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Persistence and effectiveness of nonbiologic systemic therapies for moderate-to-severe psoriasis in adults: a systematic review*

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Summary

Background The persistence and effectiveness of systemic therapies for moderate-to-severe psoriasis in current clinical practice are poorly characterized.
Objectives To systematically review observational studies investigating the persistence and effectiveness of acitretin, ciclosporin, fumaric acid esters (FAE) and methotrexate, involving at least 100 adult patients with moderate-to-severe psoriasis, exposed to therapy for ≥ 3 months.
Methods MEDLINE, Embase, the Cochrane Library and PubMed were searched from 1 January 2007 to 1 November 2017 for observational studies reporting on persistence (therapy duration or the proportion of patients discontinuing therapy during follow-up) or effectiveness [improvements in Psoriasis Area and Severity Index (PASI) or Physician's Global Assessment (PGA)]. This review was registered with PROSPERO, number CRD42018099771.
Results Of 411 identified studies, eight involving 4624 patients with psoriasis were included. Variations in the definitions and analyses of persistence and effectiveness outcomes prevented a meta-analysis from being conducted. One prospective multicentre study reported drug survival probabilities of 23% (ciclosporin), 42% (acitretin) and 50% (methotrexate) at 1 year. Effectiveness outcomes were not reported for either acitretin or ciclosporin. The persistence and effectiveness of FAE and methotrexate were better characterized, but mean discontinuation times ranged from 28 to 50 months for FAE and 7·7 to 22·3 months for methotrexate. At 12 months of follow-up, three studies reported that 76% (FAE), 53% (methotrexate) and 59% (methotrexate) of patients achieved ≥ 75% reduction in PASI, and one reported that 76% of FAE-exposed patients achieved a markedly improved or clear PGA.
Conclusions The comparative persistence and effectiveness of acitretin, ciclosporin, FAE and methotrexate in real-world clinical practice in the past decade cannot be well described due to the inconsistency of the methods used.

What's already known about this topic?

- Research examining acitretin, ciclosporin, fumaric acid esters (FAE) and methotrexate for the treatment of moderate-to-severe psoriasis has focused on safety and efficacy in randomized controlled trials.

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Conflicts of interest
The BADBIR Study Group includes Jonathan Barker; Marilyn Benham; David Burden; Fiona Browne; Ian Evans; Sagair Hussain; Brian Kirby; Linda Lawson; Tess McPherson; Ruth Murphy; Tony Ormerod; Eleanor Pearson and Josh Richards.

**Plain language summary available online*

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- The persistence and effectiveness of acitretin, ciclosporin, FAE and methotrexate since the introduction of biologic therapies in real-world clinical practice are poorly understood.

What does this study add?

- This systematic review examines the persistence and effectiveness of methotrexate, acitretin, ciclosporin and FAE for moderate-to-severe psoriasis.
- Data on the persistence and effectiveness of systemic therapies are lacking, particularly for acitretin and ciclosporin.
- The definitions of persistence and reporting of effectiveness are inconsistent.
- Further good-quality observational studies are needed to explore the real-world persistence and effectiveness of systemic treatments used for psoriasis.

Psoriasis is a chronic inflammatory skin disorder that impairs both physical and psychological health.[1] Treatment options for patients with psoriasis depend on disease severity, comorbidities and patient choice and include topical, phototherapy and systemic therapies (including biologics and small molecules).[2,3] More severe psoriasis frequently requires lifelong management, and therefore counselling patients on the likelihood of medium-to-long-term disease control is important when discussing treatment choice.

In the U.K., guidance provided by the National Institute for Health and Care Excellence (NICE) suggests the use of nonbiologic, nonsmall-molecule systemic therapies for the treatment of moderate-to-severe psoriasis that cannot be controlled with topical or phototherapies.[3] Methotrexate is recommended as first-line therapy, with ciclosporin advised in the short term and for women considering conception. Acitretin may be considered if methotrexate and ciclosporin are contraindicated or ineffective.[3]

Most of the available evidence related to systemic therapies is derived from randomized controlled trials (RCTs). These remain the gold standard for investigating new therapies, as participant randomization to receive active or comparator treatments and high internal validity facilitate causal inference of the efficacy and/or safety of the therapy under investigation between the trial arms. However, most RCTs are not fully representative of real-world clinical practice and are powered for efficacy outcomes rather than safety. Due to their relatively small sample sizes, short follow-up periods and strict inclusion criteria, RCTs may have low external validity.

