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REVIEW

Long-term Safety of Oral Systemic Therapies for Psoriasis: A Comprehensive Review of the Literature

Deepak M. W. Balak · Sascha Gerdes · Aurora Parodi · Laura Salgado-Boquete

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ABSTRACT

Oral systemic therapies are important treatment options for patients with moderate-to-severe psoriasis, either as monotherapy or in therapy-recalcitrant cases as combination therapy with phototherapy, other oral systemics or biologics. Long-term treatment is needed to maintain sufficient disease control in psoriasis, but continuous use of systemic treatments is limited by adverse events (AEs) and cumulative toxicity risks. The primary aim of this comprehensive literature review was to examine the long-term safety profiles of oral agents commonly used in the treatment of adults with psoriasis. Searches were conducted in EMBASE and PubMed up to November 2018, and 157 relevant publications were included. Long-term treatment with acitretin could be associated with skeletal toxicity and hepatotoxicity, although evidence for skeletal toxicity is mixed and hepatotoxicity is rare, particularly at low doses. Other safety issues include hyperlipidaemia and potential for teratogenicity up to 2–3 years after discontinuation of treatment. There is a paucity of data on long-term treatment with apremilast. Continued exposure to apremilast does not seem to increase the incidence of common AEs, such as gastrointestinal (GI) AEs, upper respiratory tract infections and headache, while the long-term risks for depression, suicidal thoughts and weight loss are unknown. Long-term ciclosporin treatment is associated with renal toxicity, hypertension, non-melanoma skin cancer, neurological AEs and GI AEs. Long-term methotrexate treatment is associated with hepatotoxicity, GI AEs, haematological toxicity, renal toxicity and alopecia. Finally, long-term treatment with fumaric acid esters (FAE) is associated with GI AEs, flushing, lymphocytopenia, proteinuria and elevated liver enzymes. Median drug survival estimates varied

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D. M. W. Balak (✉)
Department of Dermatology, LangeLand Ziekenhuis, Zoetermeer, the Netherlands
e-mail: balak.dmw@gmail.com

S. Gerdes
Department of Dermatology, Psoriasis-Center, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany

A. Parodi
DiSSal Section of Dermatology, University of Genoa–Ospedale-Policlinico San Martino IRCCS, Genoa, Italy

L. Salgado-Boquete
Department of Dermatology, Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain

considerably: ~ 2.9–9.7 months for apremilast; ~ 5.4 months for ciclosporin; ~ 8.6 months for acitretin; ~ 12.1–21.6 months for methotrexate; and ~ 54.8 months for FAE. These long-term safety profiles may help to guide clinicians to select the optimal oral systemic treatment for the long-term treatment of psoriasis in adults.

Keywords: Adverse events; Drug survival; Long-term; Psoriasis; Safety; Systemic therapy

Key Summary Points

Due to the chronic nature of psoriasis, long-term systemic treatment is often needed to maintain sufficient disease control. It is clinically important to consider the potential adverse events and cumulative toxicity risks associated with the long-term use of oral systemic therapies.

This comprehensive literature review discusses the long-term safety profiles and adverse events frequently associated with oral systemic therapies and the ways in which these can be managed.

Drug survival estimates differed considerably between treatments and may have been influenced by inter-study variability.

Understanding the differential risks associated with the long-term treatment of psoriasis will serve to improve risk–benefit assessment and therapeutic decision-making for clinical practice.

Further work is needed to better define 'long-term' therapy and standardise safety reporting to enable more accurate comparisons between agents.

INTRODUCTION

Oral systemic therapies represent an important component of the psoriasis treatment regimen, particularly for patients with moderate-to-severe disease and for those with mild disease who do not respond sufficiently to topical agents and/or phototherapy [1, 2]. When response to a single treatment is not sufficient, two or more treatments with different mechanisms of action and compatible safety profiles may be combined to achieve better disease control while limiting toxicity [3–5]. Such treatment strategies may include combinations of two oral systemic agents or use of an oral systemic agent together with phototherapy or a biologic. Several oral agents are currently licensed for the management of psoriasis; systemic agents with a long history of use include the so-called 'conventional' psoriasis treatments methotrexate (first used in the USA in 1958 [6]), acitretin (approved in Germany in 1992 [7]), ciclosporin (approved in Germany in 1993 [8]) and formulations of fumaric acid esters (FAE; approved in Germany in 1994 [7]) [9, 10]. More recently, two small-molecule drugs have also been approved in Europe for plaque psoriasis treatment: apremilast, an oral phosphodiesterase-4 (PDE-4) inhibitor, in 2014; and dimethylfumarate (DMF), a novel FAE monotherapy, in 2017 [11, 12]. Some of the conventional agents were developed prior to the current era of evidence-based medicine and, consequently, safety and efficacy data have been obtained predominantly from wide clinical experience, rather than from high-quality randomised controlled trials (RCTs) [2]. In contrast, for the biologic therapies in psoriasis high-quality evidence is available in support of their efficacy and safety.

In clinical practice, the question of when to choose an oral treatment versus a biologic is mostly dictated by national treatment guidelines and reimbursement criteria. In general, a patient with psoriasis is considered to be a valid candidate for systemic therapy when the affected area exceeds 10% of the body surface area, the disease involves special areas, such as scalp or genitalia, and/or topical therapy has failed [13]. Current treatment guidelines recommend a conventional

oral drug as first-line systemic treatment for moderate-to-severe psoriasis, whereas a biologic is applied as second-line treatment in case of treatment failure, intolerance or contra-indication to an oral therapy [14]. In line with this, real-world registry data demonstrate that a significant proportion of patients on systemic therapy are treated with an oral agent [9, 10]. Observations in daily clinical practice have shown that many patients discontinue and switch to an alternative psoriasis therapy during the course of their treatment. In a retrospective, longitudinal cohort study of patient data from a USA health claims database, 23% of patients switched treatment in the previous year [15]. In addition, results from a retrospective chart review of 166 patients with moderate-to-severe psoriasis indicated that on average there were 1.2 treatment changes per year, most commonly due to poor disease control or flare of psoriasis [16]. Furthermore, adverse events (AEs) are often a reason for premature discontinuation of conventional oral systemic psoriasis treatments in clinical practice [17].

Given that psoriasis is a chronic disease and all available treatments are only immune modulating, long-term treatment is often necessary to maintain sufficient disease control. However, due to the potential risks of AEs and cumulative toxicity associated with long-term treatment with systemic agents, a risk–benefit assessment individualised for each patient is required before treatment initiation. The risk–benefit ratio of systemic agents is dependent upon several factors, including drug efficacy, toxicity profiles and individual patient characteristics [18]. To allow optimal risk–benefit analysis and well-balanced decision-making for long-term psoriasis management, insight into the long-term safety profiles of the available oral systemic therapies is essential. However, a clinically oriented overview of the long-term safety profile of oral psoriasis treatments, including a comprehensive assessment of recently published data, is lacking.

