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Oral fumaric acid esters for psoriasis (Review)

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Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, Piguet V.
Oral fumaric acid esters for psoriasis.
Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD010497.
DOI: 10.1002/14651858.CD010497.pub2.

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[Intervention Review]

Oral fumaric acid esters for psoriasis

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Editorial group: Cochrane Skin Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2017.

Citation: Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, Piguet V. Oral fumaric acid esters for psoriasis. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No.: CD010497. DOI: 10.1002/14651858.CD010497.pub2.

ABSTRACT

Background

Psoriasis is a chronic inflammatory skin condition that can markedly reduce life quality. Several systemic therapies exist for moderate to severe psoriasis, including oral fumaric acid esters (FAE). These contain dimethyl fumarate (DMF), the main active ingredient, and monoethyl fumarate. FAE are licensed for psoriasis in Germany but used off-licence in many countries.

Objectives

To assess the effects and safety of oral fumaric acid esters for psoriasis.

Search methods

We searched the following databases up to 7 May 2015: the Cochrane Skin Group Specialised Register, CENTRAL in the Cochrane Library (Issue 4, 2015), MEDLINE (from 1946), EMBASE (from 1974), and LILACS (from 1982). We searched five trials registers and checked the reference lists of included and excluded studies for further references to relevant randomised controlled trials. We handsearched six conference proceedings that were not already included in the Cochrane Skin Group Specialised Register.

Selection criteria

Randomised controlled trials (RCTs) of FAE, including DMF monotherapy, in individuals of any age and sex with a clinical diagnosis of psoriasis.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Primary outcomes were improvement in Psoriasis Area and Severity Index (PASI) score and the proportion of participants discontinuing treatment due to adverse effects.

Main results

We included 6 studies (2 full reports, 2 abstracts, 1 brief communication, and 1 letter), with a total of 544 participants. Risk of bias was unclear in several studies because of insufficient reporting. Five studies compared FAE with placebo, and one study compared FAE with methotrexate. All studies reported data at 12 to 16 weeks, and we identified no longer-term studies. When FAE were compared with placebo, we could not perform meta-analysis for the primary outcome of PASI score because the three studies that assessed this outcome reported the data differently, although all studies reported a significant reduction in PASI scores with FAE. Only 1 small study designed for psoriatic arthritis reported on the other primary outcome of participants discontinuing treatment due to adverse effects (2 of 13 participants on FAE compared with none of the 14 participants on placebo; risk ratio (RR) 5.36, 95% confidence interval (CI) 0.28 to 102.1; 27 participants;

very low-quality evidence). However, these findings are uncertain due to indirectness and a very wide confidence interval. Two studies, containing 247 participants and both only reported as abstracts, allowed meta-analysis for PASI 50, which showed superiority of FAE over placebo (RR 4.55, 95% CI 2.80 to 7.40; low-quality evidence), with a combined PASI 50 of 64% in those given FAE compared with a PASI 50 of 14% for those on placebo, representing a number needed to treat to benefit of 2. The same studies reported more participants achieving PASI 75 with FAE, but we did not pool the data because of significant heterogeneity; none of the studies measured PASI 90. One study reported significant improvement in participants' quality of life (QoL) with FAE, measured with Skindex-29. However, we could not compute the mean difference because of insufficient reporting in the abstract. More participants experienced adverse effects, mainly gastrointestinal disturbance and flushing, on FAE (RR 4.72, 95% CI 2.45 to 9.08; 1 study, 99 participants; moderate-quality evidence), affecting 76% of participants given FAE and 16% of the placebo group (representing a number needed to treat to harm of 2). The other studies reported similar findings or did not report adverse effects fully.

One study of 54 participants compared methotrexate (MTX) with FAE. PASI score at follow-up showed superiority of MTX (mean Difference (MD) 3.80, 95% CI 0.68 to 6.92; 51 participants; very low-quality evidence), but the difference was not significant after adjustment for baseline disease severity. The difference between groups for the proportion of participants who discontinued treatment due to adverse effects was uncertain because of imprecision (RR 0.19, 95% CI 0.02 to 1.53; 1 study, 51 participants; very low-quality evidence). Overall, the number of participants experiencing common nuisance adverse effects was not significantly different between the 2 groups, with 89% of the FAE group affected compared with 100% of the MTX group (RR 0.89, 95% CI 0.77 to 1.03; 54 participants; very low-quality evidence). Flushing was more frequent in those on FAE, with 13 out of 27 participants affected compared with 2 out of 27 given MTX. There was no significant difference in the number of participants who attained PASI 50, 75, and 90 in the 2 groups (very low-quality evidence) whereas this study did not measure the effect of treatments on QoL. The included studies reported no serious adverse effects of FAE and were too small and of limited duration to provide evidence about rare or delayed effects.

Authors' conclusions

Evidence suggests that FAE are superior to placebo and possibly similar in efficacy to MTX for psoriasis; however, the evidence provided in this review was limited, and it must be noted that four out of six included studies were abstracts or brief reports, restricting study reporting. FAE are associated with nuisance adverse effects, including flushing and gastrointestinal disturbance, but short-term studies reported no serious adverse effects.

PLAIN LANGUAGE SUMMARY

Oral fumaric acid esters for the treatment of psoriasis

Background

Psoriasis is a long-term inflammatory skin condition that can markedly reduce the quality of life of affected individuals. Treatments taken by mouth (oral treatments), such as methotrexate, ciclosporin, and acitretin, are commonly prescribed to people with moderate to severe psoriasis. Oral fumaric acid esters (FAE) are licensed for the treatment of psoriasis in Germany but remain unlicensed in most other countries. This means that there are different treatment options offered to people in different countries.

Review question

What is the available evidence for the benefits and risks of using FAE for treating psoriasis?

Study characteristics

Our review included six randomised control trials (RCTs) that involved 544 participants. Five RCTs compared FAE with placebo, and one compared FAE with methotrexate. The outcomes we were interested in measuring were the Psoriasis Area and Severity Index (PASI), which is a psoriasis severity score, and the proportion of participants who discontinued treatment because of adverse (side) effects that are common but sufficiently serious that the drug had to be stopped, such as severe diarrhoea, infections, or cutaneous malignancy.

Key results

It was difficult to pool and compare results because outcome measures differed between the studies. Three studies reported significant benefit with FAE when compared with placebo after 12 to 16 weeks of treatment, but we could not combine these results in a statistical analysis to show the overall difference. The included studies did not fully examine the chance of discontinuing FAE treatment because of adverse effects, which is uncertain. One study showed that individuals on FAE are nearly five times more likely to develop nuisance adverse effects; the most common were diarrhoea and abdominal cramps, flushing, reversible protein loss in the urine, and raised levels of eosinophil blood cells. Two RCTs were similar enough to allow the combination of their results and found that FAE were better than placebo when measured by the proportion of individuals who experienced at least a 50% improvement in their psoriasis severity score. One study reported improvement of individuals' quality of life with FAE in comparison with placebo, but the significance of this difference could not be calculated. The benefit of FAE was similar to methotrexate after 12 weeks when changes in disease severity from the start to the end of the trial were compared. The number of individuals experiencing nuisance adverse effects with these two treatments was

not significantly different. The included studies, which were too small and of limited duration to provide evidence about rare or delayed effects, reported no serious adverse effects of FAE.

Quality of the evidence

The risk of study bias, which means any factors that may systematically deviate away from the true findings, was unclear in most studies. This may be because most of the studies were conducted decades ago or were incompletely reported. Several analyses comparing FAE with placebo and methotrexate were limited because the studies were small or did not provide enough information to establish how these treatments compare with each other. Therefore, the overall quality of the evidence was low when comparing FAE with placebo and very low when comparing FAE with methotrexate.

Future RCTs should use standard psoriasis outcome measures, including a validated quality of life scale, to enable the comparison and combination of results. They should be longer in duration or have longer follow-up phases to provide evidence about any delayed adverse effects.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. FAE compared with placebo for psoriasis

FAE compared with placebo for psoriasis

Patient or population: psoriasis
Setting: 2 reports from the Netherlands, 1 from Poland, and 2 international multicentre studies.
Intervention: FAE
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with FAE				
PASI score (scale range from 0 to 72 (higher score indicates more severe psoriasis))	PASI score reduced from a mean of 21.57 to 10.77 (FAE) and remained constant (placebo) (1 study, 99 participants; P < 0.0001); median reduction of 71% (FAE) and 6% (placebo) (1 study, 144 participants; P < 0.001); and median reduction of 67.8% (FAE) and 10.2% (placebo) (1 study, 175 participants; P < 0.001)		-	418 (3 RCTs)	⊕⊕⊖⊖ LOW[1, 2]	All 3 studies reported significant benefit with FAE at week 12 (1 study) and week 16 (2 studies), but data could not be pooled in a meta-analysis because of different ways of PASI score reporting
AEs leading to treatment discontinuation	2 participants withdrew from the FAE group (n = 13) compared with no dropouts in the placebo group (n = 14) (RR 5.36, 95% CI 0.28 to 102.12)		-	27 (1 RCT)	⊕⊖⊖⊖ VERY LOW[3, 4]	Outcome reported at week 16. Unclear if any of the reported AEs were 'serious'
Quality of life (QoL) assessed with Skindex-29 (range 0 to 100; higher scores indicate lower level of QoL)	Mean scores reduced from 54.7 at baseline to 27 at week 16 in the FAE group (n = 105) and from 54.0 to 51.1 in the placebo group (n = 70) (P < 0.001)		-	175 (1 RCT)	⊕⊕⊖⊖ LOW[1, 5]	The reporting abstract did not provide the statistical values needed to calculate the mean difference with 95% CI
	Moderate		RR 4.72 (2.45 to 9.08)	99 (1 RCT)	⊕⊕⊕⊖ MODERATE[2]	

Common nuisance AEs (not leading to treatment discontinuation)	16 per 100	76 per 100 (39 to 100)				Most commonly stomach-ache or cramps, diarrhoea, and flushing
PASI 50	Moderate		RR 4.55 (2.80 to 7.40)	247 (2 RCTs)	⊕⊕⊖⊖ LOW[1, 5]	The meta-analysis included participants who received 720 mg DMF
	14 per 100	64 per 100 (39 to 100)				
PASI 75	PASI 75 was attained by 39% of participants in the FAE group (n = 105) and 1% of those on placebo (n = 70) (1 study, week 16); and by 42% on FAE (n = 36) compared with 11% on placebo (n = 36) (1 study, week 12)		-	247 (2 RCTs)	⊕⊕⊖⊖ LOW[1, 5]	Reported to be a statistically significant difference, but data were not pooled because of significant heterogeneity (I^2 statistic = 77%)
PASI 90 - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not measured in the included studies

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

AEs: adverse effects; **CI:** confidence interval; **DMF:** dimethyl fumarate; **FAE:** oral fumaric acid esters; **PASI:** Psoriasis Area and Severity Index; **RR:** risk ratio; **RCT:** randomised controlled trial; **OR:** odds ratio; **QoL:** quality of life.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level due to risk of publication bias; data were obtained from abstract(s); full report(s) not available.
[2]Downgraded one level due to limitations in design; high risk of performance and detection bias.
[3]Downgraded one level due to indirectness; the study was designed for psoriatic arthritis where all participants also had psoriasis so may not be directly applicable to those with moderate to severe psoriasis.
[4]Downgraded two levels for imprecision; small sample size and very wide confidence interval that included the possibility of an effect in either direction (crosses line of no effect).
[5]Downgraded one level due to risk of bias; insufficient reporting.

Summary of findings 2. FAE compared with MTX for psoriasis

FAE compared with MTX for psoriasis

Patient or population: psoriasis
Setting: Departments of Dermatology, Rotterdam and Eindhoven, the Netherlands.
Intervention: FAE
Comparison: MTX

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with MTX	Risk with FAE				
PASI score (scale range from 0 to 72 (higher score indicates more severe psoriasis))	The mean PASI score was 6.7	The mean PASI score in the intervention group was 3.8 more (0.68 more to 6.92 more)	-	51 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2, 3]	PASI score was measured at week 12. The study reported no significant difference between FAE and MTX based on mean change from baseline
AEs leading to treatment discontinuation	Moderate		RR 0.19 (0.02 to 1.53)	51 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2, 3]	Based on a small sample size (FAE = 26; MTX = 25). The main reasons were elevated liver enzymes with MTX and diarrhoea with FAE. No serious AEs occurred in either group
	20 per 100	4 per 100 (0 to 31)				
Quality of life (QoL) - not measured	See comment	See comment	not estimable	(0 studies)	-	QoL was not assessed
Common nuisance AEs (not leading to treatment discontinuation)	Moderate		RR 0.89 (0.77 to 1.03)	54 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2, 3]	Only flushing was significantly more reported with FAE. Occurance of other AEs including laboratory findings were not significantly different
	100 per 100	89 per 100 (77 to 100)				
PASI 50	Moderate		RR 0.71 (0.41 to 1.22)	51 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2, 3]	Based on a small sample size (MTX = 25; FAE = 26)
	60 per 100	43 per 100 (25 to 73)				
PASI 75	Moderate		RR 0.80 (0.28 to 2.29)	51 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2, 3]	Based on a small sample size (MTX = 25; FAE = 26)
	24 per 100	19 per 100 (7 to 55)				

PASI 90	Moderate		RR 0.48 (0.05 to 4.98)	51 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2, 3]	Based on a small sample size (MTX = 25; FAE = 26)
	8 per 100	4 per 100 (0 to 40)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

AEs: adverse effects; **CI:** confidence interval; **FAE:** oral fumaric acid esters; **PASI:** Psoriasis Area and Severity Index; **MTX**: methotrexate; **RR:** risk ratio; **RCT:** randomised controlled trial; **OR:** odds ratio; **QoL:** quality of life.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for imprecision due to small sample size.
[2]Downgraded one level for study design due to the dose of MTX.
[3]Downgraded one level for study design due to study being open label.

BACKGROUND

A glossary of technical terms is available in Table 1.

Description of the condition

Psoriasis is a chronic inflammatory skin disease (Parisi 2012), which can be divided into a number of subtypes. The most common subtype is chronic plaque psoriasis, which presents as well-defined red, scaly plaques typically on the elbows, knees, and scalp (Lebwohl 2003). Other subtypes include flexural psoriasis, in which red plaques are located in the skin creases; guttate psoriasis, in which there are multiple small plaques, particularly on the trunk; generalised pustular psoriasis, involving multiple skin pustules; and erythrodermic psoriasis covering nearly all of the skin surface (Lebwohl 2003). Diagnosis is based on typical clinical features; a skin biopsy can also be helpful if there is diagnostic uncertainty (Smith 2006). Psoriatic nail changes, including onycholysis and nail pitting, occur in about 40% of people with psoriasis (Augustin 2010).

Epidemiology

Psoriasis occurs world wide and has a higher prevalence in countries further from the equator (Parisi 2012). In the United Kingdom (UK), it affects about 2% of the population (Smith 2006). Psoriasis can develop at any age; the mean age of onset may have two peaks, with the first in young adults and a second peak in about the sixth decade of life (Langley 2005). It probably affects men and women about equally (Griffiths 2007).

