in incidence rate ratios were found between the systemic treatment types. In regression analysis, increasing age was associated with causality assessed adverse events-occurrence (odds ratio 1.195; p=0.022). Comorbidity, polypharmacy, and treatment type were not associated with causality assessed adverse events-occurrence. In conclusion, increasing age was associated with a higher causality assessed adverse events-occurrence. Causality assessed serious adverse events were rare, reversible and/or manageable in clinical practice. In conclusion, the safety profile of systemic antipsoriatic therapy within this population is reassuring.

Significance

Selecting systemic therapy in older adults with psoriasis is challenging due to sparse evidence-based guidance. To investigate the safety of systemic therapy in older adults (≥ 65 years), a multicentre retrospective cohort study was conducted including causality assessment of adverse events. In this study, increasing age was associated with more causality assessed adverse events, while no association was found between comorbidity, polypharmacy and treatment type (fumarates, acitretin, methotrexate or biologicals) with causality assessed adverse event occurrence. Serious adverse events were uncommon, reversible and/or manageable in clinical practice. Therefore, the safety profile of systemic therapy within this cohort of older adults is reassuring.

Introduction

Psoriasis is a chronic inflammatory skin disease, prevalent in older adults (aged ≥ 65 years).[1-3] Due to the rapidly ageing world population, dermatologists will increasingly be confronted with this patient group. The chronic nature of psoriasis often requires patients to use antipsoriatic treatments for extended periods. Selecting the best treatment for older adults with psoriasis can be challenging and depends on the safety profile of the treatment, disease severity, comorbidity, co-medication, functional status, impact on quality of life, and patient preferences.[4-6]

Literature on this growing population is scarce, since older adults are often excluded from clinical trials.[7,8] Furthermore, conflicting results have been reported regarding treatment safety, implicating that much is still unknown in this population.[9-11] In addition, data regarding adverse events (AEs) can be difficult to interpret in any population, but especially in older adults, in whom multimorbidity and co-medication use are highly prevalent.[12] This might result in an overestimation of AE-occurrence in older adults compared with younger or healthier populations.[13] Therefore, causality assessment of AEs is key when interpreting data regarding AEs.[14]

Previous research shows that the use of systemic antipsoriatic therapy regularly differs between age groups, even though only minor differences in clinical characteristics are reported.[13,15-19] This finding could potentially be explained by a higher prevalence of certain contraindications (comorbidity and co-medication use) for systemic antipsoriatic treatment. Another suggested potential explanation for this finding is a possible reluctance amongst physicians to prescribe systemic treatment for psoriasis in older adults, which might be caused by the above-mentioned sparse evidence-based guidance available.[18]

Therefore, the aim of this study was to gain a greater understanding of treatment safety in older adults with psoriasis using systemic antipsoriatic therapy in a real-world cohort.

Methods

Study design and participants

A multicentre retrospective cohort study was performed to assess disease and treatment patterns in older adults (≥ 65 years) with psoriasis (Geriatric Psoriasis Patterns (GEPPA) study). Relevant parameters for this study were gathered from a literature review, a previous survey, and multidisciplinary brainstorm sessions.[15]

All patients were diagnosed with psoriasis by a dermatologist and treated in 1 of the 6 participating centres in the Netherlands: 1 academic medical centre (Radboud University Medical Centre, Nijmegen), 4 general hospitals (Gelderse Vallei Hospital, Ede; Canisius-Wilhelmina Hospital, Nijmegen; Bernhoven Hospital, Uden; Rijnstate Hospital, Arnhem) and 1 private practice (Padberg Clinic, Ede). In the current study only treatment episodes (TEs) of patients using systemic therapy for psoriasis were included (conventional systemic [methotrexate, dimethyl fumarate, acitretin, ciclosporin] and biological/apremilast therapies). One TE accounted for 1 continuous episode of a specific systemic antipsoriatic therapy. Approval from the medical ethics committee Arnhem-Nijmegen (reference number: 2019-5904) and written informed consent from each patient were obtained. Patients were chronologically included based on their last visit, starting from 1 January 2019, using a web-based data management system (see also **Appendix S1**).

Outcome measures

Various patient characteristics were collected, including comorbid disease status using the International Classification of Diseases – 10th Revision (ICD-10) version of the Charlson Comorbidity Index (CCI), co-medication use, and presence of polypharmacy.[20,21] The following comorbidities of interest were also separately classified: skin cancer, depression, hypertension, hyperlipidaemia, overweight, obesity and cardiovascular disease. To assess treatment patterns, the current use of systemic therapy, and TEs were collected from the age of 65 years, including: treatment duration, AE-occurrence and reasons for treatment discontinuation.

Adverse events and causality assessment

An AE was defined as any undesirable medical event of significant nature during antipsoriatic treatment. An AE was classified as serious AE (SAE) when a patient needed hospitalization, had persistent or significant disability/incapacity, and occurrence of life-threatening conditions or death (22). AEs were independently assessed on causality by 3 physician-researchers (SL, EtH, LvS) using the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment system[23] and clinical experience, followed by a consensus meeting. AEs scored < 3 using the WHO-UMC assessment system were excluded from further analysis and AEs scored as ≥ 3 using the WHO-UMC assessment system, remained included, further mentioned as causality assessed AEs (caAEs). From the available TEs, incidence rate ratios (IRR) of caAEs per year for the selected systemic therapy were computed. More details are shown in **Appendix S1**.

Statistical analyses

Descriptive analyses were performed to summarize data. Categorical data were presented as frequency/percentages. Continuous variables were presented as mean/standard deviation (SD) or median/range, when applicable. To indicate the representativeness of the study population, a comparison with other psoriasis cohorts including older adults was performed on age and sex distribution using a $\chi 2$ test and an independent T-test.[10,15,24] To analyse the IRRs of caAEs per year, negative binomial models were used. In addition, a similar analysis was performed including all AEs without selecting for caAEs only. To explore the potential relationship between age, comorbidity and AE-occurrence on current systemic treatments, and to correct for confounding variables, multivariable logistic regression analysis was performed with caAEs only, and a sensitivity analysis was performed including all reported AEs (see also **Appendix S1**). Missing values were not included in the analyses. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM, Armonk, NY, USA) and for the negative binomial analysis R (version 3.6.3) and the lme4 library (version 1.1–21) were used.[25]

Results

Study participants

In total, 117 patients with 176 TEs of systemic antipsoriatic therapy were included between 19 May 2020 and 6 March 2021: 85 (72.6%) from an academic centre and 32 (27.4%) from general hospitals/private practices. The median age at onset of psoriasis was 43.5 (range 8–79) years. Patient demographics are shown in **Table 1**. Comparison of our complete study cohort with previously described psoriasis cohorts including older adults showed that the age and sex distribution was highly comparable, indicating representativeness regarding these characteristics **(Table S1)**. The 176 TEs comprised a cumulative follow-up of 390 patient-years. Conventional systemic therapy (TE 115, 65.3%) was more often used than biologics/apremilast (TE 61; 34.7%), depicted in **Table 2**. Regarding previously used systemic therapy, 68.3% of the included patients had used more than one systemic antipsoriatic therapy previously.

Comorbidity and co-medication use

Data regarding comorbidity and body mass index (BMI) was available for 100 patients (85.5% of the total cohort) and 78 patients (66.7% of the total cohort), respectively. From these 100 patients most had 1 or more comorbid condition(s) (n = 88; 88.0%), 12% (n = 12) of patients had no comorbidity. Being overweight (n = 59; 75.6%) and hypertension (n = 47; 47.0%) were most frequently reported. The median CCI was 1

(range 0–7). Data on co-medication was available for 99 out of 117 patients (84.6%). In these 99 patients co-medication use (n = 89; 89.9%) and polypharmacy (n = 43; 43.4%) were frequently reported. More details are shown in **Table 1**.

Table 1. Patient demographics.

	Patients (n=117)
Age (years), mean ± SD	70.5 ± 4.6
median, range	70 (65 – 85)
Sex, *n (%)*, male	62 (53.0)
Type of medical centre, *n (%)*	
Academic medical centre	85 (72.6)
General hospital/private practice	32 (27.4)
Age at onset of psoriasis, years*, mean ± SD	40.2 ± 18.3
median, range	43.5 (8 – 79)
Body mass index (kg/m^2)*, mean ± SD	29.1 ± 6.0
Overweight (BMI≥25), *n (%)*	59 (75.6)
Obesity (BMI≥30), *n (%)*	31 (39.7)
Use of comedication[a], *n (%)**	89 (89.9)
Polypharmacy[b]	43 (43.4)
Comorbidity/medical history, *n (%)**	
None	12 (12.0)
Hypertension[c]	47 (47.0)
Hyperlipidaemia[c]	32 (32.0)
Myocardial infarction[d]	11 (11.0)
Cardiac failure[cd]	1 (1.0)
Cerebral vascular disease[d]	11 (11.0)
Peripheral vascular disease[d]	9 (9.1)
Cardiovascular disease[de]	35 (35.0)
Diabetes mellitus[cd]	17 (17.0)
Chronic pulmonary disease[df]	19 (19.0)
Connective tissue disorder[d]	3 (3.0)
Cancer[dg]	14 (14.0)
Metastatic[d]	2 (2.0)
Skin cancer[dh]	18 (18.0)
Chronic kidney disease[di]	15 (15.0)
Peptic ulcer[d]	4 (4.0)
Liver disease[dj]	19 (19.0)
Depression	11(11.0)
Dementia[d]	1 (1.0)
Paraplegia[d]	0 (0.0)
HIV[d]	0 (0.0)
Charlson Comorbidity Index[k]*, median (range)	1 (0 – 7)
CCI 0, *n (%)*	40 (40.0)
CCI 1, *n (%)*	21 (21.0)
CCI 2, *n (%)*	14 (14.0)
CCI ≥3, *n (%)*	25 (25.0)

Values might not add up due to missing values and combination of variables.

[a] Other than psoriasis medication. [b] Polypharmacy was defined as the simultaneous use of ≥5 medications. [c] Only counted when patients had a diagnosis and used medication. [d] The comorbidities scored in the CCI, in some cases specific comorbidities are not scored in the CCI calculation according to the ICD-10 codes by Sundarajan but are scored here in this overview. For specific definitions per comorbidity category of the CCI see the ICD-10 codes by Sundarajan.[20] [e] Cardiovascular disease included MACEs (incident myocardial infarction, stroke, cardiovascular death), heart failure, coronary artery

disease, coronary or peripheral revascularization, atrial fibrillation, transient ischemic attack, valvular disease. [f] Chronic pulmonary disease included chronic obstructive pulmonary disease, asthma, chronic bronchitis, emphysema, interstitial lung disease. [g] All types of cancer other than non-melanoma skin cancer. [h] Skin cancer included melanoma, basal cell carcinoma and squamous cell carcinoma. [i] Chronic kidney disease is defined as a GFR < 60mL/min/1.73m2 for at least 3 months. [j] Liver disease included steatosis hepatis, liver fibrosis, liver cirrhosis, hepatitis, drug induced liver injury. [k] The CCI consists of 17 comorbidities. For each comorbidity a separate weight was assigned. This index is a validated and a commonly used tool in clinical practice and research.[28] * Missing age at onset: 29, body mass index: 39, comedication: 18, comorbidity/medical history: 17, Charlson comorbidity index: 17.

BMI: body mass index; CCI: Charlson comorbidity index; HIV: human immunodeficiency virus.

Table 2. Overview of all systemic treatment episodes and AEs reported in patients aged 65 years and over, during 390 years of treatment exposure, before and after causality assessment.

	TE[ab] (n=176) n (%)	Treatment exposure, years[c]	AEs[d] (n=319) n (%)	caAEs[d*] (n=232) n (%)	SAEs (n=28) n (%)	caSAEs[*] (n=12) n (%)
Conventional systemic	115 (65.3)	224.4	187 (58.6)	134 (57.8)	10 (35.7)	4 (33.3)
Methotrexate	42 (23.9)	105.4	91 (28.5)	67 (28.9)	6 (21.4)	2 (16.7)
Dimethyl fumarate	43 (24.4)	68.1	54 (16.9)	43 (18.5)	0 (0.0)	0 (0.0)
Acitretin	26 (14.8)	47.3	39 (12.2)	21 (9.1)	4 (14.3)	2 (16.7)
Ciclosporin	4 (2.3)	3.7	3 (0.9)	3 (1.3)	0 (0.0)	0 (0.0)
Biologics/apremilast	61 (34.7)	165.4	132 (41.4)	98 (42.2)	18 (64.3)	8 (66.7)
Adalimumab	20 (11.4)	48.3	36 (11.3)	32 (13.8)	4 (14.3)	3 (25.0)
Ustekinumab	18 (10.2)	53.4	46 (14.4)	31 (13.4)	7 (25.0)	3 (25.0)
Etanercept	13 (7.4)	56.5	44 (13.8)	33 (14.2)	6 (21.4)	2 (16.7)
Secukinumab	3 (1.7)	2.5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ixekizumab	2 (1.1)	2.0	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)
Guselkumab	1 (0.6)	0.2	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Infliximab	1 (0.6)	1.3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Certolizumab-pegol	1 (0.6)	0.2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Apremilast	2 (1.1)	1.3	4 (1.3)	1 (0.4)	1 (3.6)	0 (0.0)

[a] Treatment episodes of patients aged 65 years and over were collected, exposure time to antipsoriatic treatment started accordingly from the age of 65 years and over. [b] 19 treatment episodes with patients that used double systemic antipsoriatic treatment or UV-therapy with systemic antipsoriatic treatment are excluded from analysis. The following combinations were seen: combinations with methotrexate; n=1 etanercept, n=2 adalimumab, n=1 infliximab, n=2 ustekinumab, n=5 UV-therapy. Combinations with dimethyl fumarate; n=1 adalimumab. Combinations with acitretin; n=1 etanercept, n=3 adalimumab, n=1 ustekinumab, n=2 UV-therapy. [c] Sum of total exposure to antipsoriatic treatment in years. In 17 TEs treatment duration was unknown. [d] Adverse events were only recorded occurring at the age of 65 or over and if they were of significant nature (e.g. required medical attention, dose alterations, treatment discontinuation, other medical interventions). [*] With the WHO-UMC causality assessment system, the best possible estimate of the probability of a causal relationship with the antipsoriatic treatment was assessed in a standardized way, resulting in six categories: certain, probable, possible, unlikely, conditional and unassessable.[23] The following categories were defined as causal in this study; possible, probable and certain.

TE: treatment episode; (S)AEs: (serious) adverse events; caAEs: causality assessed adverse events; caSAEs: causality assessed serious adverse events.

Treatment safety and adverse events

In total, 319 AEs were reported in 176 TEs of 117 patients. After causality assessment 232 AEs (72.7%) remained, of which 12 were SAEs (see **Table 2**). An overview of the caAEs scoring method is shown in Table SII. In patients using conventional systemic therapy 134 caAEs (57.8%) were reported and in patients using biologics/apremilast 98 caAEs (42.2%) were reported. The most common caAEs in the specific systemic treatments were infections (n = 103; 63.6%), laboratory test deviations (n = 47; 29.0%) and gastro-intestinal disorders (n = 28; 17.3%). Infections were most common in methotrexate (n = 27; 26.2%) and etanercept (n = 27; 26.2%) followed by ustekinumab (n = 23; 22.3%) and adalimumab (n = 20; 19.4%). Laboratory test deviations were most common in dimethyl fumarate (n = 16; 34.0%) and methotrexate (n = 15; 31.9%). A total of 12 caSAEs were recorded, this occurred in 10 patients across the specific systemic treatments, of which most were infections (n = 6). Based on the available data, all caSAEs were reversible and/or manageable in clinical practice. A summary of the recorded (S)AEs is given in **Table 3** and **Table S1**.

Table 3. Summary of caAEs in older adults with psoriasis using the most frequently prescribed systemic antipsoriatic treatments.

caAEs[a], number	Methotrexate (TE 42)	Dimethyl fumarate (TE 43)	Acitretin (TE 26)	Adalimumab (TE 20)	Ustekinumab (TE 18)	Etanercept (TE 13)
Total caAEs[b]	67	43	21	32	31	33
Total caSAEs[b]	2	0	2	3	3	2
Infections[c]	27 (40.3)	6 (14.0)	0 (0.0)	20 (62.5)	23 (74.2)	27 (81.8)
Laboratory test deviations[d]	15 (22.4)	16 (37.2)	6 (28.6)	5 (15.6)	3 (9.7)	2 (6.1)
Neoplasms[e]	2 (3.0)	0 (0.0)	0 (0.0)	1 (3.1)	1 (3.2)	2 (6.1)
General disorder[f]	8 (11.9)	2 (4.7)	5 (23.8)	2 (6.3)	0 (0.0)	1 (3.0)
Gastro-intestinal disorder[g]	9 (13.4)	14 (32.6)	3 (14.3)	1 (3.1)	1 (3.2)	0 (0.0)
Cardiovascular disorder[h]	1 (1.5)	3 (7.0)	1 (4.8)	1 (3.1)	0 (0.0)	0 (0.0)
Hepatobiliary disorder[i]	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neurological disorder[j]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Musculoskeletal disorders[k]	0 (0.0)	0 (0.0)	1 (4.8)	1 (3.1)	3 (9.7)	0 (0.0)
Skin disorder[l]	0 (0.0)	2 (4.7)	4 (19.0)	1 (3.1)	0 (0.0)	0 (0.0)
Eye disorders[m]	1 (1.5)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Psychological disorder[n]	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE's[o]	2 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The above shown antipsoriatic treatments were selected, based on a minimum of ten treatment episodes.

[a] Adverse events were only recorded occurring at the age of 65 or over and if they were of significant nature (e.g. required medical attention, dose alterations, treatment discontinuation, other medical interventions). All AEs presented in this table are assessed on causality; possible or probable causally related to the antipsoriatic treatment. [b] A specified overview of all reported (S)AEs is shown in the supplements, before and after causality assessment. [c] Includes; flu-like symptoms, skin infections, abscess, urinary tract infections, pneumonia, gastro-intestinal infections, oral infections, middle-ear infection, epididymitis, bacterial infection. [d] Laboratory test deviations without clinical symptoms, including; ↑transaminases, ↑gamma-glutamyl transferase,↑P3NP, ↑alkaline phosphatase, ↑creatine kinase, ↑cholesterol, ↑triglycerides, renal function deterioration, proteinuria, haematuria, deviations in urinary sediment, leukopenia, neutropenia, lymphocytopenia, anaemia. [e] Includes; actinic keratosis, non-Hodgkin lymphoma, lung cancer, tubulair adenoma, kidney cancer. [f] Includes; fatigue, sleep problems, weight loss, dizziness, hair loss, headache, dry lips, dry mouth. [g] Includes; abdominal pain, nausea, vomiting, diarrhoea, reflux, obstipation. [h] Includes; claudicatio intermittens, thrombotic event, syncope, flushing, hot flashes. [i] Includes; non-alcoholic fatty liver disease. [j] Includes; paraesthesia. [k] Includes; pain in joints, pain in muscles, muscle cramps. [l] Includes; rash, skin burn, pruritus, retinoid dermatitis, exfoliation of hand/foot palms and lips, exacerbation of psoriasis, pustels on the chest. [m] Includes; dry eyes, ablatio retinae. [n] Includes; depression. [o] Includes; pneumonitis on methotrexate.
TE, treatment episode; caAEs, causality assessed adverse events; caSAEs, causality assessed serious adverse events.

To compare caAE-occurrence per year of treatment exposure time amongst the specific systemic treatments IRRs were calculated (see **Table 4**). The IRR of etanercept (IRR 1.586; 95% confidence interval (CI) 0.695–3.813; p = 0.284), dimethyl fumarate (IRR 1.427; 95% CI 0.771–2.700; p = 0.264) and adalimumab (IRR 1.248; 95% CI 0.603–2.589; p = 0.548) were highest, but no significant differences were found among the systemic therapies. The model including all reported AEs without selecting for caAEs only showed similar results **(Table S4)**. The sensitivity analysis showed similar results, in which if the treatment duration was not known (n = 17), the mean of the specific treatment duration was used **(Table S5)**

Table 4. Negative binomial model on the incidence rate ratios of caAEs per year of selected TEs in patients aged 65 years and over.

Antipsoriatic treatment[a]	Incidence rate ratio[b]	95% CI	p-value
Methotrexate	Reference		
Dimethyl fumarate	1.427	0.771 – 2.700	0.264
Acitretin	0.739	0.330 – 1.609	0.450
Adalimumab	1.248	0.603 – 2.589	0.548
Ustekinumab	1.198	0.582 – 2.525	0.626
Etanercept	1.586	0.695 – 3.813	0.284

[a] The above shown antipsoriatic treatments were selected, based on a minimum of ten treatment episodes. [b] The IRRs are only calculated with the treatment episodes of which the treatment duration was known, 17 TEs were excluded from this analysis including corresponding AEs (n=8).
caAEs: causality assessed adverse events; IRR: incidence rate ratio; TE: treatment episode, CI: confidence interval.

To explore the potential relationship between age, comorbidity and caAE-occurrence on current specific systemic antipsoriatic therapy, a multivariable logistic regression model was used **(Table 5)**. Increasing age in years was associated with a higher odds on developing a caAE (OR 1.195; 95% CI 1.026–1.393; p = 0.022). For the comparison of systemic therapies, methotrexate was selected as reference as this was a commonly used treatment in this study. In this comparison, no significant differences for all systemic therapies regarding the odds of developing a caAE was found. Furthermore, all comorbidities, CCI, polypharmacy, age at onset of psoriasis, overweight, and sex were not associated with caAE-occurrence on current systemic therapy. The model including all reported AEs on current antipsoriatic therapy, without causality assessment showed the same results in general **(Table S6)**.

Table 5. Multiple logistic regression model on the relation of different factors with the occurrence of caAEs when using systemic antipsoriatic therapy.

Variables[a]	Odds ratio	95% CI	p-value
Age (years)	1.195	1.026 – 1.393	**0.022**
CCI score[b] (<1 vs. ≥1)	1.677	0.531 – 5.303	0.378
Polypharmacy	0.385	0.122 – 1.211	0.103
Type of systemic treatment[c]			
Methotrexate	Reference		0.062
Dimethyl fumarate	1.560	0.407 – 5.984	0.516
Acitretin	0.303	0.066 – 1.402	0.127
Biological[d]	2.889	0.754 – 11.069	0.122

[a] The following variables are also assessed in this model but did not show a significant relation: sex, age at onset of psoriasis, overweight, kidney disease, history of cancer, liver disease, cardiovascular disease.
[b] The CCI score was divided into two groups, CCI<1 and CCI≥1 based on the data distribution. [c] Six patients were excluded due to the simultaneous use of two types of antipsoriatic treatment. [d] Including etanercept, adalimumab, ustekinumab, ixekizumab.
caAEs: causality assessed adverse events; IRR: incidence rate ratio; TE: treatment episode, CI: confidence interval.

Reasons for treatment discontinuation

Of the 176 TEs, 90 (51.1%) TEs were discontinued and 85 (48.3%) TEs were currently still active at the end of the observation time. The most common reasons to discontinue systemic antipsoriatic treatment in older adults (including all systemic treatments) were adverse events (n = 37; 41.1%), ineffectiveness (n = 36; 40.0%), followed by combination of adverse events and ineffectiveness (n = 9; 10.0%), remission (n = 4; 4.4%), other reasons (n = 3; 3.3%) and unknown reason for discontinuation (n = 1; 1.1%). In conventional systemic antipsoriatic therapy the most frequently reported reasons for treatment discontinuation were AEs (n = 30; 50.0%), followed by ineffectiveness (n = 14; 23.3%). For biologics/apremilast, AEs as

reason for discontinuation was less often reported (n = 7; 23.3%) and ineffectiveness (n = 22; 73.3%) was more often reported as reason for treatment discontinuation compared with conventional systemic therapy. No significant difference was seen regarding overall treatment discontinuation frequency between conventional systemic therapy and biologics/apremilast (p = 0.663). Reasons for treatment discontinuation for the selected systemic therapies are shown in **Table S7**.