The aim of this comprehensive review of the literature is to examine the long-term safety of five common oral systemic agents that are used in the management of moderate-to-severe psoriasis and are recommended in the current European psoriasis guidelines [7].

METHODS

Scientific publications relating to the long-term safety of the systemic agents used for the treatment of psoriasis were identified through a comprehensive search of the literature, focussing on long-term safety (defined here as $\geq$ 6 months), risk–benefit profile and drug survival (defined as how long a patient remains on a given therapy continuously). Types of articles included were: primary manuscripts; review articles; case series; clinical trials; comparative studies; meta-analyses; and observational studies. Exclusion criteria were: congress abstracts; publications not in English; pre-clinical studies, including animal studies; articles in which combination treatments were used; articles describing indications other than psoriasis; articles in which patients were treated for $<$ 6 months.

In November 2018, literature searches were conducted in EMBASE (Table 1) and PubMed (using the filter 'publication date from 2018/10/01'; Table 2) to obtain the most recent literature. Additional references were found using hand searches and screening of the reference lists of identified articles.

Citations were screened by title and abstract, and additional focussed criteria were applied to narrow down the number of articles remaining for full-text screening at the next stage. Focussed criteria for inclusion were: adults with moderate-to-severe plaque psoriasis treated with monotherapy; European or North American population; exclusion of single-case studies. The full-text articles of the resulting publications were further screened before inclusion.

This article does not contain any studies with human participants or animals performed by any of the authors; therefore, ethics committee approval was not required.

RESULTS

After screening the full-text articles, 157 were included in this comprehensive review of the literature (Fig. 1; Table 3; [2, 14, 19–47]). In this section, we describe the long-term safety profile of each of five common oral systemic agents

Table 1 Abbreviated EMBASE search strategies (search date 7 November 2018)

Drug	Abbreviated search term	Results
Acitretin	'psoriasis' AND 'acitretin' AND 'safety' OR 'adverse event' AND 'long-term care'	218
	'psoriasis' AND 'acitretin' AND 'risk benefit'	34
	'psoriasis' AND 'acitretin' AND 'drug survival'	24
Apremilast	'psoriasis' AND 'apremilast' AND 'safety' OR 'adverse event' AND 'long-term care'	54
	'psoriasis' AND 'apremilast' AND 'risk benefit'	7
	'psoriasis' AND 'apremilast' AND 'drug survival'	11
Ciclosporin	'psoriasis' AND 'cyclosporine' AND 'safety' OR 'adverse event' AND 'long-term care'	448
	'psoriasis' AND 'cyclosporine' AND 'risk benefit'	114
	'psoriasis' AND 'cyclosporine' AND 'drug survival'	36
Methotrexate	'psoriasis' AND 'methotrexate' AND 'safety' OR 'adverse event' AND 'long-term care'	830
	'psoriasis' AND 'methotrexate' AND 'risk benefit'	175
	'psoriasis' AND 'methotrexate' AND 'drug survival'	115
FAE	'psoriasis' AND 'dimethylfumarate' OR 'fumaric acid' OR 'Fumaderm' AND 'safety' OR 'adverse event' AND 'long-term care'	707
	'psoriasis' AND 'dimethylfumarate' OR 'fumaric acid' OR 'Fumaderm' AND 'risk benefit'	149
	'psoriasis' AND 'dimethylfumarate' AND 'drug survival'	1

FAE Fumaric acid esters

(acitretin; apremilast; ciclosporin; methotrexate; FAE, including DMF) used to treat moderate-to-severe psoriasis in adults.

Acitretin

Acitretin is a second-generation retinoid [23] that elicits its anti-psoriatic activity via modulation of keratinocyte proliferation and downstream anti-inflammatory pathways [36]. As per the label, acitretin is indicated for severe cases of psoriasis that do not respond to other treatments (Table 3; Electronic Supplementary Material [ESM] 1) [48, 49], but some experts recommend the use of acitretin in patients with moderate-to-severe psoriasis [7] where methotrexate and ciclosporin are not appropriate [50]. In addition, acitretin is indicated for palmoplantar pustulosis [20, 25]. It has been suggested, based on clinical experience and in the absence of head-to-head RCTs, that acitretin monotherapy is less effective for psoriasis than other conventional systemic agents [2]. Because of this, acitretin may work best when combined with ultraviolet B light, psoralen and ultraviolet A light (PUVA) or other systemic therapy, or in sequential regimens [20, 21].

Skeletal toxicity, specifically hyperostosis, is thought to be the main cumulative AE of acitretin therapy [19–21, 51, 52], with some early retrospective studies reporting an increased risk of skeletal hyperostosis following long-term treatment; however, evidence for this is mixed [21]. A more recent retrospective study of acitretin given at a commonly used dosage (average 27.1 mg/day) over an average of 2.13 years found no evidence of skeletal hyperostosis [53]. In line with this finding, more recent prospective studies indicate a lower risk of acitretin-induced skeletal toxicity than previously reported [21].

There is mixed evidence for a risk of hepatotoxicity [19, 21, 24, 54] and abnormal findings on liver function tests with acitretin therapy, both of which appear to be rare at the

Table 2 Abbreviated PubMed search strategies (search date 19 November 2018)

Drug	Search query	Results
Acitretin	'psoriasis' AND 'acitretin' AND 'safety' OR 'adverse event' AND 'long-term care'	13
	'psoriasis' AND 'acitretin' AND 'risk benefit'	0
	'psoriasis' AND 'acitretin' AND 'drug survival'	0
Apremilast	'psoriasis' AND 'apremilast' AND 'safety' OR 'adverse event' AND 'long-term care'	13
	'psoriasis' AND 'apremilast' AND 'risk benefit'	1
	'psoriasis' AND 'apremilast' AND 'drug survival'	4
Ciclosporin	'psoriasis' AND 'ciclosporin' AND 'safety' OR 'adverse event' AND 'long-term care'	13
	'psoriasis' AND 'ciclosporin' AND 'risk benefit'	0
	'psoriasis' AND 'ciclosporin' AND 'drug survival'	0
Methotrexate	'psoriasis' AND 'MTX' AND 'safety' OR 'adverse event' AND 'long-term care'	13
	'psoriasis' AND 'MTX' AND 'risk benefit'	2
	'psoriasis' AND 'MTX' AND 'drug survival'	1
FAE	'psoriasis' AND 'dimethylfumarate' OR 'fumaric acid' OR 'Fumaderm' AND 'safety' OR 'adverse event' AND 'long-term care'	13
	'psoriasis' AND 'dimethylfumarate' OR 'fumaric acid' OR 'Fumaderm' AND 'risk benefit'	3
	'psoriasis' AND 'dimethylfumarate' AND 'drug survival'	0

Filter 'publication date from 2018/10/01'

initial doses commonly used in clinical practice (25–30 mg/day) [20, 21, 23, 26, 49, 54, 55]. A small retrospective study found minimal risk of hepatotoxicity, with six (14%) patients showing transient elevation in aspartate aminotransferase levels to > 41 units/L [53]. In addition, a prospective 2-year study of acitretin (25–75 mg/day) showed no biopsy-proven hepatotoxicity [55].