The cause of psoriasis is thought to be a combination of genetic and environmental risk factors (Smith 2006). A family history of psoriasis increases the risk of developing the condition, but in studies of twins, psoriasis in one identical twin does not always predict psoriasis in the other (Duffy 1993). Environmental exposures can precipitate psoriasis in some cases, such as streptococcal throat infections leading to guttate psoriasis (Telfer 1992), and medications, including beta-blockers, may trigger chronic plaque psoriasis (Basavaraj 2010). Skin trauma (e.g., due to surgery) can trigger psoriasis at the surgical site, an observation known as the Koebner phenomenon (Griffiths 2007).

Possible links with smoking, alcohol consumption, obesity, and stress remain more controversial, because these may be secondary consequences rather than primary causes (Huerta 2007).

Psoriasis is associated with psoriatic arthritis, an inflammatory arthritis that may involve the axial skeleton or more peripheral joints (Taylor 2006). Nail involvement has been shown to increase the risk of psoriatic arthritis (Griffiths 2007). Population studies suggest that severe psoriasis may be an independent cardiovascular risk factor (Mehta 2010).

Pathogenesis

Psoriasis is thought to be mediated by cells of the immune system (Baker 1984). This is supported by resolution of psoriasis after bone marrow transplants from another donor (Eedy 1990), the benefit obtained by immunosuppressive treatments, and genetic studies (Lebwohl 2003). PSORS1, located on chromosome 6, is the disease susceptibility gene locus most strongly linked with psoriasis (Trembath 1997). It contains genes encoding the major histocompatibility complex (Nestle 2009).

Cells of both the innate and adaptive immune systems are involved; in particular, type helper 1 and type helper 17 cells are important components of the immune cell cascade that results in psoriasis (Nestle 2009). These cells secrete cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-17, which cause skin inflammation (Nestle 2009). Several biologic treatments, such as anti-TNF-α therapies, have been developed to specifically target elements of the inflammatory cascade (Smith 2009).

However, pathogenic pathways in psoriasis are not limited to the immune system: keratinocytes, which are non-immune cells that form the skin barrier, also play a role by secreting chemokines that attract immune cells to the area (Nestle 2009). In addition, tissue samples have demonstrated that new blood vessel formation is a characteristic finding within psoriatic plaques, so angiogenic mediators, such as vascular endothelial growth factor, represent another potential psoriasis pathway (Heidenreich 2009).

However, understanding of pathogenesis remains incomplete.

Impact

Psoriasis is a stigmatising condition, and it can have a major impact on quality of life, equivalent to conditions such as cancer, heart disease, and diabetes (Rapp 1999). The impact of psoriasis on appearance and function can greatly affect occupational, psychological, and social elements of quality of life (Kimball 2005). The condition may profoundly restrict personal life choices (Warren 2011). Psoriasis can be itchy and painful, and application of topical therapies is time consuming and may involve mess and odour. Systemic oral therapies may have adverse effects and usually require blood-test monitoring (Menter 2007). The impact of psoriasis extends beyond individuals as it may also detrimentally affect other members of the family (Eghlileb 2007).

Description of the intervention

Oral fumaric acid esters (FAE) contain a mixture of dimethyl fumarate (DMF), thought to be the active component, and three salts of ethyl hydrogen fumarate (Mrowietz 1999). Fumaderm® initial, containing 30 mg of DMF per tablet, and Fumaderm®, containing 120 mg of DMF per tablet, are commercially available. Fumaderm® has been licensed for psoriasis in Germany since 1994 (Mrowietz 2005). At treatment initiation, gradual dose increments are recommended to improve gastrointestinal tolerance, from one tablet daily of Fumaderm® initially to a maximum of six tablets daily of Fumaderm® (Pathirana 2009). Using the recommended dosing increments, treatment benefit is usually seen after about six to eight weeks (Pathirana 2009). Most clinical data regarding efficacy relate to chronic plaque psoriasis. Although FAE are licensed and widely used in Germany, it was evident from the literature that they are also used in the Netherlands (Fallah Arani 2011; Hoefnagel 2003; Onderdijk 2014), the United Kingdom (Harries 2005; Sladden 2006), and Italy (Carboni 2004; Kokelj 2009). The European S3 guidelines recommend measuring full blood count, liver enzymes, serum creatinine, and urine sediment before starting FAE and every four weeks during the treatment period, and pregnancy status should be checked before treatment initiation (Pathirana 2009).

Adverse effects

Adverse effects of FAE occur in about two thirds of treated patients, particularly during the period of dose escalation (Pathirana 2009). These are usually mild, but can lead to treatment

discontinuation (Mrowietz 1999). The most frequent adverse effects are gastrointestinal symptoms, including diarrhoea, increased stool frequency, nausea, and abdominal pain, as well as facial flushing (Pathirana 2009). A decrease in the circulating lymphocyte count is seen in the majority of patients, but this does not usually require the discontinuation of treatment, and transient increases in the eosinophil count may occur (Hoefnagel 2003). Pregnancy and breastfeeding are considered absolute contraindications to fumaric acid esters because of a lack of safety data in this group (Pathirana 2009). Severe gastrointestinal or kidney disease are also contraindications to the use of oral fumaric acid esters (Pathirana 2009).

How the intervention might work

The exact mechanisms of action of FAE are not yet fully understood, but there is increasing evidence of anti-inflammatory effects via a number of pathways: within psoriatic plaques, dimethyl fumarate reduces the levels of several inflammatory T cell subsets (Bovenschen 2010). This may be due to decreased recruitment of inflammatory cells from the blood stream (Rubant 2008). Fumarates also induce type II dendritic cells, which have an anti-inflammatory effect mediated by the cytokine interleukin-10 (Ghoreschi 2011). In addition, FAE have been shown to inhibit the formation of new blood vessels, a process that is involved in the formation of psoriatic plaques (García-Caballero 2011; Meissner 2011).

Why it is important to do this review

Current licensed oral systemic therapies, namely methotrexate, acitretin, and ciclosporin, are not effective in all of those with psoriasis and may cause adverse effects that require discontinuation of treatment. The next licensed step in treatment is expensive biologic treatment, such as anti-TNF-α therapy (Smith 2009). Oral fumaric acid esters are a cheaper alternative systemic therapy that are licensed in Germany, and the 2011 update of European S3 guidelines recommended FAE as first-line systemic agents for moderate to severe psoriasis (Nast 2012). However, FAE are unlicensed in many other countries, which limits their clinical use and has restricted the production of guidelines to assist patients and clinicians. For example, FAE are used to treat many individuals with psoriasis in the UK (Harries 2005; Sladden 2006), but no guidance exists from the National Institute for Health and Care Excellence (NICE) or the British Association of Dermatologists. This means that there is no standardisation of prescribing schedules for oral fumaric acid esters, and many dermatologists choose not to consider their use for psoriasis because of the lack of guidance. As a result, inequalities exist in psoriasis care due to patient location. This review is intended to assist in decision-making between patients and clinicians regarding choice of systemic therapy for psoriasis.

The plans for this review were published as a protocol 'Oral fumaric acid esters for psoriasis' (Atwan 2013).

OBJECTIVES

To assess the effects and safety of oral fumaric acid esters for psoriasis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials, including cross-over trials.

Types of participants

We included individuals of either sex and any age and ethnicity, with a clinical diagnosis of psoriasis made by a medical practitioner. We included all subtypes of psoriasis.

Types of interventions

We included all randomised controlled trials that compared oral fumaric acid esters, with or without another systemic or topical active treatment, with placebo or another active treatment:

1. oral fumaric acid esters versus oral placebo;
2. oral fumaric acid esters versus active treatment;
3. oral fumaric acid esters in combination with another active treatment versus placebo; or
4. oral fumaric acid esters in combination with another active treatment versus active treatment.

We included studies that used any form of oral fumaric acid esters (FAE), including Fumaderm®, the main commercially available preparation.

Types of outcome measures

Primary outcomes

1. Psoriasis Area and Severity Index (PASI) score: scale range from 0 (no disease) to 72 (maximal disease).
2. The proportion of participants who discontinued treatment due to adverse effects that are common but sufficiently serious that the drug has had to be stopped, such as severe diarrhoea, infections, or cutaneous malignancy.

Secondary outcomes

1. Quality of life score at follow-up measured with a validated scale.
2. The proportion of participants attaining PASI 50, 75, and 90, defined as a 50%, 75%, or 90% reduction in PASI score relative to the baseline PASI score immediately prior to treatment initiation.
3. The proportion of participants experiencing any adverse effects of treatment, i.e., all nuisance side-effects that are common, but do not mean that the drug is stopped.
4. The proportion of participants experiencing serious adverse effects of treatment, defined as resulting in death, hospital admission, or increased duration of hospital stay.

Timing of outcome measures

We anticipated that the outcome measures would be of two types: those in which the treatment phase had finished and those in which the treatment phase was ongoing. We included studies of any duration, but we planned to undertake a priori subgroup analysis to investigate the influence of duration of treatment. We divided studies into short-term treatment duration of less than 12 weeks,

medium-term duration from 12 weeks to less than 6 months, and long-term duration of 6 months or greater.

Economic data

We planned to incorporate health resource usage data, if provided, to place the clinical findings in an economic context.

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 7 May 2015:

- the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 4, 2015) using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3;
- EMBASE via Ovid (from 1974) using the strategy in Appendix 4; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

Searching other resources

Trials registers

We searched the following trials registers up to 14 May 2015 using the search terms 'Fumaric acid', 'Fumarate', and 'Fumaderm':

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Handsearching

In order to identify other potential RCTs for inclusion, AA and RA handsearched the abstracts of proceedings from the following major dermatology conferences that were not already recorded in the Cochrane Skin Group Specialised Register:

- American Academy of Dermatology (AAD) (2008/2009);
- British Association of Dermatologists (BAD) (2008/2009/2010);
- European Academy of Dermatology and Venereology (EADV) (from 2006 to May 2013);
- European Society for Dermatological Research (ESDR) (2005/2006/2007/2008/2009);
- International Investigative Dermatology (IID) (from 2003 to May 2013); and
- Society for Investigative Dermatology (SID) (2007/2008/2009).

References from included and excluded studies

We checked the reference lists of included and excluded studies for further references to relevant trials.

Correspondence

We contacted by email the corresponding authors of included and excluded FAE clinical trials to check for further unpublished RCTs. We corresponded with authors where necessary to determine if a study met the criteria for inclusion and to obtain additional data where necessary.

Adverse effects

From the included studies we identified, we examined data on adverse effects of the interventions. However, we did not perform a separate search for rare or delayed adverse effects.

Data collection and analysis

Some parts of the methods section of this review uses text that was originally published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and other Cochrane reviews co-authored by JI and VP (predominantly, Ingram 2012).

Selection of studies

Two authors (AA and RA) independently compared the titles and abstracts of the studies retrieved by the searches with the inclusion criteria. They examined the full texts of studies that potentially met the criteria, as well as the studies whose abstracts did not provide sufficient information. A third author (JI) resolved any disagreements in terms of final study selection. We recorded the reasons for exclusion of studies in the 'Characteristics of excluded studies' tables.

Data extraction and management

Two authors (AA and RA) independently extracted data using a data extraction form based on the 'Checklist of items to consider in data collection or data extraction' found in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They sought the following information from the reports of included studies: study design and methodology, participants, interventions used, reported outcomes, selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other sources of bias. A third author (JI) resolved any disagreements. Two authors (AA and RA) piloted the data collection form prior to use. We entered the information collected into the 'Characteristics of included studies' tables.

Assessment of risk of bias in included studies

Two authors (AA and RA) independently assessed the risk of bias of the included studies using The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011). They graded the risk of bias as 'low', 'high', or 'unclear' for each of the following domains:
(a) random sequence generation;
(b) allocation concealment;
(c) blinding of participants, personnel, and outcome assessment;
(d) incomplete outcome data;
(e) selective outcome reporting (we checked trial databases to ensure that reported outcomes matched those prospectively listed); and
(f) other sources of bias.

Measures of treatment effect

For dichotomous outcomes, we pooled risk ratios with 95% confidence intervals (CI). For continuous outcomes, we combined either standardised or unstandardised mean differences with 95% CI, depending on whether different scales had been used and whether change scores were to be combined with follow-up scores. We used follow-up scores rather than change from baseline, as recommended by The Cochrane Collaboration (Higgins 2011). We planned to analyse ordinal data from short outcome scales using the methods for dichotomous data, by combining relevant adjacent categories to form a dichotomy. We planned to treat longer outcome scales as continuous data.

Unit of analysis issues

The unit of analysis for our review was individual participants in the context that the intervention is a systemic treatment. We planned to permit the first phase of cross-over trials and pool the results with those from equivalent parallel group RCTs. For cluster-randomised trials, we planned to deflate the sample size using the design effect reported (Higgins 2011). However, we did not include any cross-over or cluster-randomised trials.

Dealing with missing data

Whenever possible, we made contact with the original trial investigators to request any relevant unreported data. If this was unsuccessful, we planned to attempt to impute standard deviations for a small proportion of the included studies. We planned to explore the impact of missing data through sensitivity analyses. For missing dichotomous outcome data, we planned to conduct two sensitivity analyses in which we would assume all missing data to be either events or non-events.

Assessment of heterogeneity

We assessed statistical heterogeneity using the I^2 statistic. We took a narrative approach and did not perform a meta-analysis if the value of the I^2 statistic exceeded 75% because of considerable heterogeneity (O'Rourke 1989). An I^2 statistic of between 40% and 75% may represent substantial heterogeneity (Higgins 2011), and we planned to explore the potential causes where possible for the primary outcome measures.

Assessment of reporting biases

We planned to perform funnel plots and Egger's test for publication bias (Egger 1997) if 10 or more studies contributed data; however, we did not find sufficient studies to perform a funnel plot.

Data synthesis

We dealt with the primary outcome 'PASI score' as a continuous outcome (scale 0 to 72) whereas we handled the secondary outcome components, PASI 50, 75, and 90, as dichotomous outcomes. The latter represents the proportion of participants attaining 50%, 75%, or 90% reduction in baseline PASI score, respectively. We reported pooled measures of effect with 95% confidence intervals and used a fixed-effect model because we expected reasonable similarity across the included studies that involved the same disease and similar treatments and study populations. We planned to highlight with detailed justification if we used a random-effects model during the analysis because of study heterogeneity.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses on the following variables:

- treatment duration (short, medium, or long, defined as less than 12 weeks, 12 weeks to less than 6 months, or at least 6 months, respectively); and
- types of intervention and comparison (oral fumaric acid esters versus placebo, oral fumaric acid esters versus active treatment, etc.).

Sensitivity analysis

We planned to perform sensitivity analysis for studies at higher risk of bias, determined by allocation concealment and blinding of outcome assessment. We planned to conduct two sensitivity analyses in which we assumed all missing data were either events or non-events.