Discussion

This real-world multicentre retrospective cohort study assessed the treatment safety of older adults with psoriasis using systemic therapy. In total, data from 117 patients (≥ 65 years) with 176 TEs of systemic antipsoriatic therapy with a cumulative follow-up of 390 patient-years were analysed. In this study (S)AEs were thoroughly assessed on causality with the systemic antipsoriatic therapy, resulting in 232 AEs and 12 SAEs possibly related to the use of systemic antipsoriatic therapy. Causality assessed SAEs were rare, mostly infectious of nature, and were reversible and/or manageable in clinical practice. Treatment discontinuation due to adverse events was most frequently recorded in patients using conventional systemic antipsoriatic therapy and treatment discontinuation due to ineffectiveness was most often recorded in patients using biologics/apremilast. It was found that increasing age was associated with a higher caAE-occurrence (OR 1.195; p = 0.022), while no association was found between comorbidity, polypharmacy and systemic treatment type with caAE-occurrence. No significant differences in IRRs were found between the systemic treatment types.

Previous research has shown that most antipsoriatic treatments are not associated with more AEs in older adults.[9,13,15,19] Nevertheless, some systemic treatments do show a tendency of more AEs in this population, mainly in patients using ciclosporin, but also in those using dimethyl fumarate.[10,11] Causality assessment can be valuable in reporting and interpreting data on AEs. This is especially the case in older adults, as the incidence of comorbidity and related health problems/events generally increases with age and therefore misclassification of an unrelated health problem/event as AE might be more common in this population. This could lead to biased safety data in this population, potentially resulting in a disproportional treatment reluctance and undertreatment. After causality assessment 232 caAEs were reported in this study. The most common types of caAEs in the selected systemic treatments were: infections, laboratory test deviations, and gastro-intestinal disorders, in line with previous research.[9,10,26] The most common reasons to discontinue systemic

antipsoriatic treatment in older adults (including all systemic treatments) were AEs (n = 37; 40.7%), and ineffectiveness (n = 36; 39.6%), concurring with reasons for treatment discontinuation in a younger psoriasis cohort.[27]

The emergence of AEs on systemic antipsoriatic treatment may be related to numerous factors, including comorbidities, drug interactions, altered age-related drug metabolism, and decline in functional status.[9,13] As expected and in line with previous research, comorbidities and co-medication use were common in our study, with being overweight (75.6%) and hypertension (47.0%) being most reported.[10,15,17,19] Furthermore, the majority of the study population (89.9%) used co-medication and polypharmacy was common (43.4%). Multivariable regression analysis showed a higher odds of developing AEs with ageing. However, no significant association was found between the presence of comorbidity and polypharmacy on caAE occurrence. Furthermore, no significant association was found between the specific types of systemic antipsoriatic therapy on caAE-occurrence in this population of older adults. Conventional systemic therapy was more often used in our study cohort than biologics/apremilast, which is in concordance with previous studies.[15,17] The highest IRRs of caAEs per year were seen in etanercept, dimethyl fumarate and adalimumab when compared with the reference methotrexate, yet no statistical significant differences were found among the different systemic treatments. However, most caAEs were reported in the conventional systemic group compared with the biologics/apremilast group, in line with previous research.[10,13] It should be taken into account that not all studies have incorporated a thorough causality assessment of AEs, as in the current study. Out of 319 AEs, a fourth of AEs were excluded and 232 caAEs (72.2%) remained. To conclude, comparing data regarding AEs amongst different studies can be difficult, due to the possibility of reporting bias, different definitions of AEs, variability in exposure time, the possibility of indistinct causality with the treatment, and the difficulty of drawing causal relations in any study. Therefore, standardized reporting of AEs and assessing AEs on causality can be very valuable in clinical research.

Due to the retrospective and observational nature of this study, using existing data from patient records, misinterpretation and/or incomplete data might have been a source of bias. To reduce this risk of bias, we used multiple data sources from the patient records, referral notes from other medical specialists, and a second researcher manually checked 10% of the data. Nevertheless, with this cohort study we provided a total recording of AEs of a significant nature in older adult patients using systemic antipsoriatic therapy, including a causality assessment of AEs.

This study found that increasing age was associated with higher caAE-occurrence. caSAEs were rare, most were of infectious nature, and all caSAEs were reversible and/or manageable in clinical practice. Furthermore, no association was found between comorbidity, polypharmacy, and the specific types of systemic antipsoriatic therapy on the occurrence of caAEs. Therefore, the safety profile of systemic antipsoriatic treatment in this population of older adults was reassuring. This population of older adults with psoriasis is heterogeneous (e.g. in terms of functional dependency and frailty status), therefore a personalized approach including relevant patient and disease characteristics and patient preferences is important. For further treatment personalization, more real-world data is needed, particularly prospective studies on the efficacy and safety of systemic antipsoriatic treatments in older adults with psoriasis, preferably including a causality assessment on the reported (S)AEs.

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Supplemental tables

Table S1. Study population characteristics compared with target population.

	Study population[a] (n=230)	van Winden et al, 2020 (n=413)	Phan et al, 2020 (n=135)	Piaserico et al, 2014 (n=187)
Age, mean ± SD	71.1 ± 4.9	72.4 ± 5.9	73.5 ± 6.3	71.3 ± 5
Sex, n (%) Male Female	127 (55.2) 103 (44.8)	246 (59.6) 167 (40.4)	79 (58.5) 56 (41.5)	109 (58.3) 78 (41.7)

[a] Comparisons were done using the complete study population (n=230), without selection for systemic antipsoriatic treatment only.

Table S2. Overview of causality assessment of reported adverse events in systemic antipsoriatic therapy in older adults using the WHO-causality assessment tool.

WHO-scale[a]	Methotrexate (TE=42)					Dimethyl fumarate (TE=43)				
	1	2	3	4	5	1	2	3	4	5
Total AEs[b]	6	18	36	31	-	-	11	11	32	-
Total SAEs[b]	-	4	2	-	-	-	-	-	-	-
Infections	-	-	26	1	-	-	-	6	-	-
Laboratory test deviations	-	2	2	13	-	-	2	1	15	-
Neoplasms	-	7	2	-	-	-	-	-	-	-
General disorder	-	-	1	7	-	-	1	2	-	-
Gastro-intestinal disorder	-	1	1	8	-	-	-	-	14	-
Cardiovascular disorder	1	2	1	-	-	-	-	-	3	-
Hepatobiliary disorder	-	-	1	-	-	-	1	-	-	-
Neurological disorder	-	-	-	-	-	-	-	-	-	-
Musculoskeletal disorders	1	2	-	-	-	-	4	-	-	-
Skin disorder	1	-	-	-	-	-	1	2	-	-
Eye disorders	-	1	1	-	-	-	1	-	-	-
Psychological disorder	-	-	1	-	-	-	-	-	-	-
Other or unknown AE's	3	3	-	2	-	-	-	-	-	-

[a] With the WHO-UMC causality assessment system, the best possible estimate of the probability of a causal relationship with the antipsoriatic treatment was assessed in a standardized way. The following categories are displayed; unassessable (1), unlikely (2), possible (3), probable (4), certain (5). The following categories were defined as causal in this study; possible, probable and certain. The categories conditional (0) and certain (5) were not scored in this study.

[b] Adverse events were only recorded occurring at the age of 65 or over and if they were of significant nature (e.g. required medical attention, dose alterations, treatment discontinuation, other medical interventions). A specified overview of all reported (S)AEs is shown in Table SIII, before and after causality assessment.

TE: treatment episode;(S)AEs: (serious) adverse events.

	Acitretin(TE=26)					Adalimumab(TE=20)					Ustekinumab(TE=18)					Etanercept(TE=13)				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
	4	14	4	17	-	2	2	3	29	-	3	12	4	27	-	-	11	6	27	-
	-	2	1	1	-	-	1	1	2	-	1	3	1	2	-	-	4	1	1	-
	-	2	-	-	-	-	-	1	19	-	-	1	-	23	-	-	-	-	27	-
	-	3	2	4	-	-	-	-	5	-	-	1	3	-	-	-	-	2	-	-
	1	5	-	-	-	-	-	1	-	-	-	2	1	-	-	-	2	2	-	-
	-	-	-	5	-	-	-	-	2	-	-	-	-	-	-	-	-	1	-	-
	-	1	-	3	-	-	-	-	1	-	-	-	-	1	-	-	2	-	-	-
	1	2	1	-	-	1	1	1	-	-	-	1	-	-	-	-	2	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	-	-	-
	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	1	-	-
	1	-	1	-	-	1	-	-	1	-	-	3	-	3	-	-	1	-	-	-
	-	1	-	4	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	-
	-	-	-	1	-	-	1	-	-	-	-	2	-	-	-	-	1	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	2	-	-	-

Table S3. Overview of AEs in older adults with psoriasis using systemic antipsoriatic treatment before and after causality assessment, SAEs are reflected in bold.

AEs[a] (number)	Methotrexate (TE=42)	Dimethyl fumarate (TE=43)	Acitretin (TE=26)
Infections	Dermatomycosis(2) Flu-like symptoms(6) Pneumonia(6) Urinary tract infection(4) Middle ear infection(2) Oral infection(1) Abscess(1) Erysipelas(2) Other skin infection[b](2) Post-operative infection(1)	Dermatomycosis(1) Pneumonia(1) Urinary tract infection(1) Herpes zoster(1) Unknown bacterial infection(1) Other skin infection[b](1)	*Urinary tract infection(1)* *Other skin infection[b](1)*
Symptoms	Abdominal pain(4) Nausea(5) Weight loss(1) Fatigue(5) Headache(1) Sleep problems(1) *Skin bruising(1)* *Musculoskeletal[c](2)*	Abdominal pain(2) Nausea(2) Vomiting(1) Diarrhoea(9) *Hemorroïd(1)* *Hemoptoë(1)* Fatigue(2) Hot flashes(1) Flushing(2) *Skin bruising(1)* *Musculoskeletal[c](2)*	Dry eyes(1) Dry lips(2) **Severe dry mouth(1)** Exfoliation of hand/feet palms and lips(1) *Reflux laryngitis(1)* Obstipation(1) *Musculoskeletal[c](1)* Musculoskeletal[c](1) Pruritus(1) Nausea(2) Hair loss(1) *Cold feet and hands(1)* Headache(1)
Laboratory test deviations	Anaemia(4) Neutropenia(1) Leukopenia(1) ↑ Transaminase levels(5) ↑ P3NP(4) ↑*infection parameters(2)*	Lymphocytopenia(11) Leukopenia(2) *Monocytosis(1)* Proteinuria(3) Abnormal urine sediment(1) ↑ *y-GT(1)*	*Anaemia(2)* *Leucocytosis(1)* Renal function deterioration(2) ↑ Cholesterol, TG(1) ↑ Transaminase levels(1) ↑ Transaminase levels and y-GT(1) ↑ CK(1)
Neoplasms	*Basal cell carcinoma(2)* **Non Hodgkin lymphoma(1)** **Lung cancer(1)** *Angiosarcoma breast(1)* *Gallbladder polyp(1)*	None	*Squameus cell carcinoma(1)* *Lentigo maligna(1)* *MELTUMP(1)* *Myelodysplastic syndrome(1)* *Gallbladder polyp(1)*
Other AEs	Pneumonitis(2) *Fracture(2)* *Wound/injury(2)* *Actinic keratosis(2)* *Lipoma(1)* Depression(1) *Epistaxis(2)* *Thrombotic event(1)* Thrombotic event(1) *Cataract(1)* Liver cirrhosis(1) *MI(1)* *PVC(1)* Ablatio retinae(1) *Ileus(1)* *Arthrosis(1)*	*NASH(1)* *Arthrosis(1)* *Polymyalgia rheumatica(1)* Rash(2) *Ablatio retinae(1)*	*CVA(1)* **Syncope(1)** *Hypertension(1)* *Actinic keratosis(1)* *Epidermoid cyst(1)* Other skin conditions[d](2) *Unknown(1)*

	Adalimumab (TE=20)	Ustekinumab (TE=18)	Etanercept (TE=13)
	Dermatomycosis(2) Flu-like symptoms(3) **Pneumonia(1)** Urinary tract infection(4) Oral infection(1) Abscess(3) **Epididymitis(1)** **Erysipelas(1)** Lung disease with antibodies(1) Other skin infection[b](2)	Flu-like symptoms(8) **Pneumonia(2)** Urinary tract infection(6) Oral infection(1) *Paronychia(1)* Middle ear infection(1) Epididymitis(1) Herpes zoster(1) Other skin infection[b](2)	Flu-like symptoms(11) Pneumonia(2) Urinary tract infection(6) Oral infection(1) **Abdominal infection(1)** Abdominal infection(1) Other skin infection[b](5)
	Pruritus(1) Abdominal pain(1) Musculoskeletal[c](1) *Musculoskeletal[c](1)* Dizziness(2)	*Dry eyes(1)* Gastric reflux(1) *Restless limbs(1)* Dry cough(1) *Palpitations(1)*	Paraesthesia(1) Dizziness(1)
	Leukopenia(1) ↑ Cholesterol, TG(1) ↑ Transaminase levels(2) ↑ TG(1)	Anaemia(1) *Anaemia(1)* Haematuria(1) ↑ Transaminase levels and y-GT(1)	Anaemia(1) ↑ AP and y-GT(1)
	None	*Colon polyp(1)* **Kidney cancer(1)** ***Kidney cancer(1)***	*Colon polyp(1)* **Tubulair adenoma(1)** *Adrenal gland incidentaloma(1)*
	Actinic keratosis(1) Claudicatio intermittens(1) *Cataract(1)* *Aorta valve sclerosis(1)* ***Angina pectoris(1)***	*Polymyalgia rheumatica(1)* *Tendinitis(1)* *Osteoporosis(1)* *Choledocholithiasis(1)* *Fracture(1)* *Wound/injury(1)* *Cataract(1)* ***Dermatitis medicamentosa(1)***	*Tendinitis(1)* Actinic keratosis(1) *TIA(1)* *Ileus(1)* *Cataract(1)* *Cholecystolithiasis(1)* *Gastric parese(1)* *Increased risk of falling(1)* *Fracture(1)* ***Dilatation Crossover femorofemoral surgery(1)***

Table S3. Continued

AEs[a] (number)	Methotrexate (TE=42)	Dimethyl fumarate (TE=43)	Acitretin (TE=26)
Total AEs	91	54	39
caAEs	67	43	21
Total SAEs	6	0	4
caSAEs	2	0	2

Data not shown: 3 AEs occurred when using ciclosporin; hypertension (n=2) and renal function deterioration (n=1). 1 AE occurred when using ixekizumab; pneumonia (n=1), 1 AE occurred on guselkumab, proteinuria (n=1) and 4 AE's occurred on apremilast; flu-like symptoms (n=1), arthrosis (n=1), morbus bowen (n=1) and struma (SAE, n=1, unlikely related to antipsoriatic treatment). No adverse events were reported for infliximab, certolizumab pegol, and secukinumab.

[a] Adverse events were only recorded occurring at the age of 65 or over and if they were of significant nature (e.g. required medical attention, dose alterations, treatment discontinuation, other medical interventions). The (S)AEs in italics were unassessable or unlikely related to the antipsoriatic treatment. All SAEs are reflected in bold. [b] Other skin infection, including impetigo, infection of epidermoidcyste, infection of ulcus cruris, balanoposthitis and other undiagnosed skin infections. [c] Musculoskeletal conditions, including; joint pain, muscle pain, shoulder surgery, muscle cramps, bursitis. [d] Other skin conditions, including; pustels on the chest and retinoïd dermatitis.

TE: treatment episode; (S)AEs: (serious) adverse events; caAEs: causality assessed adverse events; caSAEs: causality assessed serious adverse events; MI: myocardial infarction; PVC: premature ventricular contraction; MELTUMP: melanocytic tumours of uncertain malignant potential; CK: creatine kinase; NASH: non-alcoholic fatty liver disease; y-GT: gamma-glutamyl transferase; TG: triglycerides; P3NP: amino terminal type III procollagen peptide; AP: alkaline phosphatase; ↑: elevated.

Table S4. Negative binomial model on the incidence rate ratios of caAEs per year of selected TEs of patients aged 65 years and over, with added treatment duration.

Antipsoriatic treatment[a]	Incidence rate ratio[b]	95% CI	p-value
Methotrexate	Reference		
Dimethyl fumarate	1.363	0.767 – 2.469	0.297
Acitretin	0.657	0.330 – 1.275	0.221
Adalimumab	1.390	0.704 – 2.766	0.343
Ustekinumab	1.317	0.653 – 2.713	0.445
Etanercept	1.639	0.735 – 3.844	0.238

[a] The above shown antipsoriatic treatments were selected, based on a minimum of ten treatment episodes. [b] When treatment duration was unknown (n=17), TEs were not excluded from this analysis. Instead the mean of the specific antipsoriatic treatment duration was used, consequently all cases could be included in the analysis.

CaAEs: Causality assesed adverse events; IRR: incidence rate ratio; TE: treatment episode, CI: confidence interval.

Adalimumab (TE=20)	Ustekinumab (TE=18)	Etanercept (TE=13)
36	46	44
32	31	33
4	7	6
3	3	2

Table S5. Negative binomial model on the incidence rate ratios of all AEs per year of selected TEs of patients aged 65 years and over, without selecting for causal AEs only.

Antipsoriatic treatment[a]	Incidence rate ratio[b]	95% CI	p-value
Methotrexate	Reference		
Dimethyl fumarate	1.183	0.675 – 2.072	0.557
Acitretin	1.052	0.545 – 2.029	0.880
Adalimumab	0.949	0.485 – 1.855	0.878
Ustekinumab	1.305	0.679 – 2.505	0.424
Etanercept	1.407	0.665 – 2.974	0.372

[a] The above shown antipsoriatic treatments were selected, based on a minimum of ten treatment episodes. [b] The IRRs are only calculated with the treatment episodes of which the treatment duration was known, 17 TEs were excluded from this analysis including corresponding AEs (n=8).

AEs: adverse events; IRR: incidence rate ratio; TE: treatment episode, CI: confidence interval.

Table S6. Multiple logistic regression model on the relation of different factors with the occurrence of all AEs in older adults with psoriasis, without selecting for causal AEs only.

Variables[a]	***Odds ratio***	***95% CI***	***p-value***
Age (years)	1.239	1.040 – 1.477	**0.017**
CCI score[b] (<1 vs. ≥1)	1.929	0.573 – 6.489	0.289
Polypharmacy	0.748	0.221 – 2.537	0.642
Type of systemic treatment[c]			
Methotrexate	Reference		0.342
Dimethyl fumarate	1.338	0.324 – 5.523	0.687
Acitretin	0.491	0.098 – 2.472	0.389
Biological[d]	2.451	0.576 – 10.441	0.225

[a] The following variables are also assessed in this model but did not show a significant relation: sex, age at onset of psoriasis, overweight, kidney disease, history of cancer, liver disease, cardiovascular disease.
[b] The CCI score was divided into two groups, CCI<1 and CCI≥1 based on the data distribution.
[c] Six patients were excluded due to the simultaneous use of two types of antipsoriatic treatment.
[d] Including etanercept, adalimumab, ustekinumab, ixekizumab.

AEs: adverse events; CCI: Charlson Comorbidity Index; CI: confidence interval.

Table S7. Causes of treatment discontinuation in older adults with psoriasis using systemic antipsoriatic treatment.

Causes of treatment discontinuation, n(%)	**Methotrexate (TE=42)**	**Dimethyl fumarate (TE=43)**	**Acitretin (TE=26)**	**Adalimumab (TE=20)**	**Ustekinumab (TE=18)**	**Etanercept (TE=13)**
AE	8 (19.0)	15 (34.9)	6 (23.1)	1 (5.0)	4 (22.2)	1 (7.7)
AE and ineffectiveness	3 (7.1)	2 (4.7)	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ineffectiveness	4 (9.5)	4 (9.3)	6 (23.1)	9 (45.0)	5 (27.8)	5 (38.5)
Remission	1 (2.4)	3 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[a]	1 (2.4)	1 (2.3)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Still active[b]	25 (59.5)	17 (39.5)	10 (38.5)	10 (50.0)	9 (50.0)	7 (53.8)

The above shown antipsoriatic therapies were selected, based on a minimum of ten treatment episodes.
[a] Other includes, methotrexate; fear of cancer recurrence malignancy (n=1), acitretin; dissatisfied with treatment (n=1), dimethyl fumarate; discontinuation on patient initiative during summer holiday (n=1).
[b] Including, patients that still used antipsoriatic treatment at the moment of inclusion and chart review.

TE: treatment episode; AE: adverse event.

Appendix

Appendix 1. Supplementary methods

Study design and participants

A multicentre retrospective cohort study was performed to assess disease and treatment patterns in older adults (≥65 years) with psoriasis (Geriatric Psoriasis Patterns (GEPPA) study). Relevant parameters for this study were gathered from a literature review, a previous survey, and multidisciplinary brainstorm sessions.[15] All patients were diagnosed with psoriasis by a dermatologist and treated in one of the six participating centres in the Netherlands: one academic medical centre (Radboud university medical centre, Nijmegen), four general hospitals (Gelderse Vallei Hospital, Ede; Canisius-Wilhelmina Hospital, Nijmegen; Bernhoven Hospital, Uden; Rijnstate Hospital, Arnhem) and one private practice (Padberg Clinic, Ede). In the current study only treatment episodes (TEs) of patients using systemic therapy for psoriasis were included (conventional systemic and biological/apremilast therapies). One TE accounted for one continuous episode of a specific systemic antipsoriatic therapy. Approval from the Medical Ethical Committee Arnhem-Nijmegen(reference number: 2019-5904) and written informed consent from each patient were obtained.

Outcome measures

Various patient and treatment characteristics were collected, including comorbid disease status, comedication use, and presence of polypharmacy. To measure comorbid disease status the ICD-10 version of the Charlson Comorbidity Index (CCI) was used.[20] In addition to the CCI categorisation, the following comorbidities of special interest were also separately classified, because of their (potential) relatedness to psoriasis (treatment): skin cancer, depression, hypertension, hyperlipidaemia, overweight,obesity and cardiovascular disease. Polypharmacy was defined as the simultaneous use of ≥5 medications.[21] To assess treatment patterns, the current use of systemic therapy and TEs regarding systemic antipsoriatic therapy were collected from patients charts from the age of 65, including: treatment duration, AE-occurrence and reasons for treatment discontinuation. If patients were using >1 systemic antipsoriatic treatment simultaneously or a combination of UV-therapy and systemic antipsoriatic treatment these TEs were excluded from analyses on AEs and treatment discontinuation, as it was not possible to further distinguish these outcomes in relation to the individual treatments. Furthermore, systemic treatments with <10 accounted TEs were excluded from further analysis, to avoid having multiple small treatment groups with low statistical power to draw conclusions from.

Adverse events and causality assessment

An AE was defined as any undesirable medical event of significant nature during antipsoriatic treatment (e.g.requiring a doctor's visit, dose alterations, or other medical interventions). An AE was classified as serious AE (SAE) when a patient needed hospitalisation, had persistent or significant disability/incapacity, and occurrence of life-threatening conditions or death.[22] AEs were independently assessed on causality by three physician-researchers (SL, EtH, LvS) using the WHO-UMC causality assessment system and clinical experience (23), followed by a consensus meeting. The WHO-UMC causality system consists of the following categories: certain (5), probable (4), possible (3), unlikely (2), unassessable (1) and conditional (0). AEs scored <3 were excluded. AEs scored as ≥3 remained included, further mentioned as causality assessed AEs (caAEs). From the available TEs, incidence rate ratios (IRR) of AEs per year for the selected systemic therapy were computed.