Two studies have demonstrated that patients with psoriasis identified as ineligible for biologics RCTs are at least twice as likely as eligible patients to experience serious adverse events.[4,5] Attrition with longer-term RCTs or open-label extension studies may render the interpretation of safety data difficult due to the resulting bias in the sample studied. Postmarketing observational research is complementary to prelicensing trials to enable the exploration of the persistence (duration of time from initiating to discontinuing therapy)[6] and effectiveness (response to therapy observed within real-world conditions accounting for factors that may influence the therapy's performance)[7] of psoriasis therapies in clinical practice. Discontinuation of systemic therapy is common in clinical practice, hence long-term data collection is critical to investigating therapeutic outcomes.[8,9] The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) is a well-established prospective pharmacovigilance register of patients diagnosed with psoriasis and treated with all forms of systemic therapy.[10] Observational data collected by registers such as BADBIR will provide important evidence for the persistence and effectiveness of systemic psoriasis therapies in real-world clinical practice.

We conducted a systematic review of the persistence and effectiveness of four commonly used nonbiologic, nonsmall-molecule systemic psoriasis therapies in observational studies over the past decade. The aim was to summarize and evaluate observational studies (involving $\geq$ 100 patients) investigating the persistence and/or effectiveness of acitretin, ciclosporin, fumaric acid esters (FAE) or methotrexate in adult patients with moderate-to-severe psoriasis.

Materials and methods

Literature search

A literature search was completed utilizing Embase, MEDLINE, PubMed and the Cochrane Library. Searches were limited to humans and publications dated from 1 January 2007 to 1 November 2017 to account for research published within the past decade, as the introduction of biologic therapies has influenced systemic treatment prescribing. The full search strategy and complete study protocol are listed in Appendix S1 (see Supporting Information).

Inclusion criteria

Longitudinal observational studies were eligible for review, including retrospective and prospective cohort studies. Study populations were to include ≥ 100 patients; age > 18 years; diagnosis of moderate-to-severe psoriasis; treatment with acitretin, ciclosporin, FAE or methotrexate; and follow-up time ≥ 3 months. A recent systematic review of observational studies in patients with psoriasis specified a minimum of 100 patients prescribed each therapy to increase statistical power, therefore the same requirement was applied in this review.[11]

Disease severity was ascertained through the inclusion criteria for each study (e.g. patients with moderate-to-severe psoriasis) or baseline measures of severity indicating moderate-to-severe diagnoses, namely Psoriasis Area and Severity Index (PASI) >10, involved body surface area > 10% and/or Dermatology Life Quality Index (DLQI) >10. Studies where > 50% of patients were diagnosed with psoriatic arthritis were excluded, as were studies with pooled cohorts of patients receiving systemic therapies. Case reports, RCTs and reviews were excluded.

Studies investigating persistence were included if therapy survival probabilities, mean or median time to therapy discontinuation, or the proportion of patients discontinuing therapy within the study follow-up period were reported. Studies investigating effectiveness were included if they reported absolute change in PASI, the proportion of patients achieving PASI 50, PASI 75 or PASI 90 at ≥ 3 months (50%, 75% and 90% reductions in PASI, respectively), improvements in Physician's Global Assessment (PGA) at ≥ 3 months, or the proportion of patients discontinuing therapy due to ineffectiveness.

Study selection

After the removal of duplicate reports, titles and abstracts were independently screened by two reviewers (S.W. and K.J.M.). The remaining articles were read in full, with data extracted by one reviewer (S.W.) and corroborated by the second (K.J.M.); any articles found to meet the exclusion criteria were removed. Reference lists of reviews were also hand searched to identify additional publications.

Data extraction

The study characteristics extracted from each included article were author, study design and time period, therapies studied, number of patients per therapy, mean age, sex, mean disease duration, the proportion of patients with psoriatic arthritis, the mean baseline PASI and DLQI, and the proportion of patients using combination therapy. The outcomes of interest were extracted into a separate table along with the number of patients at each follow-up, where possible.

Quality assessment

Two reviewers (S.W. and K.J.M.) determined the quality of the included observational studies using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies.[12] There are nine items included in the scale, with four items under 'selection' and four items under 'outcome' scored a maximum of one star each, with the final item 'comparability of cohorts' scored a maximum of two stars. Definitions and ratings of the biases are provided in Appendix S2 (see Supporting Information).