Mucocutaneous AEs are seen relatively often [19, 24, 25, 56]. Many of the AEs reported following acitretin therapy result from a weakening of the epithelia [22]; these include dryness of skin [23, 26, 56] and mucous membrane [19, 23, 27], pruritus [26, 56], peeling of the palms/soles [26, 57] and alopecia [19, 23–27, 56].

Acitretin has teratogenic potential [19–25]; it is associated with foetal abnormalities, with the greatest risk reported to be at weeks 3–6 of gestation. Acitretin may also be associated with increased rates of spontaneous abortions and stillbirths [21]. Thus, acitretin should not be used in pregnant women [20], and pregnancy must be avoided through the use of effective contraception for the duration of treatment and for at least 2 years after acitretin discontinuation. Some regulatory authorities (e.g. in Germany) require effective contraception for up to 3 years [19–22, 49, 58].

Hyperlipidaemia is a potential AE of acitretin [19, 20, 25–27, 59]; however, this is based mainly on reviews and short-term studies. In a clinical trial, two-thirds of patients developed hypertriglyceridaemia, one-third developed hypercholesterolaemia and 40% of patients had temporary reductions in high-density lipoproteins [28]. A longer-term retrospective study found no increases in total cholesterol of clinical significance and very little impact on low-density lipoprotein cholesterol over approximately 2 years of treatment [53]; 60% of patients demonstrated an increase in triglyceride levels of > 20 mg/dL, which was similar to

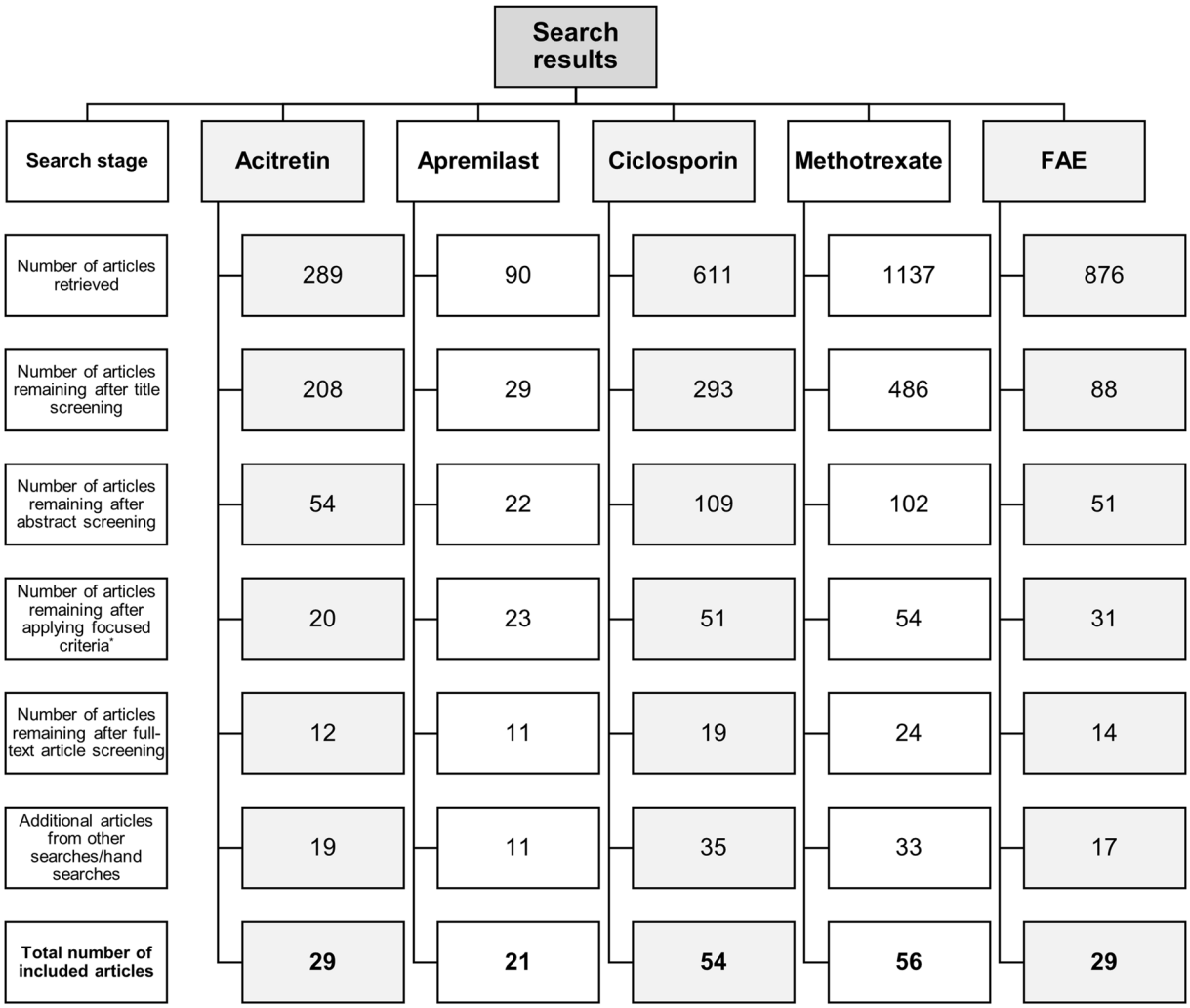

Fig. 1 Search results. *Focussed criteria for inclusion were: adults with moderate-to-severe plaque psoriasis treated with monotherapy; European or North American population; articles available in English language; exclusion of single-case studies. Note that articles may appear in more than one drug category. *FAE* Fumaric acid esters

that seen in clinical trials, with 80% of these having triglyceride levels > 200 mg/dL. Elevated lipids induced by acitretin may contribute to coronary heart disease if not managed effectively [53].

Other AEs that are attributed to acitretin, but not specifically to long-term treatment, include myalgias [19, 23, 24], arthralgia [19, 24, 27] and pseudotumour cerebri (benign intracranial hypertension) [19, 24]. Depression and other psychiatric symptoms have been reported with other retinoids, and patients should be made aware to be vigilant for possible psychiatric symptoms [28].

An advantage of acitretin is the lack of immunosuppressive AEs. A study using data from the BIOBADADERM registry (Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases) compared infection rates with different systemic drugs [60]. Of the non-biological therapies, acitretin showed the lowest risk of infection [crude risk ratio (RR) vs. methotrexate 0.6, 95% confidence interval (CI) 0.42–0.86] and a significantly lower risk of recurrent infections (adjusted RR vs. methotrexate 0.45; 95% CI 0.23–0.87; $p < 0.05$) [60].