Data collection and processing

Patients were chronologically included based on their last visit, starting from January 1, 2019. To provide an overview of the whole population of older adults with psoriasis using systemic therapy, no selection on disease severity was made. Data were obtained from the medical charts and processed anonymously using Castor Electronic Data Capture, a web-based data management system (Castor Research Inc., Hoboken, NJ, USA) (EtH, EtB). To confirm accurate data entry, 10% of the data were manually checked for discrepancies by a second researcher (EtH, SL).

Statistical analyses

Due to the explorative nature of this study, a formal power calculation was not possible. Descriptive analyses were performed to summarize data. Categorical data were presented as frequency/percentages. Continuous variables were presented as mean/standard deviation (SD) or median/range, when applicable. To indicate representativeness of our study population, a comparison with other psoriasis cohorts including older adults was performed on age and sex distribution using a chi-square test and an independent T-test.[10,15,24] To analyse the IRRs of AEs per year, negative binomial models were used. The number of caAEs in an episode was the dependent variable, and the specific systemic treatment of that episode the independent variable. The length of the episode was used as offset for the model. As episodes were clustered within patients, a multilevel model was applied with a random intercept for each patient. Additionally, a similar analysis was performed including all AEs without selecting for caAEs only. A model for SAEs regardless of causality assessment was not possible due to the low numbers.

To explore the potential relationship between age, comorbidity and AE-occurrence on current specific systemic treatments, and to correct for confounding variables, multivariable logistic regression analysis was performed with the caAEs only. In addition, a sensitivity analysis including all reported AEs was performed. After a consensus meeting and taking data availability into account other variables of potential influence included were: age at psoriasis onset, presence of psoriatic arthritis, polypharmacy, history of cancer, liver disease, kidney disease, cardiovascular disease, overweight, and sex. First, age and the CCI were assessed in the model. Then, all other variables were added to the model one by one and excluded if $p>0.2$. Subsequently, the combination of all the relevant identified variables were used in multivariable logistic regression analysis.

Missing values were not included in the analyses. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM, Armonk, NY, USA)and for the negative binomial analysis R (version 3.6.3) and the lme4 library (version 1.1–21) were used (25).

Chapter 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 centers 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, IL12/23) 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.

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.

Methods

The BioCAPTURE database

In this real-world cohort study, data were extracted from the prospective, multicenter 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 centers 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, IL12/23) 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].

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

	<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]				NA
mean ± SD	24.8 ± 12.3	41.9 ± 18.8	26.7 ± 14.2	
median, range	22.0 (0 -59)	47.0 (2- 76)	23.0 (0 – 76)	
Duration of psoriasis until start biologic, years[b,c]				0.001
mean ± SD	20.0 ± 11.9	26.5 ± 18.5	z20.7 ± 12.9	
median, range	18.2 (0.6-57.2)	17.4 (1.7-72.0)	18.2 (0.6-72.0)	
Biologic naive, *n (%)*				0.827
yes	510 (64.7)	65 (63.7)	575 (64.6)	
no	278 (35.3)	37 (36.3)	315 (35.4)	
Family history of psoriasis, *n (%)*[c]				0.311
yes	472 (66.9)	50 (59.5)	522 (66.1)	
no	234 (33.1)	33 (40.5)	268 (33.9)	
Psoriatic arthritis, *n (%)*[c]				0.447
yes	211 (32.0)	22 (27.2)	233 (31.5)	
no	448 (68.0)	59 (72.8)	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)*	
IL12-23 (*ustekinumab*)	182 (23.1)	21 (20.6)	203 (22.8)	

Table 1. Continued

	<65 years old (n = 788)	**≥65 years old (n = 102)**	**All patients (n = 890)**	**p-value[a]**
IL17	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)*	
IL23	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)*	
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
Ciclosporin	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

Not applicable (NA), 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

SD: standard deviation.

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 ($p < 0.001$).

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**.

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.

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.

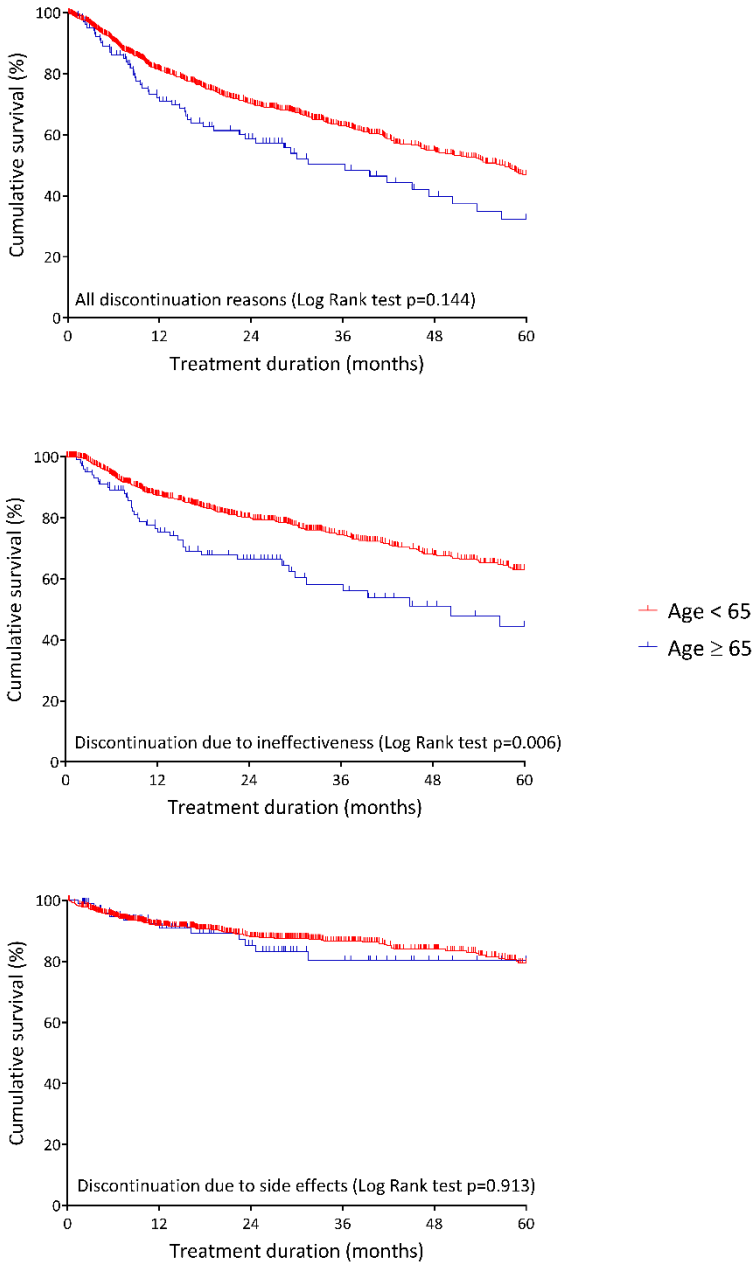

Figure 1. Five-year drug survival of older patients compared to younger patients using biologics treatment, split for discontinuation reasons

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 electronic supplementary **Tables 1 and 2**. When implementing imputed data in univariable Cox regression analyses, HRs were pointing in the same direction, showing robustness of the results.

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.

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 electronic supplementary text).

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 ($p = 0.347$).

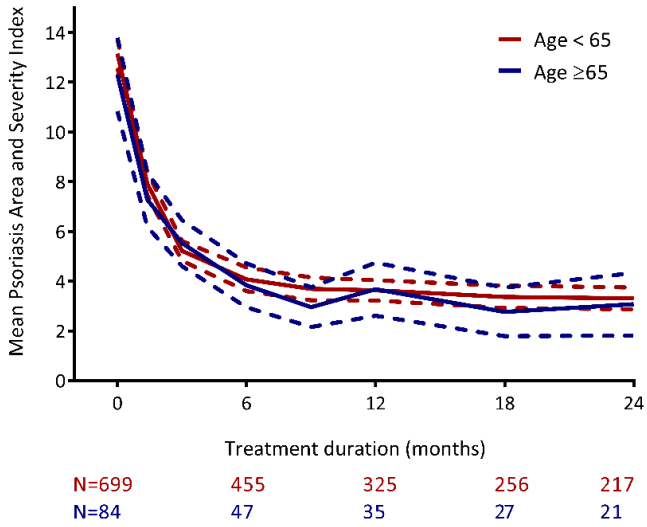

Figure 2. Mean two year PASI course + 95% confidence intervals of patients using biologics, comparing age groups

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)

Table 4. Continued

Adverse events (MedDRA classification)	<65 years old (n=103)	≥65 years old (n=12)	All patients (n=115)
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.

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, and multicenter, 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 AEs 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 materials

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

Variables	**Discontinuation for all reasons** *Event = ineffectiveness, AE, ineffectiveness + AE, other reasons, deathHR [95% CI]*		**Discontinuation due to ineffectiveness** *Event = ineffectiveness, ineffectiveness + AE HR [95% CI]*		**Discontinuation due to adverse events** *Event = AE, ineffectiveness + AEHR [95% CI]*	
	Univariate	*Multivariable*	*Univariate*	*Multivariable*	*Univariate*	*Multivariable*
Age at start of biologic	0.994 [0.982-1.004] p-value 0.235		1.000 [0.987-1.013] p-value 0.989		1.014 [0.995-1.033] p-value 0.147	
Age at onset of psoriasis	1.000 [0.991-1.010] p-value 0.993		0.999 [0.987-1.011] p-value 0.861		1.010 [0.993-1.026] p-value 0.240	
Female sex	**1.452 [1.172-1.798] p-value 0.001**	**1.474 [1.178-1.845] p-value 0.001**	**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**
Body mass index	**1.026 [1.009-1.044] p-value 0.003**	**1.022 [1.004-1.040] p-value 0.015**	**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**	
Psoriatic arthritis	1.212 [0.958-1.534] p-value 0.109		**1.362 [1.010-1.837] p-value 0.043**		1.193 [0780-1.824] p-value 0.416	
Biologic naivety	0.884 [0.712-1.098] p-value 0.266		0.815 [0.616-1.078] p-value 0.151		0.770 [0.520-1.141] p-value 0.193	
Family history of psoriasis	0.896 [0.711-1.130] p-value 0.355		0.837 [0.622-1.125] p-value 0.238		0.808 [0.538-1.215] p-value 0.306	
First-degree family history	0.937 [0.750-1.169] p-value 0.562		0.803 [0.602-1.071] p-value 0.135		1.018 [0.687-1.510] p-value 0.928	
Baseline PASI	1.004 [0.990-1.018] p-value 0.579		1.019 [1.002-1.037] p-value 0.031		0.995 [0.969-1.022] p-value 0.715	
CCI-score	**1.142 [1.013-1.288 p-value 0.030**	**1.168 [1.036-1.316] p-value 0.011**	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**

Table S1. Continued

Variables	Discontinuation for all reasons *Event = ineffectiveness, AE, ineffectiveness + AE, other reasons, deathHR [95% CI]*		Discontinuation due to ineffectiveness *Event = ineffectiveness, ineffectiveness + AE HR [95% CI]*		Discontinuation due to adverse events *Event = AE, ineffectiveness + AEHR [95% CI]*	
	Univariate	*Multivariable*	*Univariate*	*Multivariable*	*Univariate*	*Multivariable*
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**1.292	**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**
• IL-17	1.148 [0.766-1.722] p-value 0.504	[0.847-1.973] p-value 0.235	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
• IL-23	0.693 [0.342-1.405] p-value 0.309	0.388 [0.144-1.045] p-value 0.062	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

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.

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

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 3.3

Efficacy and safety of tildrakizumab in older patients: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 244 weeks

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Abstract

The evidence on treating older patients with psoriasis with modern biologics is scarce. This study compared the efficacy and safety of tildrakizumab among younger and older patients with psoriasis (< 65/≥ 65 years) in a post hoc analysis of 2 phase III trials (reSURFACE1/2, n = 1,862). Tildrakizumab 100 mg/200 mg was administered at weeks 0/4/every 12 weeks thereafter. At week 28, patients with ≥ 75% improvement in baseline Psoriasis Area and Severity Index (PASI75) in reSURFACE1 were re-randomized to the same tildrakizumab dose or placebo; in reSURFACE2, PASI75 responders to 200 mg were re-randomized to tildrakizumab 100 mg or 200 mg; PASI75 responders to 100 mg maintained their dose. At weeks 64/52 (reSURFACE1/2), PASI50 responders entered an extension period (weeks 256/244). Outcomes were proportion of patients with PASI < 3, Dermatology Life Quality Index (DLQI) 0/1, comorbidities, comedication, and side-effects. The proportion of patients with a PASI < 3 was similar and maintained (tildrakizumab 100 mg and 200 mg, week 244: 83.3% and 84.1%/92.3% and 100.0%); DLQI 0/1 proportions at week 52 were 66.8% and 72.0%/68.3% and 81.3%. Comorbidity and comedication were more common in older patients. The safety profile of tildrakizumab appeared favourable in both groups. Tildrakizumab in patients ≥ 65 years appears effective and safe in long-term psoriasis management. These findings might assist treatment selection and overcome treatment reluctance.

Significance

This study compared the efficacy and safety of tildrakizumab among younger and older adults with psoriasis (< 65/≥ 65 years). High and similar proportions of patients in both groups achieved improvement of skin lesions and disease-related quality of life during the first year, which was maintained up to 5 years. The most frequent side-effect was nasopharyngitis. Although older patients presented more comorbidities and comedication, they showed a similar and favourable safety profile, demonstrating that tildrakizumab appears to be a good and safe treatment for psoriasis in both older and younger patients with psoriasis.

Introduction

Psoriasis is a chronic inflammatory disease with a worldwide prevalence rate of approximately 2–3%.[1] Older patients (age ≥ 65 years) represent an increasing proportion of patients with psoriasis and 15% of them have moderate to severe disease.[2] With a steadily ageing population[3], physicians are faced with an increasing number of older patients with psoriasis. However, optimal treatment selection might be difficult due to the presence of comorbidities[4], comedication[5,6], and adverse events (AEs)[7], which also influence patient treatment preferences.[8]

Generally, biologics have demonstrated even better efficacy than conventional systemics[9,10], with lower rates of AE than conventional systemics.[10] However, the elderly population is often excluded from clinical trials based on age or on age-related factors (e.g. comorbidities)[11], and representation of older patients in the available trial literature is low. However, a recent registry reported that discontinuation of biologics due to AEs did not occur more frequently in older compared with younger patients.[12] Older patients tended to have more serious infections, non-melanoma skin cancer (NMSC) and malignancies than younger patients, possibly due to the ageing process and more extensive duration of disease.[9,13]

In the case of tildrakizumab (TIL), specifically, there is almost no evidence available regarding older patients, and the first report in clinical practice was provided by Ruggiero et al.[14] This study included only 6 older patients, but they reported similar results to those of randomized clinical trials.[15] Although biologics seem to be relatively safe, this limited evidence-based management could trigger treatment reluctance to prescribe (newer) biologics in older patients for fear of lower efficacy or worse tolerability. Thus, more robust, comprehensive data regarding biologics in older patients are needed.

The aim of the present study is to compare the pooled efficacy and safety of TIL 100 mg and 200 mg for 244 weeks among younger and older patients from the 2 pivotal reSURFACE trials (reSURFACE 1 and reSURFACE 2)[16], including long-term extension periods.[17,18]

Methods

This is a post hoc pooled analysis of 2 3-part, randomized, double-blind, placebo-controlled, parallel-group, phase III trials (reSURFACE 1 and reSURFACE 2, ClinicalTrials.gov NCT01722331 and NCT01729754) that evaluated the efficacy and safety of TIL in patients with moderate to severe chronic plaque psoriasis for up to 5 years.[17,18] reSURFACE 2 included etanercept as an active comparator.[16] reSURFACE 1 was conducted from 10 December 2012 to 28 October 2015. reSURFACE 2 was conducted from 12 February 2013 to 28 September 2015.

Main interventions

The main inclusion and exclusion criteria at baseline were similar between trials. Baseline study inclusion and exclusion criteria, patient characteristics, treatment, and methodology of these 2 pivotal clinical trials have been reported previously.[16,18] A total of 1,862 patients ≥ 18 years with moderate to severe chronic plaque psoriasis diagnosed ≥ 6 months prior to enrolment, with a body surface area ≥ 10%, a Physician's Global Assessment ≥ 3 and a Psoriasis Area and Severity Index (PASI) ≥ 12, were included (reSURFACE 1, n=772; reSURFACE 2, n=1,090).[16] In reSURFACE 1, patients were randomized to TIL 100 mg, 200 mg or placebo (2:2:1). In reSURFACE 2, patients were randomized to TIL 100 mg, 200 mg, placebo or etanercept 50 mg (2:2:1:2). Tildrakizumab was administered at weeks 0, 4 and every 12 weeks afterwards. Responders were defined as patients with ≥ 75% improvement in baseline PASI (PASI75). At week 28, PASI75 responders in reSURFACE 1 were re-randomized to continue with the same TIL dose or to receive placebo; in reSURFACE 2, PASI75 responders to TIL 200 mg were re-randomized to TIL 100 mg or 200 mg, while PASI75 responders to TIL 100 mg maintained the same dose. At week 64 (reSURFACE 1) or week 52 (reSURFACE 2), patients with ≥ 50% improvement from baseline PASI score entered an optional 192-week extension period, until week 256 (reSURFACE 1) or week 244 (reSURFACE 2).[17,18]

Both reSURFACE trials were conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki 1964, and its successive amendments. The study protocols received local institutional review board or ethics committee approvals. All patients gave informed consent to participate in the trials.

Main outcome measures

Medical history, including comorbidities and comedications, for each age group were summarized with descriptive statistics. Main efficacy outcomes were defined as the proportion of patients achieving absolute PASI < 3 over 5 years of treatment;

that is, at weeks 28, 52 and 244, and Dermatology Life Quality Index (DLQI)/DLQI-Relevant (DLQI-R) 0/1 responses at weeks 28 and 52. In the DLQI, non-relevant responses (NRR) are scored as having no impact on patient quality of life, artificially improving patients' DLQI scores.[19] The new DLQI-R scoring avoids the bias of the NRR option by adjusting the total score for relevant items.[20] Proportions of patients achieving absolute PASI < 5 and < 1 were also evaluated. Analyses were stratified by age groups and TIL dose, attending to the following groups: < 65 years and ≥ 65 years, TIL 100 mg and 200 mg.

Safety assessments included a description of AEs. Pre-specified treatment-emergent AEs (TEAEs) comprised severe infections, malignancies, NMSC, melanoma, confirmed extended major adverse cardiovascular events (MACE), injection site reaction and drug-related hypersensitivity reactions.[16,18] Adverse events were assessed at all study visits and classified according to age and dose split. Preferred terms from the Medical Dictionary for Regulatory Activities for each AE were assigned to the treatment dose that the patient was actively receiving when the AE occurred.

Statistical analysis

Current post hoc analyses focus on differences between age groups in demographics (including comorbidities and comedications), absolute PASI response, DLQI and DLQI-R response (by adjusting the total questionnaire score by the number of NNRs indicated by a patient)[21], and safety.

No formal hypothesis testing was performed for these post hoc analyses. All subjects randomized to TIL 100 mg and 200 mg who received at least 1 dose of study medication were included for week 28 efficacy analyses (TIL 100 mg: n = 593, 541 patients aged < 65 years and 52 patients aged ≥ 65 years; TIL 200 mg: n = 597, 547 patients aged < 65 years and 50 patients aged ≥ 65 years) **(Figure 1)**. All patients who were responders (i.e. PASI75) at week 28 and who continued treatment with the same TIL dose were included for the long-term efficacy analyses (weeks 52 and 244) (TIL 100 mg: n = 329, 303 patients aged < 65 years and 26 patients aged ≥ 65 years; TIL 200 mg: n = 227, 211 patients aged < 65 years and 16 patients aged ≥ 65 years) **(Figure 1).** Efficacy analyses used an observed case approach. A multiple imputation approach (10 imputations) was used for missing data as sensitivity analyses for the PASI outcome, as described previously.[18]

A mixed model was performed in the observed case population to evaluate possible changes in the absolute PASI at weeks 28 and 244 according to the following

independent factors: age group, treatment, week, prior biological therapy for psoriasis, smoking habit, diabetes mellitus, history of psoriatic arthritis. We also included the age group x week interaction term into the model (looking at whether the behaviour of the variable under study in the 2 age groups is different over time, regardless of treatment). The model was covaried by baseline PASI and body mass index (BMI). This analysis was repeated with a multiple imputation approach.

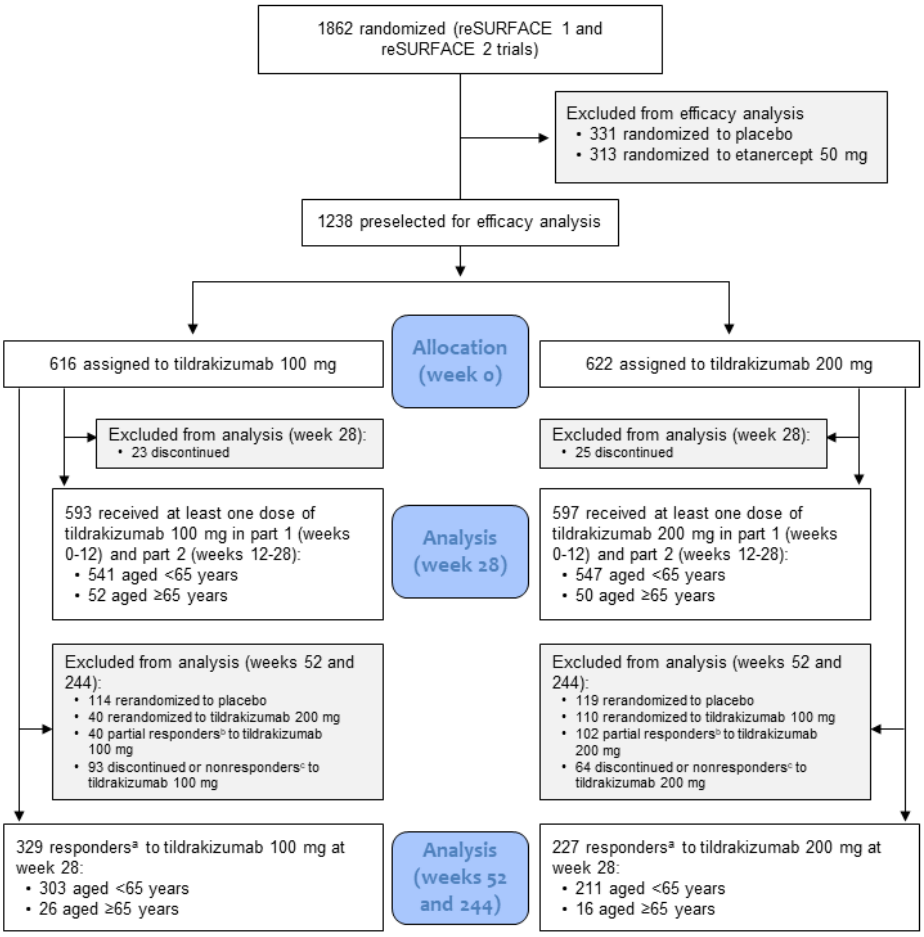

Figure 1. Patient disposition.

[a] Patients with ≥ 75% improvement in Psoriasis Area and Severity Index (PASI)

[b] patients with ≥ 50 to < 75% improvement in PASI.

[c] patients with < 50% improvement in PASI.

