JAMA Dermatology | Review

Effectiveness and Safety of Systemic Therapy for Psoriasis in Older Adults
A Systematic Review

Marieke E. C. van Winden, MD, MSc; Lara S. van der Schoot, MD; Mariluz van de L'Isle Arias, MD; Lieke J. van Vugt, MD; Juul M. P. A. van den Reek, PhD; Peter C. M. van de Kerkhof, PhD; Elke M. G. J. de Jong, PhD; Satish F. K. Lubeek, PhD

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

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

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

FINDINGS The initial search yielded 11 096 results, of which 31 unique articles with 39 561 patients were included in analysis. Overall, limited data were available per systemic agent, and overall quality of the included studies on conventional systemic therapies was low. At the end of the induction phase (12-16 weeks after start of treatment), a reduction of 75% in Psoriasis Area and Severity Index was achieved in 49% of 74 methotrexate sodium users 65 years or older, 46% to 52.6% of 178 older cyclosporin users, 27% to 47.8% of 108 older acitretin users, 15.6% to 64% of 256 etanercept users 65 years or older, 66.7% to 93% of 43 infliximab users 65 years or older, 60.7% to 65% of 100 adalimumab users 65 years or older, 56.5% of 46 ustekinumab users 65 years or older, and 86.4% of 67 secukinumab users 65 years or older. Effectiveness of acitretin, etanercept, adalimumab, and secukinumab appeared not to be associated with age; studies regarding other systemic antipsoriatic therapies did not provide age group comparisons. Older age was significantly associated with renal function deterioration in cyclosporin users and with lymphopenia in fumaric acid esters users (hazard ratio, 2.42; 95% CI, 1.65-3.55; $P < .001$). Infections were the most frequently reported adverse event in patients 65 years or older using biologics, but no significant association with age was found.

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

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Author Affiliations: Department of Dermatology, Radboud University Medical Center, Nijmegen, the Netherlands (van Winden, van der Schoot, van de L'Isle Arias, van den Reek, van de Kerkhof, de Jong, Lubeek); Department of Dermatology, Maastricht University Medical Center, Maastricht, the Netherlands (van Vugt).

Corresponding Author: Marieke E. C. van Winden, MD, MSc, Department of Dermatology, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands (marieke.vanwinden@radboudumc.nl).

JAMA Dermatol. doi:10.1001/jamadermatol.2020.2311
Published online August 19, 2020.

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

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

Key Points

Question What are the effectiveness and safety outcomes of systemic antipsoriatic therapies in patients 65 years or older?

Findings In this systematic review of 31 unique studies with 39 561 patients, the limited available data on individual antipsoriatic agents indicated a reduction of 75% in Psoriasis Area and Severity Index at weeks 12 to 16 in 27% to 53% of patients using conventional systemic therapies and 16% to 93% of patients using biologics. Scarce safety data suggest a higher chance of abnormal laboratory findings and (mild) infections in patients 65 years or older.

Meaning On the basis of the study findings, age alone should not be a limiting factor in psoriasis management; future research in this growing patient group is critical.

Methods

Search Strategy

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

Study Selection

Eligibility assessment, data extraction, quality assessment, and risk of bias assessment were performed independently by 2 reviewers (M.E.C.vW. and L.S.vdS. or M.vdLI.A.). In case of discrepancies, a third reviewer (J.M.P.A.vdR. or S.F.K.L.) was consulted. Randomized clinical trials (RCTs), cohort studies, large case series (≥10 patients), and meta-analyses assessing efficacy, effectiveness, and/or safety in patients with psoriasis 65 years or older were included. To provide a complete overview, additional studies could be included in case both reviewers agreed on the relevance of the article, for example, in case a different age cutoff value was used, or for studies in which a relatively old population was included. Studies in languages other than English, Spanish, German, French, and Dutch were excluded, as well as case reports, small case series (<10 patients), conference abstracts, oral communications, and expert opinions. At least 2 attempts were made to contact authors of the original articles if their full text could not be accessed or to request additional relevant information.

Outcome Measures

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

Data Extraction and Quality Assessment

Data were extracted using a predesigned form. Percentages were calculated by the reviewers wherever possible, if not stated in the articles. Study quality was graded according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies[8] and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for RCTs.[9] Risk of bias was assessed using the Newcastle-Ottawa Scale for cohort and case-control studies[10] and the Cochrane Risk of Bias Tool for RCTs.[6] $P < .05$ indicated significance.