Table 3 Summary of long-term safety profiles of oral systemic therapies in adult patients with psoriasis

Therapy	Chemical class	Long-term, cumulative or dose-dependent AEs	Potential severe/ irreversible AEs	Benefits	Special points for consideration
Acitretin	Retinoid	Skeletal toxicity [19–21]	Teratogenicity [19–25]; hyperlipidaemia [19, 20, 25–28]	Lack of immunosuppressive AEs [2]	Not suitable for women of reproductive age [20, 23] Especially useful for special indications (e.g. pustulosis palmoplantaris), in combination with UV treatment [20] Dosing mostly dependent on tolerability [22]
Apremilast	PDE-4 inhibitor	None	Depression, suicidal thoughts [29–31]	No increased risk for malignancies [32]; no blood monitoring required [33]; approved also for psoriatic arthritis [29, 34]	Increased caution in patients with a history of psychiatric symptoms [34]
Ciclosporin	Calcineurin inhibitor	Hypertension, nephrotoxicity, increased risk for malignancies [35]	Nephrotoxicity, gingival hyperplasia, increased risk for malignancies [35]	Quick response [35]	Useful for short treatment courses for exacerbations of psoriasis [22, 36] Not suitable for (elderly) patients with hypertension or renal disease [37]; drug–drug interactions [38]

Table 3 continued

Therapy	Chemical class	Long-term, cumulative or dose-dependent AEs	Potential severe/ irreversible AEs	Benefits	Special points for consideration
Methotrexate	Dihydrofolate reductase inhibitor	Hepatotoxicity [39]	Bone marrow toxicity, teratogenicity, pulmonary toxicity [26]; nephrotoxicity [40, 41]	Weekly administration, effects on psoriatic arthritis [42]	Not suitable for patients with increased risk for hepatotoxicity (diabetes, obesity, history of or current alcohol consumption, family history of liver disease) [43]; small therapeutic index [44]; drug–drug interactions (notably certain antibiotics) [42]; not suitable for women of childbearing potential [43]
FAE, including DMF	Fumaric acid ester	Renal impairment	Lymphopenia, leucopenia PML [14, 45]	Favourable long-term safety profile [46]; low drug–drug interactions [47]	Monitoring of lymphocyte/ leucocyte counts and application of treatment withdrawal criteria to reverse prevent lymphopenia and leucopenia [14, 45]

AE adverse event, *DMF* dimethylfumarate, *PDE-4* phosphodiesterase type-4, *PML* progressive multifocal leucoencephalopathy, *UV* ultraviolet

Due to the early appearance and dose-dependency of AEs, the dosing of acitretin is usually based on tolerability rather than efficacy [22]. Long-term therapy may be limited due to the potential for teratogenicity, AEs and potential end-organ toxicity [61], such as hepatotoxicity and skeletal toxicity, although evidence for end-organ toxicity is mixed.

The risk–benefit ratio of acitretin should be considered on an individual basis, along with AE monitoring [62].

Apremilast

Apremilast is a small molecule inhibitor of PDE-4, an enzyme which degrades cyclic adenosine

monophosphate, thereby promoting increased anti-inflammatory cytokine production and preventing synthesis of pro-inflammatory cytokines [34]. Apremilast is indicated for patients with moderate-to-severe chronic plaque psoriasis who have failed or who have a contraindication to other systemic therapy (Table 3; ESM 2) [30, 34].

Long-term clinical trials of apremilast with up to 3 years' follow-up have shown that the most common AEs include gastrointestinal (GI) AEs (nausea, diarrhoea); infections (upper respiratory tract infection, nasopharyngitis); and headache [33, 63–65]. No apparent increase in the incidence of these common AEs has been noted with continued exposure [33, 63, 66]. Infrequent and transient changes in laboratory values have been reported [66]. Real-world experience has reported similar AEs, including GI events and headache, during 7–9 months of follow-up [67–69]. A recent study reported that while apremilast is generally well tolerated in a real-world setting, the proportion of AEs resulting in treatment withdrawal was greater than that reported in RCTs [70].

Apremilast may be associated with an increased risk for depression, suicidal thoughts and behaviour and weight loss [7, 30, 31]. Uncommon cases of suicidal ideation and behaviour have been reported in clinical studies and from post-marketing experience, and completed suicide has been reported in post-marketing surveillance studies [34]. AEs of depression were reported in 1.3% of patients in short-term (16-week) studies [71]. Yet during long-term studies, the incidence of depression (reported by 2.8% of patients) did not increase over time, and the mean change in baseline body weight was only − 1.53 kg over 3 years [63]. Therefore, the long-term risks for depression and suicidal thoughts are unclear.

The risk–benefit profile of apremilast is deemed favourable when the lack of increase in common AEs with continued exposure is taken into account [33, 63, 66]; in addition, no standard blood monitoring is required [34]. Clinical vigilance for depression and suicidal thoughts is recommended [7, 30, 31].

Ciclosporin

Ciclosporin mediates its anti-psoriatic effects via selective inhibition of immunological pathways in T cells [36]. This immunosuppressant medication is indicated for the treatment of severe psoriasis when conventional therapy is ineffective or inappropriate (Table 3; ESM 3) [38, 72]. It is recommended for use as a short-term therapy [14, 36] before the initiation of more conventional, slow-acting treatments [73], as a low-dose (1.25–3 mg/kg/day) maintenance therapy and as part of a rotational strategy or combination treatment [73–75]. Occasionally, ciclosporin may be used for continuous long-term therapy for ≤ 2 years [20, 36]. However, an open cohort study showed that intermittent treatment had an improved safety profile compared with continuous treatment over 2 years [76].

Long-term ciclosporin therapy may not be possible due to AEs (in particular, nephropathy and hypertension) and risks of end-organ toxicity [61]. In addition, ciclosporin is associated with increased risks of nonmelanoma skin cancer (NMSC) and photocarcinogenic potential during long-term treatment (> 1–2 years) [14, 31], particularly in patients who have received high cumulative doses of PUVA [14, 36, 77, 78]. Another disadvantage is that ciclosporin treatment requires relatively frequent blood monitoring [35, 36, 38].

AEs with ciclosporin are common, are usually dose related and can be serious. One of the key concerns is renal dysfunction [21–24, 26, 27, 35, 37, 79–93] (reversible at doses ≤ 5 mg/kg/day [94, 95]; however, ciclosporin-induced nephrotoxicity can result in irreversible damage). Structural renal changes may be related to > 2 years of therapy (which worsen after 4 years [37, 79]) or doses > 5 mg/kg/day [35]. The most common effects include increased serum creatinine [81, 84, 90, 94, 96, 97] and urea levels [23, 94, 97].

Hypertension is more frequently experienced with longer-term ciclosporin treatment [22–24, 26, 27, 35, 37, 51, 82, 86, 87, 93, 94, 98, 99], with an incidence of 9–10% [91, 95].