Analyses of comorbidities and comedications were performed in all randomized patients (n=1,190). Concomitant medications were collected over the 5-year study period. Safety analyses were performed in all patients who received at least 1 dose of study drug by treatment received (n=1,800). Safety data from week 0 to 5 years were pooled between reSURFACE 1 (up to week 256) and reSURFACE 2 (up to week 244) and presented for patients who received TIL during any part of the study with age of 65 years as the comparison threshold. Safety data are reported as number of events per 100 patient-years of exposure; exposure-adjusted incidence rates and 95% confidence intervals (95% CIs) were calculated as described previously.[16,18]

Analyses were performed with SAS software, version 9.4 (TS1M7) (© 2016 by SAS Institute INC, Cary, NC, USA), on the X64_10PRO platform for Windows, extension package SAS/STAT® software, version 15.2.

Results

Demographic and baseline characteristics

A summary of baseline characteristics is shown in **Table 1**. The percentage of women was slightly higher in the older vs younger group and baseline DLQI score was significantly lower in older vs younger patients ($p = 0.002$). The median (range) age for each age group was 44.0 (18.0–64.0) years in the younger, and 68.0 (65.0–82.0) years in the older group **(Figure S1).** Both age groups showed no differences in previous experience with systemic biologic or non-biologic treatments.

The most common comorbidities in patients < 65 years vs ≥ 65 years were musculoskeletal and connective tissue disorders (26.4% vs 43.1%, $p < 0.001$), metabolic and nutrition disorders (26.0% vs 56.9%, $p < 0.001$), vascular disorders (24.4% vs 70.6%, $p < 0.001$), and immune system disorders (22.3% vs 20.6%, $p = 0.80$). The complete medical history, with comorbidities, by age group is shown in **Table S1**. The proportions of patients < 65 years vs ≥ 65 years taking comedication at baseline were 56.3% vs 87.3%. **Table S2** shows comedication reported by patients over the 5-year study period.

Table 1. Demographic and baseline characteristics of the study population by age group and tildrakizumab dose.

	<65 years			≥65 years			p-value[c]
	100mg (n=541)	200mg (n=547)	Total (n=1088)	100mg (n=52)[a]	200mg (n=50)[b]	Total (n=102)	
Age, years, *n*, mean (SD)	541, 43.2 (11.3)	547, 43.8 (11.9)	1088, 43.5 (11.6)	52, 70.2 (4.6)	50, 68.4 (3.6)	102, 69.3 (4.3)	NA
Female, *n* (%)	161/541 (29.8)	142/547 (26.0)	303/1088 (27.9)	19/52 (36.5)	19/50 (38.0)	38/102 (37.3)	0.04
BMI, kg/m2, *n*, mean (SD)	540, 30.0 (7.1)	547, 29.8 (7.5)	1087, 29.9 (7.3)	51, 31.4 (7.5)	50, 30.1 (7.5)	101, 30.7 (7.5)	0.24
Weight, kg, *n*, mean (SD)	541, 89.1 (23.1)	547, 89.1 (23.2)	1088, 89.1 (23.1)	52, 91.2 (23.1)	50, 85.0 (17.8)	102, 88.2 (20.8)	0.70
PASI score, *n*, mean (SD)	541, 20.2 (7.9)	547, 20.3 (8.0)	1088, 20.2 (8.0)	52, 18.9 (6.2)	50, 19.8 (8.5)	102, 19.4 (7.4)	0.29
BSA,(%), *n*, mean (SD)	541, 31.7 (18.4)	542, 31.3 (17.4)	1083,31.5 (17.9)	52, 29.0 (13.2)	50, 32.4 (19.1)	102, 30.7 (16.3)	0.65
DLQI score, n, mean (SD)	538, 14.4 (7.0)	541, 13.5 (7.0)	1079, 13.9 (7.0)	52, 12.8 (7.6)	50, 10.4 (6.1)	102, 11.7 (6.9)	0.002
PsA, *n* (%)	89/541 (16.5)	87/547 (15.9)	176/1088 (16.2)	9/52 (17.3)	11/50 (22.0)	20/102 (19.6)	0.37
PGA ≥4, *n* (%)	177/541 (32.7)	185/547 (34.0)	362/1088 (33.4)	16/52 (30.8)	14/50 (28.0)	30/102 (29.4)	0.42
Previous experience with systemic biologic treatment, *n* (%)	94/541 (17.4)	95/547 (17.4)	189/1088 (17.4)	11/52 (21.2)	11/50 (22.0)	22/102 (21.6)	0.29
Previous experience with systemic non-biologic treatment, *n* (%)[d]	174/541 (32.1)	194/547 (35.5)	368/1088 (33.8)	16/52 (30.8)	10/50 (20.0)	26/102 (25.5)	0.09

[a] n=26 after W28 re-randomization

[b] n=16 after W28 re-randomization

[c] Students t-tests are used for numerical variables and $\chi 2$ tests for categorical data. Comparisons involve the 2 total age groups;

[d] Excluding phototherapy.

When presenting percentages, numerator and denominator are reported.

BMI: body mass index; BSA: body surface area; DLQI: Dermatology Life Quality Index; NA: not applicable; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; PsA: psoriatic arthritis; SD: standard deviation; w: week.

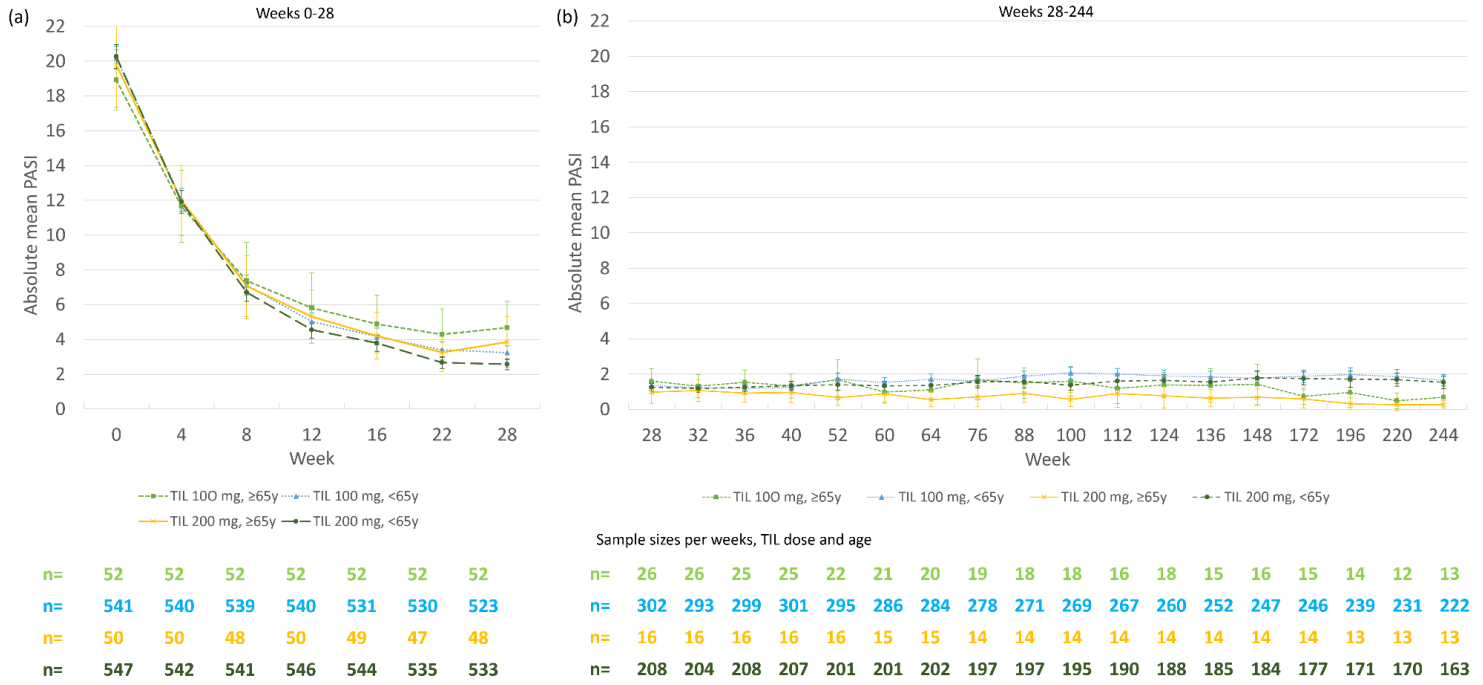

Figure 2. Mean of absolute Psoriasis Area and Severity Index (PASI) by age group and Tildrakizumab (TIL) dose over time (observed case approach).

(**a**) 0-28 weeks.

(**b**) 28-244 weeks.

Bars indicate the 95% confidence interval. The number of patients with available PASI scores over time is shown at the bottom.

y: years.

Efficacy outcomes

PASI score. **Figure 2** shows the absolute mean PASI score over time by age group and TIL dose. Throughout the first 28 weeks, and especially between weeks 0 and 8, a decrease in the absolute mean PASI was observed in the 2 age groups and for each dose, from mean scores of ≥ 19 at baseline to means ≤ 6 from week 12. This trend was then maintained until week 244. The proportion (95% CI) of TIL-treated patients aged < 65 vs ≥ 65 years achieving an absolute PASI < 3 for TIL 100 mg at week 28 was 66.4% (62.1–70.4%) vs 51.9% (37.6–66.0%). At week 244, it was 83.3% (77.8–88.0%) vs 92.3% (64.0–99.8%). The proportion (95% CI) of TIL-treated patients aged < 65 vs ≥ 65 years achieving an absolute PASI < 3 for TIL 200 mg at week 28 was 70.4% (66.3–74.2%) vs 58.3% (43.2–72.4%). At week 244, it was 84.1% (77.5–89.3%) vs 100.0% (75.3–100.0%) (comparison by age groups (combining TIL doses) week 244: p = 0.09). The proportions of patients with PASI < 5 coincided with those found for PASI < 3, with no differences between age groups at week 244. The proportions of patients with PASI < 1 was lower compared with PASI < 3 and < 5, with a slight tendency to show a benefit in patients aged ≥ 65 vs < 65 years at week 244 (see **Appendix S1**)**.**

Absolute mean PASI and absolute PASI < 3, < 5 and < 1 results evaluated by the sensitivity analysis (multiple imputation) is shown in **Figure S2** and **Appendix S2**, respectively.

There was no effect of age group on absolute PASI at weeks 28 and 244. There was a significant effect of baseline PASI, treatment, week and smoking status (p < 0.001) on absolute PASI at week 28. At week 244, there were significant effects on absolute PASI for baseline PASI (p < 0.001), treatment (p = 0.02), BMI (p = 0.001), prior biological therapy for psoriasis (p = 0.01), smoking status (p = 0.007), and the interaction term age group × week (p = 0.003) **(Table S3)**. The mixed model on PASI course for sensitivity analysis with multiple imputation is shown in **Table S4**.

DLQI and DLQI-R. The proportion (95% CI) of TIL-treated patients aged < 65 vs ≥ 65 years achieving a DLQI 0/1 for TIL 100 mg at week 28 was 53.8% (49.5–58.2%) vs 53.9% (39.5–67.8%), and at week 52, it was 66.8% (61.1–72.1%) vs 68.2% (45.1–86.1%). The proportion (95% CI) of TIL-treated patients aged < 65 vs ≥ 65 years achieving a DLQI 0/1 for TIL 200 mg at week 28 was 61.1% (56.8–65.3%) vs 60.4% (45.3–74.2%), and at week 52 it was 72.0% (65.2–78.1%) vs 81.3% (54.4–96.0%) (see **Figure 3**) (comparison by age groups (combining TIL doses) at week 52: p = 0.54). The absolute mean DLQI scores and DLQI-R results are shown in **Appendix S3**. The mean absolute DLQI and DLQI-R scores were similar, except for patients aged ≥ 65 years for TIL 100

mg at week 28, where the mean DLQI-R was higher (4.5 (5.2) vs 3.4 (3.9)). The proportions of patients for each age group maintained the same trend for DLQI-R as those observed for DLQI, although the proportions are lower for the former.

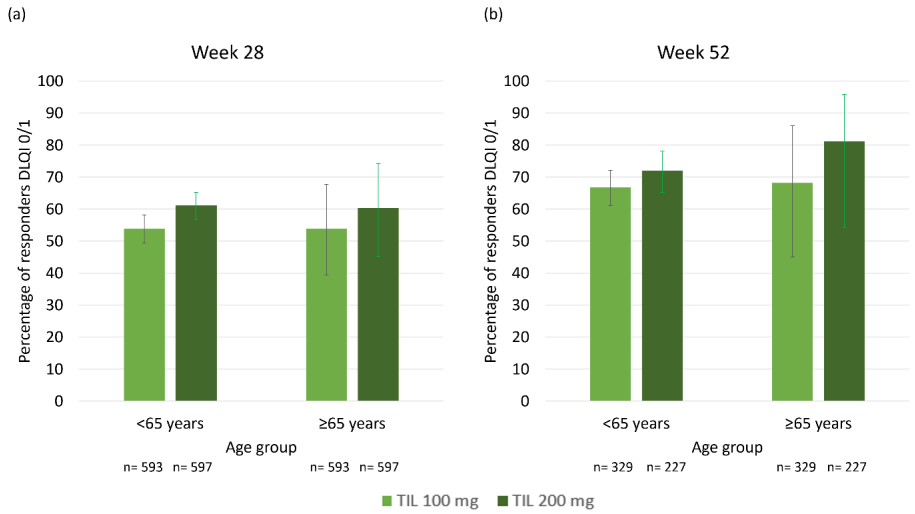

Figure 3. Percentage of patients achieving Dermatology Life Quality Index (DLQI) 0/1 by age group and tildrakizumab (TIL) dose at weeks 28 and 52 (observed case approach).
Bars indicate the 95% confidence interval (95% CI).

Safety outcomes

Summary of exposure adjusted rates of AEs attending TIL dose and age are shown in **Table 2**. The cumulative incidence of TEAEs for TIL 100 mg/TIL 200 mg in patients < 65 vs ≥ 65 years was 4,717/5,032 vs 515/545 per 100 patient-years of exposure, within which the highest cumulative incidence of infections were 621/592 vs 23/51 per 100 patient-years of exposure for nasopharyngitis, followed by 168/203 vs 11/10 for other upper respiratory tract infection, and 76/94 vs 3/10 for influenza.

With regards to TEAEs of special interest, the cumulative incidence for TIL 100 mg/TIL 200 mg in patients < 65 years vs patients ≥ 65 years was 17/11 vs 4/6 per 100 patient-years of exposure for malignancy excluding NMSC, 6/10 vs 8/6 for NMSC, and 14/21 vs 1/3 for confirmed extended MACEs.

A total of 6 (0.2%) drug-related serious AEs (SAEs) per 100 patient-years of exposure (100 mg TIL)/4 (0.2%) (200 mg TIL) led to discontinuation in the younger group, and 3 (12.5%)/1 (0.5%) in the older group. The specific drug-related SAEs are shown in **Table 4**.

Table 2. Exposure-adjusted rates of adverse events (AEs) and treatment-emergent AEs (TEAEs) by age group and tildrakizumab dose.

	<65 years		≥65 years	
	100mg (n=793)	**200mg (n=846)**	**100mg (n=79)**	**200mg (n=82)**
Total follow-up, patient-year	2487.7	2531.6	200.7	221.9
Any SAE	205 (8.2) [7.1-9.4]	206 (8.1) [7.0-9.3]	44 (21.9) [15.3-28.5]	39 (17.6) [12.0-23.2]
Drug-related SAEs	18 (0.7) [0.4-1.1]	11 (0.4) [0.2-0.7]	6 (3.0) [0.6-5.4]	5 (2.3) [0.2-4.3]
SAEs leading to discontinuation	22 (0.9) [0.5-1.3]	16 (0.6) [0.3-1.0]	9 (4.5) [1.5-7.5]	7 (3.2) [0.8-5.5]
Drug-related SAEs leading to discontinuation	6 (0.2) [0.0-0.4]	4 (0.2) [0.0-0.3]	3 (1.5) [0.0-3.2]	1 (0.5) [0.0-1.4]
Any TEAE	4717 (189.6) [184.1-195.1]	5032 (198.8) [193.2-204.4]	515 (256.6) [234.0-279.2]	545 (245.6) [224.6-266.7]
Drug-related TEAEs	752 (30.2) [28.1-32.4]	989 (39.1) [36.6-41.6]	41 (20.4) [14.1-26.8]	51 (23.0) [16.6-29.4]
TEAEs leading to discontinuation	42 (1.7) [1.2-2.2]	30 (1.2) [0.8-1.6]	10 (5.0) [1.8-8.1]	10 (4.5) [1.7-7.4]
Drug-related AEs leading to discontinuation	16 (0.6) [0.3-1.0]	8 (0.3) [0.1-0.5]	3 (1.5) [0.0-3.2]	2 (0.9) [0.0-2.2]
Deaths	9 (0.446) [0.1-0.6]	4 (0.2) [0.0-0.3]	2 (1.0) [0.0-2.4]	1 (0.5) [0.0-1.4]
TEAEs of special interest				
Severe infection[a]	31 (1.3) [0.8-1.7]	41 (1.6) [1.1-2.1]	7 (3.5) [0.9-6.1]	7 (3.2) [0.8-5.5]
Malignancy excluding NMSC	17 (0.7) [0.4-1.0]	11 (0.4) [0.2-0.7]	4 (2.0) [0.0-4.0]	6 (2.7) [0.5-4.9]
NMSC	6 (0.2) [0.0-0.4]	10 (0.4) [0.2-0.6]	8 (4.0) [1.2-6.8]	6 (2.7) [0.5-4.9]
Confirmed extended MACE	14 (0.6) [0.3-0.9]	21 (0.8) [0.5-1.2]	1 (0.5) [0.0-1.5]	3 (1.4) [0.0-2.9]
Injection-site reaction	66 (2.7) [2.0-3.3]	81 (3.2) [2.5-3.9]	1 (0.5) [0.0-1.5]	5 (2.3) [0.2-4.3]
Drug-related hypersensitivity reaction	14 (0.6) [0.3-0.9]	5 (0.2) [0.0-0.4]	0	0

Data shown as *n* (number of events per 100 patient-years of exposure) [95% CI]. [a] Severe infection was defined as any infection meeting the regulatory definition of a serious AE (i.e. resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or required intervention to prevent 1 of the other outcomes listed), or any infection requiring intravenous antibiotic.
95% CI: 95% confidence interval; MACE: major adverse cardiovascular event; NMSC: non-melanoma skin cancer; SAEs: serious AEs.

Table 3. Drug-related exposure-adjusted rates of serious adverse events by age group and tildrakizumab dose.

		< 65 years
	100 mg (*n* = 793)	**200 mg (*n* = 846)**
Total follow-up, patient-year	2,487.7	2,531.6
Angina pectoris	1 (0.0) [0.0- 0.1]	0
Appendicitis	1 (0.0) [0.0- 0.1]	0
Benign biliary neoplasm	0	0
Bile duct stone	0	0
Bone tuberculosis	0	1 (0.0) [0.0- 0.1]
Breast cancer	1 (0.0) [0.0- 0.1]	1 (0.0) [0.0- 0.1]
Carotid artery stenosis	1 (0.0) [0.0- 0.1]	0
Cellulitis	0	1 (0.0) [0.0- 0.1]
Cerebral infarction	1 (0.0) [0.0- 0.1]	0
Cerebrovascular accident	1 (0.0) [0.0- 0.1]	0
Chronic obstructive pulmonary disease	0	1 (0.0) [0.0- 0.1]
Diverticulitis	1 (0.0) [0.0- 0.1]	0
Epiglottitis	0	1 (0.0) [0.0- 0.1]
Gastroenteritis	1 (0.0) [0.0- 0.1]	0
Headache	0	0
Hypertensive crisis	1 (0.0) [0.0- 0.1]	0
Large intestine infection	0	1 (0.0) [0.0- 0.1]
Large intestine polyp	0	1 (0.0) [0.0- 0.1]
Lung neoplasm malignant	1 (0.0) [0.0- 0.1]	0
Meningitis viral	0	1 (0.0) [0.0- 0.1]
Mesenteric artery thrombosis	1 (0.0) [0.0- 0.1]	0
Metastatic carcinoma of the bladder	1 (0.0) [0.0- 0.1]	0
Non-Hodgkin's lymphoma	1 (0.0) [0.0- 0.1]	0
Pneumonia	1 (0.0) [0.0- 0.1]	0
Pneumonia mycoplasma	0	1 (0.0) [0.0- 0.1]
Psoriasis	0	1 (0.0) [0.0- 0.1]
Rectal adenocarcinoma	1 (0.0) [0.0- 0.1]	0
Thyroid cancer	1 (0.0) [0.0- 0.1]	0
Thyrotoxic crisis	1 (0.0) [0.0- 0.1]	0
Tonsillitis	1 (0.0) [0.0- 0.1]	0
Urosepsis	0	0
Wound infection	0	1 (0.0) [0.0- 0.1]
		≥ 65 years

Table 3. Continued

	100 mg (n = 79)	200 mg (n = 82)
Total follow-up, patient-year	200.7	221.9
Appendicitis	0	1 (0.5) [0.0- 1.4]
Basal cell carcinoma	0	1 (0.5) [0.0- 1.4]
Bladder transitional cell carcinoma	1 (0.5) [0.0- 1.5]	0
Cardiac failure chronic	1 (0.5) [0.0- 1.5]	0
Diffuse large B-cell lymphoma	1 (0.5) [0.0- 1.5]	0
Gastric polyps	0	1 (0.5) [0.0- 1.4]
Herpes zoster	0	1 (0.5) [0.0- 1.4]
Loss of consciousness	1 (0.5) [0.0- 1.5]	0
Peripheral arterial occlusive disease	1 (0.5) [0.0- 1.5]	0
Peritonitis	0	1 (0.5) [0.0- 1.4]
Septic arthritis staphylococcal	1 (0.5) [0.0- 1.5]	0

Data shown as n (number of events per 100 patient-years of exposure) [95% confidence interval (CI)].

Discussion

The increasing number of elderly patients (≥65 years) with moderate to severe psoriasis in daily practice represents a challenge for dermatologists. However, evidence in this patient population is limited to a few biological agents and small-molecule inhibitors.[22] This is one of the first studies to depict the efficacy and safety data of TIL for older vs younger patients from randomized clinical trials. This comparison is important because of possible differences in patient profile and the increasing number of older patients with psoriasis needing a safe and effective treatment. TIL in patients ≥ 65 years appears to be effective and safe in long-term psoriasis management, which was comparable to younger patients.

Differences in comorbidities were evident between both age groups. The current study found a higher proportion of musculoskeletal, metabolic, and vascular disorders, proportionally, in older patients. These disorders are more common in old age[23-25], and have been (partially) related to the existence of psoriasis.[26-28] Biologics appear to have a good safety profile and are usually well tolerated. In addition, in terms of comedication, older patients had a higher intake of drugs related to cardiac or gastric problems. Since TIL is cleared from the body by general protein catabolism processes, and is not eliminated by renal or hepatic pathways, no interaction between TIL and the comedications taken in this population has been described.[29]

Although the current study found some differences among the presence of comorbidities and comedication, comparable long-term PASI and DLQI responses were found in younger and older patients, independently of the administration dose, without safety concerns. In the long-term (week 244), the current study found that more than 80% and 90% of younger and older patients, respectively, showed a PASI < 3. These results are consistent with other studies on the long-term effects of different biologics on PASI responses.[30]

The proportion of subjects with at least 1 NRR in the DLQI was higher for the older group, which also showed a significantly lower baseline DLQI level. Non-relevant responses on the DLQI may be associated with an underestimation of disease severity.[31] In patients with psoriasis who marked 1 or more NRRs, the DLQI-R seems more sensitive compared with the DLQI[32], with the rates of patients with psoriasis with NRRs being higher for older patients.[33] The current study showed that the proportions of patients with DLQI-R 0/1 were similar and/or slightly lower compared with the DLQI 0/1. In this sense, the improved measurement properties of the new DLQI-R score in psoriasis are well established.[21, 34–36]

Safety analysis showed a favourable tolerability profile in both age groups. Adverse events were consistent with the rates observed in other clinical trials with biologics.[37] In terms of infection, both age groups showed a similar profile, sharing the highest incidence of nasopharyngitis and other respiratory tract infection, in line with those of phase II–III trials with biologics[38,39] and available real-world evidence (RWE) registries[40], with no new safety evidence. However, in terms of TEAEs of special interest, older patients showed proportionally more cases of cardiovascular events, NMSC and other malignancies compared with younger patients, as previously described in the literature[13], most likely related to the ageing process and the longer psoriatic disease duration, and not due to the psoriatic treatment administered. In general, these results demonstrate the potential benefit of TIL in older patients without affecting their safety profile.