This review is reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and is registered with PROSPERO (CRD42018099771; date 19 June 2018).

Results

The initial search produced 656 articles, with 411 remaining after deduplication (n = 245; Fig. 1). After excluding 335 articles by title screening, 76 abstracts remained. Fifty-seven articles were excluded by abstract. Two additional articles were found through hand searching the reference lists of the included studies, with 21 articles read in full and assessed for eligibility. Of the 13 articles next excluded, three studies were removed by title or abstract due to having a cohort of < 100 patients (Appendix S3; see Supporting Information)[13–15] and 10 articles were excluded for ineligibility (Appendix S4; see Supporting Information).[16–25] No studies were excluded based on outcome definition alone. The remaining eight articles were included in the systematic review (Table 1).

Study characteristics

Acitretin, ciclosporin and methotrexate were included in one study,[26] FAE and methotrexate in one study,[27] methotrexate in two studies[28,29] and FAE in four[30–33] (Table 1). Four studies were retrospective and performed at a single centre,[27,28,30,31] while four were multicentre studies, three of which were prospective[26,29,33] and one retrospective.[32] All eight studies were European, with follow-up conducted from 2003 to 2014 and published in 2009–2017.

One study reported only the number of treatment cycles instead of the number of patients (158 cycles of FAE, 174 cycles of methotrexate)[27] and one study reported the baseline characteristics for the entire cohort instead of patients registering to each therapy.[29] Four studies reported the proportions of patients with no previous exposure to systemic psoriasis therapy (incident users).[26,28,31,32] Two of these four studies investigated FAE and reported 60%[31] and 81%[32] of the cohort as incident users, one study reported 67% of a methotrexate cohort as incident users[28] and one study reported the proportions of incident users of acitretin, ciclosporin and methotrexate as 54%, 46% and 51%, respectively.[26] One article reported the number of first-line treatment cycles for FAE (n = 116, 73%) and methotrexate (n = 70, 40%) as opposed to the number of systemic-naive patients.[27]

Seven of the eight articles examined therapy discontinuation time,[26–29,31–33] with six also reporting the proportion of patients discontinuing therapy (Table 2).[26–28,31–33] All eight studies reported effectiveness outcomes (Table 2 and Table S1;

Table 1 Newcastle characteristics of the studies included in the systematic review

Study	Design	Baseline Characteristics*		
Arnold *et al.*[26]	Retrospective, single centre, 2003–2014	**FAE:** n = 158 treatment courses Age (SD): 50·4 years (15·2) Females: 33·9% PASI (SD): 13·0 (7·8) 116 courses first-line systemic therapy	**Methotrexate:** n = 174 treatment courses Age (SD): 51·7 years (12·6) Females: 42·5% PASI (SD): 12·3 (7·0) 70 courses first-line systemic therapy	
Cabello *et al.*[27]	Retrospective, single centre, 2007–2014	**Methotrexate:** n = 218 Age (SD): 45·8 years (15) PASI (SD): 7·4 (6·7); DLQI (SD): 8·2 (5·1) Systemic naïve: 67% *Combination therapies:* 87% monotherapy, 13% receiving another systemic treatment		
Davila-Seijo *et al.*[25]	Prospective, multicentre (BIOBADADERM), 2008-2013, (Median follow-up (range): 3·3 years (0-5·1))	**Acitretin=**n = 340 Age (SD): 55 years (15) Females: 31% PASI (SD): 9 (6) Systemic naïve: 54% *Combination therapies:* 2 cycles MTX, 3 cycles CsA	**Ciclosporin=**n = 356 Age (SD): 43 years (14) Females: 49% PASI (SD): 13 (9) Systemic naïve: 46% *Combination therapies:* 5 cycles MTX, 5 cycles ACI	**Methotrexate:** n = 638 Age (SD): 49 years (15) Females: 45% PASI (SD): 9 (6) Systemic naïve: 51 *Combination therapies:* 11 cycles CsA, 8 cycles ACI
Inzinger *et al.*[29]	Retrospective, single centre (PsoRA), 2004-2011	**FAE:** n = 200 Age (SD): 40·4 years (13·3) PASI (SD): 11·6 (5)		
Ismail *et al.*[30]	Retrospective, single centre, 2003-2012	**FAE:** n = 249 Age (range): 44·5 years (17-82); females: 36% PASI (range): 9·2 (0-22·2); DLQI (range): 13·4 (0-27) Systemic naïve: 60%		
Maul *et al.*[28]	Prospective, multicentre (SDNTT), 2011-2014	**Methotrexate**†: n = 119 (total 158) Age: 47·1 years; females: 31·6% PASI (SD, range): 9·2 (6·1: 0·0-32·4); DLQI (SD, range): 10·7 (6·6: 0·0-27·0)		
Reich *et al.*[31]	Retrospective, multicentre (FUTURE), dates not provided	**FAE:** n = 984 Age (SD, range): 50·5 years (13·18, 15-105); females: 41·8% Systemic naïve: 80·6%		
Walker *et al.*[32]	Prospective, multicentre (74 private practices and 4 hospitals in Germany)	**FAE:** n = 249 Age (range): 49·7 years (18-89); females: 44% PASI: 16·83; DLQI: 9·95 *Combination therapies:* 35·4% concomitant medication		