Ciclosporin may also be associated with an increased risk of malignancies [especially squamous cell carcinoma (SCC) in patients with a previous history of PUVA treatment] [23, 35, 77, 78, 94, 100–102]. A prospective long-term (≤ 5 years) cohort study found that > 2 years of treatment (compared with < 2 years) was associated with a higher risk of malignancy (particularly NMSC) [77].

Neurological AEs, including headache [26, 35, 37, 87, 91, 103, 104], paraesthesia [23, 26, 35, 37, 91, 94, 103, 104] and tremor [35, 37, 87, 94, 104], are also seen with long-term therapy. Pseudotumour cerebri has been reported in very rare cases [103]. Finally, GI AEs, such as nausea [37, 91, 104] and GI discomfort [26, 35, 87, 94, 103], may be apparent with long-term therapy.

Abnormal values from laboratory tests can also occur, including measurements indicating hypercholesterolaemia [35, 37], hypertriglyceridaemia [35, 37, 87], hyperkalaemia [23], hypomagnesaemia [23], hyperbilirubinaemia [37, 91, 94] and decreased haemoglobin levels [94].

Ciclosporin is associated with an increased risk of infection [23]. A multicentre, prospective cohort study with a mean follow-up of 3.3 years showed a 58% higher risk compared with methotrexate (adjusted RR 1.58, 95% CI 1.17–2.15) [60]. Other ciclosporin AEs, although not always specifically associated with long-term treatment, include hypertrichosis [23, 24, 26, 35, 37, 82, 87, 93, 94, 103–105], gingival hyperplasia [23, 24, 26, 37, 87, 93, 94, 98, 104, 105], fatigue [37, 82, 91, 104, 105], myalgia [37], temperature hypersensitivity in extremities [37] and pulmonary AEs (cough, rhinitis and dyspnoea) [103].

Ciclosporin treatment has a risk–benefit ratio that is considered acceptable for short-term treatment [20, 73] or in cases for which there are limited treatment options. Ciclosporin may be less acceptable for patients who are at increased risk of some of the serious AEs, including renal impairment or hypertension (e.g. elderly patients) [20, 83]. The risk–benefit ratio of ciclosporin could be improved by changing the dose strategy, by using ciclosporin in combination with other psoriasis treatments (e.g. topical therapies) [106] and by keeping the cumulative dosing time to < 2 years.

Methotrexate

Methotrexate is presumed to alleviate psoriasis symptoms via the inhibition of DNA and RNA synthesis in activated T cells and keratinocytes, thereby initiating anti-proliferative and immunomodulatory mechanisms [36]. Methotrexate is indicated for the treatment of severe psoriasis (Table 3; ESM 4) [42, 107] and is also used to treat moderate-to-severe psoriasis [7]. As a DNA synthesis inhibitor, methotrexate has greater toxic effects on cells with higher division rates [108]. When used in a treatment regimen, methotrexate requires expert supervision because it can have severe wide-ranging AEs leading to GI, kidney, liver and lung toxicity. Liver enzymes and leucocyte counts need to be periodically monitored [109, 110].

Long-term studies show that AEs occur in around 61–95% of patients treated with methotrexate [26, 40, 111, 112]. However, a meta-analysis based on 2763 patient-safety years reported that AEs were treatment-limiting in only 6.9% of patients treated for 6 months [113].

Progressive and dose-dependent hepatotoxicity is a concern with long-term methotrexate therapy [20–24, 26, 39, 74, 114–119]. Increases in hepatic enzyme levels occur in 23–33% of patients on long-term treatment with this medication [39, 40, 112]. A 2-year retrospective chart review showed a 23% incidence of severe hepatotoxicity and an association with increased risk for diabetes mellitus [39]. Liver toxicity is rare in the absence of key risk factors, including excessive alcohol intake, concomitant non-steroidal anti-inflammatory drug (NSAID) use, diabetes mellitus, obesity, hypoalbuminaemia and high total cumulative dose [111]. Low-dose methotrexate rarely causes clinically significant liver damage in the absence of excessive alcohol intake [115]. Therefore, alcohol use should be avoided and patients with hepatic inflammation should be monitored [120]. Acute increases in liver enzymes may indicate hepatic inflammation, and if alanine or aspartate aminotransferase

levels exceed ≥ 3-fold the upper limit of normal, then methotrexate should be discontinued [120]. Liver biopsies can be subject to sampling error, intra- and inter-observer variability, procedural pain and morbidity; therefore, liver biopsies are not considered to be the test of choice and non-invasive tests should be sought as an alternative [121–123]. Accordingly, the latest guidelines have removed the requirement for liver biopsies for patients without risk factors (e.g. obesity and diabetes) [23, 43], and the British Association of Dermatologists [124] and the German S3 guidelines [7] no longer recommend liver biopsies to monitor methotrexate-induced hepatotoxicity.

GI symptoms [20, 24, 40, 112], including nausea [23, 26, 27, 40], vomiting [23, 40] and abdominal discomfort [23], are associated with long-term methotrexate therapy. Subcutaneous or intramuscular methotrexate administration may overcome some of the limitations of oral therapy regarding GI symptoms; however, to date no studies have directly compared these two routes of administration in patients with psoriasis [125]. Dose reductions of methotrexate may help to avoid GI symptoms and the addition of folic acid to the therapeutic regimen is also helpful, although high doses of folic acid can diminish the therapeutic effect of methotrexate [108].

Reported subjective AEs lasting longer than the first few days of drug administration include fatigue [40], headache [24, 40] and malaise [24]. Haematological toxicity can occur, specifically pancytopenia [21, 23, 24, 26, 40]. Following dose reduction or temporary withdrawal, haematopoietic suppression usually improves [40].

Kidney function was affected in around 3% of patients on long-term methotrexate therapy [40, 41]. Methotrexate is teratogenic and is contraindicated in pregnancy [2, 23, 24, 26, 126, 127]. Pulmonary toxicity is a risk of methotrexate therapy [20, 26, 108, 117, 118, 128]; lung fibrosis [23, 24] and pneumonitis [24] have been reported.

Treatment with methotrexate has been associated with an increased incidence of certain malignancies, such as lymphoma [24, 100] and SCC in patients having received PUVA [100]. A prospective study indicated that high-dose exposure to methotrexate was a significant independent risk factor for developing SCC (high versus low/no exposure: RR 2.1, 95% CI 1.4–2.8) [129].

Alopecia was seen in 4% of patients on long-term therapy [26, 40]. Severe skin reactions have also been associated with methotrexate treatment [20].

