ORIGINAL ARTICLE

Safety Assessment of Conventional and Biological Systemic Therapy in Older Adults with Psoriasis, a Real-world Multicentre Cohort Study

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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.

Key words: psoriasis; elderly; geriatric psoriasis; older adults; systemic treatment; treatment safety.

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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.

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.

MATERIALS AND 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 theWorld Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment system and clinical experience (23), 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 χ^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,

Table I. Patient demographics

Characteristics	Patients (n = 117)
Age, years, mean±SD	70.5±4.6
Median, range	70 (65–85)
Sex, male, *n* (%)	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 co-medication[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[c,d]	1 (1.0)
Cerebral vascular disease[d]	11 (11.0)
Peripheral vascular disease[d]	9 (9.1)
Cardiovascular disease[d,e]	35 (35.0)
Diabetes mellitus[c,d]	17 (17.0)
Chronic pulmonary disease[d,f]	19 (19.0)
Connective tissue disorder[d]	3 (3.0)
Cancer[d,g]	14 (14.0)
Metastatic[d]	2 (2.0)
Skin cancer[d,h]	18 (18.0)
Chronic kidney disease[d,i]	15 (15.0)
Peptic ulcer[d]	4 (4.0)
Liver disease[d,j]	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 (CCI)[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 ischaemic 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 <60 ml/min/1.73 m2 for at least 3 months. [j]Liver disease included steatosis hepatitis, 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: n = 29, body mass index: 39, co-medication: 18, comorbidity/medical history: 17, Charlson Comorbidity Index: 17.
BMI; body mass index; CCI: Charlson Comorbidity Index; HIV: human immunodeficiency virus; SD: standard deviation.

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 (SPPS) 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 I**. 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 SI). 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 II**. 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 I.

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 II). 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 III** and Table SIII.

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

	Treatment episode[ab] ($n=176$) *n* (%)	Treatment exposure, years[c] *n*, %	Adverse events[d] ($n=319$) *n* (%)	Causality assessed adverse events[d]* ($n=232$) *n* (%)	Serious adverse events ($n=28$) *n* (%)	Causality assessed serious adverse events* ($n=12$) *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 (TEs) 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]Nineteen treatment episodes with patients who used double systemic antipsoriatic treatment or ultraviolet (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, $n=5$ ultraviolet (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 years or over and if they were of significant nature (e.g. required medical attention, dose alterations, treatment discontinuation, other medical interventions). *With the World Health Organization-Uppsala Monitoring Center 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 6 categories: certain, probable, possible, unlikely, conditional and unassessable (23). The following categories were defined as causal in this study; possible, probable and certain.

Table III. Summary of causality assessed adverse events (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 AEs[o]	2 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Adverse events (AEs) were only recorded if they occurred at the age of 65 years 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,↑ amino terminal type III procollagen peptide (P3NP), ↑alkaline phosphatase, ↑creatine kinase, ↑cholesterol, ↑triglycerides, renal function deterioration, proteinuria, haematuria, deviations in urinary sediment, leukopaenia, neutropaenia, lymphocytopaenia, anaemia. [e]Includes; actinic keratosis, non-Hodgkin lymphoma, lung cancer, tubular 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, pustules on the chest. [m]Includes; dry eyes, retinal detachment. [n]Includes; depression. [o]Includes; pneumonitis on methotrexate.
TE: treatment episode; caAEs: causality assessed adverse events; caSAEs: causality assessed serious adverse events. The above shown antipsoriatic treatments were selected: based on a minimum of 10 treatment episodes (TEs).

To compare caAE-occurrence per year of treatment exposure time amongst the specific systemic treatments IRRs were calculated (see **Table IV**). 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 SIV). 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 SV).

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 V**). Increasing age in years was associated with a higher odds on developing a caAE (OR 1.195; 95% CI 1.026–1.393; $p=0.022$).

Table IV. Negative binomial model on the incidence rate ratios of causality assessed adverse events per year of selected treatment episode in patients aged 65 years and over

Antipsoriatic treatment[a]	IRR[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 10 treatment episodes. [b]The incidence rate ratio (IRRs) are only calculated with the TEs, of which the treatment duration was known, 17 TEs were excluded from this analysis including corresponding adverse events ($n=8$). CI: confidence interval.

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 SVI).

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

Table V. Multiple logistic regression model on the relation of different factors with the occurrence of causality assessed adverse events 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[c]	0.385	0.122–1.211	0.103
Type of systemic treatment[d]			0.062
Methotrexate	Reference		
Dimethyl fumarate	1.560	0.407–5.984	0.516
Acitretin	0.303	0.066–1.402	0.127
Biological[e]	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 Charlson Comorbidity Index (CCI) score was divided into 2 groups, CCI<1 and CCI≥1 based on the data distribution. [c]Polypharmacy was defined as the simultaneous use of ≥5 medications. [d]Six patients were excluded due to the simultaneous use of 2 types of antipsoriatic treatment. [e]Including etanercept, adalimumab, ustekinumab, ixekizumab.
95% CI: 95% confidence interval.

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 SVII.

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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