RESULTS

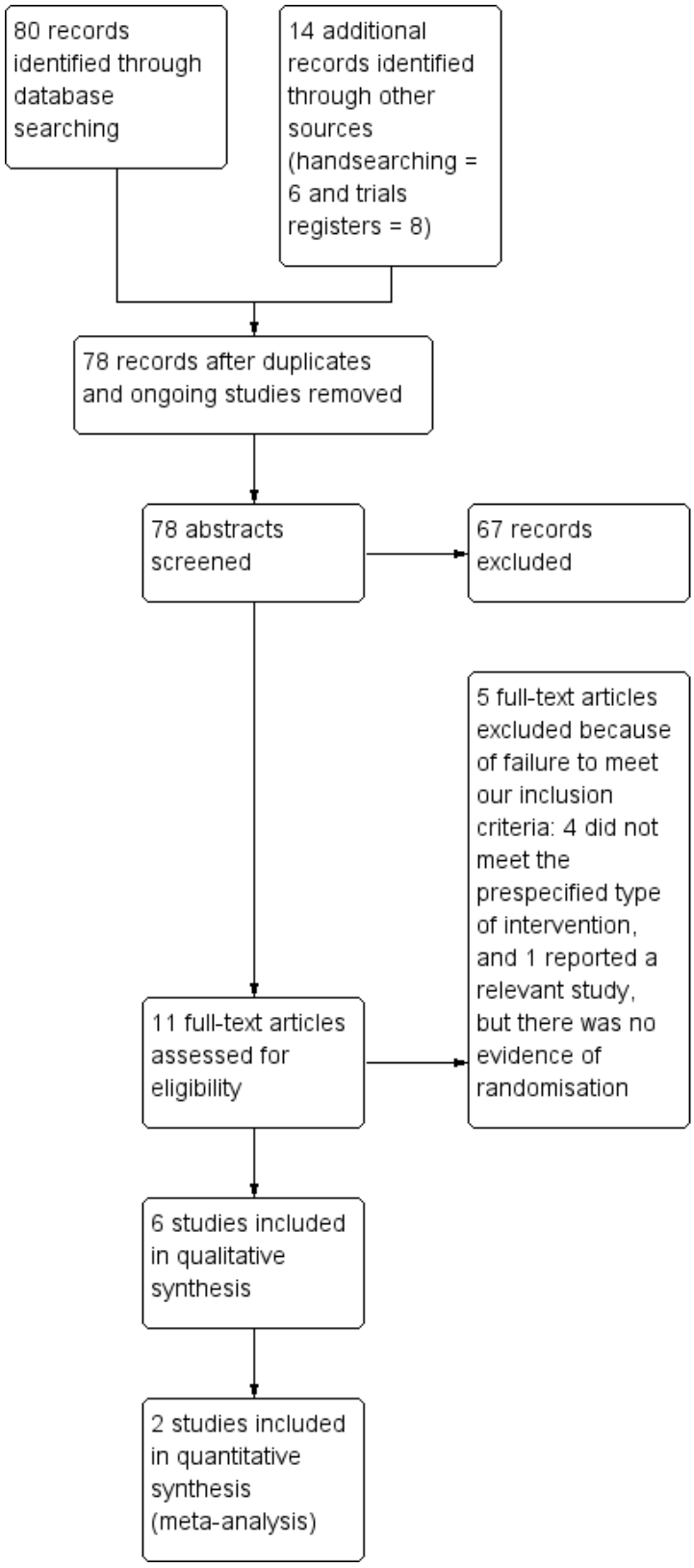
Description of studies

Please see the 'Characteristics of included studies' tables and the 'Characteristics of excluded studies' tables.

Results of the search

The database searches identified a total of 80 records. We identified 6 additional records by handsearching and 8 by searching the trials registers (Figure 1), giving a total of 78 records after the removal of duplicates and ongoing studies. We list details of the eight ongoing studies in the 'Characteristics of ongoing studies' tables. Two authors independently screened the titles and abstracts yielding 11 potentially eligible reports of studies. After obtaining the full texts of these reports, we excluded five, and the remaining six were eligible for inclusion in the review. Two of the included studies were published in full reports (Altmeyer 1994; Fallah Arani 2011), one in a brief communication (Nugteren-Huying 1990), one in a letter (Peeters 1992), and two as abstracts (Langner 2004; Mrowietz 2006). We could not obtain full reports of published abstracts by contacting the authors (see 'notes' in the 'Characteristics of included studies' tables of Langner 2004 and Mrowietz 2006).

Figure 1. Study flow diagram.



Included studies

Please see the 'Characteristics of included studies' tables.

Six studies met the inclusion criteria, with a total of 544 participants.

Setting

Three of the included studies were carried out in the Netherlands (Fallah Arani 2011; Nugteren-Huying 1990; Peeters 1992), one in Poland (Langner 2004), and two were international multicentre studies (Altmeyer 1994; Mrowietz 2006).

Participants

One trial was designed to measure the treatment effect in psoriatic arthritis (PsA), but contact with the author confirmed that all participants also had psoriasis (Peeters 1992). We included this study to obtain data on adverse effects (AEs). All of the included studies reported participants to be adults of at least 18 years of age except Langner 2004, which did not mention the age range of the participants. Two studies included only participants with chronic plaque psoriasis (Fallah Arani 2011; Mrowietz 2006); two included chronic plaque, guttate, pustular, and erythrodermic types (Altmeyer 1994; Langner 2004); but two studies did not report the type (Nugteren-Huying 1990; Peeters 1992). For participants to be eligible, 1 study, Fallah Arani 2011, required them to have a Psoriasis Area and Severity Index (PASI) score ≥ 10 at baseline; 1 study, Mrowietz 2006, ≥ 12; and 1 study, Langner 2004, 16 to 24. Two studies used body surface area (BSA) to assess severity for eligibility, being at least 10% in 1 study, Nugteren-Huying 1990, and more than 10% in another, Altmeyer 1994. One study, which was specifically designed for PsA, did not include psoriasis severity for eligibility assessment (Peeters 1992). Fallah Arani 2011 was the only study to provide details of previous psoriasis therapies, including phototherapy in 53%, conventional systemic agents in 61%, and biologic therapies in 7%. The wash-out period was four weeks prior to randomisation.

Design

Four of the included trials had a two-arm parallel design, and of these, three compared oral fumaric acid esters (FAE) with placebo (Altmeyer 1994; Mrowietz 2006; Peeters 1992), and one compared FAE with methotrexate (Fallah Arani 2011). One study had a four-group dose-finding placebo-controlled design (Langner 2004), and one compared FAE versus octylhydrogen fumarate plus magnesium and zinc monoethyl fumarate (MEF) versus placebo (Nugteren-Huying 1990).

Interventions

There were some variations in the dose increments between studies. Four studies, Altmeyer 1994; Fallah Arani 2011; Nugteren-Huying 1990; Peeters 1992, used tablets containing a mix of dimethyl fumarate (DMF) and salts of MEF. The proportion of this mix was the same, containing 120 mg DMF and 95 mg MEF. The interventions in the other 2 studies, Langner 2004; Mrowietz 2006, respectively, were BG-12 and Panaclar™, formerly BG00012, which contained 120 mg DMF. Low-strength tablets (containing 30 mg DMF) were given in the first 2 weeks of the intervention in Altmeyer 1994 and the first 3 weeks in Fallah Arani 2011 whereas the other studies did not mention treatment initiation with low-strength tablets (Langner 2004; Mrowietz 2006; Nugteren-Huying 1990; Peeters 1992). Altmeyer 1994 increased the 120 mg DMF tablets by 1 tablet daily from week 3 to a maximum of 6 tablets daily compared with an increase of 1 tablet weekly from week 4 in Fallah Arani 2011 to a maximum of 6 tablets daily at week 9. Mrowietz 2006 titrated over 7 days the maximum dose of 720 mg DMF (6 tablets). Two studies reported a gradual increase from one to six tablets daily with no further information (Nugteren-Huying 1990; Peeters 1992). Finally, Langner 2004 provided no information regarding dose increments in the groups who received 360 mg and 720 mg DMF daily. In the one study that compared FAE with methotrexate (Fallah Arani 2011), the methotrexate group started with an initial dose of 5 mg per week and then the dose gradually increased up to 15 mg per week orally. After 12 weeks, the study gradually reduced the dose until stopping it after week 16.

Outcomes

Timing of outcome reporting was of medium-term duration for all studies, namely at week 12 (Fallah Arani 2011; Langner 2004) and week 16 (Altmeyer 1994; Mrowietz 2006; Nugteren-Huying 1990; Peeters 1992).

Not all trials reported on all outcomes prespecified in our review. The included studies reported the following outcomes: PASI score (Altmeyer 1994; Fallah Arani 2011; Langner 2004; Mrowietz 2006); proportion of participants who discontinued treatment because of adverse effects (Fallah Arani 2011; Peeters 1992); quality of life score (Mrowietz 2006); proportion of participants attaining PASI 50, PASI 75 (Fallah Arani 2011; Mrowietz 2006), and PASI 90 (Fallah Arani 2011); proportion of participants experiencing any AEs (Altmeyer 1994; Fallah Arani 2011); and proportion of participants experiencing serious AEs (Fallah Arani 2011). None of the included studies reported data on economic evaluations.

Excluded studies

Please see the 'Characteristics of excluded studies' tables.

We excluded five studies from the review. Four of these did not meet our prespecified type of intervention (Balak 2015; Friedrich 2001; Gollnick 2002; Nieboer 1990), and one did not have evidence of randomisation (Nieboer 1989).

Risk of bias in included studies

We provide details of the 'Risk of bias' assessment in the 'Risk of bias' tables (see the 'Characteristics of included studies' tables). Overall, there was insufficient reporting in most of the included studies to permit judgement of 'low risk' or 'high risk' (Figure 2; Figure 3). One reason is the publication type of some included studies, which included two abstracts (Langner 2004; Mrowietz 2006), one letter (Peeters 1992), and one brief communication (Nugteren-Huying 1990). The fact that some studies were about 20 years old may also be a possible factor for insufficient reporting (Altmeyer 1994; Peeters 1992).

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

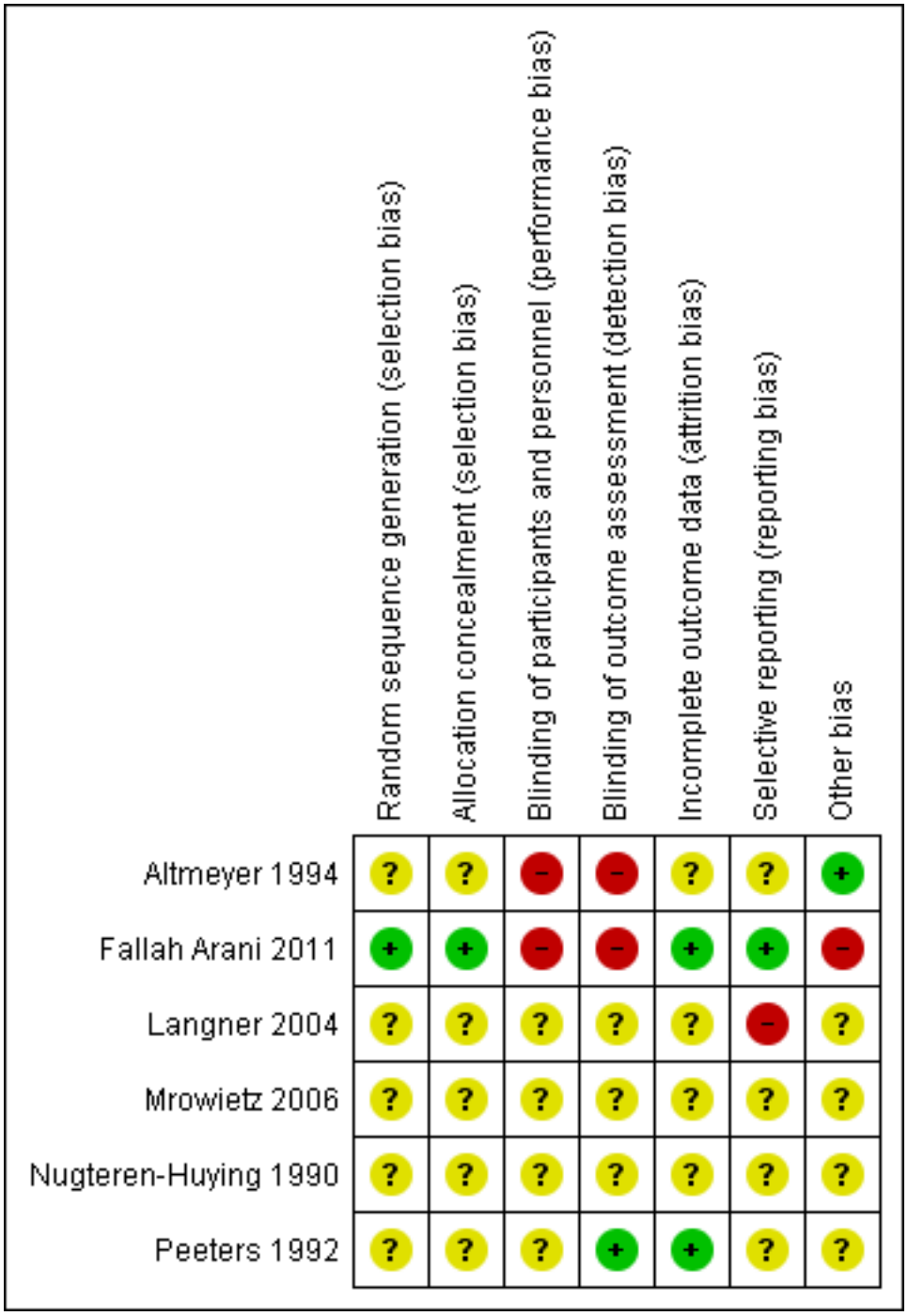
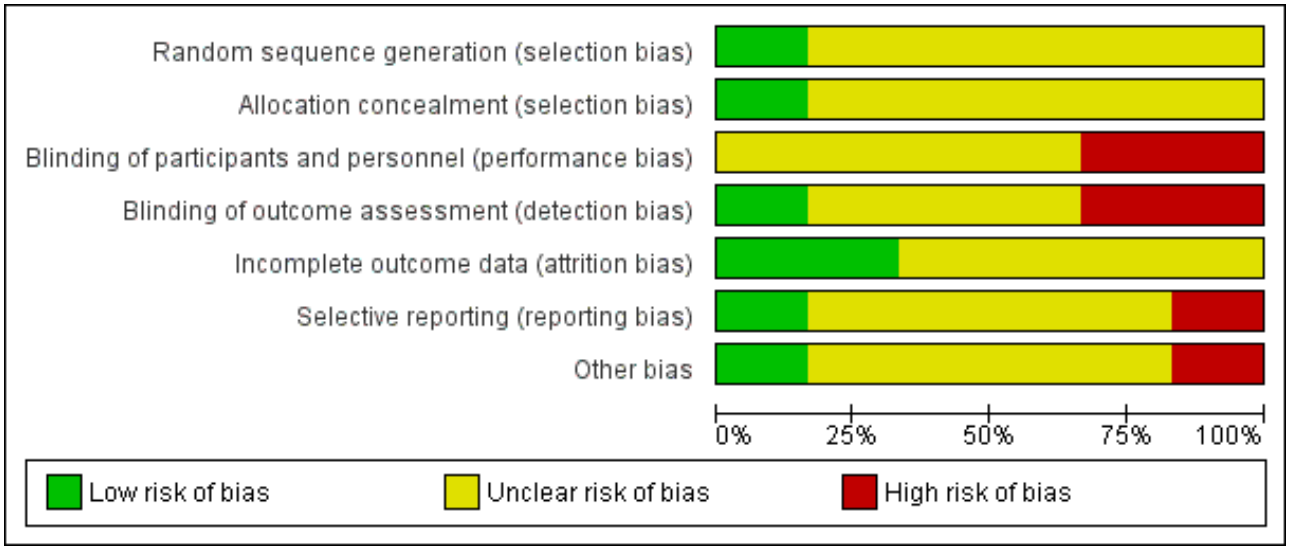


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.