Other AEs that have been associated with methotrexate treatment—although not specifically with long-term therapy—include reactivation of phototoxic reactions [24] and ulcerative stomatitis [24]. Methotrexate is also associated with an increased risk of infections [20, 23, 130]; a multicentre, prospective cohort study with a mean follow-up of 3.3 years reported a 40% higher risk of infection versus acitretin (crude acitretin RR 0.6, 95% CI 0.42–0.86) and a 58% lower risk of infection versus ciclosporin (adjusted ciclosporin RR 1.58, 95% CI 1.17–2.15) [60].

Methotrexate may reduce the incidence of cardiovascular-related disease in patients with psoriasis [131]. Two different meta-analyses of observational studies concluded that low-dose methotrexate was associated with a decreased risk of cardiovascular events [132, 133]. These analyses included a study that showed a significantly reduced risk of vascular disease for those who were prescribed methotrexate compared with those who were not (RR 0.73, 95% CI 0.55–0.98) [132–134].

Interestingly, dermatology guidelines for methotrexate recommend more intensive monitoring than do rheumatology guidelines for methotrexate. Consequently, abnormal test results are observed more frequently in patients with psoriasis than in those with psoriatic arthritis [135].

Long-term therapy with methotrexate may not be possible due to AEs and end-organ toxicity potential [61] and administration should ideally be time-limited and carefully monitored [109, 110].

Another clinically relevant issue is potential interactions between methotrexate and other drugs, including drugs that may decrease methotrexate binding to serum albumin; probenecid, which may inhibit tubular secretion;

drugs with known kidney or liver toxicity; and alcohol. In addition, certain NSAIDs should not be administered at the same time of day as methotrexate [14].

Clinicians prescribing methotrexate should be alert for potential dosing errors. Dosing errors may occur with methotrexate (in particular with oral dosing formulations) due to patient mistakes or prescribing/dispensing errors. Recent recommendations to avoid such errors include restricting who can prescribe methotrexate, changing the packaging/warnings and providing educational materials [136].

Methotrexate has been reported to have an acceptable risk–benefit profile [112]; however, this must be carefully evaluated and continuously monitored in each patient due to the potential for serious AEs [20]. Taken together, with proper treatment monitoring and physician vigilance, methotrexate continues to play an important role as a systemic psoriasis therapy [137].

Fumaric Acid Esters

A fixed combination of FAE that includes DMF and different monoethylfumarates is licensed in Germany as Fumaderm® (Biogen Idec) for the treatment of moderate-to-severe plaque psoriasis (hereafter referred to as FAE) [7, 46]. DMF [as monotherapy; marketed as Skilarence® (Almirall Limited)] is approved for the treatment of moderate-to-severe plaque psoriasis that requires systemic therapy (Table 3; ESM 5) [45, 138]. DMF, via its active metabolite monomethylfumarate, is believed to elicit its immunomodulatory effects through several pathways, including glutathione-mediated nuclear factor kappa-light-chain-enhancer of activated B-cell inhibition to promote downstream anti-inflammatory pathways [139, 140].

AEs with FAE occurred in 49% of patients in a retrospective analysis over a mean period of 3.6 (range 0.1–32.5) years [141], and in 73% of patients in a study of patients with severe psoriasis with $\leq$ 14 years of follow-up [142]. A 16-week RCT of FAE and DMF found a similar percentage of patients experiencing AEs (84.1 and 83.9%, respectively) [143]. A prospective follow-up study of DMF found that 86% of patients experienced AEs over a median period of 28 months [144].

The most commonly reported AEs with FAE and DMF are GI complaints [7, 16, 20, 46, 141, 143–151] (most commonly abdominal pain), flushing [7, 16, 20, 46, 141, 142, 144–146, 148–151] and white blood cell count abnormalities [7, 16, 141, 142, 149, 151, 152]. In an 8-month study of FAE, 68% of patients developed GI AEs and/or flushing; these AEs settled without intervention in most cases [146]. A retrospective analysis of patients with $\leq$ 4 years of treatment found that at the beginning of treatment, GI complaints were the most frequent AEs with FAE; however, the authors do not state how this changed with longer-term treatment [147]. A retrospective cohort study found that 42% of patients experienced diarrhoea and 55% experienced flushing over $\leq$ 14 years of treatment with FAE [142]. Approximately 30% of patients experienced GI disorders and 14% experienced flushing in a retrospective observational study with a mean duration of FAE therapy of 3.6 years [141]. A real-world study of FAE reported GI disturbances in 25% of patients and flushing in 12% [149]. GI disorders were the most frequently reported AEs in a phase 3 trial with both FAE (63%) and DMF (63%); most events reported were considered 'mild' in intensity. Flushing was also commonly reported (16 and 18%, respectively) [143]. A prospective follow-up study of DMF found that 58% of patients experienced GI AEs and 65% experienced flushing over a median period of 28 months [144].

Abnormalities in monitoring blood tests or urinalysis were observed in 45% of patients in an 8-month study of FAE [146]. Transient proteinuria (defined as dipstick urinalysis positive and 24-h urine collection > 0.14 g protein) was seen in 13% of patients treated with FAE over a mean period of 3.6 years; however, only a few cases of disturbed renal function were documented [141].

The use of FAE may be associated with lymphopenia [7, 16, 141, 142, 149, 151, 152]. A retrospective cohort study found relative lymphopenia in 76% of patients over $\leq$ 14 years of

treatment with FAE [142]. A retrospective cross-sectional study of FAE reported that 41% of patients experienced lymphopenia after 24 months [152]. Lymphopenia < 500/μL (grade 3 and 4) was observed at some point during treatment in 17% of patients in a retrospective observational study (mean FAE duration 3.6 years) [141]. A real-world study of FAE reported lymphopenia in 10% of patients [149]. Regular monitoring of lymphocyte counts (every 4 weeks for FAE [7]; every 3 months for DMF [45]) and discontinuation of DMF treatment if counts fall to < 700/μL [45] are recommended to avoid prolonged exposure to severe lymphopenia and to minimise the potential risk of opportunistic infections such as progressive multifocal leucoencephalopathy (PML). In patients with lymphocyte counts of 700–1000/μL, monthly monitoring is required until levels are ≥ 1000/μL [45]. A recent review of the literature identified 19 cases of PML (14 in patients with psoriasis) on FAE therapy, with the onset of symptoms occurring after a median of 31 months [153].

Leucopenia may be observed with long-term treatment with FAE [7, 141, 151, 152]. A retrospective cross-sectional study reported that 12% of patients experienced leucopenia after 24 months of treatment with FAE [152]. Reduced leucocyte levels (< 3000/μL) were observed in 5% of patients in a retrospective observational study (mean FAE duration 3.6 years) [141].

Another potential AE of FAE treatment is eosinophilia, which is usually transient [7, 141, 142, 151]. A retrospective cohort study found transient eosinophilia in 14% of patients over ≤ 14 years of FAE treatment [142]. Similarly, transient abnormal eosinophil levels (25% above the upper limit of normal) were observed in 16% of patients in a retrospective observational study (mean FAE duration 3.6 years) [141]. German guidelines for psoriasis treatment conclude that eosinophilia is temporary and generally observed between weeks 4 and 10 of therapy [154]. Eosinophilia rarely leads to intervention or treatment discontinuation [141, 142].