Results

Study Characteristics

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

Methotrexate Sodium

Three articles[11-13] assessed methotrexate effectiveness in older adults, and 4 studies[11,26,28,31] assessed methotrexate safety and

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

Cyclosporine

Three studies[11,14,15] assessed cyclosporine effectiveness in a cumulative number of 178 older adults, and 3 studies[11,31,32] assessed cyclosporine safety and tolerability in patients 65 years or older. At week 12, 46% to 52.6% of the included patients reached PASI75. No data were available regarding long-term effectiveness. The most frequently reported adverse events were hypertension and renal insufficiency,[11,32] the latter being significantly more prevalent in patients 65 years or older (4 of 12 patients [33%]) compared with patients younger than 65 years (10 of 110 patients [9%]; $P = .03$).[32] Other frequently reported adverse events in older cyclosporine users were hypercholesterolemia, hypertriglyceridemia, and infections (eTable 2 in the Supplement).[32,40] Cyclosporine use in patients 65 years or older was associated with a significantly higher overall rate of adverse events (1.4 per patient-year) compared with methotrexate (0.12 per patient-year; $P < .001$).[11]

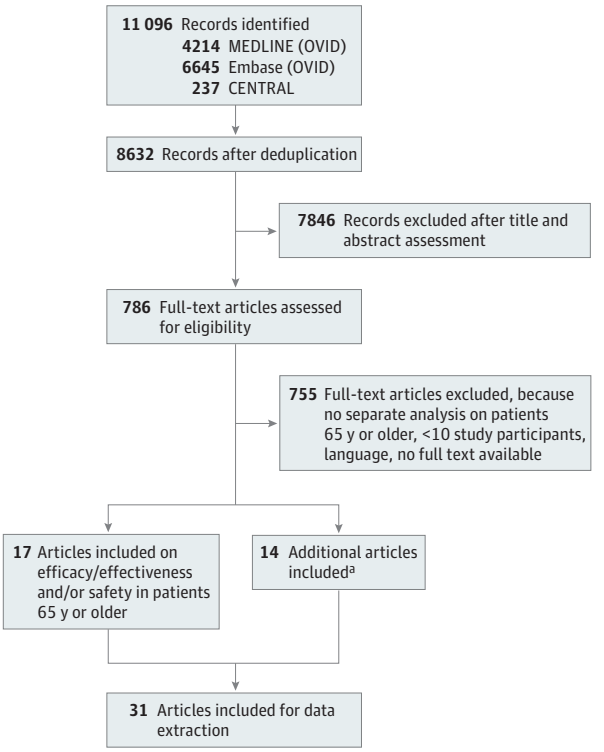
Retinoids

Two studies[11,16] assessed acitretin effectiveness in a cumulative number of 108 older adults, and 4 studies[11,16,28,31] assessed acitretin safety and tolerability in older adults. None of the studies described a combination of acitretin and UV phototherapy in older adults. At weeks 12 to 16, 27% to 47.8% of the included patients achieved PASI75,[11,16] and no significant association between age and treatment failure or response rate was seen.[16] The effectiveness of acitretin (PASI75 achieved by 27%) was significantly lower compared with the effectiveness of other systemic therapies (49% [$P = .01$] for methotrexate, 64% [$P < .001$] for etanercept, 65% [$P < .01$] for adalimumab, and 93% [$P < .05$] for infliximab).[11] No data were available regarding long-term effectiveness. The most common adverse effects were alopecia, xerophthalmia, cheilitis, and fatigue (eTable 2 in the Supplement). One study[16] reported on the association between acitretin safety and age; no correlation was found between the incidence of adverse effects and age ($P = .62$, not otherwise specified).

Fumaric Acid Esters

No studies were identified examining effectiveness of fumaric acid esters in patients 65 years or older. However, 1 study[17] reported similar PASI75 responses in 88 patients older than 55 years compared with 221 patients 55 years or younger (51 [58.0%] vs 111 [50.2%]; $P = .22$). In this study, PASI75 was achieved at different time points, which limits comparison with other studies. Older age was significantly associated with the development of T-cell lymphopenia (hazard ratio, 2.42; 95% CI, 1.65-3.55; $P < .001$) during treatment with fumaric acid esters (eTable 2 in the Supplement).