Allocation

Only one study, Fallah Arani 2011, reported adequate sequence generation and allocation concealment. The other studies did not report the method of sequence generation or allocation concealment.

Blinding

Five of the six included studies were described as double-blind (Altmeyer 1994; Langner 2004; Mrowietz 2006; Nugteren-Huying 1990; Peeters 1992). Blinding of participants and personnel (performance bias) was of unclear risk in four of these studies and high risk in one (Altmeyer 1994). Blinding of outcome assessment (detection bias) was of low risk in one study (Peeters 1992), high risk in one (Altmeyer 1994), and unclear risk in the remaining three double-blinded studies (Langner 2004; Mrowietz 2006; Nugteren-Huying 1990). The sixth study included in our review, Fallah Arani 2011, had an open label design, so performance and detection biases were of high risk.

Incomplete outcome data

Two studies had low risk of attrition bias (Fallah Arani 2011; Peeters 1992). We noted unclear risk of attrition bias in the remaining four studies (Altmeyer 1994; Langner 2004; Mrowietz 2006; Nugteren-Huying 1990).

Selective reporting

The protocol of one study was prospectively registered (Fallah Arani 2011). We noted slight variations between the registered protocol and published report, but contact with the author confirmed that the relevant ethics committee had approved some minor changes after registering the protocol. We observed high risk of selective reporting in one study that mentioned PASI, Physician's Clinical Global Impression, Patient's Global Assessment, and Skindex-29 in the methodology, but only reported PASI in the results of the published abstract (Langner 2004). The risk was unclear in other studies (Altmeyer 1994; Mrowietz 2006; Nugteren-Huying 1990; Peeters 1992). We did not perform funnel plots and Egger's test to assess publication bias because fewer than 10 studies contributed data in our review.

Other potential sources of bias

The risk of other potential sources of bias was low in one study (Altmeyer 1994), unclear in four studies (Langner 2004; Mrowietz 2006; Nugteren-Huying 1990; Peeters 1992), and high in one study (Fallah Arani 2011).

Effects of interventions

See: **Summary of findings for the main comparison** FAE compared with placebo for psoriasis; **Summary of findings 2** FAE compared with MTX for psoriasis

All of the included studies had a medium duration (12 weeks to less than 6 months), so we did not perform a subgroup analysis for different treatment durations. We did not perform sensitivity analysis because the risk of bias in the included studies was mostly unclear. Five studies compared oral fumaric acid esters (FAE) with placebo, and one study compared FAE with methotrexate. We discuss these two comparisons individually in our review and summarise them in two 'Summary of findings' ('SoF') tables (see Summary of findings for the main comparison; Summary of findings 2).

We have mainly used a narrative approach to present the effects of FAE in the treatment of psoriasis because of a lack of opportunities for meta-analysis. We combined data from 2 reports comparing FAE with placebo in a meta-analysis for one of the secondary outcomes, PASI 50 (see Data and analyses). Of note, reduction in PASI score is a beneficial outcome, while PASI 50 refers to the proportion of participants achieving a 50% decrease in baseline PASI, so a higher PASI 50 represents greater treatment success. None of the included studies reported data on economic evaluations, so this was not possible to measure in our review.

Comparison of oral fumaric acid esters with placebo

Five studies compared FAE with placebo for the treatment of psoriasis (Altmeyer 1994; Langner 2004; Mrowietz 2006; Nugteren-Huying 1990; Peeters 1992), one of which was designed to measure the treatment effect in psoriatic arthritis (PsA) where all participants also had psoriasis (Peeters 1992). Three studies used a mixture of dimethyl fumarate (DMF) plus monoethyl fumarate (MEF) in enteric-coated tablets as an intervention (Altmeyer 1994; Nugteren-Huying 1990; Peeters 1992) whereas the other two studies used DMF alone (Langner 2004; Mrowietz 2006).

The following studies reported our prespecified outcomes: Altmeyer 1994; Langner 2004; Mrowietz 2006 (PASI score); Peeters 1992 (proportion of participants who discontinued treatment because of adverse effects); Mrowietz 2006 (quality of life (QoL) score); Langner 2004; Mrowietz 2006 (proportion of participants attaining PASI 50 and PASI 75); and Altmeyer 1994 (proportion of participants experiencing common nuisance adverse effects). The quality of the evidence was 'moderate' for proportion of participants experiencing any common nuisance adverse effects; 'low' for PASI score, quality of life, and proportion of participants attaining PASI 50 and PASI 75; and 'very low' for proportion of participants who experienced adverse effects that led to treatment discontinuation (see Summary of findings for the main comparison).

The included studies did not report serious adverse effects, and it was unclear whether any of the adverse effects leading to treatment discontinuation were serious. A meta-analysis of results from 2 studies was possible for PASI 50 and PASI 75 data; however, we reported only the PASI 50 meta-analysis results because of significant heterogeneity for the PASI 75 data. Meta-analyses were not possible for all other outcomes, so we did not report these in a narrative manner.

Primary outcomes

PASI score

Altmeyer 1994 reported a reduction of PASI score from a mean of 21.57 at baseline to 10.77 after 16 weeks of FAE treatment whereas in the placebo group, it remained constant. The study reported the difference between groups at week 16 to be statistically significant ($P < 0.0001$). The text did not report mean PASI scores at baseline and week 16 for the placebo group. We attempted to obtain these values from the line graph provided in the study report by using a magnified Excel worksheet to read the values. This highlighted differences compared with the text of the report for the PASI scores relating to the FAE group. Attempts to contact the authors to seek clarification were unsuccessful, so on balance, we decided that the text values for the FAE group PASI scores were more likely to be accurate and avoided calculation of a mean difference with confidence intervals to prevent introduction of potential error into our review.

Langner 2004, which compared 3 doses of FAE (120 mg, 360 mg, 720 mg) with placebo, reported the median percentage reduction from baseline PASI as 31%, 52%, 71%, and 6%, respectively, after 12 weeks. The study reported this to be statistically significant for the 360 mg and 720 mg dose groups compared with placebo ($P < 0.001$). The paper did not report mean PASI scores at baseline and follow-up.

Similarly, Mrowietz 2006 reported the median PASI score at week 16 in 2 groups that received either FAE (n = 105) or placebo (n = 70). The study reported the median score to be lower with FAE at 5.8 compared with 14.2 with placebo ($P < 0.001$), which represented a 67.8% and 10.2% reduction, respectively. The study also did not report mean PASI scores at baseline and follow-up, but reported an effect size of 7.4 (95% confidence interval (CI) 5.40 to 9.40).

The other two studies comparing FAE with placebo did not include a PASI score and instead measured the disease severity by estimating the body surface area (BSA) involved (Nugteren-Huying 1990; Peeters 1992), "scoring the degree of infiltration and scaling of the plaques from 0 (no infiltration or scaling) to 8 (very severe infiltration or scaling)" (Nugteren-Huying 1990), or scoring the degree of erythema and scaling on a scale range from 0 to 8 (Peeters 1992).

Proportion of participants who discontinued treatment due to adverse effects

Only one study accounted for the number of participants who dropped out solely due to adverse effects (AE) (Peeters 1992). In this 16-week study, 2 participants from the FAE group (n = 13) withdrew from the study (1 after 6 weeks because of diarrhoea that could not be controlled by lowering the treatment dose and 1 after 12 weeks because of proteinuria and elevated serum creatinine levels, which were reversible several weeks after treatment discontinuation), compared with no withdrawals from the placebo group (n = 14) (risk ratio (RR) 5.36, 95% CI 0.28 to 102.12; 1 study, 27 participants; very low-quality evidence) (Analysis 1.1). However, these findings were uncertain because of indirectness and a very wide confidence interval.

Nugteren-Huying 1990 reported that of the 39 participants equally randomised to receive FAE (DMF plus MEF), octylhydrogen fumarate plus magnesium and zinc salts of MEF, or placebo, 34 completed the study. The number of participants who completed the study in each group showed one dropout from the FAE group, three from the octylhydrogen fumarate plus magnesium and zinc salts of MEF group, and one from the placebo group, but the reasons were unclear. The study reported that all 13 participants in the FAE group had diarrhoea, and 1 became ill as a result of renal insufficiency.

In another study (Altmeyer 1994), the number of dropouts due to AEs alone was not possible to establish because FAE was terminated prematurely in 19 (38.8%) participants because of AEs (n = 4), deterioration (n = 5), and several reasons including "no change, increase in the extent and side effects" (n = 10). In comparison, 29 (58.0%) in the placebo group withdrew because of worsening (n = 22), gastrointestinal disturbances (n = 1), and general dissatisfaction with treatment outcome (n = 6).

The two studies published in abstracts, Langner 2004; Mrowietz 2006, did not report the number of participants who completed the study and whether there were any dropouts due to AEs.

Secondary outcomes

Quality of life (QoL) score

One study, Mrowietz 2006, reported quality of life assessment using Skindex-29 (range = 0 to 100; higher scores indicated a lower level of QoL). Mean Skindex-29 scores reduced from 54.7 at baseline to 27.0 at week 16 in the FAE group (n = 105) compared with a reduction from 54.0 to 51.1 in the placebo group (n = 70). This reduction

correlated to a 47% improvement in quality of life with FAE with a reported between-group difference of -19.27 (P < 0.001).

Proportion of participants attaining PASI 50, 75, and 90

The included studies reported PASI 50 and PASI 75 (Langner 2004; Mrowietz 2006). The number of participants who achieved PASI 50 was greater with FAE compared with placebo (RR 4.55, 95% CI 2.80 to 7.40; P < 0.00001; I^2 statistic = 0%; 2 studies, 247 participants; low-quality evidence) (Analysis 1.2). More participants on FAE therapy also attained PASI 75, but due to substantial heterogeneity (I^2 statistic = 77%) between these 2 studies, we could not combine them.

Altmeyer 1994 reported the change of PASI by calculating the remission index. This was categorised into bands different from the standard PASI 50, 75, and 90 as follows: > 95%, 70% to 95%, 30% to 69%, < 30%, 0%, and < 0%; hence, we could not integrate these into the above calculations.

The remaining two studies, Nugteren-Huying 1990; Peeters 1992, did not use PASI for severity assessment.

Proportion of participants experiencing any adverse effects of treatment

Based on one study (Altmeyer 1994), the number of participants experiencing AEs was higher with FAE compared with placebo (RR 4.72, 95% CI 2.45 to 9.08; 1 study, 99 participants; moderate-quality evidence) (Analysis 1.3). The authors also stated the total number of times that an AE was reported, including multiple reports from the same participant. These included stomach ache or cramps (35 times versus twice), diarrhoea (27 times versus twice), flushing (21 times versus none), skin burning (twice versus once), and itching (once versus none). Laboratory findings showed no change in haemoglobin and erythrocyte count, with no differences between groups or within groups. The study noted a mild decrease in leukocytes at week eight in both groups with no changes thereafter. Although between-group analysis at week 16 showed no significant difference, within-group comparison showed a statistically significant decrease in the FAE group (P = 0.0163). The eosinophil count was unchanged in the placebo group, but increased in the FAE group from 2% (day 0) to 3.4% at 4 weeks (P < 0.05), with a further insignificant increase to 4.7% at week 12. Eosinophilia at 28% was noted in 1 participant (unknown time point). Lymphocyte count was unchanged in the placebo group whereas the study reported a non-significant reduction in the FAE group between baseline and week 16. No significant changes were noted in platelet count or levels of bilirubin, urea, creatinine, glucose, alkaline phosphatase, transaminases, gamma glutamyltransferase (GGT), cholesterol, triglycerides, urinalysis, and creatinine clearance in either group.

One study, Peeters 1992, reported diarrhoea, nausea, headache, and flushing as the most common side-effects in both FAE and placebo groups, but provided no numerical values to compute the difference. The study reported these adverse effects to be temporary in most participants and improved after reducing the dose or altering the dietary regimen (no further details). Within-group analysis showed a statistically significant reduction in the erythrocyte sedimentation rate (ESR) (P = 0.007) and alkaline phosphatase (P = 0.005) with FAE whereas haemoglobin, leucocytes, lymphocytes, platelets, and serum creatinine did not significantly change in either group. Comparison between the 2 groups showed statistically significant lower ESR in the FAE group (P = 0.02), lower leucocyte levels (P = 0.02), lower platelet levels (P = 0.02), and lower alkaline phosphatase activity (P = 0.005). However, as participants had psoriatic arthritis, the effect on these markers may not have been representative for individuals with psoriasis alone.

In Nugteren-Huying 1990, 3 groups were treated with FAE (DMF plus several types of MEF) (group 1 = 13), octylhydrogen fumarate plus magnesium MEF (5 mg) and zinc MEF (3 mg) (group 2 = 13), or placebo (group 3 = 13). Group 1 reported the most common adverse effects as flushing (n = 12), diarrhoea (n = 13), fatigue (n = 7), and nausea (n = 6). One participant showed a rise of serum creatinine up to 238 umol/L and reduction of creatinine clearance rate by 51%; this was reported to be reversible. Twelve participants in group 2 developed diarrhoea as a main adverse effect. Group one (n = eight) and group two (n = four) reported transient elevation of liver enzymes. Other abnormalities observed in group one were transient eosinophilia (five participants) and lymphopenia (four). The study provided no information about dropouts in the placebo group, and it was unclear which of the mentioned AEs led to treatment discontinuation in each group.

Mrowietz 2006 did not report the number of participants experiencing AEs. The abstract reported that 58% of FAE-treated participants compared with 23% of those receiving placebo had gastrointestinal AEs. Eighty-two per cent of these were classified as mild to moderate in severity (unclear if some, or all, of the remaining 18% dropped out because of severe symptoms). Forty-two per cent of participants reported flushing in the FAE group compared with 9% in the placebo group. There were no clinically relevant trends to abnormal values in haematology, chemistry, renal, or hepatic function studies. The study reported the adverse events to be generally mild to moderate in severity and transient.