Limitations

This study has some limitations. The main limitation is the relatively small number of older patients. In addition, older patients with extensive multimorbidity and/or polypharmacy are less likely to be included in clinical trials. The investigated older patients may still be a relatively healthy older group, as they passed the clinical trial inclusion and exclusion criteria. In this vein, exclusion criteria for reSURFACE trials are not based on (or represent) RWE. For example, some of the common comorbidities associated with psoriasis or its variants (psoriatic arthritis, erythrodermic psoriasis) were exclusion criteria in the reSURFACE studies, as well as recurrent infections.[41-43] In addition, patients with extensive pre-treatment were excluded, as they had to wait until their psoriasis showed a PASI ≥ 12. In clinical practice, this is not feasible, under-representing to the trial populations what clinicians see in daily clinical practice. Despite the fact that some data indicate that patients treated in routine practice with TIL differed substantially from those included in phase III studies[44], a RWE study has recently confirmed that there is no efficacy-effectiveness gap for TIL.[45] Further research with a larger number of older patients in a real-world setting is needed to confirm these preliminary results. Another limitation is the lack of age-randomized groups and control settings.

Conclusion

In these current post hoc analyses, TIL demonstrated long-term control with a favourable safety in patients below and above 65 years of age. This confirms the limited RWE on the clinical effectiveness of TIL in older patients with moderate to severe psoriasis. Despite the differences between the age groups in terms of comorbidities and comedications, these results indicate a similar percentage improvement in disease severity in the 2 age groups, with comparable improvements in quality of life and without major safety issues. Further confirmatory studies are desirable, with dedicated and real-world trials to better understand the profile of biological management of this group of patients.

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Supplemental material

Table S1. Medical history, including comorbidities[a], by age group.

	<65 years n=1088	**≥65 years n=102**	**P value**
Blood and lymphatic system disorders	23 (2.1)	1 (1.0)	.71
Cardiac disorders	50 (4.6)	13 (12.8)	.002
Congenital, familial and genetic disorders	21 (1.9)	2 (2.0)	1.00
Ear and labyrinth disorders	32 (2.9)	11 (10.8)	.001
Endocrine disorders	55 (5.1)	15 (14.7)	.001
Eye disorders	63 (5.8)	17 (16.7)	<.001
Gastrointestinal disorders	164 (15.1)	26 (25.5)	.010
General disorders and administration site conditions	35 (3.2)	7 (6.9)	.08
Hepatobiliary disorders	39 (3.6)	6 (5.9)	.27
Immune system disorders	243 (22.3)	21 (20.6)	.80
Infections and infestations	146 (13.4)	17 (16.7)	.37
Injury. poisoning and procedural complications	64 (5.9)	5 (4.9)	.83
Metabolism and nutrition disorders	283 (26.0)	58 (56.9)	<.001
Musculoskeletal and connective tissue disorders[b]	287 (26.4)	44 (43.1)	<.001
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	45 (4.1)	11 (10.8)	.006
Nervous system disorders	136 (12.5)	16 (15.7)	.35
Pregnancy, puerperium and perinatal conditions	4 (0.4)	0 (0)	NA
Psychiatric disorders	194 (17.8)	23 (22.6)	.23
Renal and urinary disorders	50 (4.6)	8 (7.8)	.15
Reproductive system and breast disorders	52 (4.8)	16 (15.7)	<.001
Respiratory, thoracic and mediastinal disorders	124 (11.4)	20 (19.6)	.02
Social circumstances	39 (3.6)	9 (8.8)	.02
Surgical and medical procedures	221 (20.3)	31 (30.4)	.02
Vascular disorders	265 (24.4)	72 (70.6)	<.001

Data shown as No. (%).[a] Comorbidities defined as diseases in the medical history that are classically considered to be associated/related/derived from psoriasis; [b] Including psoriatic arthritis.
NA: Not Applicable.

Table S2. Concomitant medications over the 5-year study period.

	From baseline to W28		W28 to W52		W52 to W244	
	≥65 years (n=102)	<65 years (n=1088)	<65 years (n=514)	≥65 years (n=42)	<65 years (n=514)	≥65 years (n=42)
ACE inhibitors	23 (22.6)	81 (7.4)	37 (7.2)	9 (21.4)	65 (12.7)	12 (28.6)
Acetic acid derivatives	2 (2.0)	38 (3.5)	3 (7.1)	15 (2.9)	62 (12.1)	6 (14.3)
Amides	3 (2.9)	18 (1.7)	3 (7.1)	9 (1.8)	41 (8.0)	4 (9.5)
Aminoalkyl ethers	3 (2.9)	29 (2.7)	1 (2.4)	17 (3.3)	28 (5.5)	3 (7.1)
Angiotensin II antagonists	23 (22.6)	73 (6.7)	37 (7.2)	9 (21.4)	35 (6.8)	9 (21.4)
Angiotensin II receptor blockers	NA	NA	NA	NA	47 (9.14)	11 (26.2)
Anilides	11 (10.8)	188 (17.3)	74 (14.4)	7 (16.7)	149 (29.0)	13 (31.0)
Benzodiazepine derivatives	5 (4.9)	57 (5.2)	30 (5.8)	3 (7.1)	57 (11.1)	9 (21.4)
Beta blocking agents	17 (16.7)	54 (5.0)	26 (5.1)	6 (14.3)	35 (6.8)	7 (16.7)
Biguanides	13 (12.8)	62 (5.7)	31 (6.0)	4 (9.5)	46 (9.0)	6 (14.3)
First generation cephalosporins	3 (2.9)	21 (1.9)	1 (2.4)	6 (1.2)	31 (6.0)	1 (2.4)
Third generation cephalosporins	1 (1.0)	14 (1.3)	1 (1.0)	14 (1.3)	27 (5.3)	3 (7.1)
Dihydropyridine derivatives	17 (16.7)	46 (4.2)	8 (19.1)	20 (3.9)	37 (7.2)	13 (31.0)
Fluoroquinolones	2 (2.0)	31 (2.9)	1 (2.4)	16 (3.1)	69 (13.4)	5 (11.9)
Glucocorticoids	5 (4.9)	40 (3.7)	29 (5.6)	5 (11.9)	78 (15.2)	8 (19.1)
Heparin	3 (2.9)	6 (0.6)	NA	9 (1.8)	26 (5.1)	2 (4.8)
HMG CoA reductase inhibitors	34 (33.3)	98 (9.0)	52 (10.1)	11 (26.2)	74 (14.4)	18 (42.9)
Influenza vaccines	8 (7.8)	29 (2.7)	6 (14.3)	13 (2.5)	34 (6.6)	9 (21.4)
Macrolides	8 (7.8)	32 (2.9)	2 (4.8)	14 (2.7)	53 (10.3)	6 (14.3)
Mucolytics	4 (3.9)	17 (1.6)	1 (2.4)	7 (1.4)	29 (5.6)	4 (9.5)
Opioids combined with non-opioid analgesics	NA	NA	NA	NA	32 (6.2)	2 (4.8)
Combination of penicillins (including beta-lactamase inhibitors)	NA	12 (1.1)	NA	12 (1.1)	35 (6.8)	3 (7.1)
Penicillins with extended spectrum	6 (5.9)	36 (3.3)	6 (5.9)	36 (3.3)	68 (13.2)	8 (19.1)
Propionic acid derivatives	12 (11.8)	188 (17.3)	95 (18.5)	6 (14.3)	171 (33.3)	12 (28.6)
Proton pump inhibitors	17 (16.7)	83 (7.6)	54 (10.5)	13 (31.0)	107 (20.8)	14 (33.3)

Table S2. Continued

	From baseline to W28		W28 to W52		W52 to W244	
	≥65 years (n=102)	<65 years (n=1088)	<65 years (n=514)	≥65 years (n=42)	<65 years (n=514)	≥65 years (n=42)
Salicylic acid & derivatives	31 (30.4)	98 (9.0)	51 (10.5)	12 (28.6)	85 (16.5)	14 (33.3)
Selective beta-2-adrenoceptor agonists	5 (4.9)	30 (2.8)	5 (4.9)	30 (2.8)	36 (7.0)	1 (2.4)
Selective serotonin reuptake inhibitors	7 (6.9)	62 (5.7)	35 (6.8)	3 (7.1)	48 (9.3)	6 (14.3)
Thyroid hormones	14 (13.7)	42 (3.9)	29 (5.6)	8 (19.1)	33 (6.4)	8 (19.1)

Data shown as No. (%). Only concomitant medications present in at least 5% of one of the groups are reported.
ACE: Angiotensin-Converting-Enzyme; HMG CoA: Hydroxymethylglutaryl-CoA; NA: Not Applicable; W: week.

Table S3. Mixed model on the evolution of absolute PASI at weeks 28 and 244 (observed case approach).

	Week 28	Week 244
Effect	**P value**	
Age group	.53	.10
PASI baseline	<.001	<.001
Treatment	<.001	.02
BMI (kg/m^2)	.30	.001
Week	<.001	.15
Prior biological therapy for psoriasis	.37	.014
Smoking habit	<.001	.007
Diabetes	.54	.57
History of psoriatic arthritis	.14	.86
Age group x week	.46	.003

BMI: Body Mass Index; PASI: Psoriasis Area and Severity Index.

Table S4. Mixed model on the evolution of absolute PASI at weeks 28 and 244 (multiple imputation approach).

	Week 28	Week 244
Effect	**P value**	
Intercept	<.001	.94
Age group	.18	.07
PASI baseline	<.001	<.001
Treatment	<.001	.13
BMI (kg/m^2)	.32	.02
Week		
0 versus 28 (W28) / 28 versus 244 (W244)	<.001	.01
4 versus 28 (W28) / 32 versus 244 (W244)	<.001	.001
8 versus 28 (W28) / 36 versus 244 (W244)	<.001	.001
12 versus 28 (W28) / 40 versus 244 (W244)	<.001	.008
16 versus 28 (W28) / 52 versus 244 (W244)	<.001	.71
22 versus 28 (W28) / 60 versus 244 (W244)	.31	.18
64 versus 244 (W244)	NA	.75
76 versus 244 (W244)	NA	.98
88 versus 244 (W244)	NA	.28
100 versus 244 (W244)	NA	.22
112 versus 244 (W244)	NA	.10
124 versus 244 (W244)	NA	.23
136 versus 244 (W244)	NA	.47
148 versus 244 (W244)	NA	.20
172 versus 244 (W244)	NA	.09
196 versus 244 (W244)	NA	.10
220 versus 244 (W244)	NA	.27
Prior biological therapy for psoriasis	.44	.002
Smoking habit		
Current user versus never used tobacco	<.001	.004
Ex user versus never used tobacco	.59	.79
Diabetes	.69	.62
History of psoriatic arthritis	.12	.79
Age group x week		
0 versus 28 (W28) / 28 versus 244 (W244)	.02	.05
4 versus 28 (W28) / 32 versus 244 (W244)	.13	.06
8 versus 28 (W28) / 36 versus 244 (W244)	.45	.04
12 versus 28 (W28) / 40 versus 244 (W244)	.65	.11

Table S4. Continued

	Week 28	Week 244
16 versus 28 (W28) / 52 versus 244 (W244)	.82	.27
22 versus 28 (W28) / 60 versus 244 (W244)	.83	.49
64 versus 244 (W244)	NA	.60
76 versus 244 (W244)	NA	.21
88 versus 244 (W244)	NA	.37
100 versus 244 (W244)	NA	.63
112 versus 244 (W244)	NA	.70
124 versus 244 (W244)	NA	.46
136 versus 244 (W244)	NA	.62
148 versus 244 (W244)	NA	.73
172 versus 244 (W244)	NA	.92
196 versus 244 (W244)	NA	1.00
220 versus 244 (W244)	NA	.78

BMI: Body Mass Index; NA: Not Applicable; PASI: Psoriasis Area and Severity Index; W: week.

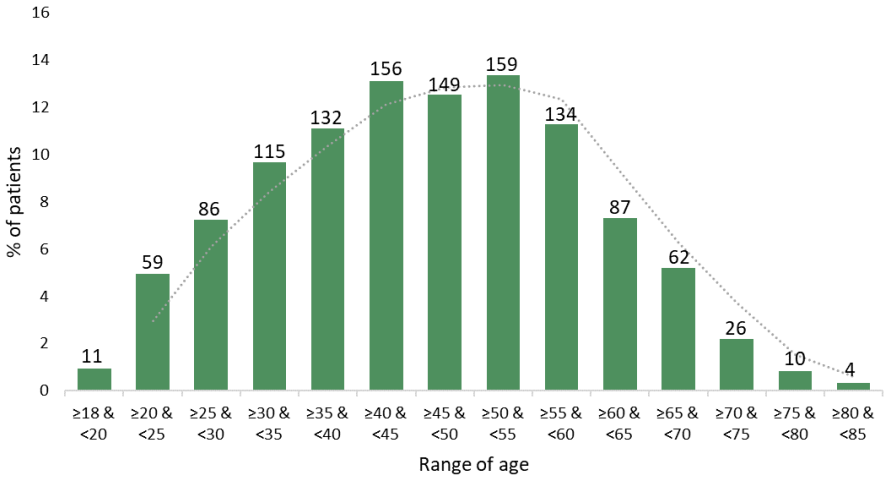

Figure S1. Percentage distribution of patients by age quintiles.

Pooled dose subgroups: n=593 (TIL 100 mg) + n=597 (TIL 200 mg), total n=1,190. In columns, number of patients. Line: moving average.

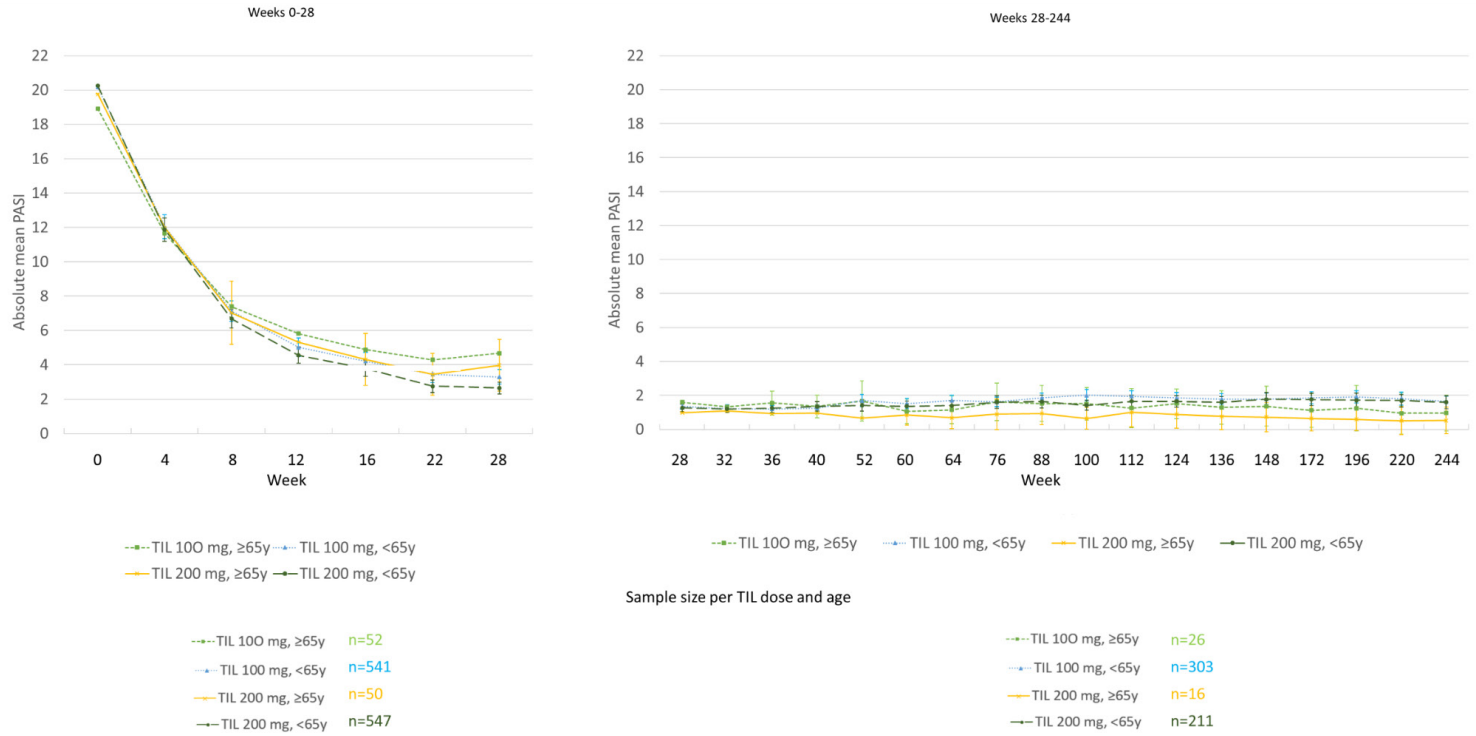

Figure S2. Mean of absolute PASI by age group and TIL dose over time (sensitivity analysis with the multiple imputation approach).

The bars indicate the 95% CI. The number of patients with available PASI scores over time is shown at the bottom. Multiple imputation (10 imputations): if there are equal values for 10 imputations, the 95% CI is not calculated.

CI: Confidence Interval; PASI: Psoriasis Area and Severity Index; TIL: Tildrakizumab.

Supplemental appendices

APPENDIX S1

Efficacy outcomes: PASI score <5 and <1 using the observed case approach

The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<5 for TIL 100 mg at week 28 was 78.4% (74.6-81.9%) versus 65.4% (50.9-78.0%). At week 244, it was 91.0% (86.4-94.4%) versus 100.0% (75.3-100.0%). The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<5 for TIL 200 mg at week 28 was 82.1% (78.7-85.3%) versus 68.8% (53.8-81.4%). At week 244, it was 91.4% (86.0-95.2%) and 100.0% (75.3-100.0%) (comparison by age groups [combining TIL doses] at week 244: *P*=.113).

The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<1 for TIL 100 mg at week 28 was 41.1% (36.9-45.5%) versus 26.9% (15.6-41.0%). At week 244, it was 51.4% (44.6-58.1%) versus 61.5% (31.6-86.1%). The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<1 for TIL 200 mg at week 28 was 44.5% (40.2-48.8%) versus 37.5% (24.0-52.7%). At week 244, it was 58.3% (50.3-65.9%) versus and 92.3% (64.0-99.8%) (comparison by age groups [combining TIL doses] at week 244: *P*=.025).

APPENDIX S2

Efficacy outcomes: PASI score <3, <5 and <1 using the multiple imputation approach

The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<3 for TIL 100 mg at week 28 was 65.9% (61.8-69.9%) versus 51.9% (37.6-66.0%). At week 244, it was 75.7% (70.5-80.5%) versus 71.5% (50.9-87.0%). The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<3 for TIL 200 mg at week 28 was 69.4% (65.4-73.3%) versus 57.2% (42.4-71.1%). At week 244, it was 77.8% (71.6-83.2%) versus 93.1% (69.7-99.1%) (comparison by age groups [combining TIL doses] at week 244: *P*=.39).

The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<5 at week 28 for TIL 100 mg was 78.2% (74.5-81.6%) versus was 65.4% (50.9-78.0%). At week 244, it was 87.0% (82.7-90.6%) versus 88.1% (69.6-97.1%). The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<5 for TIL 200 mg at week 28 was 81.4% (77.9-84.6%) versus 67.6% (52.9-80.1%). At week 244, it was 88.5% (83.5-92.5%) versus 96.3% (73.8-99.8%) (comparison by age groups [combining TIL doses] at week 244: *P*=.49).

The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<1 for TIL 100 mg at week 28 was 40.9% (36.8-45.2%) versus 26.9% (15.6-41.0%). At week 244, it was 45.6% (39.9-51.4%) versus 46.5% (27.1-66.9%). The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving an absolute PASI<1 for TIL 200 mg at week 28 was 43.8% (39.6-48.1%) versus 36.2% (23.1-51.0%). At week 244, it was 52.7% (45.7-59.6%) versus 83.1% (56.7-96.5%) (comparison by age groups [combining TIL doses] at week 244: *P*=.23).

APPENDIX S3

DLQI and DLQI-R using the observed case approach

The absolute mean (standard deviation, SD) DLQI in TIL-treated patients aged <65 years versus ≥65 years for TIL 100 mg at week 28 was 3.0 (3.9) versus 3.4 (4.3). At week 52, it was 2.1 (3.4) versus was 1.5 (2.9). The absolute mean (SD) DLQI in TIL-treated patients aged <65 years versus ≥65 years for TIL 200 mg at week 28 was 2.3 (3.5) versus 2.7 (4.3). At week 52, it was 1.5 (2.9) versus 1.1 (2.0).

The mean change from baseline (SD) in DLQI in TIL-treated patients aged <65 years versus ≥65 years for TIL 100 mg at week 28 was -11.5 (7.0) versus -9.4 (6.1). At week 52, it was -12.7 (7.0) versus -10.6 (5.6). The mean change from baseline (SD) in DLQI in TIL-treated patients aged <65 years versus ≥65 years for TIL 200 mg at week 28 was -11.2 (7.0) versus -7.6 (6.7). At week 52, it was -11.6 (6.5) versus -10.3 (6.5).

The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving a DLQI-R 0/1 for TIL 100 mg at week 28 was 49.1% (42.9-55.35%) versus 36.0% (18.0-57.5%). At week 52, it was 65.0% (57.8-71.6%) versus 54.6% (23.4-83.3%). The proportion (95% CI) of TIL-treated patients aged <65 years versus ≥65 years achieving a DLQI-R 0/1 for TIL 200 mg at week 28 was 60.44% (54.3-66.2%) versus 54.66% (32.2-75.6%). At week 52, it was 66.7% (56.3-76.0%) versus 87.5% (47.4-99.7%) (comparison by age groups [combining TIL doses] at week 52: *P*=.80).

The mean absolute (SD) DLQI-R in TIL-treated patients aged <65 years versus ≥65 years at week 28 for TIL 100 mg was 3.2 (4.4) versus 4.5 (5.2). At week 52, it was 1.9 (3.0) versus 2.3 (4.1). The mean absolute (SD) DLQI-R in TIL-treated patients aged <65 years versus ≥65 years at week 28 for TIL 200 mg was 2.3 (3.6) versus 2.4 (4.5). At week 52, it was 1.4 (2.3) versus 0.6 (1.1). The mean change from baseline (SD) in DLQI-R in TIL-treated patients aged <65 years versus ≥65 years at week 28 for TIL 100 mg was -12.5 (7.4) versus -9.5 (6.8). At week 52, it was -13.9 (7.0) versus -12.4 (6.4). The mean change from baseline (SD) in DLQI-R in TIL-treated patients aged <65 years versus ≥65 years at week 28 for TIL 200 mg was -12.0 (7.3) versus -7.5 (5.5). At week 52, it was -12.0 (6.5) versus -9.4 (5.2).