Figure 1. Flow Diagram of the Literature Search



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

Etanercept

Four studies[11,18-20] assessed etanercept effectiveness in a cumulative number of 256 patients 65 years or older, and 6 studies[11,18,28-31] assessed safety and tolerability in etanercept users 65 years or older. PASI75 was attained by 15.6% to 64% of patients 65 years or older at week 12[11,18,20] and by 83.6% to 86.9% after 1 to 3 years (Figure 3).[18] Response rates varied between etanercept doses (Table 2). Two studies[19,20] comparing patients 65 years or older with patients younger than 65 years found no difference in effectiveness between age groups. As is shown in eTable 3 in the Supplement, the most frequently reported adverse events were mild infections (eg, flulike symptoms).[11,18,29] No significant difference was seen in incidence of serious infections in etanercept users 65 years or older compared with methotrexate users 65 years or older.[28] One article[36] with participants with a high overall mean age reported an increased risk for malignant neoplasms for tumor necrosis factor inhibitors, although a separate analysis including only etanercept did not reach significance (odds ratio [OR], 1.37; 95% CI, 0.94-2.01; $P = .10$). One study[30] reported on the association between etanercept safety and age; serious adverse events were more frequently seen in patients 65 years or older compared with patients younger than 65 years, although according to the authors none of these were associated with etanercept use (not further specified).

Infliximab

Two retrospective studies[11,21] assessed infliximab effectiveness with a cumulative inclusion of 43 patients 65 years or older, and

Table 1. Studies Included for Data Extraction on the Efficacy or Effectiveness of Systemic Antipsoriatic Therapies in Older Adults[a]

Source	Study design and methodological approach[b]	Treatment	Age, y		Baseline PASI, mean (SD) [range]	No. of patients	
			Cutoff	Mean (SD) [range]		Aged ≥65 y[c]	Aged <65 y
Piaserico et al,[11] 2014	Retrospective, NRI	Methotrexate, 11.7 mg OW (mean)	65	71.3 (5) [65-NR][d]	12.7 (5.8) [4-32]	74	NA
Fairris et al,[12] 1989	NR[e]	Methotrexate; mean dose, NR (minimum, 2.5 mg/wk)	50	NR (NR) [50-93]	NR	23 (>50 y)	NA
Kaur et al,[13] 1995	Retrospective, NR[e]	Methotrexate, 25-30 mg OW	50	55.4 (NR) [51-65]	NR	14 (>50 y)	NA
Piaserico et al,[11] 2014	Retrospective, NRI	Cyclosporin, 3.5 mg/kg (mean)	65	71.3 (5) [65-NR][d]	17 (5.9) [6-32]	36	NA
Timonen et al,[14] 1990	Integrated analysis of 5 dose-finding studies, ITT, LOCF	Cyclosporin, 1.25-5.00 mg/kg/d	40	42 (NR) [18-75][d]	25 (NR) [NR][d]	120 (>40 y)	129 (≤40 y)
Abe et al,[15] 2007	Prospective, as treated	Cyclosporin, 2.5 mg/kg/d	NA	59.7 (7.75) [NR]	NR (NR) [12-18]	19[d]	NA
Piaserico et al,[11] 2014	Retrospective, NRI	Acitretin, 0.38 mg/kg (mean)	65	71.3 (5) [65-NR][d]	14.8 (6.9) [2-32]	62	NA
Borghi et al,[16] 2015	Retrospective, as treated	Acitretin, 22.5 mg/d (mean)	NA	61.4 (15.3) [28-90]	20.3 (7.8) [10-41.4]	46[d]	NA
Dickel et al,[17] 2019[g]	Retrospective, as treated	Dimethyl fumaric acid, 345.8 (167.0) mg for monotherapy and 416.8 (196.2) for combination therapy (mean [SD])	55	47.8 (14.6) [9-90][d]	22.3 (8.1) [2.4-43.2][d]	88 (>55 y)	221 (≤55 y)
Esposito et al,[18] 2012	Retrospective, ITT, LOCF[e]	Etanercept, 50mg TW (wk 0 to wk 12); 25mg TW/50 mg OW (after wk 12)	65	70.0 (NR) [65-82]	11.3 (NR) [0.4-68.3]	15 (wk 0-NR) 46 (wk 0-156)	NA
Giunta et al,[19] 2014	Retrospective, LOCF	Etanercept, dose NR	65	50.7 (NR) [18-83][d]	11.50 (NR) [NR]	56	244
Gordon et al,[20] 2006	Integrated analysis, 3 RCTs, LOCF	Etanercept, 50 mg OW/TW	65	45.4 (12.2) [NR][d]	18.8 (8.4) [NR][d]	25, placebo 32, OW 24, TW	389, placebo 383, OW 334, TW
Piaserico et al,[11] 2014	Retrospective, NRI	Etanercept, dose NR	65	71.3 (5) [65-NR][d]	14.9 (6.4) [3-35]	83	NA
Chiricozzi et al,[21] 2016	Retrospective, as treated	Infliximab dose NR, at 0, 2, 6, and every 8 wk	65	72 (5.2) [65-85]	15.6 (10.2) [NR]	27	NA
Piaserico et al,[11] 2014	Retrospective, NRI	Infliximab dose NR	65	71.3 (5) [65-NR][d]	14.8 (5.7) [4-20]	16	NA
Esposito et al,[18] 2012	Retrospective, ITT, LOCF[e]	Adalimumab, 80 mg ID and 40 mg EOW	65	69.3 (NR) [65-75]	10.4 (NR) [0.4-23.8]	11 (wk 0-NR) 17 (wk 0-156)	NA
Menter et al,[22] 2010	PHA: 1 RCT, ITT, NRI	Adalimumab, 80 mg ID and 40 mg EOW	65	NR	NR	30 placebo 54 adalimumab	368 placebo 760 adalimumab
Piaserico et al,[11] 2014	Retrospective, NRI	Adalimumab dose NR	65	71.3 (5) [65-NR][d]	14.3 (4.1) [9-20]	18	NA
Hayashi et al,[23] 2014	Retrospective, analysis NR	Ustekinumab, 45 mg at wk 0 and 4 and every 12 wk for ≥1y[f]	65	73.1 (7.4) [65-88]	12.9 (7.9) [3.0-30.2]	24	NA
Megna et al,[24] 2016	Retrospective, analysis NR[e]	Ustekinumab, 45 mg (<100 kg) and 90 mg (>100 kg) at wk 0 and 4 and every 12 wk for ≥2 y	65	70.3 (4.6) [65-79]	13.7 (5.1) [5.4-28.2]	22	NA
Körber et al,[25] 2018	PHA: 3 RCTs, ITT, NRI	Secukinumab, 300 mg OW for wk 0-4 and every 4 wk for wk 8-48	65	≥65 y: 69.3 (NR) [NR]; <65 y: 42.9 (NR) [18-64]	≥65 y: 20.2 (7.5) [NR]; <65 y: 22.9 (9.4) [NR]	67	842