Acitretin (ACI): ciclosporin (CsA): fumaric acid esters (FAE): methotrexate (MTX): psoralen ultraviolet A (PUVA): ultraviolet B (UVB): standard deviation (SD): psoriatic arthritis (PsA): Psoriasis Area and Severity Index (PASI): Physician Global Assessment (PGA): Dermatology Life Quality Index (DLQI): Psoriasis Register Austria (PsoRA): Swiss Dermatology Network for Targeted Therapies (SDNTT): Dermatology Clinical Effectiveness Research Network (DCERN) *Mean age, disease duration, PASI and DLQI values presented with range. †Baseline characteristics provided only for total systemic cohort including FAE (27), CsA (6), and retinoids (6)

see Supporting Information), with six studies reporting the proportion of patients discontinuing therapy due to ineffectiveness[26–28,31–33] and the other two studies reporting the mean PASI, PASI 75 and PASI 90;[29] and PASI 50, PASI 75 and PASI 90 at 3-, 6- and 12-month time points.[30]

Persistence

Davila-Seijo *et al.* reported the probability of drug survival at 1 year as 42·3% for acitretin [95% confidence interval (CI) 36·9–47·6], 23·3% for ciclosporin (95% CI 19·0–27·8) and 50·3% for methotrexate (95% CI 46·3–54·2), with median discontinuation times of 0·72, 0·45 and 1·01 years, respectively (Table 2).[26] Over the 5-year study period 34%, 26% and 30% of patients discontinuing acitretin, ciclosporin and methotrexate, respectively, did so for ineffectiveness (Table S1), with 14%, 18% and 17% discontinuing for adverse events.[26]

One study reported mean treatment durations of 35·6 months (95% CI 27·8–43·5) and 22·3 months (95% CI 17·6–27·1) for FAE and methotrexate, respectively; the most common reasons for discontinuation during the 5-year study

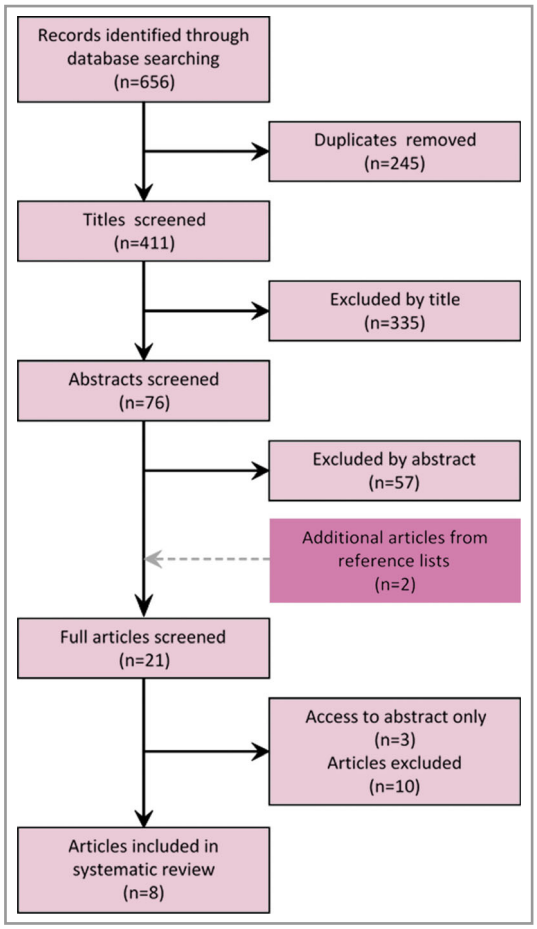

Fig 1. Flowchart of the article selection. Studies were identified by searching Embase, MEDLINE, PubMed and the Cochrane Library then filtered according to title, abstract and eligibility. Additional articles were identified by manually searching reference lists.