Langner 2004 reported that the most common AEs were flushing, minor plasma elevations of the liver enzyme alanine aminotransferase (ALT), common colds, and a low rate of gastrointestinal events. (There were no numerical values to show if this was dose-dependant or severe enough to cause treatment discontinuation.)

Proportion of participants experiencing serious adverse effects

None of the studies reported whether any of the adverse events that led to treatment discontinuation were serious.

Comparison of FAE with methotrexate

Only one study with an open label design compared FAE with methotrexate (MTX) (Fallah Arani 2011). Reported outcomes included PASI score; proportion of participants who discontinued treatment because of adverse effects; proportion of participants who achieved PASI 50, 75, and 90; and proportion of participants experiencing common nuisance and serious adverse effects. We graded the quality of the evidence for these outcomes as 'very low' (see Summary of findings 2).

Primary outcomes

PASI score

After 12 weeks of treatment, the mean PASI score decreased from 14.5 (standard deviation (SD) 3.0) at baseline to 6.7 (SD 4.5) in the 25 participants treated with MTX compared with a reduction from

18.1 (SD 7.0) at baseline to 10.5 (SD 6.7) in the 26 participants treated with FAE. After adjustment for baseline values, the absolute difference (FAE minus MTX) at 12 weeks was 1.4 (95% CI -2.0 to 4.7; P = 0.417). However, when we compared the PASI scores at follow-up (week 12), as recommended by The Cochrane Collaboration, this difference was in favour of MTX (mean difference (MD) 3.80, 95% CI 0.68 to 6.92; 1 study, 51 participants; very low-quality evidence) (Analysis 2.1).

Proportion of participants who discontinued treatment due to adverse effects

Five of the 25 participants treated with MTX dropped out due to AEs (4 because of elevated liver enzymes and 1 because of recurrent angina) compared with 1 dropout in the 26 treated with FAE because of diarrhoea. This difference was not significant (RR 0.19, 95% CI 0.02 to 1.53; 1 study, 51 participants; very low-quality evidence) (Analysis 2.2). The study reported the elevated liver enzymes to be transient and normalised four to eight weeks after treatment cessation.

Secondary outcomes

Quality of life (QoL) score

Quality of life was not assessed in this study.

Proportion of participants attaining PASI 50, 75, and 90

There was no significant difference in the number of participants who attained PASI 50 (Analysis 2.3), 75 (Analysis 2.4), and 90 (Analysis 2.5) in the 2 groups. Eleven of the 26 participants treated with FAE and 15 of the 25 treated with MTX achieved PASI 50 after 12 weeks (RR 0.71, 95% CI 0.41 to 1.22; 1 study, 51 participants; very low-quality evidence). Five participants who received FAE attained PASI 75 compared with 6 in the MTX group (RR 0.80, 95% CI 0.28 to 2.29; 1 study, 51 participants; very low-quality evidence), while PASI 90 was observed in 1 participant in the FAE group and 2 in the MTX group (RR 0.48, 95% CI 0.05 to 4.98; 1 study, 51 participants; very low-quality evidence).

Proportion of participants experiencing any adverse effects of treatment

The number of participants experiencing adverse effects of treatments was not significantly different between the two groups. Whereas 24 of the 27 participants in the FAE group reported AEs, all 27 in the MTX group experienced AEs (RR 0.89, 95% CI 0.77 to 1.03; 1 study, 54 participants; very low-quality evidence) (Analysis 2.6). However, more participants experienced flushing in the FAE group (13 versus 2) (RR 6.50, 95% CI 1.62 to 26.09). Participants in the FAE group reported influenza-like symptoms less commonly than those in the MTX group (1 versus 7), but this difference was not significant (RR 0.14, 95% CI 0.02 to 1.08). There was no significant difference in reported laboratory findings between the two groups. Transient elevation of liver enzymes (100% to 200% of the values at screening visit) was observed in 3 of the 27 participants in the FAE group and 8 of the 27 participants in the MTX group (RR 0.38, 95% CI 0.11 to 1.26). There was transient eosinophilia (maximum measured level 1.55 x 10^9 L^{-1}) in 5 participants in the FAE group compared with none of those in the MTX group (RR 11.00, 95% CI 0.64 to 189.65) and transient leucocytopenia (2.1 x 10^9 L^{-1}) in 1 participant in the FAE group compared with none in the MTX group (RR 3.00, 95% CI 0.13 to 70.53), and there were similar findings for lymphocytopenia. Transient thrombocytosis (with a maximum level of 422 x 10^9 L^{-1}) was not noted in the FAE group compared with 1 occurrence in the MTX group (RR 0.33, 95% CI 0.01 to 7.84), and finally, an equal number of 8 participants from each group showed transient proteinuria (RR 1.00, 95% CI 0.44 to 2.28).

Proportion of participants experiencing serious adverse effects

This study reported that none of the participants experienced any serious or irreversible adverse effects.

DISCUSSION

Summary of main results

The aim of this review was to provide the best available evidence on the efficacy and safety of oral fumaric acid esters (FAE) for the treatment of psoriasis. We included 6 randomised controlled trials (RCTs), with a total of 544 participants, in this review. Five of these studies compared FAE with placebo. We could not pool data from these studies in meta-analyses because of variations in reported outcomes and insufficient reporting; the only exception was for the Psoriasis Area and Severity Index (PASI) 50, which 2 studies reported. The meta-analysis included 247 participants and demonstrated a combined PASI 50 of 64% for those given FAE compared with a PASI 50 of 14% for those on placebo, representing a number needed to treat to benefit (NNTB) of 2. This favourable NNTB result should be viewed in the context that PASI 50 has been superseded by PASI 75 as the standard psoriasis outcome measure (Smith 2009), and some have argued that in the era of biologic therapies, PASI 90 should be the treatment goal. Three of the studies reported statistically significant reduction of PASI scores with FAE when compared with placebo, but we could not evaluate the mean difference. We obtained the dropout rate due to adverse effects (AEs) from one study with uncertain findings due to indirectness and a very wide confidence interval. Combining data on PASI 50 from 2 studies showed significant benefit in favour of FAE compared with placebo; unfortunately, PASI 75 data showed significant heterogeneity (I^2 statistic = 77%), so we did not combine these studies. One report indicated 47% improvement in quality of life (QoL) with FAE with a reported between-group difference of -19.27 (P < 0.001). Another study reported a significantly higher number of participants experiencing common AEs with FAE, mostly stomach-ache or cramps, diarrhoea, flushing, and eosinophilia.

One of the included studies showed that the effect of FAE on PASI score was comparable to methotrexate (MTX) in terms of change from baseline. However, comparing PASI scores between groups at the endpoint showed favour of MTX due to a disparity in baseline disease severity between the two groups. The number of participants achieving PASI 50, 75, and 90 was not significantly different, and dropout rates because of AEs were similar. The overall number of participants experiencing common nuisance AEs (not leading to treatment discontinuation) was not significantly different between the two groups; however, flushing was more likely for FAE compared with MTX. No serious AEs were observed in any of the participants, and unfortunately, the included studies did not assess the effects on participants' QoL.

Overall completeness and applicability of evidence

The small number of included studies and insufficient reporting of outcomes were major limitations to address the objectives of this review. Some studies included participants with various types of psoriasis, but the outcomes reported did not indicate whether the response to FAE varied between these different types. The

majority of studies comparing FAE with placebo did not report the number of participants who completed the study or dropped out because of AEs. We were also unable to draw conclusions regarding whether the variations in dose increments had an impact on the magnitude of treatment effect or risk of AEs. More recently, the European S3 psoriasis guidelines has standardised the schedule of dose increments (Pathirana 2009). We were unable to establish if the use of dimethyl fumarate (DMF) alone has a similar efficacy and safety profile as the mixture of DMF plus monoethyl fumarate (MEF). Methotrexate (MTX) is used as a first-line oral treatment for psoriasis in many countries, so it was useful to compare MTX with FAE in one of the included studies. However, the maximum dose of MTX used in this study may have been suboptimal as higher doses can be administered in routine clinical practice and also the time of assessment at 12 weeks might have been too brief to evaluate true efficacy. Although the study reported no significant difference in the percentages of participants who achieved PASI 75 and PASI 90 in week 16 after oral treatment was stopped, it must be noted that the dose of MTX was reduced gradually from week 12. So it is unclear if this difference would remain insignificant if MTX was continued at the same dose. Unfortunately, none of the included studies reported long-term follow-up data; therefore, we could not establish the long-term efficacy and safety of FAE from the included trials. Also, none of the included studies reported data on economic evaluations, so this was not possible to measure in our review.

Quality of the evidence

We obtained data presented in this review from six reports, including two abstracts, one brief communication, and one letter. Incompletely reported studies have their limitations; however, we felt it was important to include them in this review because of the overall lack of eligible RCTs. These 6 studies included 544 adult participants in total. Five studies compared FAE with placebo in a double-blind fashion, and one compared FAE with an active comparator, methotrexate, in an open label study. Four studies reported PASI score as a primary outcome, which they presented in different ways as mean scores at baseline and endpoint, percentage of median reduction from baseline, and median scores at endpoint. Insufficient reporting did not allow us to conduct multiple meta-analyses in order to draw robust conclusions. Overall, the evidence for reported outcomes was of low quality in studies that compared FAE with placebo and very low quality in those that compared FAE with methotrexate (see Summary of findings for the main comparison; Summary of findings 2). It is worth noting that some of the included studies were conducted before the requirement for trial registration. Also, we were unable to perform funnel plot or Egger's test to assess the risk of publication bias because of the small number of included studies.

Potential biases in the review process

To our knowledge, we have identified all of the studies related to this review. In addition to electronic searches performed by the Trials search co-ordinator in the Cochrane Skin Group (CSG), one author (AA) searched other resources (including trial registers, handsearching, and grey literature). To minimise the possibility of missing reports, two authors (AA, JRI) independently screened the titles and abstracts to identify potential relevant studies. Following this, two authors (AA, RA) read the full papers of identified studies and extracted data from the eligible ones using the same data extraction form. The two authors resolved discrepancies in 'Risk of bias' assessment between them or with the judgment of a third author (JRI) if they reached no initial agreement. When queries about included studies emerged, one author (AA) contacted study authors (please see 'notes' in the 'Characteristics of included studies' tables for details). In some cases, we did not receive replies, in part due to the length of time that had elapsed since the studies were performed. We regularly sought and followed advice from the CSG throughout the review process. It is worth noting that the use of different cut-off points for the PASI score (i.e., PASI 50, 75, and 90) is likely to be highly correlated with the absolute PASI score and therefore an update of this review should consider selecting only one of these outcomes. We planned to avoid meta-analysis if the value of the I^2 statistic exceeded 75%, so did not combine PASI 75 data for Langner 2004 and Mrowietz 2006, although we concede that this is a somewhat arbitrary threshold for assessing heterogeneity, which may depend on several factors (section 9.5.2: Higgins 2011).

Agreements and disagreements with other studies or reviews

We identified one systematic review for treatments of severe psoriasis including FAE (Griffiths 2000). Griffiths 2000 included five studies, two of which we excluded from our review (Nieboer 1989; Nieboer 1990) - please see the 'Characteristics of excluded studies' studies for the reasons for exclusion. Griffiths 2000 excluded Peeters 1992 as it was essentially designed for psoriatic arthritis rather than psoriasis. However, our contact with the author confirmed that all participants also had psoriasis and we therefore included this study in our review, mainly to obtain adverse effects data.

The Griffiths 2000 review dealt with variations in reporting of average PASI scores by dichotomising the response in terms of 'successful' or 'unsuccessful' treatment in order to report the treatment success rate as a risk difference (RD). This permitted a meta-analysis from which the authors of the Griffiths 2000 review concluded that FAE was superior to placebo with a pooled RD value of 0.47 (95% confidence interval (CI) 0.33 to 0.61) (combined results of Altmeyer 1994; Nugteren-Huying 1990). Griffiths 2000 performed no meta-analyses regarding adverse effects or other outcomes specified in our review.

Mustafa 2013 performed a systematic review that included 21 RCTs reporting efficacy of systemic treatments for moderate to severe psoriasis. The Mustafa 2013 review included 16 RCTs in meta-analyses where risk difference (RD) was reported to measure treatment effect whereas tolerability was assessed from rates of withdrawal and adverse effects. Although the review stated that it would study systemic treatments approved for moderate to severe psoriasis, it only reported results for biologics. The abstract of Mustafa 2013 mentioned, 'Rates of withdrawals due to adverse events were highest for methotrexate and oral fumaric acid esters', but the paper provided no other information. We contacted the author on 9 July 2014 for clarifications and had received no response at the point of submitting this review.

More recently, Schmitt 2014 conducted a systematic review to measure the efficacy and safety of systemic treatments, including biologics and conventional systemic therapies, for moderate to severe psoriasis. The review included only fully published RCTs and excluded review papers, letters, and abstracts. With regard to FAE, Schmitt 2014 included two studies (Altmeyer 1994; Fallah Arani 2011). The review found that FAE is superior to placebo based on mean PASI change (Altmeyer 1994) and has similar efficacy to

MTX (absolute risk difference 0.05, 95% CI -0.18 to 0.27) (Fallah Arani 2011), in agreement with the findings of our Cochrane review, which calculated risk ratios. In keeping with our review, Schmitt 2014 reported that the rates of adverse effects and withdrawals did not differ between FAE and MTX, but did not undertake statistical analysis.

A systematic review by Ceglowska 2014 in a conference proceeding reported clinical effectiveness of FAE for psoriasis and psoriatic arthritis. This review included three studies, Altmeyer 1994; Fallah Arani 2011; Peeters 1992, and presented the results in narrative form as in our review. It concluded that FAE have similar clinical efficacy to MTX in the treatment of moderate to severe psoriasis, based on the difference in mean change from baseline PASI score, and are more effective than placebo in the treatment of psoriasis and psoriatic arthritis. Measuring the efficacy of FAE in the treatment of psoriatic arthritis was not a prespecified outcome in our review. The Ceglowska 2014 review did not examine the safety of FAE to compare with our findings. The quality of included studies in Ceglowska 2014 was scored from three to four points on the Jadad scale (range from zero, low quality, to five, higher quality). In comparison, our review determined the evidence to be of low quality when FAE were compared with placebo and very low quality when FAE were compared with MTX using the Cochrane GRADEpro tool.

The findings in our review reinforce the statement mentioned in the European S3 guidelines that "although the use of fumarates for psoriasis has been evaluated in clinical trials, only a small number of these have followed the criteria of evidence-based medicine" (Pathirana 2009). The guidelines included a few open label non-RCTs, which provided some data on the long-term safety of FAE; we did not include these in our review, which was restricted to relatively short RCTs.