The mean (SD) DLQI NRRs in TIL-treated patients aged <65 years versus ≥65 years for TIL 100 mg at week 28 was 0.4 (1.0) versus 0.6 (0.9). At week 52, it was 0.4 (1.0) versus 0.9 (0.8). The mean (SD) DLQI NRRs in TIL-treated patients aged <65 years versus ≥65 years for TIL 200 mg at week 28 was 0.4 (1.2) versus 0.8 (1.2). At week 52, it was 0.4 (0.9) versus 0.3 (0.5).

Chapter 4

Summary, discussion, recommendations, and future perspectives

The growing population of older adults with psoriasis has been an underexposed group in research. Managing psoriasis in older adults can be challenging in daily clinical practice, as this population is notably diverse in terms of patient-related factors such as ageing-related changes in organ functioning, comorbidity, comedication use, frailty, and functional status. The aim of this thesis was to contribute to more evidence-based guidance for the personalised management of psoriasis in older adults.

4.1 Summary

In **chapter 2.1**, patient, disease, and treatment characteristics of older adults (≥65 years) with psoriasis compared to younger adults (<65 years) were investigated in a nationwide patient survey. This survey was sent to all members of the Dutch Psoriasis Association (n=3310). A total of 985 (29.7%) patients returned the survey, of which 414 (43.6%) were ≥65 years old. Comparable disease characteristics and disease severity were reported among the studied age groups. Comorbidity, comedication use, and functional dependency with using psoriasis treatment were significantly more common among older adults compared to younger adults. Still, no significant differences were observed between age groups concerning the use of systemic psoriasis treatment in general (38.3% in ≥65 years vs. 42.3% in <65 years; p=0.219) and the different types of systemic therapies used. Somewhat unexpectedly, treatment-related side effects were less often reported by older adults compared to younger adults in this study (19.8% in ≥65 years vs. 25.9% in <65 years; p=0.015). However, since this was a self-assessed survey, it is likely that patients did not report treatment-related asymptomatic laboratory deviations. Based on the findings of this survey, chronological age alone should not be a primary determinant when selecting a treatment for patients with psoriasis. Even though a favourable tolerability profile was reported in this study, specific attention to patient-related differences (e.g., comorbidity, comedication, functional dependency) is important, given their higher prevalence among older patients and their potential consequences.

With the increasing availability of treatment options for patients with psoriasis and the growing population of older adults affected by this disease, it is also important to evaluate potential unmet needs and treatment preferences in this population. In **chapter 2.2**, the second part of the earlier-described patient survey provided insight in the most bothersome disease aspects, quality of life (QoL), patient preferences, and treatment goals in older adults with psoriasis compared

to younger adults. Both age groups reported pruritus, scaling, and the visibility of psoriasis to be the most bothersome aspect of psoriasis. Psychological problems and stigmatization due to psoriasis were less often reported as bothersome by older patients compared to younger patients. The impact on health related QoL was measured by the Dermatology Life Quality Index (DLQI). A higher DLQI score represents a more severely impaired QoL. In younger patients, a higher mean DLQI score was reported compared to older patients (3.89 ± 4.55 vs. 2.98 ± 3.5; p=0.006). This finding indicates that older patients with psoriasis experience a lower QoL-impairment due to their skin disease compared to younger patients, even though a comparable disease severity was reported in this study population (see chapter 2.1). However, since some DLQI-items (e.g., sports and work) are often considered not relevant by older patients, in contrast to younger patients, correction for these items is important for an accurate interpretation of the influence of psoriasis on QoL. When correcting for these 'not relevant responses' (NRRs) using the Dermatology Life Quality Index-Relevant (DLQI-R), this significant difference among age groups dissolved. In this study, the use of the original DLQI in older adults resulted in an underestimation of the impact of psoriasis on QoL in this specific population. Based on our findings, it is therefore advised to use the DLQI-R instead of the DLQI when assessing QoL in older adults with psoriasis. This study also showed that patient preferences differed between age groups. Older adults valued minimizing topical treatment use, reducing subcutaneously administered treatment, decreasing hospital visits, and minimizing laboratory assessments as significantly more important than younger patients. For both age groups, a reduction of treatment-related adverse events (AEs) was valued as the most important patient preference. Treatment goals were highly comparable between age groups; to be free of pruritus, scaling, and visible psoriasis lesions were reported as the most relevant treatment goals in both age groups. However, visibility-related treatment goals, like complete clearance of all skin lesions, to be free of redness, and to be free of scaling were regarded as more important by older patients compared to younger patients (p=0.009, p=0.006, and p=0.003, respectively). Although comparable bothersome disease aspects and treatment goals were reported among the age groups, individual outcomes were very heterogeneous. This highlights the need of individualised attention for bothersome disease aspects, patient preferences, and treatment goals. As older adults with psoriasis are often excluded from randomized controlled trials (RCTs), a knowledge gap has emerged regarding this growing population. This exclusion is often based on chronological age (direct exclusion criterion), but also on excluding patients with certain comorbidities that affect older adult patients disproportionately (indirect exclusion criteria). Therefore, the external validity and generalizability of RCT findings might be limited when applied

to older adults with psoriasis. To determine the extent and repercussions of this exclusion, a comparison of comorbid disease status of older adults with psoriasis to the general population was conducted, and the impact of RCT exclusion criteria on a real-world psoriasis cohort was quantified in **chapter 2.3**. In this real-world study (n=230), a more extensive comorbid disease burden in older adults with psoriasis compared to older adults without psoriasis was observed. Depression ($p < 0.001$), skin cancer ($p < 0.001$), obesity ($p < 0.001$), hyperlipidaemia ($p < 0.05$) and being overweight ($p < 0.05$) were more prevalent in older adults with psoriasis compared to the general older Dutch population. This fits the general hypothesis that psoriasis increases the comorbidity risk considerably and underscores the need for prevention and management of psoriasis-associated comorbidity. Furthermore, in this real-world study chronological age, cardiovascular disease, and (history of) malignancy were identified as the most prevalent RCT exclusion criteria, thereby having the largest impact on the generalizability of evidence from RCTs to the real-world population of older adults with psoriasis. Considering this, there could be risks regarding medication safety, along with potential variation in efficacy outcomes. Therefore, it is crucial to be aware of these limitations when applying RCT results to this specific population. In addition, generating real-world evidence (RWE) for this age group is vital to establish the differences between the real-world population and patients included in RCTs.

While a comparable disease severity between older adults and younger adults with psoriasis has been reported, some research indicates that older adults tend to receive less systemic therapy.[1-3] To further investigate this possible treatment inequality and the role of healthcare providers in this context, a mixed-methods study comprising a survey and semi-structured interviews was conducted, as described in **chapter 2.4**. With this study, insights were gained into the prescribing patterns, comfort levels, barriers, and needs of Dutch dermatologists and dermatology residents when prescribing systemic therapy in older adults with psoriasis. Most survey respondents (67% of 73 respondents) reported applying systemic therapy to the same extent in older adults compared to younger patients with psoriasis. Moreover, around 69% of the respondents reported being not reluctant to prescribe systemic therapy in older adults. Nevertheless, age-based systemic treatment differences were still common in this study, as 27% of respondents were reluctant to use systemic therapy in older adults. Comorbidity, comedication use, and the risk of AEs were the most frequently reported reasons for this reluctance. Furthermore, most respondents (68%) performed additional actions when prescribing systemic treatment to older adults, e.g., more intensive monitoring of comorbidity and comedication use, (additional) consultations

with other specialists, prescribing lower dosages than standard practice, more frequent laboratory check-ups, more (directive) guidance during the treatment selection process, and more often initiating home care. Moreover, respondents in this study had less experience with prescribing biologics in this population compared to conventional systemic therapy, which is in line with other literature.[3] Respondents were least comfortable with prescribing ciclosporin and infliximab and most comfortable with methotrexate, acitretin, ustekinumab, and adalimumab in older adults with psoriasis. By conducting additional in-depth interviews with respondents, further insights were gained into the barriers and needs when prescribing systemic treatment in older adults with psoriasis. The identified barriers were similar to the most frequently reported reasons to be reluctant according to the survey: comorbidity, comedication use, and worry about AEs. Sparse evidence-based guidance regarding efficacy and safety of systemic treatment in geriatric psoriasis was also mentioned as an important reason for being reluctant to prescribe systemic treatment, especially in frail patients. The challenge of accurate frailty assessment and preventing misjudgement of patients' vulnerability (e.g., cognitive function, comprehension, mobility, and social support system), particularly within the limited consultation time available in clinical practice, was defined as a barrier. More evidence-based guidance, education, consultation time, and the use of frailty screening in individual situations were expressed needs to improve psoriasis management and prevent undertreatment in older adults with psoriasis.

In general, chronological age is often considered inadequate to predict treatment feasibility and treatment outcomes. However, frailty and (diminished) functional status, which become more prevalent with age, have been shown to be significantly related to adverse treatment outcomes in other medical fields. For patients with psoriasis, no research had been conducted on the presence and impact of frailty and functional dependency before. In the multicentre cross-sectional cohort study presented in **chapter 2.5**, we therefore investigated the extent of frailty and functional dependency in older adults with psoriasis and the possible implications for psoriasis management. In 102 older adults with psoriasis, three different frailty screening tools were applied: the Geriatric-8 (G8), Groningen Frailty Index (GFI), and Clinical Frailty Scale (CFS). These tools showed that 42.2% (G8), 26.0% (GFI), and 13.7% (CFS) of patients were (potentially) frail. Dependency regarding activities of daily living (ADL) and instrumental activities of daily living (iADL) were also prevalent among older adults with psoriasis, in 14.3% and 37.6% respectively. Approximately one quarter (27%) of the included patients required help with applying or using their psoriasis therapy, and these patients were more often frail or functional dependent compared to patients who did not require help with psoriasis

therapy. Furthermore, frail and functional dependent patients reported lower treatment satisfaction with their psoriasis therapy, measured by the Treatment Satisfaction Questionnaire for Medication (TSQM), than non-frail and functionally independent patients. Given the prevalence of frailty and functional dependency identified in this study and the management implications thereof, incorporating a frailty assessment tool into clinical practice could be beneficial for aiding treatment decision-making in geriatric psoriasis care. For instance, employing the CFS in clinical practice could be useful for identifying patients needing tailored management, since most management implications were observed among patients identified as frail through this screening tool. Moreover, the CFS is easy to use and can be rapidly deployed.

With the expanding range of systemic therapeutic options for psoriasis, guidance is crucial for selecting the most optimal and safe treatment, particularly in older adults. Factors influencing treatment selection include the safety profile, comorbidity, comedication use, functional status, disease severity, and patient preferences. Previous research showed considerable variability in AE rates and tolerability profile among older adults with psoriasis using systemic therapy.[4-6] As the prevalence of comorbidity and related health events increase with age, misclassification of an unrelated health event as a treatment-related AE might be more common in older adults. Consequently, interpreting safety data in older adults without causality assessment can be challenging. Therefore, in chapter 3.1, we investigated the reported AEs among a cohort of older patients using systemic therapy and provided an overview of these AEs, including a causality assessment. In this study, 117 patients (≥65 years) with psoriasis using systemic therapy, with 176 treatment episodes and a follow-up of 390 patients-years, were analysed. All AEs were assessed for causality with the used systemic therapy, using the WHO-UMC assessment system, consisting of five categories: certain (5), probable (4), possible (3), unlikely (2), unassessable (1) and conditional (0). The systemic therapies used were fumarates, acitretin, methotrexate, or biologicals. In total, 319 AEs and 28 serious adverse events (SAEs) were reported, of which 232 (72.7%) AEs and 12 (42.9%) SAEs were classified as possibly or probably related to the use of systemic therapy for psoriasis. Of the 12 SAEs occurring in 10 patients using systemic therapy, most concerned infections. Reassuringly, the possibly/probably related SAEs were reversable and/or manageable in clinical practice. Interestingly, increasing chronological age was associated with a higher AE rate (possibly/probably related AEs), but the presence of comorbidity and polypharmacy were not associated with a higher AE rate (possibly/probably related AEs) in this cohort. Moreover, no significant difference was observed between the types of systemic

therapy and possibly/probably related AE occurrence. To conclude, this study showed the importance of causality assessment of AEs, and the safety profile of systemic therapy in older adults with psoriasis in this study was reassuring.

Biologics are one of the latest additions to the array of therapeutic options for psoriasis. Selecting the most appropriate biological for an older adult might be challenging as the body of evidence regarding biologics in older adults is limited. To further strengthen this evidence, a comparison of drug survival, safety, and effectiveness of biologics between older adults and younger patients was performed in a multicentre real-world setting **(chapter 3.2)**. Reassuringly, the overall drug survival and drug survival regarding AEs were high and comparable between age groups. However, drug survival regarding effectiveness was significantly lower in older patients compared to younger patients. Hence, older adults discontinued their biologic treatment due to ineffectiveness more often than younger patients. Remarkably, PASI scores at discontinuation were slightly lower in older patients, although this difference was not statistically significant (median 7.8 (2.6 - 14.8) in ≥65 years vs. median 9.6 (0.00 – 34.4) in <65 years; p=0.347), possibly indicating a difference in needs or treatment burden among older adults. Aging-related factors, such as increased comorbidities, functional dependency, or polypharmacy may again explain this finding. In both age groups, infections were the most frequently observed AEs resulting in treatment discontinuation. Comfortingly, no SAEs resulting in treatment discontinuation were observed among older adults. Bearing in mind all results of this study, the treatment of older adults with the investigated biologics appears a well-tolerated and effective therapeutic choice.

As the development of new biologics for psoriasis is ongoing, safety and efficacy of these new agents need to be studied. Tildrakizumab (an IL-23 inhibitor) is one of the latest additions. The evidence on treating older adults with psoriasis using these newer biologics is very limited. Therefore, in **chapter 3.3**, the effectiveness and tolerability of tildrakizumab among older adults compared to a younger psoriasis population was investigated, using data from two RCTs. Even though older patients (≥65 years) had a more extensive comorbid disease history and comedication use, the use of tildrakizumab in this patient group seemed both effective and safe for the management of psoriasis. After 244 weeks, PASI scores <3 were observed for more than 80% of younger and 90% of older patients, respectively. Improvements in QoL were comparable across the age groups. Safety analysis revealed a favourable tolerability profile for both age groups. Respiratory tract infections were the most common AEs in both older and younger patients. In older adults, proportionally more cases of cardiovascular events, non-melanoma skin cancer, and other

malignancies were observed during treatment compared to younger patients. This is most likely related to the aging process and a longer duration of psoriatic disease, and thereby a longer time to develop associated comorbidities. To conclude, this study showed that despite a difference in comorbidity and comedication use between older and younger patients, the use of tildrakizumab resulted in similar improvement in disease severity and QoL across age groups, with no major safety concerns observed.

4.2 Discussion

In this thesis, older adults with psoriasis were placed in the spotlight, after being an underexposed patient group in psoriasis research before. Since exclusion rates of older adults with psoriasis from RCTs are high, a knowledge gap is present. To provide evidence-based guidance for older adults with psoriasis, it is important to gain an in-depth understanding of psoriasis especially in the patients in their '*Golden Years*'.

For this thesis, geriatric psoriasis has been extensively investigated using various data sources comprising real-world and RCT data, and various designs such as patient and healthcare provider surveys and interviews, a multicentre retrospective cohort study, multicentre prospective cohort studies, and existing data from two previously performed RCTs. In this discussion, an outline and analysis will be given of the findings presented in this thesis, in the light of existing literature and future perspectives. Furthermore, based on the findings, recommendations are presented for dermatologists and other healthcare professionals to optimize care in older adults with psoriasis.

Firstly, treatment patterns in older adults with psoriasis were investigated. It was reassuring to see that in **chapter 2.1**, including a large patient survey study, no significant differences in the frequency of prescribed (systemic) therapies for psoriasis between older and younger patients were observed. When focusing on type of systemic treatment used in older adults, in the studies included in **chapter 2.1 and 3.1**, modern systemic therapy (e.g., biologics and small molecule inhibitors) was less frequently used compared to conventional systemic therapy in older adults, which was also observed in younger patients. This is in contrast to previously reported results from scarce available literature on this topic, where significant differences in prescribed therapies for psoriasis between older and younger patients were observed.[7,8] Specifically, modern systemic therapy was less

often prescribed in older adults versus younger patients, suggesting potential undertreatment in geriatric psoriasis.[1,3,7,9] Given that the difference in treatment patterns across age groups was not evident in the recent studies included in this thesis, it is possible that the potential undertreatment in geriatric psoriasis is not as substantial (anymore) as previously indicated. A possible explanation for the difference between prior research and the studies reported in this thesis could be the increasing trend in the prescription of (modern) systemic therapies over time, as healthcare providers have developed more experience and therefore also become more comfortable with prescribing these agents in older adults.

To delve deeper into treatment patterns in geriatric psoriasis, a mixed-methods study **(chapter 2.4)** was conducted. Reassuringly, the majority of dermatologists and dermatology residents included in this study applied systemic therapy to the same extent in older adults compared to younger patients. Even so, differences in treatment management among the age groups still existed. For instance, approximately a quarter of the survey respondents were reluctant to use systemic therapy in older adults. Comorbidity, comedication use, the risk of adverse events, and the sparse evidence-based guidance available were the main reasons to be reluctant with systemic therapy in this population. Furthermore, the majority of the responders performed additional actions when prescribing systemic therapy in older adults compared to younger patients (e.g., more intensive monitoring of comorbidity and comedication use, (additional) consultations with other specialists, prescribing lower dosages than standard practice, more frequent laboratory check-ups, more (directive) guidance during the treatment selection process, and initiating home care). Moreover, given that psoriasis disease severity is often comparable between age groups, as reported in **chapter 2.1** and in literature, the need for systemic therapy might be equally warranted in both age groups.[1,2] Not many other studies have been conducted on treatment reluctance of systemic therapy in older psoriasis patients. One small, 5-question survey study reported comorbidity, immunosenescence, and cognitive decline as the main reasons for treatment reluctance with systemic therapy in geriatric psoriasis.[10] Cognitive decline and increased infection risk were also reported reasons for treatment reluctance in **chapter 2.4,** but to a lesser extent. Moreover, undertreatment of older adults is prevalent across various medical fields, with comorbidity, polypharmacy and ageism commonly cited as contributing factors.[11,12] The World health organisation defines ageism as "the stereotyping, prejudice, and discrimination against people on the basis of their age".[13] Ageist assumption about health status or treatment preferences often lead to suboptimal healthcare for older adults.[14] As treatment reluctance is common in other medical fields[15-17], there could be an opportunity to learn from

other medical specialities that apparently struggle with comparable challenges. An initial step could be to consult a primary care provider (general practitioner or elderly care physician) in case of doubt, which may lead to valuable educational insights in both directions. Hesitation to employ systemic therapy for psoriasis can be rational and necessary, particularly when potential contraindications are present. However, at times, this treatment reluctance can become disproportional and can result in undertreatment. To overcome ageist stereotypes and barriers to prescribing systemic therapy for psoriasis in older adults, we believe that this thesis provides additional evidence regarding systemic treatment (effectiveness and safety), which can be used in future guidelines for geriatric psoriasis.

Secondly, to better comprehend the population of older adults, treatment goals, patient preferences, the most bothersome disease aspects, and influence of psoriasis on the quality of life were investigated in **chapter 2.2**. Interestingly, treatment goals were highly comparable between older and younger patients, but patient preferences differed significantly between the age groups. Older adults valued minimizing topical treatment use, reducing subcutaneously administered treatment, decreasing hospital visits, and minimizing laboratory assessments as significantly more important than younger patients. It is often assumed that the burden of visible psoriasis plaques is lower in older adults. However, the older adults included in chapter 2.2 identified the visibility of psoriasis as one of the most burdensome aspects of psoriasis and valued visibility-related treatment goals as more important than younger patients. The findings from **chapter 2.2** show that certain aspects such as visibility should not be disregarded due to age-based assumptions. In general, to provide the most optimal therapy for any patient, it is important to understand how the disease affects a patients QoL. In **chapter 2.2**, the use of the DLQI resulted in an underestimation of the true impact on QoL due to the not-relevant responses, especially in older adults. Therefore, the DLQI-R, which considers the NRRs, is recommended as a tool for evaluating impact of psoriasis on QoL in clinical practice and research **(chapter 2.2)**.

As observed in **chapter 2.4**, healthcare providers may hesitate with prescribing systemic therapy due to comorbidity and comedication, and/or they may perform additional actions in older adults with psoriasis. Since the prevalence of most comorbidities generally increase with advancing age, and specifically for older psoriasis patients, a more extensive comorbid disease burden compared to older patients without psoriasis is reported **(chapter 2.3)**, treatment reluctance based on comorbidity can disproportionately affect older adults with psoriasis. Naturally, (relative) contra-indications for systemic therapies should always be considered

when deciding upon treatment for any patient, regardless of age. In addition to specific contraindications, multimorbidity or polypharmacy can be seen as obstacles when deciding upon systemic treatment in older patients, as they may require extra investigation such as checking for drug interactions, consulting other specialists, or performing additional laboratory assessments (as detailed in **chapter 2.4**). These extra investigations could lead to undertreatment, as they often require more time, particularly compared to patients without comorbidity. An underlying factor in treatment reluctance due to comorbidity or polypharmacy seems to be the concerns about adverse events of systemic therapy in geriatric psoriasis **(chapter 2.4)**.[11] These concerns might arise from the lack of evidence-based guidance and inexperience with systemic treatment in this patient population **(chapter 2.3 and 2.4)**. As the development of new systemic therapies has progressed rapidly over the last decade, it is understandable that not every healthcare provider has experience with these new therapies in all patient populations.[2,7] Continuing on the concerns about AEs, in general, older adults are more at risk for adverse events when using systemic medication due to comorbidity and age-related alterations in drug metabolism.[18] In the older adult psoriasis population described in **chapter 3.1**, comorbidity and polypharmacy were very common. Reassuringly, they were not associated with an increased risk of AE occurrence in older patients using systemic therapy for psoriasis. These findings suggest that treatment reluctance due to comorbidity and increased concern for AEs in older patients might not always be warranted. Furthermore, withholding effective therapies due to treatment reluctance can be harmful for older patients. However, these findings are based on group data, so it will remain important to assess the (potential) risks individually when systemic therapy is preferred. Furthermore, it is important that healthcare providers are aware that treatment reluctance, stemming from comorbid disease status or comedication use, can disproportionately affect older adults with psoriasis. Moreover, it is crucial for healthcare providers to reflect on whether this treatment reluctance is based on rational, evidence-based arguments or arguments solely based on perceived emotional distress or gut feelings. Understanding safety data, especially in older adults with multiple health problems, can be challenging. Misclassification of unrelated health problems as treatment-related adverse events is more likely in older adults. To prevent overestimation of AEs in older adults, causality assessment is crucial. In **chapter 3.1**, over a quarter (27.3%) of the reported AEs were deemed unrelated to systemic psoriasis treatment in older adults. Furthermore, the reported AEs that were considered possibly related to the use of systemic therapy were reversible and/or manageable in clinical practice. Therefore, besides causality assessment, assessing the reversibility of AEs is also important for a correct interpretation of the safety risks associated with systemic therapy in geriatric psoriasis.