period were adverse events and ineffectiveness (42% and 21%, respectively, for FAE; 22% and 21% for methotrexate; Table S1).[27] Two studies reported the mean duration of FAE therapy as 28 months (range 1 week to 106 months)[31] and 50 months (no range),[32] with another two studies reporting mean durations of methotrexate therapy of 17·2 ± 13·6 months[28] and 7·7 months (range 0–36;[29] Table S1). The most common reasons for discontinuation among studies reporting the proportion of patients discontinuing FAE were adverse events (46% over 4 years;[31] 43% over 1 year)[33] and ineffectiveness (22% over 36 months),[32] and adverse events for methotrexate (22% over 48 weeks;[28] Table S1).

Effectiveness

Mean PASI values at baseline and 12 months were reported in two studies; Walker *et al.* reported mean PASI of 16·8 and 5·6, respectively, for patients receiving FAE,[33] while Maul *et al.* reported mean PASI of 11·4 and 2·2, respectively, for patients receiving methotrexate (Table 2).[29] Two studies reported that 76% of FAE patients on therapy at 1 year achieved PASI 75[30] and PGA of markedly improved or clear.[32] Two studies reported that 53%[28] and 59%[29] of patients on methotrexate remaining on therapy at 1 year achieved PASI 75 (Table 2). Two studies also reported discontinuations due to ineffectiveness for FAE (40% over 4 years;[31] 11% over 1 year)[33] and one for methotrexate (21% over 48 weeks;[28] Table S1). Effectiveness outcomes with PASI or PGA were not reported for ciclosporin or acitretin.

Quality assessment

Two studies were rated as 'high quality'[26,27] (scored > 7), with the remaining six studies rated 'medium quality'[28–33] (scored 4–6). None of the six studies rated as 'medium quality' adjusted for age, sex or any other confounding factors in their persistence or effectiveness analyses.[28–33] A meta-analysis was not conducted due to the diverse study designs, outcome definitions and analytical approaches used (Table 3).

Discussion

This systematic review found that in the treatment of moderate-to-severe plaque psoriasis the probability of drug survival at 1 year was 23% for ciclosporin, 42% for acitretin and 50% for methotrexate.[26] Discontinuations due to adverse events (42% FAE and 22% methotrexate,[27] 46% FAE,[31] 43% FAE,[33] 22% methotrexate)[28] were more common for FAE than for methotrexate. There were mixed results for discontinuations due to ineffectiveness (44% acitretin, 21% ciclosporin and 33% methotrexate;[26] 22% FAE).[32] No studies reported effectiveness outcomes for acitretin or ciclosporin. The persistence and effectiveness of FAE and methotrexate were better characterized, but mean discontinuation times ranged from 28 to 50 months (FAE)[27,31,32] and 7·7 to 22·3 months (methotrexate).[26–29] Proportions of patients achieving PASI 75 at 12 months were reported for FAE (76%)[30] and methotrexate (53%[28] and 59%),[29] with 76% of patients on FAE achieving a PGA of markedly improved or clear at 12 months.[32]

A significant limitation to the current literature investigating the persistence of systemic therapy is the lack of survival analyses. Survival analyses are essential when using observational methods to explore drug persistence, because without them, differing lengths of follow-up will not be accounted for. NICE recommends that ciclosporin use should not exceed 1 year unless patients have severe and/or unstable disease and biologic therapy is contraindicated. As ciclosporin is usually prescribed for short durations, the lack of long-term persistence should not be viewed as a proxy for poor safety or ineffectiveness of this therapy.[3] Of the eight studies identified, one conducted a survival analysis on the time to drug discontinuation for patients using each systemic therapy.[26] Three additional studies also conducted survival analyses; however, one pooled all systemic therapies into a systemic cohort,[29] the second reported treatment courses rather than patients,[27] and the third study did not provide the definition for discontinuation