An observational prospective study by Walker 2014 examined the effectiveness, dosing, and adverse effects of Fumaderm®, the marketed brand of FAE, in daily practice. Biogen Idec GmbH, the manufacturer of Fumaderm®, funded it. The study recruited 249 adult participants with psoriasis who started Fumaderm® during their routine clinical care from 78 German dermatology centres and followed them up at 3, 6, and 12 months. It was reported that mean PASI and dermatology life quality index (DLQI) scores in the study population decreased by 66.6% and 67.2% at 12 months, respectively. In comparison, 1 of our included studies, Mrowietz 2006, reported 47% improvement in mean Skindex-29 score at 16 weeks. The Walker 2014 study did not report PASI 50 at 12 or 16 weeks to allow comparison with our findings. Of the 249 participants in this report, 104 dropped out, but the study only documented reasons for this for 76 participants. Among these, 43.4% dropped out because of adverse effects. This rate was measured after 1 year of treatment whereas Peeters 1992 and Fallah Arani 2011 measured the dropout rates because of adverse effects at 16 weeks and reported them as affecting 15.4% (2 of 13 participants) and 3.8% (1 of 26 participants), respectively.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review should be interpreted with caution because of the relatively small number of participants treated in the qualifying randomised controlled trials (RCTs) and lack of meta-analyses due to outcome measure heterogeneity in the pre-Psoriasis Area and Severity Index (PASI) era when some studies were conducted. The limited data obtained from this review provide evidence that oral fumaric acid esters (FAE) are superior to placebo and may be similar in efficacy to methotrexate (MTX). Because of the different ways of reporting changes in PASI scores in studies comparing FAE with placebo, we could only establish the magnitude of benefit for PASI 50. This was 4.5 times more likely to be achieved with FAE after 12 to 16 weeks, with a number needed to treat to benefit of 2. The single study comparing FAE with MTX demonstrated a similar reduction in mean PASI scores from baseline after 12 weeks, with a 7.6-point reduction for the FAE group compared with a 7.8-point reduction for those given MTX. Data from only one relatively small study, in which all participants had psoriatic arthritis, suggest that FAE are not associated with a higher rate of treatment discontinuation compared with placebo. However, this is at odds with clinical experience and the results of the prospective observational study by Walker 2014. The concomitant psoriatic arthritis may have affected this finding, so larger studies of participants selected primarily with cutaneous psoriasis are needed to provide a definitive answer. Commonly reported adverse effects associated with FAE include gastrointestinal symptoms (58% of participants in 1 study), flushing (42%, 48%, and 95% in 3 studies), eosinophilia (18.5% and 38.5% in 2 studies), and reversible proteinuria (29.6% in 1 study). However, the RCTs examined did not report long-term follow-up data, so the review cannot comment on long-term safety of FAE for psoriasis, which is important because FAE may be taken for several years in routine clinical practice.

Implications for research

This review has highlighted several important gaps in the evidence base for the treatment of psoriasis with FAE. One of the main issues is outcome measure heterogeneity as some included RCTs were conducted prior to PASI and quality of life becoming the accepted efficacy measures for psoriasis. This will permit meta-analysis of efficacy data. Comparison with active controls, such as methotrexate, is to be encouraged because these are well established as effective, licensed systemic therapies. The relative efficacy of FAE compared with other systemic psoriasis therapies is also important to establish in the context of the relatively high cost of FAE in most countries. This may be addressed by the ongoing trials, which aim to compare FAE with different active comparators, such as acitretin and biologic therapies (etanercept, adalimumab, and secukinumab). It is worth noting that the status of some of these ongoing trials is unknown (see Ongoing studies), so it is unclear whether they were ever completed or whether there might be any issue of publications bias.

The current RCTs available have not fully established the timescale in which FAE produce benefit in psoriasis. There is now consensus regarding gradual dose increments for FAE (Pathirana 2009) following treatment initiation, which should allow RCTs to compare speed of FAE action with other systemic therapies. Hence, an important future clinical trial would be a comparison of FAE with MTX both dosed using standardised increments and ensuring 12 weeks of treatment at the maximum dose prior to measuring the primary efficacy outcomes of PASI 75 and quality of life, as well as clear reporting of treatment discontinuation due to adverse effects.

This review also highlighted problems in the reporting of AE data, with much of this data either absent or

not reported to Consolidated Standards of Reporting Trials (CONSORT) (www.consort-statement.org). Following these clinical trial standards and ensuring consistency in reported outcomes based on the Core Outcome Measures in Effectiveness Trials (COMET) initiative are necessary to enhance the quality and robustness of evidence. Following the schedule of dose increments according to the European S3 guidelines will allow an accurate measure of adverse effects associated with FAE and the rate of treatment discontinuation because of these adverse effects. There is still a need to establish long-term safety of FAE with a large enough patient cohort to detect rare adverse effects; this evidence should be available in the relatively near future from registers of biologic interventions for psoriasis that contain a systemic medications arm, such as the UK British Association of Dermatologists Biologic Interventions Register (BADBIR) database (Burden 2012).

ACKNOWLEDGEMENTS

The authors would like to thank Chris Taylor who commented on the Plain Language Summary, Glossary, and the readability of the very first draft of the review.

The authors would like to thank the Cochrane Skin Group for their editorial support and guidance throughout the review process.

The Cochrane Skin Group editorial base wishes to thank Hywel Williams who was the Dermatology Editor for this review; Ben Carter and Esther van Zuuren who were the Statistical and Methods Editors, respectively; the clinical referees, Robert Chalmers and Laurence Le Cleach; and the consumer referee, Carolyn Hughes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Altmeyer 1994

Methods	• 2 arms, parallel group, multicentre, double-blind RCT for 16 weeks • Study site(s) not clearly reported, but the authors' affiliations were in Germany and Switzerland
Participants	• 100 participants of both sexes entered the study • The number of participants allocated to each group was not stated (from percentages of dropouts, we calculated the numbers to be 49 in the FAE group (based on 19 (38.8%) prematurely terminated) and 50 in the placebo group (based on 29 (58.0%) prematurely terminated)) • Aged 18 to 70 years (FAE group: mean of 41.1 years (range of 21 to 69 years); placebo group: mean of 39 years (range of 19 to 67 years)) • Participants had psoriasis (chronic plaque type, exanthematic guttate type, pustular type, psoriatic erythroderma) for at least 2 years, and only those with more than 10% of the body surface area affected were included • FAE: 19 (38.8%) dropouts - 4 due to AEs, 5 deteriorated, and 10 for several reasons (including "no change, increase in the extent, and side effects"). Placebo group: 29 (58.0%) dropouts - 22 due to worsening, 1 due to gastrointestinal disturbances, and 6 because of general dissatisfaction with treatment outcome
Interventions	**Intervention 1** A mixture of dimethyl fumarate and monoethyl hydrogen fumarate. It was available in 2 different enteric-coated formulations: low-strength tablets containing 105 mg of ester mixture (30 mg dimethyl fumarate/75 mg monoethyl hydrogen fumarate as calcium, magnesium, zinc salts) and as "forte" tablets containing 215 mg of ester mixture (120 mg dimethyl fumarate/95 mg monoethyl hydrogen fumarate as calcium, magnesium, zinc salts). The dose escalation was as follows: "In the first week 105 mg of the ester mixture daily, in the second week 210 mg per day. After the second week the "forte" form was given and the dose increased by 215 mg per day (week 3) up to a maximum dose of 1290 mg ester mixture per day (week 16)" **Intervention 2** Oral placebo - "patients receiving placebo were given the corresponding numbers of tablets"
Outcomes	• Remission Index (RI) at week 16 (RI was based on the difference in PASI score) • Pruritus, arthralgia, and nail deformities were assessed on the basis of a clinical score from 0 to 4 (0 = none to 4 = very severe) • Adverse effects
Notes	We obtained the author's email address from Google search (not provided on the paper). We sent an email to Peter J Altmeyer on the identified email address (p.altmeyer@klinikum-bochum.de) on 12 July 2013 regarding full study data – there was no response to date (20 May 2015). There was no declaration regarding whether the study was sponsored or whether any conflict of interest existed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 978): "One hundred patients of both sexes were admitted to the study" Comment: there was no information on the method of randomisation

Altmeyer 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	The allocation concealment was not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 978): "Patients receiving placebo were given the corresponding number of tablets" Comment: there were no further details. The high rate of flushing and GI adverse effects is likely to have caused a degree of unblinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was described as 'double-blinded', but the method of blinding was not stated. The high rate of flushing and GI adverse effects is likely to have caused a degree of unblinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the number of participants allocated into each group was not mentioned Quote (page 978): "One hundred patients of both sexes were admitted to the study" Quote (page 980): "Treatment was terminated prematurely in 19 patients (38.8%) in the drug group and 29 (58.0%) in the placebo group" Comment: intention-to-treat analysis using last observation carried forward was performed, which should have limited the impact of attrition bias for efficacy data. We graded the risk of attrition bias as 'unclear' as the reasons for dropout in 10 FAE participants was a combination of no change, worsening of disease severity, and adverse effects
Selective reporting (reporting bias)	Unclear risk	The study protocol was not registered
Other bias	Low risk	We detected no risk of other bias

Fallah Arani 2011

Methods	• Multicentre, prospective, open label, parallel group RCT for 20 weeks (16-week intervention period followed by a 4-week follow-up period)
Participants	• At least 18 years old with moderate to severe chronic plaque psoriasis and a PASI of at least 10. Participants with other clinical forms of psoriasis (e.g., guttate or pustular psoriasis) were excluded • Participants were recruited between October 2006 and February 2009 from the Departments of Dermatology at Erasmus MC, Rotterdam, and from the Catharina Hospital, Eindhoven - the Netherlands • 72 participants were screened, 60 of whom were randomised in 1:1 ratio to receive 16 weeks of treatment with either MTX or FAE (30 participants in each group) • 6 participants (3 in the MTX group and 3 in the FAE group) were subsequently excluded as 5 were not eligible and 1 withdrew consent • 27 participants received assigned treatment in each group. The mean age in the MTX group (16 men (59%) and 11 women (41%)) was 41 years (SD = 14 years) and 43 years (SD = 16 years) in the FAE group (20 men (74%) and 7 women (26%)) • **Week 12:** 26 participants in the FAE group and 25 in the MTX group were evaluated in primary analysis (1 in the FAE group and 2 in the MTX group dropped out because of non-appearance). **Weeks 12 to 16:** 4 dropped out from the FAE group (1 due to AEs, 3 due to lack of response), and 6 dropped out in the MTX group (5 due to AEs, 1 due to non-compliance). **Weeks 16 to 20:** 4 participants were lost to follow up in the FAE group (18 finished follow-up); all 19 in the MTX group finished follow-up
Interventions	**Intervention 1**

Fallah Arani 2011 *(Continued)*

	Fumarates consisting of dimethyl fumarate and salts of monoethyl fumarate (Magistrale Bereider Oud-Beijerland, the Netherlands). Participants received 30 and 120 mg fumarates orally according to a standard progressive dosage regimen (Pathirana 2009). After week 9, the therapy was continued at the maximum dose of 720 mg of fumarate **Intervension 2** Oral methotrexate started with an initial dose of 5 mg per week with laboratory controls after 3 days and 1 week. Thereafter, the dose was gradually increased up to 15 mg per week orally according to the Weinstein scheme as 15 mg weekly in 3 equal doses of 5 mg each 12 hours apart. The dose was tapered to 12.5 mg weekly at week 13, 10 mg weekly at week 14, 5 mg weekly at week 15, and 2.5 mg weekly at week 16. The treatment was stopped after 16 weeks, and all of the participants were followed up for another 4 weeks
Outcomes	• Mean change from baseline PASI after 12 weeks of treatment • Adverse events
Notes	Mean changes in PASI were evaluated using repeated-measurements of ANOVA. This analysis included time (week of treatment) as a fixed factor and used the baseline PASI as a covariate. Analysis was by intention-to-treat, and 2-sided P values of 0.05 were considered to indicate statistical significance Funding sources: none Conflicts of interest: none declared We documented communication with the author in the corresponding 'Risk of bias' table 'selective reporting' section

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 856): "All eligible patients were randomly assigned on a 1:1 basis to receive 16 weeks of treatment...Randomization was performed centrally according to a computer-generated randomisation list"
Allocation concealment (selection bias)	Low risk	Quote (page 856): "Only the research nurse, who had no contact with the patients before randomisation, had insight into the allocation schedule"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 856): "Randomization could not be blinded because treatment intake differed in both groups"
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts due to adverse clinical events and laboratory findings were stated Quote (page 857): "Analysis was by intention-to-treat and two-sided p-values of 0.05 were considered to indicate statistical significance"
Selective reporting (reporting bias)	Low risk	This study was registered with trialregister.nl, number ISRCTN76608307. In the trial registry, the primary outcome was PASI score (endpoint was not specified). Secondary outcomes were PGA and blood/urine samples (PGA was not reported). Also, in the registry, it was stated: "[The] study is designed to determine which of the two therapies induce a PASI 75 first" (not reported) We contacted the author for clarifications (8 June 2013), who replied (7 October 2013): "There have been some minor changes, approved by the METC, to

Fallah Arani 2011 *(Continued)*

		the protocol after registering the study at trialregister.nl. The protocol and the published paper are identical"
Other bias	High risk	The MTX dosing schedule may have diminished the true efficacy results in this group

Langner 2004

Methods	• Multicentre, double-blind, placebo-controlled, dose-finding, phase 2 study • Study outcomes were reported at 12 weeks then "patients who completed the double-blind phase or who withdrew after 8 weeks due to lack of efficacy were eligible to enrol in an open-label, 24-week, follow-up study"
Participants	• Eligible participants had chronic plaque, exanthematic guttate, erythrodermic, palmoplantar, or pustular psoriasis for at least 1 year and a baseline PASI of 16 to 24 • A total of 144 participants enrolled into the study. The number of participants in each group was not stated, but we assume it was 36 in each of the 4 groups based on the following quote: "patients were equally randomised" • The numbers of dropouts, in total and from each group, were not stated • The study site(s) was/were not mentioned, but the authors' affiliations were in Poland
Interventions	• "Patients were equally randomised to 1 of 4 treatment groups: placebo or BG-12 120 mg (1 capsule), 360 mg (3 capsules), or 720 mg (6 capsules), each capsule contained dimethyl fumarate. Study drug (placebo or active) was administered 3 times daily for 12 weeks" • Participants who completed the double-blind phase or who withdrew after 8 weeks because of lack of efficacy were eligible to enrol in an open label, 24-week, follow-up study of 360 mg of BG-12 daily, which could have been increased to 720 mg if the PASI was greater than 12
Outcomes	• Median percentage reduction from baseline PASI • Physician's Clinical Global Impression • Patient's Global Assessment • Skindex-29 (to measure the effects on quality of life) • Adverse events
Notes	Systemic and topical therapies were discontinued before study enrolment (unknown washout period), with the exception of topical salicylic acid and emollients. There was no declaration regarding whether the study was sponsored or whether any conflict of interest existed (abstract). We obtained the author's email address from a web search. We emailed the author on 16 and 20 May 2013 regarding the full study report, and the University of affiliation in Poland was also emailed on 23 May 2013; all mails failed to be delivered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were equally randomised to 1 of 4 treatment groups" Comment: there was no information on the method of randomisation
Allocation concealment (selection bias)	Unclear risk	No information was provided on allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	The trial was described as 'double-blind', but the method of blinding was not stated