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

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

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

[c] In case the number of patients 65 years or older was unclear (eg, in case a different age cutoff was used, or in case of a population with a relatively overall high mean age), the total number of patients was given.

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

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

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

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

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

Study characteristics		Outcomes <52 wk		Outcomes ≥52 wk		Overall quality [b]/risk of bias[c]
Source	Treatment	Patients aged ≥65 y	Patients aged <65 y	Patients aged ≥65 y	Patients aged <65 y	
Piaserico et al,[11] 2014	Methotrexate	Wk 12: PASI75, NR (49%)	NA	NA	NA	B/5
Fairris et al,[12] 1989	Methotrexate	Wk 12: PASI75, NR[d]	NA	NA	NA	C/2[e]
Kaur et al,[13] 1995	Methotrexate	Wk 12: PASI75, NR; mean time to PASI75, 7.1 wk	NA	NA	NA	C/4[e]
Piaserico et al,[11] 2014	Cyclosporin	Wk 12: PASI75, NR (46%)	NA	NA	NA	B/5
Timonen et al,[14] 1990	Cyclosporin	Wk 12: PASI75, 57 (47%; >40 y)	PASI75: 51 (40%) (≤40 y)[f]	NA	NA	B/4
Abe et al,[15] 2007	Cyclosporin	Wk 12: PASI75, 10 (52.6%)[j]	NA	NA	NA	C/4
Piaserico et al,[11] 2014	Acitretin	Wk 12: PASI75, NR (27%)	NA	NA	NA	B/5
Borghi et al,[16] 2015	Acitretin	Wk 10-16: PASI50, 40 (87%)	NA	NA	NA	A/6
		Wk 10-16: PASI75, 22 (47.8%)				
		After wk 16: PASI75, 31 (67.4%)[g]				
Dickel et al,[17] 2019[h]	Dimethyl fumaric acid	PASI75: 51 (58.0%), >55 y, different time points	PASI75: 111 (50.2%), ≤55 y, different time points[f]	NA	NA	B/5
Esposito et al,[18] 2012	Etanercept	Wk 12: PASI50, NR (82.0%)	NA	Wk 52: PASI50, NR (90.2%)	NA	B/4[e]
		Wk 12: PASI75, NR (54.1%)		Wk 52: PASI75, NR (83.6%)		
		Wk 24: PASI50, NR (90.2%)		Wk 104: PASI50, NR (91.8%)		
		Wk 24: PASI75, NR (78.7%)		Wk 104: PASI75, NR (86.9%)		
				Wk 156: PASI50, NR (91.8%)		
				Wk 156: PASI75, NR (83.6%)		
Giunta et al,[19] 2014	Etanercept	Wk 12: PASI50, NR (83.9%)	Wk 12: PASI50, NR (91.4%)[f]	NA	NA	B/5
		Wk 24: PASI75, NR (64.3%)	Wk 24: PASI75, NR (71.3%)[f]			
Gordon et al,[20] 2006	Etanercept	Wk 12: PASI75, 0 (placebo)	Wk 12: PASI75, 13 (3.3%) (placebo)	NA	NA	B/4
		Wk 12: PASI75: 5 (15.6%) (OW)	Wk 12: PASI75, 134 (35.0%) (OW)[i]			
		Wk 12: PASI75: 14 (58.3%) (TW)	Wk 12: PASI75, 163 (48.8%) (TW)[i]			
Piaserico et al,[11] 2014	Etanercept	Wk 12: PASI75, NR (64%)	NA	NA	NA	B/5