Table 2 Summary of evidence

Drug (reference)	Number of Patients	Results
Persistence		
Probability of drug survival at 12 months		
ACI[25]	340	42·3% (95% CI 36·9%-47·6%)
CsA[25]	356	23·3% (95% CI 19·0%-27·8%)
MTX[25]	638	50·3% (95% CI 46·3%–54·2%)
Therapy discontinuation time		
ACI[25]	340	Median; 0·72 years (no range)
CsA[25]	356	Median; 0·45 years (no range)
FAE[26]	158*	Mean; 35·6 months (95% CI 27·8-43·5)
FAE[30]	249	Mean; 28 months (1 week-106 months)
FAE[31]	984	Mean; 50 months (no range)
MTX[25]	638	Median; 1·01 years (no range)
MTX[26]	174*	Mean; 22·3 months (95% CI 17·6–27·1)
MTX[27]	218	Mean; 17·2 months (SD; 13·6)
MTX[28]	119	Mean; 7·7 months (range 0–36)
Effectiveness		
Mean PASI Values		
FAE[32]	Baseline: 249	16·83
	12 months: 145	5·61
MTX[28]	Baseline: 119	11·4
	3 months: 80	3·3
	6 months: 55	2·2
	12 months: 28	2·2
Proportion of patients achieving improvements in disease severity: n (%)		
FAE[29]	3 months: 115	PASI50: 87 (76%); PASI75: 54 (47%); PASI90: 10 (9%)
	6 months: 73	
	12 months: 41	PASI50: 60 (82%); PASI75: 46 (63%); PASI90: 20 (27%)
		PASI50: 37 (90%); PASI75: 31 (76%); PASI90: 14 (34%)
FAE (PGA markedly improved/clear)[31]	3 months: 953	294 (30·8%)
	6 months: 941	630 (67·0%)
	12 months: 936	713 (76·2%)
	24 months: 901	701 (77·8%)
	36 months: 566	465 (82·1%)
	>36 months: 566	473 (83·6%)
MTX[27]	Not provided for separate time points	PASI75: Week 12: 32·5%; Week 16: 34·4%; Week 24: 44·7%; Week 36: 50·0%; Week 48: 52·8%
MTX[28]	3 months: 81	PASI75: 30 (37%); PASI90: 11 (13·6%)
	6 months: 56	PASI75: 30 (53·6%); PASI90: 16 (28·6%)
	12 months: 29	PASI75: 17 (58·6%); PASI90: 13 (44·8%)

Acitretin (ACI); ciclosporin (CsA); fumaric acid esters (FAE); methotrexate (MTX); 95% CI (95% confidence interval); Psoriasis Area and Severity Index (PASI); Physician Global Assessment (PGA). *Treatment courses. †Number discontinuing therapy.

used in the survival analysis,[28] making the results difficult to interpret.

A further limitation to the studies exploring therapy persistence is the inconsistent definition of drug discontinuation. Of the seven studies reporting therapy persistence, four did not provide any definition of drug discontinuation.[29,31–33] One study defined discontinuation as 'a suspension of medication' due to a range of possibilities, however, it did not specify what a 'suspension' was or a time frame.[28] Two studies provided a sufficient definition of a discontinuation, providing a time frame for how long patients were not using therapy.[26,27] Due to the lack of, and difference in, a definition of discontinuation, it is difficult to ascertain whether short-term breaks in therapy have been accounted for. Definitions of drug discontinuation and time frames are particularly important when interpreting ciclosporin survival, as this is generally given for short periods of time.

Many of the included studies lack complete reporting and analysis of baseline characteristics. Evidence shows there are differences in the prescribing patterns of psoriasis therapies for different patients,[34] while the definition of moderate-to-severe psoriasis remains inconsistent, resulting in a range of baseline severities used between countries and healthcare systems. It would therefore be beneficial to assess the baseline characteristics of the therapy cohorts separately to identify differences between them. One study pooled the characteristics of the different therapy cohorts[29] and five studies did not report three or more of the baseline measurements