Frailty and functional dependency become more prevalent with age, and are linked to negative health outcomes in patients undergoing medical interventions in various medical fields.[19-21] Furthermore, assessing these factors in clinical practice has been proven beneficial in guiding medical decision-making across several populations of older adults.[20] While these factors are recognized as significant in the treatment decision-making process in other medical fields, they were unexplored in older adults with psoriasis until now. In **chapter 2.5**, the prevalence and extent of frailty and functional dependency were investigated in a multicentre observational cohort of older adults with psoriasis by using and comparing different screening tools. In this study, frailty and functional dependency were common. Furthermore, older psoriasis patients who were frail and functional dependent often expressed lower satisfaction with their therapy compared to non-frail and functionally independent older patients, suggesting a possible difference in treatment needs. Moreover, frail and functionally dependent patients required assistance in applying or using their psoriasis treatment more often compared to patients who were non-frail or functionally independent **(chapter 2.5)**. These findings indicate that frail and/or functionally dependent patients with psoriasis might require a different approach in clinical practice. Therefore, it is important to address these factors in the treatment decision-making process, including consideration of (expected) treatment burden, the need for assistance, and therapy compliance. We investigated several screening tools, of which the CFS performed best as it identified the majority of management implications (needing help with psoriasis therapy and lower treatment satisfaction). Therefore, utilizing the CFS in clinical practice may prove beneficial for choosing appropriate treatment, organizing (home) care, deciding to involve family/support system, and determining the frequency of follow-up appointments in this population **(chapter 2.5)**. The CFS is a frequently studied tool to screen for frailty based on clinical judgement that has been used in different healthcare and community-based settings around the world.[22] The CFS ranges from 1 (very fit) to 9 (terminally ill). The CFS has been associated with relevant frailty-related aspects and outcomes in different populations, and its simplicity and rapid deployment make it a valuable asset in multiple settings.[22-25] Therefore, the CFS may also be suitable for use in dermatology consultations, especially considering the limited time available. Future research concentrating on the implementation of the CFS and the consequences of implementation in daily practice care for older adults with psoriasis is warranted. Additionally, it is important that frailty measures in general are more frequently included in clinical research for this population, as this could enhance the interpretation and comparison of research findings. Nonetheless, it is also essential to acknowledge that being frail or functional dependent should not necessarily preclude systemic treatment, provided that

appropriate precautions are taken, e.g., initiating home care, medication roll dispenser, informing and involving family/support team, considering alternatives for hospital visits like phone or digital consultations, tailored to each individual.

Currently, modern systemic therapies, such as biologics, occupy a prominent place in the treatment landscape for psoriasis. However, previous research on older patients using biologics was limited with small sample sizes. The research in this thesis contributes significantly to the evidence on geriatric psoriasis and biologics, covering various aspects. In **chapter 3.1**, infections were the primary adverse event associated with biologics in older adults. SAEs were rare and mainly comprised clinical manageable infections. **Chapter 3.2** compared biologic drug survival and safety in older versus younger patients using real-world prospective observational data. Consistent with chapter 3.1, infections were also the most frequently reported AE resulting in treatment discontinuation in older adults in chapter 3.2. For younger patients, infections were also the most frequently reported AE resulting in treatment discontinuation. In both age groups, upper respiratory infections/flu-like symptoms were the most frequently reported infections. Consistent with our findings, infections emerge as the most frequently observed AE of biologics in both older adults and younger patients in previous literature.[4,26-29] Considering the differences in immune functioning between older and younger patients, it can be assumed that older patients using biologics might face a higher infection risk. Additionally, the higher prevalence of some comorbidities and/or comedication use associated with infection risk among older adults in general might explain an additional risk for infections among older biological users.[30-33] However, in **chapter 3.2** and **3.3**, infections were common in both older and younger patients and comprised similar infection profiles (e.g. (upper) respiratory tract infections). Furthermore, a systematic review conducted in 2020 found no significant association between infection rates, biologics use, and advancing age in psoriasis.[4] The position of vaccination for a broad range of infections for patients on biologics is currently discussed and could be especially important for older patients with psoriasis since infections can have a worse disease course in older patients.[31] Furthermore, it remains unclear whether it is preferable to continue or temporarily pause biologic treatment during general infections.[34] While guidelines often recommend temporary discontinuation during (severe) concurrent infections, there is growing awareness that continuing biologics may be possible and sometimes preferable[35], as it prevents deterioration of psoriatic disease. It would be interesting to study this in more detail in the future, specifically including the impact of age, (baseline) immune functioning, and immunosenescence. Encouragingly, in **chapter 3.2** no SAEs leading to treatment discontinuation were reported in older adults, and

overall drug survival was comparable between included age groups. In **chapter 3.3**, analysis of RCT data, with a 244-week follow-up compared the effectiveness and safety of tildrakizumab in older versus younger patients, showing no major safety concerns in long-term psoriasis treatment for older adults. Overall, the available evidence from this thesis, supported by the limited previous literature, indicates that biologics for psoriasis are a safe and effective management option for older adults, where awareness of comorbidity and comedication use is vital.[4,9,36-43]

Although biologics are increasingly available and used in psoriasis management, conventional systemic treatments are still the most commonly prescribed systemic treatment options for psoriasis and have been used for decades. Nevertheless, safety concerns in older adults using conventional systemic treatments are still raised. In **chapter 3.1**, increasing AEs with advancing age were observed, though no significant differences among the different systemic treatment types were observed, possibly due to lack of study power. The most frequently observed AEs possibly related to conventional systemic therapy in **chapter 3.1** align with existing literature.[4,5,44] These include infections and elevated liver enzymes for methotrexate, lymphopenia and gastrointestinal disorders for dimethyl fumarate, and dry mucous membranes of mouth and nose, elevated liver enzymes, and renal function deterioration for older patients using acitretin. Somewhat expected, only a handful of patients received ciclosporin in **chapter 3.1**. This could probably be explained by the fact that literature shows an increase in AEs associated with age for ciclosporin, mainly consisting of hypertension and renal dysfunction.[4,5] In the absence of new insights/data, precaution in elderly patients remains important when prescribing ciclosporin in older adults. Reassuringly, SAEs on conventional systemic therapy were scarce, and AEs were often reversible with dose adjustments, treatment discontinuation, or appropriate treatment of the occurred AE. Therefore, age alone should not restrict treatment choice, but choosing and monitoring of the right treatment requires a more holistic view (e.g., considering comorbidities, comedication, and functional status), independent of age. In general, for populations at risk for (S)AE (depending on patient profile and medication profile) monitoring of physical and laboratory alterations and appropriate treatment adjustments (e.g., dose adjustments, discontinuation, switching treatment) are crucial for both biologics and conventional systemic treatment.

Despite the rapid growth of the older adult population with psoriasis, current national and international guidelines for psoriasis offer limited recommendations for older adults. As mentioned previously in this thesis, the need for more evidence-based guidance for the management of geriatric psoriasis is warranted, especially given the

barriers regarding prescription of systemic therapy in this population. When examining this lack of evidence-based guidance in geriatric psoriasis, it is evident that while research on systemic therapy exists, older adults are frequently excluded from RCTs based on chronological age limits and/or comorbidities.[45] Consequently, data from existing RCTs are less generalizable to older adults with psoriasis, complicating relevant guideline recommendations for this specific group. The findings from **chapter 2.3** indicate that besides age, cardiovascular disease, and malignancy are the main factors impacting the generalizability of RCT data to the real-world geriatric psoriasis population. This underscores the importance of real-world observational studies with very long follow-ups to specifically provide evidence regarding the maintenance phase of treatment in a chronic disease like psoriasis, especially given the fact that the life expectancy of older patients continues to increase. Additionally, there is a potential for better utilization of existing data from RCTs, as research teams and/or pharmaceutical companies often possess raw data on older patients with psoriasis potentially suitable for additional analyses. These datasets could offer valuable insights, as illustrated by the data presented in **chapter 3.3**. Furthermore, including specific variables such as frailty and functional dependency in RCTs and real-world studies could enable valuable subgroup analysis within the heterogeneous group of older adults. If the research questions permit, future RCTs should preferably become more pragmatic and try to align as closely as possible with daily clinical practice, with broader inclusion criteria and minimal exclusion criteria. Alongside pragmatic RCTs, real-world observational studies remain important, as they can encompass long follow-ups of large and more diverse patient groups.

It is important to realize that a part of the elderly population is not represented in this thesis, as they do not visit a dermatologist. Examples of these patients include those treated in primary care or those who do not visit a healthcare provider for their psoriasis at all (e.g., older adults with multimorbidity where treatment of their skin disease is not a priority). The extent of this unrepresented group remains uncertain, and no recommendations can be formulated for this population based on this thesis. Future research exploring the size of this group and their unmet needs might provide interesting additional insights.

With this thesis, a significant contribution to the evidence-based guidance for the personalised management of psoriasis in older adults was made. Besides considering disease-specific aspects, it is evident that in the management of geriatric psoriasis, significant factors like comorbidity, comedication use, frailty, and functional dependency may be present and require significant attention in the decision-making process. As the population of older adults is very heterogeneous,

management decisions based on chronological age alone and age-based assumptions should be avoided. Advanced age may serve as an indicator to further evaluate frailty and functional dependency. Moreover, incorporating patient preferences, treatment goals, treatment burden, and treatment feasibility into shared decision-making is essential.

> *'Age is just a number. It's totally irrelevant unless, of course, you happen to be a bottle of wine." – Joan Collins*

4.3 Guidance for a personalised approach in Geriatric Psoriasis

For the personalised management of older adults with psoriasis, the following recommendations can be provided:

1. As the population of older adults is very heterogeneous, ageist stereotypes and assumptions based solely on chronological age should be avoided in treatment decision-making.
2. In addition to disease characteristics, considering patient-related factors (e.g., comorbidity, comedication use, frailty, functional dependency) is crucial for optimal treatment selection. Assessment of treatment feasibility and burden is essential, especially for older patients facing cognitive decline, frailty, and functional dependency. Explore alternatives like phone or digital consultations to reduce the burden of hospital visits.
3. The burden of psoriasis in older adults should not be overlooked. Older adults consider the visible aspect of psoriasis to be one of the most bothersome aspects.
4. The use of the original DLQI in older adults can lead to an underestimation of the impact of psoriasis on the quality of life. Therefore, the use of the DLQI-R in research and clinical practice should be preferred over the original DLQI scoring method, especially in older adults.
5. Frailty screening tools such as the CFS appear promising for identifying frailty and functional dependency in clinical practice before and during treatment, offering opportunities to improve treatment satisfaction and reduce treatment burden in older patients.
6. Multidisciplinary consultation with other healthcare providers (e.g., general practitioner, geriatrician, elderly care physician) should be considered with a low threshold in case of complex multimorbidity, cognitive decline, frailty, or functional dependency.

7. Biologics and most conventional systemic treatments are safe to use in older adults, although caution is advised with the use of ciclosporin in this population.
8. Interpretating safety data in older adults can be challenging. For a better understanding of the (potential) risks of therapy, incorporating a causality assessment of adverse events is crucial, as well as evaluating the reversibility of adverse events.
9. Alongside real-world studies, future pragmatic RCTs including a broader group of older adults and thereby better matching the heterogeneous real-world setting are of significant value for assessing both new and established systemic agents in geriatric psoriasis.

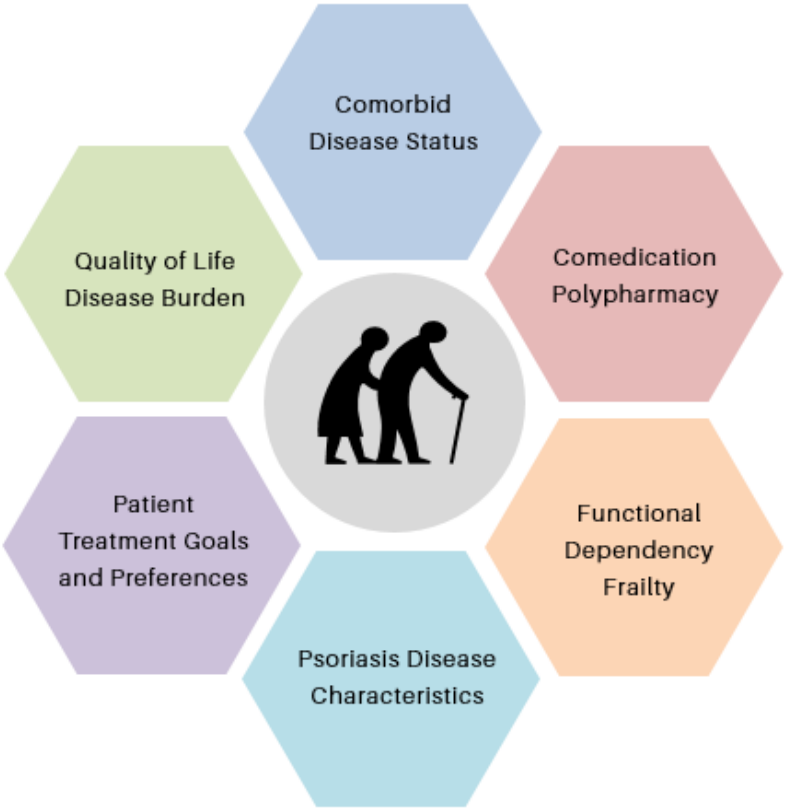

Figure 1. Overview of important factors to consider when deciding upon a treatment for older adults with psoriasis.

4.4 Future perspectives

In dermatology, the population of older adults with psoriasis currently represents a substantial proportion of patients, and this demographic is expected to further increase in the future, requiring safe and effective treatments tailored to individual needs. In this thesis, recommendations and guidance for the management of geriatric psoriasis were provided. However, due to the diverse nature of the older adult population, drawing uniform conclusions across this group is not preferable. Therefore, more research employing various approaches is still required to provide the most optimal and personalised treatment for older adults with psoriasis. Naturally, RCTs investigating the safety and efficacy of (new) systemic therapies in psoriasis are always needed. In addition, new pragmatic RCTs focusing on older adults with psoriasis, with broader inclusion criteria and detailed reporting of adverse events including causality assessments, are necessary. Furthermore, unpublished data from RCTs stratified for older adults should be published. Besides RCTs, which can be costly, there is a need for more (long-term) real-world evidence, including data from registries like the Dutch BioCAPTURE registry (used in chapter 3.2). These registries are essential for understanding the daily clinical practice population, especially the geriatric psoriasis population as they are often excluded from RCTs. To further personalize treatment for older adults with psoriasis, it is important to address the heterogeneity of this population in medical research. Thus, focusing on factors such as comorbidity, comedication use, frailty, and functional dependency in geriatric psoriasis research is a necessary direction.

With this thesis, insights have been acquired regarding the management of psoriasis in older adults. Several interventions have been suggested, such as longer consultation times, assessing frailty/functional dependency in clinical practice, substituting physical consultations with telemedicine, providing home care, involving social support systems, and integrating nurse practitioners into geriatric psoriasis care. Moreover, providing training of dermatologists in the field of frailty could also be a significant intervention, and expanding guidelines with an emphasis on older patients continues to be important. Even so, there remains ample terrain for exploration, particularly in determining which patients benefit from specific interventions, a crucial aspect of providing personalised medicine. Therefore, future research is needed to explore the potential value of integrating the suggested interventions such as the frailty/functional dependency screening tools into daily clinical practice. As indicated in this thesis, frail and/or functional dependent patients expressed lower treatment satisfaction and more frequently required assistance with their psoriasis therapy compared to non-frail/functionally independent patients.

It would be interesting to explore the impact of integrating frailty screening tools like the CFS into clinical practice on treatment outcomes and decisions in geriatric psoriasis. Encouragingly, the focus on and interest in older patients with psoriasis is currently also demonstrated by the recent initiative of the International Psoriasis Council (IPC), a global network of physician experts dedicated to enhancing the health of psoriasis patients around the world. In April 2024, they launched 'Expert Insights' on psoriasis in older patients, a discussion publication on epidemiology, clinical features and treatment.[46] Establishing treatment goals for this population, is among the key initiatives that will be addressed by the IPC in the future.

This thesis was partly compiled during the COVID-19 pandemic, during which less urgent in-hospital patient visits were temporarily restricted or reduced, and remote patient monitoring was established. Currently, telemedicine appears to be a viable option for monitoring patients with chronic and stable disease like psoriasis using systemic therapy.[47] For older patients (especially the frail and functional dependent), a hospital visit can be very burdensome, especially when a sufficient support system is lacking. It would be interesting to explore whether older adults with psoriasis would specifically benefit from using telemedicine instead of certain outpatient visits. In addition to utilising digital innovations, transferring some geriatric psoriasis care from hospitals to general practitioners, or for nursing home residents to elderly care physicians, might enhance healthcare accessibility and relieve the burden of hospital visits for elderly patients, especially with appropriate remote guidance/consultation from a dermatologist.

Considering that technical innovations are being developed rapidly and cautiously implemented in clinical practice, the role of dermatologists will evolve as well. E-health applications and AI-supported systems can aid in the management of psoriasis in older adults, especially for complex patients with multimorbidity, polypharmacy, frailty, and functional dependency. These technical advancements have the potential to reduce time-consuming procedures and improve quality of care, allowing healthcare providers to dedicate their time and effort towards more personalised management of their patients. Examples of these technical advancements include automated medical chart documentation and medication verification, as well as clinical decision support systems using predictive analytics. However, consideration must be given to the technical or digital skills of older adults and their social support system. The use of these technologies should always be seen as a means, not an end.

There is a group of older adults that has not been addressed in this thesis, namely those who are not under the care of a dermatologist, but who are treated in

primary care, or those who do not visit a physician at all for their psoriasis. Since this population has not been sufficiently studied, new research in this patient group would be a logical next step following this thesis. As this is uncharted territory, a good starting point would be to assess the size of this patient group, identify any unmet needs, and what the impact of psoriasis on this patient group. Furthermore, the older adult psoriasis population could be a valuable group for studies on the cumulative effects of long-lasting psoriasis, including psoriasis-associated comorbidities and the cumulative life course impairment of psoriasis. Lessons learned in these areas might provide insights leading to beneficial interventions for psoriasis patients in their younger years as well.

Psoriasis care is continuously evolving, with new therapeutic options being established every year, allowing numerous patients to achieve adequate disease control. Despite ongoing progress in psoriasis care for older adults, there is still plenty of work to be done. The pursuit of knowledge knows no bounds; it is a lifelong endeavour.

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Chapter 5

Nederlandse samenvatting

Door de vergrijzing van de wereldbevolking zullen dermatologen en andere zorgverleners steeds vaker ouderen met huidaandoeningen tegenkomen in de dagelijkse praktijk. Psoriasis, een veelvoorkomende chronische ontstekingsziekte van de huid, kan een aanzienlijke impact op de kwaliteit van leven hebben van patiënten en komt voor in alle leeftijdsgroepen, inclusief ouderen. De behandeling van ouderen met psoriasis kan uitdagend zijn vanwege bijkomende factoren zoals multimorbiditeit, polyfarmacie, kwetsbaarheid, functionele afhankelijkheid en verouderings-gerelateerde orgaanstoornissen. Aangezien oudere patiënten met psoriasis vaak worden uitgesloten van deelname aan gerandomiseerde gecontroleerde onderzoeken (Engels: *Randomized Controlled Trials*; RCTs), bestaat er een kenniskloof tussen oudere patiënten met psoriasis in vergelijking met andere leeftijdsgroepen. De rol van onderzoek naar ervaringen uit de dagelijkse klinische praktijk (Engels: *Real-World Evidence;* RWE) wordt dan ook steeds belangrijker. Er is momenteel beperkt wetenschappelijk bewijs uit onderzoek verwerkt in richtlijnen en beschikbaar ter ondersteuning van de behandeling van ouderen met psoriasis (Engels: *evidence-based guidance*). Het doel van dit proefschrift was bij te dragen aan meer kennis en richtlijnen voor de behandeling van ouderen met psoriasis, om zo de gepersonaliseerde zorg te bevorderen voor deze populatie.

In een landelijk vragenlijstonderzoek (n=985) beschreven in **hoofdstuk 2.1** werden patiëntkenmerken, psoriasiskenmerken en behandelingen van oudere patiënten (≥65 jaar) met psoriasis vergeleken met jongere patiënten (<65 jaar) met psoriasis. In deze studie werden andere medische aandoeningen (comorbiditeit), gebruik van comedicatie en functionele afhankelijkheid van zorgverleners en/of familieleden met betrekking tot de psoriasisbehandeling significant vaker gerapporteerd door oudere patiënten in vergelijking tot jongere patiënten. Desondanks werden er geen significante verschillen gezien tussen de leeftijdsgroepen met betrekking tot het gebruik van systemische medicatie voor psoriasis (38,3% in patiënten ≥65 jaar versus 42,3% in patiënten <65 jaar; p=0,219). Opvallend was dat ouderen minder vaak bijwerkingen rapporteerden tijdens de psoriasisbehandeling in vergelijking met jongere patiënten (19,8% bij ≥65 jaar versus 25,9% bij <65 jaar; p=0,015). Echter, gezien dit een door patiënt zelf gerapporteerde vragenlijstonderzoek betrof, is het mogelijk dat asymptomatische laboratoriumafwijkingen niet zijn gemeld. Daarnaast zijn redenen om met voorgaande behandelingen te stoppen niet geëvalueerd in deze studie. Hoewel een gunstig tolerantieprofiel werd gerapporteerd in deze studie onder oudere patiënten, is specifieke aandacht voor patiënt gerelateerde verschillen (zoals comorbiditeit, gebruik van comedicatie en functionele afhankelijkheid) belangrijk, zeker gezien de hogere prevalentie hiervan in de oudere populatie.

Met de toenemende beschikbaarheid van psoriasisbehandelingen en een toenemend aantal ouderen met psoriasis, is het belangrijk om onvervulde behoeften binnen deze populatie te identificeren. In **hoofdstuk 2.2** werd het tweede deel van het nationale patiënten vragenlijstonderzoek beschreven. Ouderen rapporteerden andere behandelvoorkeuren dan jongere patiënten, waarbij zij meer belang hechtten aan het verminderen van medicijngebruik, ziekenhuisbezoeken en bloedcontroles. Voor beide leeftijdsgroepen was het verminderen van bijwerkingen de voornaamste behandelvoorkeur. Hoewel de algemene behandeldoelen (zoals vrij zijn van jeuk, schilfering en zichtbare plekken) vergelijkbaar waren tussen de leeftijdsgroepen, waren individuele uitkomsten zeer uiteenlopend. Dit benadrukt de behoefte aan individuele evaluatie van ziekte- en behandellast, patiëntvoorkeuren en behandeldoelen. Kwaliteit van leven kan gemeten worden met de DLQI (*Dermatology Life Quality Index)*. Omdat sommige DLQI-items (zoals sport en werk) vaak als niet relevant worden beschouwd door oudere patiënten in vergelijking met jongere patiënten, is correctie voor deze items essentieel voor een nauwkeurige interpretatie van de kwaliteit van leven. De DLQI-R is een alternatieve scoringsmethode die rekening houdt met de items die door de patiënt als "niet relevant" zijn aangemerkt. Er werd geen significant verschil in DLQI-R score gemeten tussen de leeftijdsgroepen.

Omdat ouderen met psoriasis vaak worden uitgesloten van RCTs vanwege hun leeftijd en comorbiditeit, kan de toepasbaarheid en de vertaling van RCT-resultaten naar deze populatie moeilijker zijn. In **hoofdstuk 2.3** werd de impact van RCT-exclusiecriteria onderzocht onder ouderen met psoriasis uit de dagelijkse praktijk (n=230). Ouderen met psoriasis hadden meer comorbiditeit in vergelijking tot ouderen zonder psoriasis. Depressie, huidkanker, obesitas, hyperlipidemie en overgewicht kwamen significant vaker voor bij ouderen met psoriasis dan zonder psoriasis. Kalenderleeftijd, cardiovasculaire aandoeningen en maligniteiten werden in deze studie geïdentificeerd als de meest voorkomende RCT-exclusiecriteria, met de grootste impact op de toepasbaarheid van RCT-resultaten in de dagelijkse praktijk voor oudere patiënten. Deze bevindingen benadrukken de beperkingen van het vertalen van RCT-resultaten naar deze specifieke populatie, zoals de risico's op medicatieveiligheid en variatie in effectiviteitsuitkomsten. Het generen van RWE voor deze leeftijdsgroep is essentieel om de verschillen tussen RCTs en de dagelijkse praktijk vast te stellen.