Chiricozzi et al,[21] 2016	Infliximab	Wk 12: PASI50, 21 (77.8%)	NA	NA	NA	B/5
		Wk 12: PASI75, 18 (66.7%)				
		Wk 12: PASI90, 13 (48.1%)				
Piaserico et al,[11] 2014	Infliximab	Wk 12: PASI75, NR (93%)	NA	NA	NA	B/5
Esposito et al,[18] 2012	Adalimumab	Wk 12: PASI50, NR (85.7%)	NA	Wk 52: PASI50, NR (78.6%)	NA	B/4[e]
		Wk 12: PASI75, NR (60.7%)		Wk 52: PASI75, NR (67.9%)		
		Wk 24: PASI50, NR (82.1%)		Wk 104: PASI50, NR (82.1%)		
		Wk 24: PASI75, NR (71.4%)		Wk 104: PASI75, NR (71.4%)		
				Wk 156: PASI50, NR (82.1%)		
				Wk 156: PASI75, NR (71.4%)		

(continued)

Table 2. Study Outcomes, Quality, and Risk of Bias[a] (continued)

Study characteristics		Outcomes <52 wk		Outcomes ≥52 wk		Overall quality [b]/risk of bias[c]
Source	Treatment	Patients aged ≥65 y	Patients aged <65 y	Patients aged ≥65 y	Patients aged <65 y	
Menter et al,[22] 2010	Adalimumab	Wk 16: PASI75, NR (3%) (placebo)	Wk 16: PASI75, NR (7%) (40-64 y) and 6% (<40 y) (placebo)	NA	NA	B/5
		Wk 16: PASI75, NR (61%) (adalimumab)	Wk 16: PASI75, NR (70%) (40-64 y) (adalimumab)[f]			
			Wk 16: PASI75, NR (74%) (<40 y) (adalimumab)			
Piaserico et al,[11] 2014	Adalimumab	Wk 12: PASI75, NR (65%)	NA	NA	NA	B/5
Hayashi et al,[23] 2014	Ustekinumab	Wk 16: PASI50, NR (87.0%)	NA	Wk 52: PASI50, NR (95.0%)	NA	B/5
		Wk 16: PASI75, NR (56.5%)		Wk 52: PASI75, NR (60.0%)		
		Wk 28: PASI50, NR (81.8%)				
		Wk 28: PASI75, NR (59.1%)				
Megna et al,[24] 2016	Ustekinumab	Wk 28: PASI50, NR (86.4%)	NA	Wk 52: PASI50, NR (90.9%)		B/4[e]
		Wk 28: PASI75, NR (63.6%)		Wk 52: PASI75, NR (86.4%)		
		Wk 28: PASI90, NR (13.6%)		Wk 52: PASI90, NR (54.5%)		
		Wk 28: PASI100, NR (4.5%)		Wk 52: PASI100, NR (36.4%)		
				Wk 76: PASI50, NR (95.4%)		
				Wk 76: PASI75, NR (90.9%)		
				Wk 76: PASI90, NR (77.3%)		
				Wk 76: PASI100, NR (54.5%)		
				Wk 100: PASI50, NR (100%)		
				Wk 100: PASI75, NR (90.9%)		
				Wk 100: PASI90, NR (86.4%)		
				Wk 100: PASI100, NR (54.5%)		
Körber et al,[25] 2018	Secukinumab	Wk 16: PASI75, NR (86.4%)	Wk 16: PASI75, NR (89.0%)[i]	Wk 52: PASI75, NR (81.8%)	Wk 52: PASI75, NR (79.4%)[i]	B/5
		Wk 16: PASI90, NR (72.7%)	Wk 16: PASI90, NR (74.3%)			
		Wk 16: PASI100, NR (40.9%)	Wk 16: PASI100, NR (40.9%)			

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

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

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

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

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

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

[f] Indicates no significant difference between age groups.