Langner 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as 'double-blind', but there was no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At week 12, median percentage reductions from baseline PASI were reported in the 4 groups on unknown number of participants. Most commonly reported adverse events were mentioned with no statistical figures and no information if these resulted in treatment discontinuation. There was insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	High risk	Only PASI (including PASI 50 and PASI 75) was reported in the results. Common adverse events were mentioned but with no statistical figures. The paper stated that "approximately 100 patients have been enrolled in the 24-week follow-up phase" - the proportion of how many completed the double-blind phase against those who withdrew after 8 weeks due to lack of efficacy was unknown
Other bias	Unclear risk	We extracted data from 1 abstract, and there was insufficient reporting to highlight other potential bias

Mrowietz 2006

Methods	• Multicentre, double-blind, placebo-controlled, parallel group RCT • The study had a 16-week double-blind treatment phase, followed by an optional 8-week treatment-free observational phase
Participants	• 175 participants ≥ 18 years old with moderate to severe psoriasis vulgaris (PASI ≥ 12; mean PASI: 18.2) • Participants were recruited from 5 European countries (Sweden: Stockholm; Denmark: Aarhus; the Netherlands: Nijmegen; France: Nice; Germany: Berlin, Dresden, Frankfurt, Gottingen, Kiel, Tubingen) • Participants were randomised 3:2 to dimethyl fumarate (n = 105) or placebo (n = 70) for 16 weeks • There was no information on dropouts or number of participants who completed the study
Interventions	**Intervention 1** BG00012 (in 1 abstract mentioned as "Panaclar™, formerly BG00012), was administered orally as enteric-coated microtablets each of 120 mg dimethyl fumarate in a dose of 240 mg (2 x 120 mg) 3 times daily (daily dose: 720 mg) for 16 weeks" The study drug was titrated over 7 days (no more information) **Intervention 2** Oral placebo (no more information)
Outcomes	• Median PASI at week 16 • PASI 50 and PASI 75 • Skindex-29 • Adverse events
Notes	The study was declared to be supported by Biogen Idec Inc. and Fumapharm AG. U Mrowietz and K Reich: research support, speaker, and consultant for Biogen Idec Inc. and Fumapharm AG. M Spellman: employee of Biogen Idec Inc. We contacted Professor Mrowietz 17 May 2013 for clarifications about the full report/raw data, who replied (18 May 2013): "The study was finalized as a joint venture between the former company Fumapharm and Biogen Idec. Soon after study completion Fumapharm was acquired by Biogen Idec and all activities in the indication psoriasis were stopped. The filing for registration in

Mrowietz 2006 *(Continued)*

psoriasis of BG-12 was retracted and the drug only developed further for the indication multiple sclerosis. Therefore we have not been able to publish the study in a peer-reviewed journal apart from the abstracts you have retrieved. Therefore I am unable to provide you with a respective literature or the data. Hope that this information is helpful for you. Kind regards, Ulrich Mrowietz"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised 3:2…" Comment: no information was provided on the method of randomisation
Allocation concealment (selection bias)	Unclear risk	No information was provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as 'double-blind', but the method of blinding was not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The paper mentioned 'double-blind', but there was no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	The study protocol was not registered (author's explanation provided above)
Other bias	Unclear risk	Supported by Biogen Idec Inc. and Fumapharm AG. U Mrowietz and K Reich: research support, speaker, and consultant for Biogen Idec Inc. and Fumapharm AG. M Spellman: employee of Biogen Idec Inc. We extracted data from abstracts and conference proceedings; there was insufficient reporting to highlight potential bias

Nugteren-Huying 1990

Methods	• 3-arm, double-blind, placebo-controlled RCT for 16 weeks
Participants	• 39 psoriasis participants (men = 27; women = 12), age range = 20 to 73 years (mean of 44 years) • The study site(s) was not mentioned, but the authors' affiliations were in the Netherlands • Participants had to have involvement of at least 10% of the body surface and stable disease • Participants were randomly assigned to 3 groups. The randomisation ratio/number of participants in each group were not reported, but we assumed it to be 1:1:1 (i.e., 13 in each group) based on reported results "out of 39 patients, 34 completed the study" "(group 1, n = 12), (group 2, n = 10), (group 3, n = 12)" • At baseline, no significant differences were found among the 3 groups with regard to sex ratio, age, type and duration of psoriasis, extent and severity of the skin lesions, and preceding antipsoriatic therapy
Interventions	**Group 1**

Nugteren-Huying 1990 *(Continued)*

	Treated orally with enteric-coated tablets containing 120 mg dimethyl fumarate, 87 mg calcium monoethyl fumarate, 5 mg magnesium monoethyl fumarate, and 3 mg zinc monoethyl fumarate **Group 2** Treated orally with enteric-coated tablets containing 284 mg octylhydrogen fumarate, 5 mg magnesium monoethyl fumarate, and 3 mg zinc monoethyl fumarate **Group 3** Given orally administered placebo tablets. All tablets had the same appearance, size, and colour. The dosage schedule called for a gradual increase from 1 to 6 tablets daily
Outcomes	• "Extent and activity of skin disease were assessed by estimating the percentage of body surface affected with psoriasis and by scoring the degree of infiltration and scaling of the plaques (from 0 = no infiltration or scaling to 8 = very severe infiltration or scaling)" • In the results, reduction in the mean percentage of body surface affected and reduction in the mean score of the degree of infiltration and scaling of the plaques were reported at 16 weeks • Adverse events were reported in all 3 groups but unclear whether they led to treatment discontinuation in some participants
Notes	It was reported in 'Participants and methods' that 'All tablets [were] provided by Fumapharm AG, Muri, Switzerland'; it was unclear whether conflicts of interest existed. All study participants received topical treatment with 5% salicylic acid in white petrolatum. The report did not provide authors' contact details. A web search including PubMed publications was unsuccessful. We emailed the university in the affiliation (Leiden University – the Netherlands) at wetenschap@bb.leidenuniv.nl; communicatie@leidenuniv.nl; nieuws@leidenuniv.nl on 5 September 2013 to enquire about any of the study authors. We received a reply from communicatie@leidenuniv.nl on 9 September 2013 suggesting visiting Leiden University Medical Centre website (www.lumc.nl) to seek this information. The Dermatology section on the website did not include email addresses for enquiries; several attempts were made by calling a provided phone number (+31 71 5262497) on 9 September 2013 and 10 September 2013 with no success The second author's affiliation (van der Schroeff JG) from a literature search appeared to be at Bronovo Hospital, The Hague, the Netherlands. His email address was not provided in the publications identified. We sent an email to Bronovo hospital (info@bronovo.nl) on 16 February 2015 to enquire about his contact details. We received a reply from Dr van der Schroeff's email address on 20 February 2015. We sent a list of queries to him on the same day, highlighting the need to submit our review soon. We have received no response to date (20 May 2015)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to three groups" Comment: there was no information on the method of randomisation
Allocation concealment (selection bias)	Unclear risk	The intent or method (or both) to conceal allocation was not specifically reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as 'double-blind', but the method of blinding was not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as "double-blind", but there was no further information

Nugteren-Huying 1990 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Out of 39 patients, 34 completed the study" Comment: it was unclear how many participants were initially allocated to each group; there was no explanation of dropout and from which group and reasons. The study presented results on participants who completed the study only
Selective reporting (reporting bias)	Unclear risk	The study protocol was not registered; outcomes were not clearly specified
Other bias	Unclear risk	We are uncertain whether the company had any input into the trial report

Peeters 1992

Methods	• Double-blind, placebo-controlled RCT comparing FAE vs placebo in the treatment of psoriatic arthritis
Participants	• 27 participants with psoriatic arthritis were randomly assigned to 2 groups for a 16-week study • The study was conducted at Leiden University Hospital, Departments of Rheumatology and Dermatology, the Netherlands • Group 1 (FAE group) had 13 participants (10 male, 3 female) with a mean age of 42 years (SD = 12.7 years) and suffered from psoriasis for a mean of 10.6 years (SD = 7.9 years) and from arthritis for a mean of 6.5 years (SD = 6.6 years). Group 2 (placebo arm) had 14 participants (3 female, 11 male) with a mean age of 39.4 years (SD = 9.6 years) who had suffered from psoriasis for a mean of 12.8 years (SD = 10.6 years) and from arthritis for a mean of 6.5 years (SD = 7.2 years) • The groups were well balanced with regard to demographic data and disease activity parameters • Of the 27 participants, 25 completed the study; 1 participant in the fumarate group stopped trial medication prematurely after 6 weeks because of diarrhoea that could not be controlled by lowering the dosage of the drug. A second participant in the fumarate group stopped medication after 12 weeks because of proteinuria and an increase in serum creatinine levels. Several weeks after the drug was discontinued, proteinuria disappeared and serum creatinine normalised
Interventions	**Group 1** Orally enteric-coated tablets containing 120 mg dimethyl fumarate, 87 mg calcium monoethyl fumarate, 5 mg magnesium monoethyl fumarate, and 3 mg zinc monoethyl fumarate **Group 2** Placebo tablets The dosage schedule called for a gradual increase from 1 to 6 tablets daily
Outcomes	• Clinical efficacy parameters of arthritis and skin lesions (BSA, skin infiltration 0 to 8, skin erythema 0 to 8) • Treatment discontinuation due to adverse events was reported in the text • Common nuisance adverse events were mentioned with no statistical values
Notes	There was no declaration regarding whether the study was sponsored or whether any conflict of interest existed. There was no evidence in the paper that all participants did have psoriasis on the skin. We obtained the author's contact address from Free University Hospital (25 September 2013). We posted an enquiry letter on 26 September 2013 and received an email reply from AJ Peeters on 11 November 2013 confirming that all participants had psoriasis and psoriatic arthritis. A follow-up email was sent to Dr Peeters on 30 January 2015 for further queries about the study, and we received no response. The third author's affiliation (van der Schroeff JG) from a literature search appeared to be at Bronovo Hospital, The Hague, the Netherlands. His email address was not provided in the publications identified. We sent an email to Bronovo hospital (info@bronovo.nl) on 16 February 2015 to enquire about his contact details and received a reply from Dr van der Schroeff's email address on 20 February 2015. We sent

Peeters 1992 *(Continued)*

a list of queries to him on the same day, highlighting the need to submit our review soon. We have received no response to date (20 May 2015)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 502): "Twenty-seven patients with psoriatic arthritis were randomly assigned to two groups for a 16-week, double-blind, placebo-controlled study" Comment: no further details on the randomisation method were stated
Allocation concealment (selection bias)	Unclear risk	The intent or method (or both) to conceal the allocation sequence was not specifically reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 502): "Twenty-seven patients with psoriatic arthritis were randomly assigned to two groups for a 16-week, double blind, placebo-controlled study" Quote (page 503): "Clinical efficacy parameters of arthritis and skin lesions were measured by a rheumatologist and a dermatologist who were not aware of adverse reactions" Quote (page 503): "Dosage was adjusted on the basis of adverse reactions by a physician who was not involved in measuring the efficacy parameters" Comment: there was no explanation of whether blinding of participants was effective
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 503): "Clinical efficacy parameters of arthritis and skin lesions were measured by a rheumatologist and a dermatologist who were not aware of adverse reactions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (page 503): "Of the 27 patients, 25 completed the study; one participant in the fumarate group stopped trial medication prematurely after 6 weeks... A second participant in the fumarate group stopped medication after 12 weeks" Data were presented in a table (quote (page 503): "after 16 weeks of therapy or at the time of premature discontinuation")
Selective reporting (reporting bias)	Unclear risk	The study protocol was not registered Common nuisance adverse events were mentioned with no statistical values
Other bias	Unclear risk	Quote (page 503): "All patients were asked to follow the dietary guidelines strictly" The paper did not report exclusion criteria, concurrent medications, and washout periods. It was unclear whether all participants had matching severity of psoriasis on the skin at baseline

AEs: adverse effects.
ANOVA: analysis of variance.
BSA: body surface area.
FAE: oral fumaric acid esters.
GI: gastrointestinal.
PASI: Psoriasis Area and Severity Index.
PGA: Physician Global Assessment.
METC: Medical Ethics Review Committee.

MTX: methotrexate.
RCT: randomised controlled trial.
SD: standard deviation.
vs: versus.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Balak 2015	This trial did not meet the prespecified type of intervention. 50 participants were randomly assigned to 2 groups in 1:1 ratio. All participants received FAE, but 1 group received additional cetirizine 10 mg once daily whereas the other received additional placebo. The aim was to assess whether the addition of oral histamine H1 receptor antagonist to FAE would reduce the incidence of AEs
Friedrich 2001	The paper did not meet the prespecified type of intervention. 44 participants were randomly assigned to 2 groups. All participants received FAE, but 1 group received additional pentoxifylline (PTX). The aim was to examine if addition of PTX reduced the risk of AEs
Gollnick 2002	The paper did not meet the prespecified type of intervention. 143 participants were randomly assigned to 2 groups. All participants received FAE, but 1 group had additional topical calcipotriol. The aim was to investigate whether the addition of calcipotriol had an additive efficacy
Nieboer 1989	The paper reported observations from 5 studies of which study 3 might have been eligible, but there was no evidence of randomisation
Nieboer 1990	The paper did not meet the prespecified type of intervention. 45 participants were randomly assigned to 2 groups. All participants received dimethyl fumarate (DMF), but 1 group had additional MEF. The aim was to assess the therapeutic efficacy of DMF alone compared with combination of DMF plus MEF

AEs: adverse effects.
DMF: dimethyl fumarate.
FAE: oral fumaric acid esters.
MEF: monoethyl fumarate.
PTX: pentoxifylline.