Increases in liver enzymes and serum creatinine levels may be seen with long-term treatment with FAE [16, 141, 148, 152]. A retrospective cohort study found liver enzyme elevations in 25% of patients over ≤ 14 years of FAE treatment; these events were isolated elevations that mostly resolved spontaneously or with dose reduction [142]. A retrospective cross-sectional study of FAE reported that 13% of patients experienced liver enzyme increases after 3 months and 6% experienced an increase in creatinine levels after 24 months [152]. Additionally, abnormal creatinine levels (> 1.2 mg/dL) were observed in 12% of patients in a retrospective observational study (mean FAE treatment duration 3.6 years) [141].

In the context of potential drug–drug interactions, a preclinical in vitro assessment of DMF as an inhibitor of cytochrome P450 (CYP) enzymes did not find any inhibitory activity of DMF or its main metabolite monomethylfumarate, suggesting that DMF is unlikely to influence other compounds metabolised by CYP enzymes [155] (Almirall S. A., Barcelona, Spain; data on file). Therefore, DMF may be combined safely with other therapies metabolised via CYP enzymes. Accordingly, a retrospective study of patients treated with FAE and at least one other medication over a mean of 27.4 months reported no clinical drug–drug interactions with FAE [47].

A 2017 Cochrane systematic review and meta-analysis of systemic pharmacological treatments for chronic plaque psoriasis found no significant differences between FAE and placebo in terms of the risk of developing serious AEs [156]; over 1 year, FAE had a similar rate of serious AEs as other systemic drugs. In another study, the rates of AEs for FAE and other systemic drugs were also similar, with the exception of higher rates of GI disorders (13.1 vs. 8.4 per 100 patient-years, respectively) and blood and lymphatic disorders (4.1 vs. 1.0 per 100 patient-years) and lower infection rates (3.0 vs. 6.0 per 100 patient-years) [157].

Current guidelines recommend treatment with FAE for induction and long-term treatment [14, 150]. A European consensus group that was convened to deliver real-world guidance on the clinical use of DMF in moderate-to-severe chronic plaque psoriasis recommended managing patient expectations before starting treatment because AEs are mostly experienced

during the onset of therapy. The consensus group considered the long-term safety profile of FAE treatment to be favourable [46].

Data from a phase 3 clinical trial indicate that DMF is superior to placebo in terms of efficacy and comparable to FAE in terms of efficacy and safety profile [143].

Taken together, FAE therapy is associated with a favourable risk–benefit profile [158] and may thus be a useful treatment option for patients with moderate-to-severe psoriasis, including those for whom potentially more toxic therapies are contraindicated [20].

Drug Survival

Taking into consideration that long-term AEs could negatively impact drug survival, we also reviewed drug survival estimates (Table 4; [17, 135, 157, 159–168]). Variability in drug survival rates in daily clinical practice may reflect important differences in the safety profile (the percentages of patients discontinuing due to AEs are presented in ESM 6), but also efficacy, patient treatment satisfaction, convenience and/or economic factors.

A multicentre, prospective cohort study of patients in the BIOBADADERM registry reported that drug survival probabilities in the first year of treatment were 23.3%, 42.3% and 50.3% for ciclosporin, acitretin and methotrexate, respectively [159]. A quarter of patients stopped treatment after 0.30, 0.22 and 0.38 years, respectively; the median survival times were 0.72, 0.45 and 1.01 years, respectively [159].

A retrospective assessment of drug survival rates found that 1-year survival rates ranged from 16% for ciclosporin to 37% for acitretin, 43% for methotrexate and 46% for FAE; the 5-year survival rates ranged from 10% for methotrexate, to 16% for acitretin and 25% for FAE. For ciclosporin the survival rate was 0% at 20 months [17]. A retrospective analysis of the Italian PsoReal registry data found that the average treatment duration of conventional agents (9.0 ± 10.0 months) and biologics (13.7 ± 11.6 months) was lower than that of FAEs (28.1 ± 20.1 months) [169].

Assessment of the factors associated with drug survival using a large public healthcare database (Clalit Health Services) in Israel found similar mean drug survival times for acitretin and methotrexate (25.5 and 25.9 months, respectively) [160]. Five-year drug survival rates were 23% for acitretin and 19.6% for methotrexate. Young age was a risk factor for treatment termination in both the acitretin and methotrexate treatment groups. This was attributed to concern for the potential of future morbidities, emergence of AEs, alteration in disease severity and teratogenic properties [160].

Additionally, a prospective analysis of drug survival of psoriasis treatments in the Swiss Dermatology Network for Targeted Therapies found mean drug survival times of 7.7 months for methotrexate and 9.3 months for FAE [167]. After 18 months, 50% of patients treated with a systemic agent had discontinued therapy (due to contraindication, AE or treatment success) [167]. Finally, median drug survival times reported for apremilast ranged from ~ 2.9 to ~ 9.7 months [161–165].

Differences in discontinuation rates may be accounted for by the fact that some studies have looked at drug survival in combination with additional systemic treatments (associated with better drug survival) [170] and differing healthcare insurance systems [163]. Drug survival estimates for methotrexate, for example, also vary considerably—likely indicating variable long-term tolerability. Data from a prospective Dutch registry of patients treated with methotrexate (MTX-CAPTURE) showed drug survival rates of 63%, 30% and 15% after 1, 3 and 5 years, respectively; the median drug survival was 1.8 years [166, 171]. Other studies showed the duration of the first treatment course to be, on average, 18.8 months [135] and that 68% of patients discontinued methotrexate after an average of ~ 4.2 months [172]. Median drug survival of FAE was measured in a 1-year registry study and was found to be 54.8 months compared with 51.1 months for other conventional systemic treatments ($p = 0.40$) [157]. Data from a retrospective, single-centre study from Ireland reported a 4-year drug survival rate of

Table 4 Summary of drug survival rates for the systemic agents used to treat moderate-to-severe psoriasis