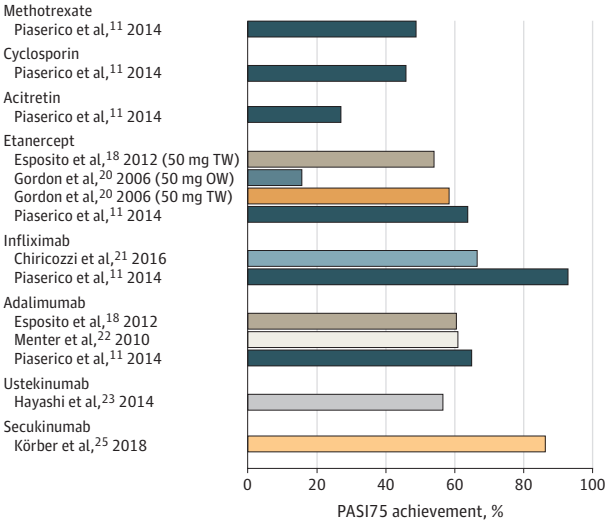
[g] No difference was seen between age of those who achieved PASI75 (mean [SD] age, 60.8 [15.9] y) and nonresponders (mean [SD] age, 62.7 [14.5] y; $P = .96$).

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

[i] Statistical comparison not reported.

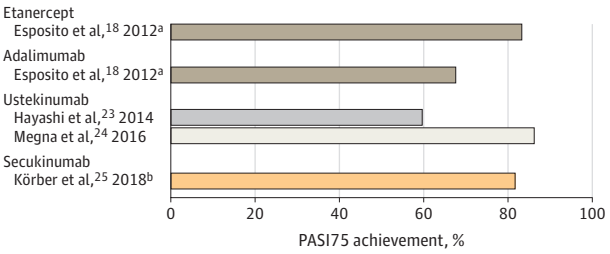
[j] Total study population, including other age groups.

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



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

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



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

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

[b] The study used intention-to-treat analysis with nonresponder imputation.

5 studies[11,21,28,29,33] assessed safety and tolerability in infliximab users 65 years or older. PASI75 response at week 12 ranged from 66.7% to 93%,[11,21] including 6 patients using combination therapy with methotrexate, 7.5 to 15.0 mg/wk.[21] No data were available regarding long-term effectiveness. As is shown in eTable 4 in the Supplement, the most frequently reported adverse events were mild infections.[21,29,33] Two studies described a trend of an increased infection rate with rising age, although the differences found were not statistically significant (11 of 117 [9.4%] patients aged ≥65 years vs 28 of 647 [4.3%] patients aged <65 years; $P = .06$)[33] or not reported (4 of 6 [66.7%] patients aged ≥76 years vs 2 of 22 [9.1%] patients aged ≤75 years; *P* value not reported).[29] Comorbidities were associated with an increased incidence of infections, especially respiratory disease.[33] Fiorentino et al[36] reported an increased risk for malignant neoplasms in older patients using tumor necrosis factor inhibitors, although a separate analysis including only infliximab did not reach significance (OR, 1.01; 95% CI, 0.59-1.74; $P = .96$).

Adalimumab

Three studies[11,18,22] assessed adalimumab effectiveness in a cumulative number of 100 patients 65 years or older, and 5 studies[11,18,27,28,31] assessed safety in adalimumab users 65 years or older. At weeks 12 to 16, PASI75 was achieved in 60.7% to 65% of patients 65 years or older[11,18,22] and in the longer term (1-3 years) in 67.9% to 71.4%.[18] No statistically significant association was seen between PASI75 response and age.[22] One study[27] reported on the association between adalimumab safety and age; a similar frequency of adverse events was seen in patients older than 65 years (2 of 16 [12.5%]) compared with patients 65 years or younger (13 of 101 [12.9%]; *P* value not reported), most commonly infections (eTable 5 in the Supplement). No statistically significant difference was seen in incidence of infections in adalimumab users 65 years or older compared with methotrexate users 65 years or older.[28] An increased risk for malignant neoplasms in older patients using tumor necrosis factor inhibitors was reported by Fiorentino et al,[36] although a separate analysis including only adalimumab did not reach significance (OR, 1.37; 95% CI, 0.93-2.02; $P > .99$).