Hoewel vergelijkbare ziekte-ernst tussen oudere en jongere patiënten met psoriasis is gerapporteerd, en wij in hoofdstuk 2.1 geen verschil zagen in het gebruik van systemische therapie tussen ouderen en jongeren, zijn er enkele studies waar dat wel

gezien werd. Om een mogelijke behandelingsongelijkheid en de rol van zorgverleners hierin verder te onderzoeken, werd een mixed-methods studie uitgevoerd (**hoofdstuk 2.4**). Deze studie omvatte een vragenlijstonderzoek en interviews, die inzicht gaven in voorschrijfpatronen, barrières en behoeften van Nederlandse dermatologen en artsen in opleiding tot dermatoloog bij het voorschrijven van systemische therapie aan ouderen met psoriasis. Uit het vragenlijstonderzoek bleek dat 67% van de respondenten systemische therapie even vaak voorschrijft aan ouderen als aan jongeren, en 69% aangeeft niet terughoudend te zijn met het voorschrijven van systemische therapie aan ouderen. Echter, 27% gaf aan wel terughoudend te zijn, vooral vanwege comorbiditeit, gebruik van comedicatie en het (vermeende) bijwerkingenrisico onder oudere patiënten. Daarnaast nam 68% van de respondenten extra maatregelen bij ouderen, zoals intensievere monitoring van comorbiditeit en gebruik van comedicatie, vaker multidisciplinair overleg, lagere dosering voorschrijven en frequenter bloedonderzoek. De gedefinieerde barrières uit de interviews kwamen overeen met de voornaamste redenen voor terughoudendheid zoals gerapporteerd in bovengenoemde vragenlijstonderzoek. Zorgverleners gaven aan dat de verbetering van de behandeling van ouderen met psoriasis vraagt om meer evidence-based richtlijnen, meer educatie, meer tijd voor consulten en het implementeren van kwetsbaarheidsscreening in individuele gevallen.

Patiëntfactoren zoals kwetsbaarheid en verminderde functionele status, welke vaker voorkomen op oudere leeftijd, zijn gerelateerd aan nadelige behandeluitkomsten. In **hoofdstuk 2.5** zijn deze factoren onder oudere patiënten met psoriasis onderzocht (n=102). Drie instrumenten om op kwetsbaarheid te screenen werden gebruikt: de Geriatric-8 (G8), de Groningen Frailty Index (GFI) en de Clinical Frailty Scale (CFS). Deze instrumenten toonden aan dat respectievelijk 42,2% (G8), 26,0% (GFI) en 13,7% (CFS) van de patiënten (mogelijk) kwetsbaar waren. Afhankelijkheid met betrekking tot activiteiten van het dagelijks leven (ADL) en instrumentele activiteiten van het dagelijks leven (iADL) kwamen voor bij 14,3% en 37,6% van de patiënten. Ongeveer 27% van de patiënten had hulp nodig bij het gebruik van psoriasismedicatie, wat significant vaker voorkwam bij kwetsbare en/of functioneel afhankelijke patiënten. Bovendien rapporteerden kwetsbare en functioneel afhankelijke patiënten lagere tevredenheid over hun psoriasismedicatie. Gezien de prevalentie en beleidsimplicaties van kwetsbaarheid en functionele afhankelijkheid die in deze studie werden geïdentificeerd, kan het nuttig zijn om in de praktijk een instrument te gebruiken om op kwetsbaarheid te screenen. Dit kan de besluitvorming bij ouderen met psoriasis ondersteunen. Omdat de meeste beleidsimplicaties werden waargenomen bij patiënten die als kwetsbaar waren

geïdentificeerd met de CFS, en omdat dit een makkelijk toepasbaar instrument is, kan de CFS waardevol zijn om te gebruiken in de dagelijkse praktijk.

Om een veilige behandelkeuze te maken, zijn data over bijwerkingen van geneesmiddelen essentieel. Deze data kunnen soms lastig te beoordelen zijn omdat het niet altijd duidelijk is of een bijwerking daadwerkelijk gerelateerd is aan een geneesmiddel of een andere oorzaak heeft. Zeker bij ouderen kan dat moeilijk zijn vanwege polyfarmacie en comorbiditeit. In **hoofdstuk 3.1** werden alle gerapporteerde bijwerkingen onderzocht op causaliteit bij 117 patiënten (≥65 jaar) die systemische therapie (fumaarzuur, acitretine, methotrexaat, en biologicals) voor psoriasis gebruikten. Van de 319 gerapporteerde bijwerkingen en 28 ernstige bijwerkingen, werden 232 (72,7%) bijwerkingen en 12 (42,9%) ernstige bijwerkingen geclassificeerd als mogelijk gerelateerd aan de psoriasisbehandeling bij aanvullende beoordeling op mogelijke causaliteit. Dit benadrukt het belang van een causaliteitbeoordeling bij het interpreteren van veiligheidsdata. Het was geruststellend dat de meeste bijwerkingen reversibel en/of goed te behandelen waren in de praktijk. Bovendien werd er geen significant verschil waargenomen tussen de verschillende typen psoriasismedicatie en de frequentie van bijwerkingen in deze studie. Concluderend, het veiligheidsprofiel van de onderzochte middelen was geruststellend.

Biologicals zijn één van de nieuwste therapeutische opties voor psoriasis. In **hoofdstuk 3.2** is de drug survival (DS, de duur van het gebruik van een geneesmiddel), veiligheid en effectiviteit van biologicals vergeleken tussen oudere en jongere patiënten in de dagelijkse praktijk. Hoewel ouderen een lagere DS hadden met betrekking tot effectiviteit en vaker stopten vanwege ineffectiviteit (23,5% bij <65 jaar versus 34,3% bij ≥65 jaar), was de algehele DS en DS met betrekking tot bijwerkingen hoog en vergelijkbaar tussen de leeftijdsgroepen. Infecties waren de meest voorkomende bijwerkingen die resulteerden in het stoppen van de biological in beide leeftijdsgroepen (4,9% ≥65 jaar en 3,2% <65 jaar). Geruststellend was dat er geen ernstige gerelateerde bijwerkingen werden waargenomen die resulteerden in het stoppen van de behandeling bij ouderen. Op basis van deze bevindingen lijkt het gebruik van biologicals voor psoriasis bij ouderen over het algemeen veilig en effectief.

Tildrakizumab, een IL-23-remmer, is recent toegevoegd aan het arsenaal van biologicals. In **hoofdstuk 3.3** werd de effectiviteit en veiligheid van dit middel onderzocht bij oudere patiënten in vergelijking met jongere patiënten, gebaseerd op data uit twee RCTs. Ondanks een uitgebreidere medische voorgeschiedenis en

meer gebruik van comedicatie bij oudere patiënten, bleek tildrakizumab effectief en veilig voor beide leeftijdsgroepen. Na 244 weken toonde tildrakizumab verbetering van de PASI-score (ziekte-ernst) tot <3 bij 80% van de jongere patiënten en bij 90% van de oudere patiënten. De kwaliteit van leven verbeterde vergelijkbaar in beide leeftijdsgroepen. De veiligheidsanalyse toonde een gunstig profiel bij zowel oudere als jongere patiënten, met luchtweginfecties als meest voorkomende bijwerking. Bij oudere patiënten werden echter meer cardiovasculaire voorvallen, niet-melanoom huidkanker en andere maligniteiten waargenomen, waarschijnlijk gerelateerd aan een gevorderde leeftijd en het hebben van psoriasis voor een langere tijdsduur. Concluderend, ondanks verschillen in gezondheidsstatus en medicatiegebruik, toonde tildrakizumab vergelijkbare verbetering in ziekte-ernst en kwaliteit van leven bij oudere en jongere patiënten, zonder significante veiligheidsrisico's.

Conclusie

Dit proefschrift biedt inzicht in verschillende aspecten van de behandeling van psoriasis bij ouderen, waarin een gepersonaliseerde aanpak cruciaal is. Naast het overwegen van ziektespecifieke kenmerken, is het belangrijk om rekening te houden met patiënt gerelateerde kenmerken zoals comorbiditeit, gebruik van comedicatie, kwetsbaarheid en functionele afhankelijkheid in deze populatie. Op basis van dit proefschrift en de heterogeniteit van deze populatie, zijn behandelbeslissingen puur op basis van kalenderleeftijd ongewenst en moeten leeftijdsgebonden aannames worden vermeden. Een gevorderde leeftijd kan wel een signaal zijn om kwetsbaarheid en functionele afhankelijkheid verder te evalueren. Hierbij kan het toepassen van een kwetsbaarheidsbeoordeling, multidisciplinair overleg en (aanvullende) telefonische consulten waardevol zijn. Daarnaast is het essentieel om patiëntvoorkeuren, behandeldoelen, belasting door een behandeling en haalbaarheid van een behandeling mee te nemen in de gezamenlijke besluitvorming.

Chapter 6

Research data management

Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants. All studies described in this thesis were conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO). The medical and ethical review board Committee of Research Involving Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands (METC Oost-Nederland) has reviewed and given approval to conduct the studies (chapters 2.1 and 2.2), or waived ethical approval due to the nature of the study (chapters 2.3, 2.4, 2.5, 3.1, and 3.2). For the multicenter studies described in chapter 2.3, 2.5, 3.1, and 3.2 local approval from the participating centers was obtained. Furthermore, written informed consent was obtained from all participating patients included in this thesis. Written informed consent was also obtained from the dermatologists and dermatology residents participating in the interview study described in chapter 2.4. For the survey part of chapter 2.4, respondents were informed that the results will be used for publication and returning the survey was construed as informed consent. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage, when applicable).

Data collection and storage

For chapter 2.1, 2.2, 2.3, 2.5, 3.1, and 3.2 were collected through electronic Case Report Forms (eCRF) using CASTOR EDC. From Castor EDC data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA. For chapter 2.1 and 2.2 besides a paper-based version, survey data was anonymously collected using a web-based survey system Qualtrics (XM 2020, Provo, UT, USA) which is password protected. In chapter 2.4, survey data was also collected using Qualtrics. 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 on the department. In chapters 2.3, 2.5, 3.1, and 3.2 patient data were also gathered from collaborating hospitals. Written informed consents, questionnaires and patient identification keys are stored by the local sub-investigator at the dermatology department within their hospital premises. Chapter 3.3 is a post-hoc pooled analysis of 2 three-part randomized, double blind, placebo-controlled, parallel-group phase III trials (Resurface 1 and Resurface 2, ClinicalTrials.gov NCT01722331 and NCT01729754), no data has been stored at the department of Dermatology, Radboudumc, as data belongs to Almirall.

Availability of data

The majority of studies are 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. The anonymous datasets that were used for analysis are available from the corresponding author upon reasonable request.

Appendices

List of abbreviations

ACE	Angiotensin-Converting-Enzyme
ADL	Activities of Daily Living
AE	Adverse Event
AP	Alkaline Phosphatase
BioCAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry with Biologics
BMI	Body Mass Index
caAE	causality assessed Adverse Event
caSAE	causality assessed Serious Adverse Event
CBS	Statistics Netherlands
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI	Confidence interval
CK	Creatin Kinase
COVID-19	Coronavirus Disease 2019
DC	Dendritic cell
DLQI	Dermatology Life Quality Index
DLQI-R	Dermatology Life Quality Index Relevant
eCRF	electronic Case Report Forms
G8	Geriatric-Eight
GCP	Good Clinical Practice
GEPPA	Geriatric Psoriasis Patterns Assessment
GFI	Groningen Frailty Indicator
GFR	Glomerular filtration rate
GP	General practitioner
HBO	Hoger beroepsonderwijs
HMG CoA	Hydroxymethylglutaryl coenzym A
HR	Hazard Ratio
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases-Tenth Revision
ICH	International Council for Harmonisation
IPC	International Psoriasis Council
IFN	Interferon
IGA	Investigator Global Assessment
IL	Interleukin
IRR	Incidence Rate Ratio
JAK/STAT	Janus kinase/Signal Transducer and Activator of Transcription
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular event
MEDRA	Medical Dictionary for Regulatory Activities
MELTUMP	Melanocytic Tumour of Uncertain Malignant Potential
METC	The medical and ethical review board Committee of Research Involving Subjects
MI	Myocardial Infarction

NA	Not applicable
NASH	Non-Alcoholic Steatosis Hepatis
NCR	Netherlands Cancer Registry
NK	Natural killer
NMSC	Non-melanoma skin cancer
NR	Not reported
NRR	Non-relevant response
OR	Odds ratio
P3NP	Amino terminal type 3 procollagen peptide
PASI	Psoriasis Area and Severity Index
PASI75	75% improvement in baseline PASI
PGA	Patient Global Assessment
PsA	Psoriatic arthritis
PUVA	Psoralenen + uv-A
PVC	Premature Ventricular contraction
QoL	Quality of life
RCT	Randomized controlled trial
RIVM	Dutch National Institute for Public Health and the Environment
RWE	Real-world evidence
SAE	Serious Adverse Event
SAPASI	Self-Administered Psoriasis Area Severity Index
SD	Standard deviation
SF-36	Short Form Survey 36
SMI	Small-molecule inhibitor
SPSS	Statistical Package for Social Sciences
SPR	Standardized prevalence ratio
SRQR	Standard for Reporting Qualitative Research
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TE	Treatment Episode
TEAE	Treatment-Emergent Adverse Event
TG	Triglycerides
TH	T-helper cell
TIL	Tildrakizumab
TNF	Tumour Necrosis Factor
TSQM	Treatment Satisfaction Questionnaire for Medication
TYK2	Tyrosine kinas 2
UV	Ultraviolet
VAS	Visual Analogue Scale
W	Week
WMO	Medical Research Involving Human Subjects Act
y-GT	Gamma-Glutamyl Transferase
yo	Years old
yrs	Years

List of publications

Publications related to this thesis

ter Haar ELM, van den Reek J, Sadat Chenarani Moghadam M, Schoon Y, Kleinpenning MM, de Jong EMG, Lubeek SFK Frailty and functional dependency in a multicenter cohort of older adults with psoriasis: Prevalence and extent of and implications for psoriasis management. *Journal of the American Academy of Dermatology*. Sep 6 2024

ter Haar ELM, van den Reek J, Ten Bruin EE, Bronkhorst EM, Borgonjen RJ, Kleinpenning MM, Kop EN, Visch MB, van de Kerkhof PCM, de Jong EMG, Lubeek SFK. Exclusion by age, cardiovascular comorbidity and malignancies are the main factors that impact generalizability of evidence from trials to the real-world situation in older adults with psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV*. Dec 2023;37(12):e1471-e1474.

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*Authors contributed equally.

Publications not related to this thesis

Knipping S, **ter Haar ELM**, Alkemade H, Bronkhorst E, Falk M, Hueskes K, Nij Bijvank C, Spillekom-van Koulil S, Lubeek SKF. Translation and Validation of the Dutch Version of the Sun Exposure and Protection Index. Dermatology (Basel, Switzerland). 2024;240(2):282-90.

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PhD portfolio

Department: Dermatology
PhD Supervisor: Prof. dr. E.M.G.J. de Jong
PhD Co-supervisor(s): Dr. S.F.K. Lubeek and Dr. J.M.P.A. van den Reek

Training activities	Hours
Courses	
EPIC introduction course (2020)	8
Literature Review for your PhD: how to search & where to publish (2020)	4
EndNote Workshop UMC (2020)	1
RIHS - Introduction course for PhD candidates (2020)	15
Radboudumc - eBROK course (2020)	42
RU - Scientific Writing for PhD candidates (2021)	84
RU - Statistics for PhD's by using SPSS (2021)	60
RU - Project management for PhD candidates (2021)	52
Radboudumc - Scientific integrity (2021)	20
RU - The Art of Finishing Up (2021)	10
Workshop: negotiating skills (2022)	1
RU - The Art of Presenting Science (2022)	36
Seminars	
Research round: Inflammatory disease (2020)	1
Psoriasis patiënten Nederland - Webinar: Personalized care (oral presentation) 2021)	3
IQVIA: real-world evidence symposia (2021)	7
EADV review (2021)	2
Annual BioCapture meeting (presenter) (2022)	2
VUK-UP night seminar organised by Radboud university, Radboudumc (2022)	2
Dermatology - various clinical seminars (2020-2022)	6
Research integrity Round (2023)	1
Conferences	
Annual meeting Nederlandse Vereniging Experimentele Dermatologie (NVED) (2020)	16
European Academy of Dermatology and Venereology (EADV): poster presentation (2020)	7
European Academy of Dermatology and Venereology (EADV): poster presentation (2021)	7
Psoriasis from Gene to Clinic - virtual conference: poster presentation (2021)	24
Annual meeting Nederlandse vereniging Experimentele Dermatologie (NVED): poster presentation (2022)	16
PhD retreat (2022)	14
Skin Inflammation and Psoriasis International Network (SPIN): oral presentation (2022)	24
European Academy of Dermatology and Venereology (EADV) congress: poster presentation (2022)	24

Other	9
Radboudumc - General Radboudumc introduction for research personnel (2020)	1.5
Webinar verder kijken dan de huid (2021)	1.5
Research Integrity Round: The Dark Side of Science (2021)	78
Research presentations Dermatology (2022)	78
Journal club dermatology (2023)	10
NVDV - Werkgroeplid richtlijnherziening Psoriasis (2023-2024)	
Teaching activities	
Supervision of internships / other	
Supervision research internship master medical student (2020)	50
Supervision research internship master medical student (2022)	50
Total	**767**

Curriculum Vitae

Elke ter Haar werd geboren op 3 september 1992 te 's-Hertogenbosch en is opgegroeid in het nabijgelegen Rosmalen. Na het behalen van haar VWO diploma aan het Sint-Janslyceum te 's-Hertogenbosch, begon zij in 2012 aan haar bacheloropleiding Biomedische Wetenschappen aan de Radboud Universiteit te Nijmegen. Na het behalen van haar bachelordiploma in 2015 is zij na een schakeljaar ingestroomd in de masteropleiding Geneeskunde aan dezelfde universiteit, waarvan zij in 2019 haar diploma heeft behaald. In haar laatste opleidingsjaar heeft zij een keuze-coschap gelopen als beleidsadviseur van de directie van ZonMw in Den Haag, alsmede een senior-coschap en wetenschappelijke stage bij de afdeling Dermatologie in het Radboudumc te Nijmegen. Tijdens haar studie heeft zij meerdere functies bekleed in de studentmedezeggenschap: zo is ze voorzitter geweest van de Studenten Organisatie voor Onderwijs en Studie (SOOS, 2014-2015), vicevoorzitter van het congresbestuur van het Landelijk Medisch Studenten overleg (LMSO, 2015-2016), en tweemaal verkozen tot lid van de Facultaire Studentenraad en de UMC-Raad van het Radboudumc (2015-2016, 2018-2019).

Na het behalen van haar artsenbul begon ze in januari 2020 als arts-promovendus bij de afdeling Dermatologie van het Radboudumc. Tijdens dit promotietraject werd ze begeleid door prof. dr. E.M.G.J. de Jong (promotor), en dr. S.F.K. Lubeek en dr. J.M.P.A. van den Reek (copromotoren). Van oktober 2022 tot en met oktober 2023 heeft zij haar promotietraject in deeltijd voortgezet, naast een voltijdsfunctie als arts niet in opleiding (ANIOS) op de afdeling Dermatologie van het Radboudumc. Nadien heeft ze haar promotietraject weer voltijds opgepakt, waarna ze in juli 2024 is begonnen als ANIOS Ouderengeneeskunde bij Novicare in de regio Arnhem-Nijmegen.

Het onderwerp van haar promotietraject betrof psoriasis bij ouderen, met bijzondere aandacht voor behandelpatronen, veiligheid en personalised medicine. Tijdens haar onderzoek heeft zij meerdere studies uitgevoerd en samengewerkt met verschillende ziekenhuizen in Nederland. Haar onderzoeksactiviteiten hebben geleid tot de publicatie van acht peer-reviewed artikelen in toonaangevende tijdschriften. Deze publicaties zijn gebundeld in dit proefschrift.

Dankwoord

De afgelopen jaren heb ik met veel plezier aan dit proefschrift gewerkt, maar dit zou zonder de begeleiding, hulp en ondersteuning van anderen niet mogelijk zijn geweest. Iedereen die hieraan bij heeft gedragen wil ik bedanken!

In het bijzonder wil ik alle patiënten en zorgprofessionals bedanken voor hun waardevolle deelname aan de verschillende onderzoeken opgenomen in dit proefschrift.

Beste Elke, Juul en Satish: zonder jullie prachtige ideeën, volharding en altijd een open deur was dit proefschrift niet tot stand gekomen. Ik wil jullie bedanken dat jullie mij geïnspireerd hebben, mij hebben laten groeien en ontwikkelen, en dat we samen een bijdrage hebben kunnen leveren voor oudere patiënten met psoriasis. Naast dat we hard gewerkt hebben, was er ook altijd ruimte voor gezelligheid, etentjes, congressen, koffiemomentjes, etc. Ik dank jullie voor het vertrouwen in mij.

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Lieve paranimfen Sarah en Maartje: de cirkel is rond, wat een eer dat jullie vandaag naast mij staan. We zijn samen begonnen als arts-onderzoekers bij de dermatologie maar zijn op dit moment alle drie werkzaam in een ander specialisme. Ondertussen is onze vriendschap de afgelopen jaren blijven groeien. Ontzettend bedankt voor de gezelligheid, de lach en huil momentjes en onze avondjes uit in de afgelopen jaren.

Lieve biebchickies, (arts)-onderzoekers; Marieke, Tamara, Finola, Jade, Lara, Marloes, Mirjam, Sarah, Maartje, Claire, Sophie, Malak, Nikki, Linda, Charlotte, Liana, Josje,

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Evi: het voelt al weer lang geleden dat we samen lief en leed deelde in de bieb, die regelmatig omgetoverd werd tot kerstshow of café. Na de verhuizing naar de nieuwbouw op de 7e verdieping hebben we toch nog wat van onze eigen werkplekken kunnen meenemen, hopelijk blijft die kerstbal er altijd hangen! Ik wil jullie bedanken voor alle gezelligheid, etentjes, sinterklaasactiviteiten, stapavondjes, congresbezoeken, etc. Het was altijd een feest! Het bezoek aan Milano was onvergetelijk, grazie mille Laar en Saar!

Lieve Marieke, veel dank voor jouw begeleiding en humor tijdens mijn wetenschappelijke stage. Mede door jou zag ik in hoe leuk een promotietraject kon zijn!

Lieve Marisol en Thea, jullie zijn de motor achter het klinisch onderzoek van onze afdeling. Als er iets achter de schermen geregeld moest worden wisten jullie altijd raad. Heel veel dank voor jullie hulp en gezelligheid!

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Lieve Lian, veel dank voor de gezellige en fijne momenten samen op de afdeling. We moeten nog steeds een keer samen naar het theater gaan!

Beste stafleden, A(N)IOS, physician assistants, verpleging, administratie, stafbureau en medisch fotografen, heel erg bedankt voor jullie interesse en de fijne samenwerking tijdens de afgelopen jaren.

Alle onderzoekers van het lab, veel dank voor jullie hulp op het lab als er iets voor een trial geregeld moest worden, maar vooral bedankt voor alle gezelligheid tijdens de derma uitjes en het jaarlijkse NVED congres.

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Lieve Milou, als nichtje maar zeker ook als goede vriendin en ceremoniemeesteres heb jij een grote rol in mijn leven. Proost op dat dat voor altijd zo mag blijven!

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Lieve Joey, wat ben ik dankbaar dat ik jou mijn man mag noemen. Jouw onvoorwaardelijke steun, je grapjes, je relativeringsvermogen, en je eerlijkheid zijn van onschatbare waarde geweest. Je weet ondertussen meer van psoriasis dan mijn mede arts vriendinnen buiten de dermatologie. Ook ben ik dankbaar hoe je bent met Teddy, dat betekent veel voor mij. Ik kijk uit naar de avonturen die gaan komen, en een komt al heel gauw. Morgen gaan we!! - Dum spiro te amo

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