	Drug survival probability	Mean/median drug survival	References
Acitretin	42.3% (95% CI 36.9–47.6) at 1 year	Median (50%): 0.72 years (~ 8.6 months)	Dávila-Seijo et al. [159]
	23% after 5 years	Mean (SE): 25.5 (0.5) months	Shalom et al. [160]
	37% at 1 year, 16% at 5 years		Arnold et al. [17]
Apremilast	67.6% at Week 24 (~ 5.5 months)	Mean: 224.7 days (~ 7.4 months)	Papadavid et al. [161]
		Median: 295 days (~ 9.7 months)	Lee et al.[162]
		Mean: 348 days (~ 11.4 months)	
		Median: 200 days (~ 6.6 months)	Santos-Juanes et al. [163]
		Median: 12.5 weeks (range 1–87) (~ 2.9 months)	Vujic et al. [164, 165]
Ciclosporin	23.3% (95% CI 19.0–27.8) at 1 year	Median (50%): 0.45 years (~ 5.4 months)	Dávila-Seijo et al. [159]
	16% at 1 year, 0% at 20 months		Arnold et al. [17]
Methotrexate	50.3% (95% CI 46.3–54.2) at 1 year	Median (50%): 1.01 years (~ 12.1 months)	Dávila-Seijo et al. [159]
	19.6% after 5 years	Mean (SE): 25.9 (0.47) months	Shalom et al. [160]
	63%, 46%, 30% and 15% after 1, 2, 3 and 5 years	Median: 1.8 years (~ 21.6 months)	Otero et al. [166]
		Mean: 18.8 months	Busger op Vollenbroek et al. [135]
	43% at 1 year, 10% at 5 years	Mean (SD): 7.7 (7.2) months	Maul et al. [167]
			Arnold et al. [17]
FAE[a]	46% at 1 year, 25% at 5 years		Arnold et al. [17]
	60% at 4 years	Mean: 28 months	Ismail et al. [168]
		Mean (SD): 9.3 (9.3) months	Maul et al. [167]
		Median: 54.8 months	Augustin et al. [157]

CI confidence interval, *FAE* fumaric acid esters; *SD* standard deviation; *SE* standard error

[a] It is assumed that these drug survival rates relate to the fixed combination of FAE (Fumaderm®); however, this was not clearly stated in the source publications

60% for FAE; the mean length of treatment was 28 months [168].

DISCUSSION

We have comprehensively assessed the literature on the long-term safety profiles of five commonly used oral systemic treatments for psoriasis. The characterisation of long-term safety profiles may help to guide therapeutic decision making for oral systemic therapy in clinical practice, allowing healthcare professionals to select the most optimal treatment for each individual. In addition, the information provided by this literature review has the potential to improve treatment-monitoring practices and management of AEs.

The clinical evidence to-date indicates that long-term treatment with acitretin and methotrexate may be limited due to potential cumulative organ-toxicity risks and must be avoided in female patients of reproductive age due to teratogenic potential [48, 107, 109, 110]; however, acitretin and methotrexate remain useful and widely used therapeutic options if patients are selected carefully and monitored regularly. Methotrexate should be avoided in patients who drink alcohol excessively and in patients with diabetes, obesity, concomitant NSAID use and hypoalbuminaemia due to increased risk of hepatotoxicity [111], while acitretin should not be used in pregnant women [20]. Apremilast has a favourable long-term safety profile; there is no increased risk in common AEs with continued exposure and no standard blood monitoring is required [7, 30, 31]. European guidelines do not recommend ciclosporin for the long-term treatment of psoriasis given its safety concerns; however, it may be used occasionally for $\leq$ 2 years. Ciclosporin may not be suitable for those patients, particularly the elderly, who are at increased risk for some of the more serious AEs, such as renal impairment or hypertension [20, 83]. FAE (including DMF) show a promising long-term efficacy and safety profile [138, 141, 144]. GI AEs (most commonly abdominal pain and diarrhoea) and flushing are an important concern for many patients; however, symptoms are generally mild-to-moderate and often resolve with continued treatment [141, 151]. Exposure to severe lymphopenia should be minimised to reduce the risk of PML; consequently, absolute lymphocyte counts should be monitored every 4 weeks for FAE and every 3 months for DMF, and treatment should be stopped if lymphocyte counts decrease to $< 700/\mu L$ on two repeated measurements [45]. FAE should be avoided in patients with pre-existing leukopenia [7, 141, 152] and/or lymphopenia [7, 16, 141, 142, 149, 152].

Long-term safety profiles are also useful in the context of combination therapy, which might be used in patients with psoriasis who are recalcitrant to monotherapy with the aim of improving efficacy while limiting toxicity. Different strategies can be employed: two or more therapies with different mechanisms of action can be used in combination, or rotational therapy or sequential therapy may be used. Rotational therapy involves rotating psoriasis therapies every 2–3 years to minimise cumulative toxicity, while sequential therapy involves switching between different agents for rapid clearance versus long-term maintenance [3]. The European S3 guidelines provide recommendations on specific therapeutic combinations along with the benefits and limitations of each [14]. Recent guidelines from the American Academy of Dermatology and National Psoriasis Foundation focussing on the efficacy and safety of systemic non-biological treatments suggest that ciclosporin may be used as a bridge therapy for patients who are transitioning to a long-term treatment with an improved safety profile. Recommended combination therapies include methotrexate with tumour necrosis factor (TNF) inhibitors or narrow-band-UVB phototherapy, or acitretin with PUVA or broad-band-UVB phototherapy [173]. The Medical Board of the National Psoriasis Foundation indicated the following preferences for combination therapies with biologics: biologic + methotrexate, biologic + acitretin and biologic + phototherapy [5]. However, the number of available trials assessing the efficacy and safety of combination therapies in psoriasis is limited [3–5]; these are warranted in future research.

One major challenge when reviewing the literature was the definition of 'long-term' therapy. This review included articles that investigated safety over an arbitrarily chosen duration of $\geq$ 6 months; however, psoriasis is a lifelong condition that can require continuous treatment for many years. Variability in the definition of 'long-term' care, therefore, meant that comparison between agents was challenging. In addition, although long-term data are available for all of the conventional systemic agents, limited data are available on the newer agents, such as DMF and apremilast, which have not been extensively used over the long term. Hence, the availability of long-term safety data for these recently approved therapies was limited compared with that for conventional agents such as methotrexate and ciclosporin. Moreover, it was not always clear which AEs were due specifically to cumulative treatment over long periods of time and which were associated with very early treatment. An additional challenge was the collation of data in a meaningful way due to the reporting differences across publications. Direct inter-study and inter-agent comparisons should, therefore, be interpreted with caution. Finally, another potential limitation to this review is the small number of studies that were included, particularly for the newer agents.

In terms of the drug survival of these systemic agents, estimates varied considerably. Understanding the long-term safety profile will help to further elucidate the drivers of long-term drug survival, inform better treatment strategies and improve patient outcomes. Importantly, drug survival and RR estimates must be interpreted with caution because differences in study design, patient inclusion and selection introduce variability, thus influencing findings.

CONCLUSION

Oral systemic agents continue to play an important role in the long-term management of psoriasis. The characterisation of the long-term safety profile of oral systemic psoriasis treatments is essential to optimise risk–benefit analysis and well-balanced therapeutic decision-making and helps to guide adequate treatment-monitoring practices in clinical practice. In terms of improving future studies, a clearer definition of what constitutes 'long-term' therapy in psoriasis is needed to better define treatment regimens. Moreover, consistent reporting of safety data will better enable comparison and help to further elucidate the long-term safety profile of systemic agents.

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