Ustekinumab

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

Secukinumab

One study assessed secukinumab effectiveness and safety in 67 patients 65 years or older.[25] PASI75 was achieved by 86.4% of patients 65 years or older at week 16 compared with 89.0% of patients younger than 65 years (*P* value not reported). Long-term effectiveness (52 weeks) was achieved by 81.8% of patients 65 years or older and 79.4% of patients younger than 65 years (*P* value not reported). As is shown in eTable 7 in the Supplement, the most frequently reported adverse events were infections, which were seen in 36 of 67 patients (53.7%) 65 years or older vs 527 of 839 (62.8%) younger than 65 years ($P \geq .05$, not otherwise specified).[25] Cardiac disorders were seen in 8 of 67 patients (11.9%) 65 years or older

vs 24 of 839 (2.9%) younger than 65 years (*P* value not reported), although patients 65 years or older also had significantly more preexistent cardiovascular comorbidities at baseline (eg, hypertension in 71.8% of patients aged ≥65 years vs 20.8% of patients aged <65 years [*P* < .001]; myocardial infarction in 7.7% of patients aged ≥65 years vs 1.9% of patients aged <65 years [*P* = .02]; coronary artery disease in 10.3% of patients aged ≥65 years vs 1.7% of patients aged <65 years [*P* < .001]). Treatment-related serious adverse events were seen in 4.5% of patients 65 years or older and in 1.8% of patients younger than 65 years (*P* values not reported, not otherwise specified).[25]

Apremilast

No studies were identified studying the effectiveness of apremilast in patients 65 years or older. Dommasch et al[28] found no significant increase in risk of serious infections in apremilast users 65 years or older compared with methotrexate users 65 years or older (propensity score–adjusted hazard ratio, 0.51; 95% CI, 0.05-5.60; *P* = .58). No other studies were identified assessing apremilast safety and tolerability in older adults (eTable 8 in the Supplement).

Discussion

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

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

For conventional systemic treatment, the most important adverse events in patients 65 years or older included liver dysfunction in methotrexate users,[26,34,35,38,39] hypertension and renal function deterioration in cyclosporine users,[11,32,40] and lymphopenia in fumaric acid ester users.[17] Literature is inconsistent on methotrexate-related hepatotoxicity and the association with age. Whereas some studies have identified age as a risk factor for hepatotoxicity,[50,51] more recent studies found no such association.[26,52,53] Cyclosporine should be prescribed in patients 65 years or older with absolute caution, because it appears to be associated with the highest adverse events rate of all antipsoriatic systemic therapies,[11] and an association of adverse events with increasing age was identified.[32,37] However, most adverse events associated with conventional systemic therapies were reversible after dose adjustment or discontinuation or were successfully treated (eg, hypertension, laboratory changes).[16,32,39,40]

Infections were the most frequently reported adverse events in patients 65 years or older using biologics. In this systematic review, no evidence was found of differences in infection risk by age category.[25,28,33] Other previous studies are inconsistent regarding the association between age and infection risk; Kalb et al[54] found a higher risk of serious infections with increasing age in 11 466 patients with psoriasis (mean [SD] age, 48.5 [13.8] years), in contrast to a meta-analysis[55] with a cumulative number of 17 739 patients (mean [SD] age, 49.1 [14.6] years). In rheumatoid arthritis and inflammatory bowel disease, an increased infection risk was seen in patients 65 years or older using biologics.[56] However, multiple studies have suggested that adverse events in patients with psoriasis might differ from those seen in patients with other immune-mediated inflammatory diseases owing to differences in the underlying immunologic changes.[56-58] Moreover, combination therapy with other immunomodulators is maintained far more frequently (15%-79%) than in dermatological daily practice.[56] In line with previous research, no increased risk of malignant neoplasms (excluding nonmelanoma skin cancer) was seen in methotrexate and ustekinumab users (mean [SD] age, 59.9 [10.9] years).[36,59] Although tumor necrosis factor inhibitors (etanercept, adalimumab, and infliximab) were associated with a higher risk for malignant neoplasms after at least 12 months, analysis per agent did not show significant associations, possibly owing to a lack of statistical power.[36] No data were available for patients 65 years or older specifically. Therefore, results of real-world studies are needed to identify rare long-term adverse events of antipsoriatic therapies and the association with older age (≥65 years).