Table 3 Newcastle–Ottawa Quality Assessment Scale for Cohort Studies

Study	Arnold[27]	Cabello Zurita[28]	Davila-Seijo[26]	Inzinger[30]	Ismail[31]	Maul[29]	Reich[32]	Walker[33]
Selection (maximum one star per item)								
Representativeness of exposed cohort	(b) *	(b) *	(a) *	(b) *	(b) *	(a) *	(a) *	(a) *
Selection of nonexposed cohort	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ascertainment of exposure	(a) *	(a) *	(a) *	(a) *	(a) *	(b) *	(b) *	(b) *
Outcome not present at baseline	(a) *	(a) *	(a) *	(a) *	(a) *	(a) *	(a) *	(a) *
Comparability of cohorts (maximum two stars)								
Matching	(a, b) **	0	(a) *	0	0	0	0	0
Outcome (maximum one star per item)								
Assessment of outcome	(b) *	(b) *	(b) *	(b) *	(b) *	(b) *	(b) *	(b) *
Length of follow-up	(a) *	(a) *	(a) *	(a) *	(a) *	(a) *	(a) *	(a) *
Adequacy of follow-up	(d)	(d)	(b) *	(b) *	(b) *	(a) *	(a) *	(c)
Total score	7	5	7	6	6	6	6	5

N/A, not applicable. See Appendix S2 in the Supporting Information for descriptions of the letter codes.

listed.[27,28,30,32,33] This lack of detail makes the quality assessment both within and between studies more difficult.

There is little acknowledgment of prevalent-user bias throughout the current literature. A prevalent user can be defined as a patient who previously used the therapy of interest before the start of the study follow-up, then restarted the same therapy during the study period.[35] The inclusion of such patients within an analysis can bias results as they may have been exposed to a specific therapy previously and could be prescribed this again due to a previous positive response, or they could be exposed to a new therapy if their initial treatment failed. One study reported the proportion of incident users within the entire cohort and one reported the proportion of treatment courses that were first line,[27] while only four studies provided the proportions of incident users for individual therapies.[26,28,31,32] It would be beneficial to conduct sensitivity analyses with and without prevalent users to identify whether prevalent-user bias is present.

The discontinuation of previous therapy could also influence the disease severity recorded prior to initiating a new one, particularly if there are minimal washout periods or overlaps between them. By reporting both the aggregate estimates and estimates stratified by therapy, we can understand better whether previous therapy exposure affects drug persistence or effectiveness. Another factor that influences the persistence or effectiveness of therapies is medication adherence. Patients with psoriasis registering to BADBIR on acitretin, ciclosporin, FAE or methotrexate were almost twice as likely to be nonadherent (29·2%) as patients receiving etanercept or adalimumab (16·4%, $P < 0{\cdot}001$).[36] Medication adherence should be assessed when investigating treatment response, particularly whether nonadherence is intentional (e.g. medication perceived to be ineffective) or unintentional (e.g. lower persistence related to habit strength).

The results of this review reflect the contemporary evidence for the persistence and effectiveness of systemic psoriasis therapies within the real-world environment. Since performing our database search, one conference abstract has been published as a manuscript. The authors performed a single-centre, retrospective study of 626 patients with psoriasis receiving FAE monotherapy, and demonstrated a median duration of therapy of 1·7 years, with 188 patients (30%) discontinuing therapy.[37] The introduction of biologic and small-molecule therapies in the past decade is likely to have influenced the persistence of acitretin, ciclosporin, FAE and methotrexate in clinical practice, which is yet to be addressed in the literature. Future analyses should stratify by year of initiation to account for changes in the prescribing environment and thus the persistence of these therapies over time.

The complexity of studying persistence and effectiveness of therapy in clinical practice is highlighted by the varying results, study cohorts and methods of reporting. The inconsistent methods of reporting prevented a meta-analysis from being conducted. There was also the potential to introduce bias via the outcome definition specified in the protocol for this systematic review. Although no studies were excluded based on outcome definition alone (Appendix S4; see Supporting Information), future reviews of this topic should consider the use of a more robust definition to minimize the risk of excluding a study that used a different but relevant outcome definition.

In conclusion, this systematic review highlights how evidence for the persistence and effectiveness of systemic therapies for psoriasis in clinical practice is lacking. There are few studies exploring acitretin or ciclosporin, and those that have examined FAE or methotrexate are difficult to compare due to incomplete reporting of baseline characteristics, insufficient survival analyses and differing definitions of drug discontinuation. There is therefore a need for good-quality observational research, with an additional need for uniform methods of analysis and reporting to allow for meta-analyses.

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Appendix

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 The characteristics of the studies included in the systematic review.

Appendix S1 Study protocol: persistence and effectiveness of systemic psoriasis therapies.

Appendix S2 Definitions of the biases assessed within the included studies.

Appendix S3 Studies excluded due to including < 100 patients.

Appendix S4 Studies excluded due to ineligibility.