Some studies have reported a higher incidence of serious adverse events in patients 65 years or older, irrespective of whether or not an association with antipsoriatic treatment was suspected.[60] However, the definition of serious adverse events in RCTs entails hospitalization and emergency department visits, regardless of association with the treatment. Patients 65 years or older frequently have more comorbidities and a higher a priori chance of hospitalization than younger patients. It is therefore questionable whether the results on serious adverse events in these studies, frequently lacking a control group with patients of the same age, can be attributed to antipsoriatic treatment. Considering the risk-to-benefit ratio remains important in every individual patient. Because coronavirus disease 2019 (COVID-19) is at present a global threat to older adults,

many dermatologists might hesitate to prescribe or continue immunomodulatory therapies. Clinical guidelines advise not to cease systemic antipsoriatic therapies unless COVID-19 symptoms arise.[61] The scarce available data do not imply a more severe course of the disease in patients using antipsoriatic therapies, some of which possibly even ameliorate the organ damage associated with severe COVID-19.[62-66] However, much is still unknown, and further research, specifically in older adults, is needed to clarify recommendations.

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

Limitations

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

Conclusions

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

ARTICLE INFORMATION

Accepted for Publication: June 5, 2020.

Published Online: August 19, 2020. doi:10.1001/jamadermatol.2020.2311

Author Contributions: Drs van Winden and Lubeek had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: van Winden, van der Schoot, van Vugt, van den Reek, van de Kerkhof, de Jong, Lubeek.
Acquisition, analysis, or interpretation of data: van Winden, van der Schoot, van de L'Isle Arias, van Vugt, van den Reek, de Jong, Lubeek.
Drafting of the manuscript: van Winden, van der Schoot, van de L'Isle Arias, van den Reek, Lubeek.
Critical revision of the manuscript for important intellectual content: van Winden, van der Schoot, van Vugt, van den Reek, van de Kerkhof, de Jong, Lubeek.
Statistical analysis: van Winden, van de L'Isle Arias, de Jong, Lubeek.
Obtained funding: Lubeek.
Administrative, technical, or material support: van Winden, van Vugt, Lubeek.
Supervision: van den Reek, van de Kerkhof, de Jong, Lubeek.

Conflict of Interest Disclosures: Dr van Winden reported performing investigator-initiated research with financial support from Almirall SA and performing clinical trials for AbbVie, Celgene Corporation, Janssen Pharmaceutica, Leo Pharma A/S, Eli Lilly and Company, and Novartis International AG. Dr van der Schoot reported receiving grants from ZonMw during the conduct of the study and participating in trials sponsored by Almirall SA, Janssen Pharmaceutica, and Novartis International AG outside the submitted work. Dr van Vugt reported receiving grants from ZonMw during the conduct of the study and participating in trials sponsored by AbbVie, Janssen Pharmaceutica, Celgene Corporation, and Novartis International AG outside the submitted work. Dr van den Reek reported receiving grants from ZonMw during the conduct of the study; participating in trials sponsored by Janssen Pharmaceutica, AbbVie, and Celgene Corporation outside the submitted work; receiving speaking fees from Janssen Pharmaceutica and AbbVie; and receiving reimbursement for attending a symposium from Janssen Pharmaceutica, Pfizer, Inc, Celgene Corporation, and AbbVie. Dr van de Kerkhof reported serving as the chief medical officer of the International Psoriasis Council and receiving fees for lectures and consultancies from Bristol-Myers Squibb, UCB, Leo Pharma, Eli Lilly and Company, Dermavant Sciences, Almirall SA, Celgene Corporation, Novartis International AG, Janssen Pharmaceutica, and AbbVie. Dr de Jong reported receiving research grants for the independent research fund of the Department of Dermatology of the Radboud University Medical Centre Nijmegen from AbbVie, Pfizer, Inc, Novartis International AG, Janssen Pharmaceutica, and Leo Pharma; and consulting or serving as a paid speaker for and/or participating in research sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Janssen Pharmaceutica, Novartis International AG, Eli Lilly and Company, Celgene Corporation, Leo Pharma, UCB, and Almirall SA. Dr Lubeek reported receiving research grants for investigator-initiated research by Almirall SA. No other disclosures were reported.

Funding/Support: This study was supported by Almirall SA (independent research fund of the Department of Dermatology of Radboud University Medical Centre Nijmegen).

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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