Characteristics of ongoing studies *[ordered by study ID]*

DRKS00000716

Trial name or title	Regulatory T cell function in psoriasis vulgaris
Methods	Randomised, active-controlled, single-blinded trial
Participants	**Inclusion criteria** • Clinical diagnosis of plaque-type psoriasis for > 6 months • PASI > 10 and psoriasis-affected body surface > 10% • Men and women aged 18 years up to 65 years
Interventions	**Intervention 1** Adalimumab (Humira®) 80 mg initially and 40 mg every other week subcutaneously over a time period of 24 weeks **Intervention 2**

DRKS00000716 *(Continued)*

	Etanercept (Enbrel®) 50 mg twice weekly subcutaneously for 12 weeks and 25 mg twice weekly subsequently for another 12 weeks **Intervention 3** Oral fumaric acid esters (Fumaderm®) was given up to 6 doses per day orally over a time period of 24 weeks
Outcomes	**Primary outcomes (week 8)** • PASI score • DLQI • Skin biopsy for immunohistology and T cells in peripheral blood **Secondary outcomes (week 24)** • PASI score • DLQI skin biopsy for immunohistology and T cells in peripheral blood
Starting date	February 2011
Contact information	Arnd Jacobi Baldingerstrasse 35043 Marburg Germany Telephone: 06421 5862919 Email: Arnd.Jacobi@med.uni-marburg.de Affiliation: Klinik für Dermatologie und Allergologie Philipps-Universität Marburg
Notes	Recruitment status: complete Follow-up: complete Accessed on the World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch) on 14 May 2015

EudraCT Number 2012-000035-82

Trial name or title	A 2:1 randomised, double-blinded, placebo-controlled study to evaluate the efficacy and safety of Fumaderm® in young patients aged 10 to 17 years with moderate to severe psoriasis vulgaris (KIFUderm study)
Methods	Randomised, double-blinded, placebo-controlled
Participants	**Inclusion criteria** • Male and female patients aged 10 to 17 years and weight > 30 kg • Moderate to severe psoriasis vulgaris according to the rule of 10 (PASI ≥ 10 or BSA ≥ 10 or CDLQI/DLQI ≥ 10) • History of psoriasis vulgaris for at least 6 months
Interventions	Fumaderm® vs placebo

EudraCT Number 2012-000035-82 *(Continued)*

Outcomes	**Primary outcome**
	• PASI 75, PGA 0 or 1 (clear or almost clear), or both, during a 20-week treatment phase
	Secondary outcomes
	• To evaluate the efficacy and tolerability as assessed by the following:
	  • PASI means
	  • PASI 50, 75, and 90
	  • PGA
	  • CDLQI/DLQI
	  • NS AE/SAE and laboratory values

Starting date	September 2012
Contact information	SCIderm GmbH Drehbahn 1 to 3 Hamburg 20354 Germany Telephone: +49 40554401115 Fax: +49 40554401291 Norbert.berenzen@SCIderm.com
Notes	Currently ongoing Accessed on clinicaltrialsregister.eu on 14 May 2015

EudraCT Number 2012-000055-13

Trial name or title	A multi-center, randomised, double-blind, three-arm, 16 week, adaptive phase III clinical study to investigate the efficacy and safety of LAS41008 vs LASW1835 and vs placebo in patients with moderate to severe plaque psoriasis
Methods	A multicentre, randomised, clinical trial
Participants	**Inclusion criteria** • Men and women aged 18 years or older with a diagnosis of moderate to severe chronic plaque psoriasis for at least 12 months • PASI > 10 • BSA > 10% • PGA moderate to severe
Interventions	Dimethyl (E)-butenedioate (code: LAS41008) vs Fumaderm® (code: LASW1835) vs placebo
Outcomes	**Primary outcomes** • Superiority of LAS41008 versus placebo based on PASI 75 at week 16 compared with baseline • Superiority of LAS41008 versus placebo based on the proportion of participants achieving a score of "clear" or "almost clear" in the Physician's Global Assessment (PGA) after 16 weeks of treatment

EudraCT Number 2012-000055-13 *(Continued)*

	• Non-inferiority of LAS41008 compared with LASW1835 regarding PASI 75 after 16 weeks of treatment **Secondary outcomes** • Superiority of LAS41008 versus placebo based on changes in PASI; PGA after 3 and 8 weeks; and BSA after 3, 8, and 16 weeks • Non-inferiority of LAS41008 compared with Fumaderm® regarding PASI 75 after 3 and 8 weeks of treatment • Assessment of the safety of LAS41008 compared with Fumaderm® and placebo for both treatment periods (30/120 mg dimethyl fumarate) • Assessment of the safety and efficacy of LAS41008 and Fumaderm® when administered concomitantly with medicines known to have potential nephrotoxic effects, e.g., angiotensin-converting enzyme, angiotensin II inhibitors, and statins
Starting date	August 2012
Contact information	Almirall SA Dr med Veronica Tebbs Rda. General Mitre 151 Barcelona 08022 Spain Telephone: +49 4072704242 Fax: +49 4072704295 Email: veronica.tebbs@almirall.com
Notes	Currently ongoing Accessed on clinicaltrialsregister.eu on 14 May 2015

EudraCT Number 2012-005685-35

Trial name or title	A randomised, double blind, double dummy, active comparator and placebo controlled confirmative non-inferiority trial of FP187 compared to Fumaderm® in moderate to severe plaque psoriasis
Methods	A randomised, double-blind, double dummy, active comparator, and placebo-controlled confirmative non-inferiority trial
Participants	**Inclusion criteria** • Participants of either sex at least 18 years of age • Plaque psoriasis with BSA > 10%; PASI > 10; sPGA ≥ 3
Interventions	FP187 vs Fumaderm®
Outcomes	**Primary outcome** • PASI75 and the responder rate of sPGA as co-primary endpoint at week 20 **Secondary outcomes**

EudraCT Number 2012-005685-35 *(Continued)*

	• Compare the efficacy of 500 mg FP187 (250 mg BID) with 720 mg Fumaderm® (240 mg TID) and placebo at weeks 4, 8, 12, 16, and 20 for the following:
	  • proportion of participants achieving sPGA of 'clear' or 'almost clear' or at least a 2-point improvement from baseline
	  • proportion of participants achieving PASI 50 and PASI 90
	  • the absolute and relative change in PASI and in BSA
	  • proportion of responders on the combined PASI 50 and DLQI ≤ 5
	  • the participant achieving DLQI ≤ 5
	  • the participant-rated DLQI
	  • pruritus measured on a VAS scale
	  • Patient Benefit Index
	  • improvement on nail disease using the NAPSI score
	• Assess pain relief in participants with psoriasis arthritis
	• Investigate laboratory safety on haematology and renal function, liver enzymes, and standard biochemistry in the 3 treatment arms
	• Assess safety and tolerability of FP187 during the full duration of the trial based on AE and SAE reporting and supportive questionnaire

Starting date	July 2013
Contact information	Forward Pharma GmbH Deutscher Platz 5A Leipzig 04103 Germany Telephone: 49341993 9988 Email: FP187.trial@forward-pharma.com
Notes	Currently ongoing Accessed on clinicaltrialsregister.eu on 14 May 2015

EudraCT Number 2014-005258-20

Trial name or title	A 24-week, randomised, controlled, multicenter, open label study with blinded assessment of the efficacy of subcutaneous secukinumab compared to Fumaderm® in adults with moderate to severe plaque psoriasis
Methods	A randomised, controlled, multicentre, open label study with blinded assessment of the efficacy
Participants	**Inclusion criteria** • Men or women ≥ 18 years of age • Chronic plaque-type psoriasis for at least 6 months • Moderate to severe plaque psoriasis (PASI score of > 10; affected BSA > 10%; DLQI > 10)
Interventions	Secukinumab auto-injector vs Fumaderm®
Outcomes	**Primary outcome** • PASI 75 at week 24

EudraCT Number 2014-005258-20 *(Continued)*

	Secondary outcomes • Raw PASI and PASI 50/75/90/100 response rates at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 • BSA at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 • IGA at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 • DLQI at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 • SF-36 response at weeks 4, 16, and 24 • NAPSI response at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24
Starting date	March 2015
Contact information	Novartis Pharma GmbH Roonstr. 25 Nürnberg 90429 Germany Telephone: 00491802232300 Fax: 004991127312160 Email: infoservice.novartis@novartis.com
Notes	Currently ongoing Accessed on clinicaltrialsregister.eu on 14 May 2015

NCT00811005

Trial name or title	Fumaric acid ester-PUVA therapy versus acitretin-PUVA therapy in pustular palmoplantar psoriasis
Methods	Prospective, randomised, controlled, single-blinded study
Participants	**Inclusion criteria** • Age 18 to 90 years of both sexes • Participants with pustular palmoplantar psoriasis
Interventions	FAE-PUVA combination vs acitretin-PUVA combination for a maximum period of 12 weeks
Outcomes	**Primary outcome** • Duration of remission **Secondary outcomes** • Percentage of participants achieving remission • Number of PUVA exposures required for inducing remission • Total UVA exposure dose required for inducing remission • Frequency and quality of adverse reactions
Starting date	October 2008
Contact information	Adrian Tanew, MD

NCT00811005 *(Continued)*

	Division of Special and Environmental Dermatology Vienna, Austria, 1180
Notes	"The recruitment status of this study is unknown because the information has not been verified recently" Verified September 2009 by Medical University of Vienna Accessed on ClinicalTrials.gov on 18 July 2014 with a second check on 14 May 2015

NCT01088165

Trial name or title	The influence of adalimumab vs fumaric acid esters on cardiovascular and metabolic risk factors in the therapy of patients with moderate to severe psoriasis vulgaris
Methods	Randomised, double-blind, parallel group RCT
Participants	**Inclusion criteria** • Age 18 to 80 years of either sex • Chronic severe plaque type psoriasis (PASI < 10) requiring systemic treatment. Non-response or contraindication to previous systemic, light treatment, or both • PASI ≥ 10; BSA ≥ 10
Interventions	Adalimumab subcutaneous injections vs oral FAEs provided as Fumaderm® No reduction of 50% minimum of baseline PASI by week 12: additional narrow band UVB radiation, 3 x/week until the participants achieve PASI reduction of 75% or greater or over a maximum period of another 12 weeks
Outcomes	**Primary outcome** • The influence of adalimumab treatment in comparison with FAE on the functional integrity of the endothelium will be monitored by flow-mediated dilatation **Secondary outcomes** • The measurement of carotid artery intima-media thickness (IMT) by ultrasound will serve as a morphological substrate for evaluating the potential effect of adalimumab on signs of atherosclerosis within the vessel wall • Influence of adalimumab in comparison with FAE on biochemical cardiovascular and metabolic risk factors
Starting date	March 2010
Contact information	Gregor Holzer, MD 40400 ext 7701 gregor.holzer@meduniwien.ac.at Medical University Vienna Department of Dermatology Vienna, Austria, 1090
Notes	"The recruitment status of this study is unknown because the information has not been verified recently" Verified January 2012 by Medical University of Vienna

NCT01088165 *(Continued)*	
	Accessed on ClinicalTrials.gov on 18 July 2014 with a second check on 14 May 2015

NCT01321164	
Trial name or title	Fumaric acid versus fumaric acid plus narrow band type B ultraviolet (UVB) for psoriasis
Methods	Randomised, investigator-blinded, parallel group RCT
Participants	**Inclusion criteria** • Men and women aged 18 to 80 years • Moderately severe to severe psoriasis (BSA ≥ 10 and PASI ≥ 10)
Interventions	**Group 1** Oral fumaric acid esters monotherapy **Group 2** Combination therapy of oral fumaric acid esters plus narrow band type B UVB
Outcomes	**Primary outcome** • Mean reduction in PASI (time frame: baseline and 6 weeks) **Secondary outcomes** • Mean cumulative FAE dose required to reach PASI 75 (time frame: 6 months) • Mean reduction in PASI (time frame: baseline and 6 months) • Mean reduction in PLASI (time frame: baseline and 6 months) • Mean reduction in DLQI (time frame: baseline and 6 months) • Mean white blood cells (leukocytes and lymphocytes) count (time frame: baseline and 6 months) • Correlation between the mean white blood cells (leukocytes and lymphocytes) count and PASI reduction and between the mean white blood cells count and cumulative FAE dose
Starting date	April 2011
Contact information	Professor Adrian Tanew Medical University of Vienna Department of Dermatology Division of General Dermatology Vienna, Austria, 1090
Notes	This study has been completed Accessed on ClinicalTrials.gov on 14 May 2015

AE: adverse effects.
BID: twice a day.
BSA: body surface area.
CDLQI: Children's Dermatology Life Quality Index.
DLQI: Dermatology Life Quality Index.
FAE: oral fumaric acid esters.
IGA: Investigator's Global Assessment.
IMT: intima-media thickness.

PASI: Psoriasis Area and Severity Index.
PGA: Physician Global Assessment.
PLASI: Psoriasis Log-based Area and Severity Index.
PUVA: psoralen combined with ultraviolet A.
NAPSI: Nail Psoriasis Severity Index.
NS: non-significant.
RCT: randomised controlled trial.
SAE: serious adverse effects.
SF-36: 36-Item Short Form Health Survey.
sPGA: Static Physician global Assessment.
TID: three times a day.
UVA: ultraviolet therapy.
VAS: visual analogue scale.
vs: versus.

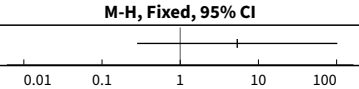
DATA AND ANALYSES

Comparison 1. FAE vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AEs leading to treatment discontinuation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 PASI 50	2	247	Risk Ratio (M-H, Fixed, 95% CI)	4.55 [2.80, 7.40]
3 Common nuisance AEs (not leading to treatment discontinuation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

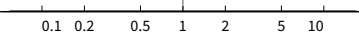
Analysis 1.1. Comparison 1 FAE vs placebo, Outcome 1 AEs leading to treatment discontinuation.

Study or subgroup	FAE n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Peeters 1992	2/13	0/14		5.36[0.28,102.12]



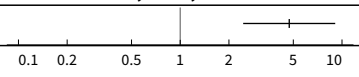
Analysis 1.2. Comparison 1 FAE vs placebo, Outcome 2 PASI 50.

Study or subgroup	FAE n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Langner 2004	23/36	5/36		29.41%	4.6[1.97,10.76]
Mrowietz 2006	68/105	10/70		70.59%	4.53[2.51,8.19]
Total (95% CI)	**141**	**106**		**100%**	**4.55[2.8,7.4]**
Total events: 91 (FAE), 15 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=6.11(P<0.0001)					



Analysis 1.3. Comparison 1 FAE vs placebo, Outcome 3 Common nuisance AEs (not leading to treatment discontinuation).

Study or subgroup	FAE n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Altmeyer 1994	37/49	8/50		4.72[2.45,9.08]

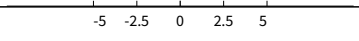


Comparison 2. FAE vs MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PASI score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 AEs leading to treatment discontinuation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 PASI 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 PASI 75	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 PASI 90	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Common nuisance AEs (not leading to treatment discontinuation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 FAE vs MTX, Outcome 1 PASI score.

Study or subgroup	FAE N	FAE Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Fallah Arani 2011	26	10.5 (6.7)	25	6.7 (4.5)		3.8[0.68,6.92]

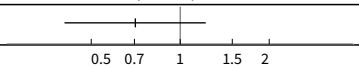


Analysis 2.2. Comparison 2 FAE vs MTX, Outcome 2 AEs leading to treatment discontinuation.

Study or subgroup	FAE n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah Arani 2011	1/26	5/25		0.19[0.02,1.53]

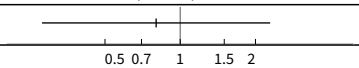
Analysis 2.3. Comparison 2 FAE vs MTX, Outcome 3 PASI 50.

Study or subgroup	FAE n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah Arani 2011	11/26	15/25		0.71[0.41,1.22]



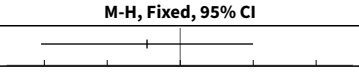
Analysis 2.4. Comparison 2 FAE vs MTX, Outcome 4 PASI 75.

Study or subgroup	FAE n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah Arani 2011	5/26	6/25		0.8[0.28,2.29]



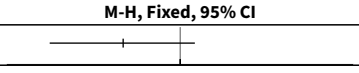
Analysis 2.5. Comparison 2 FAE vs MTX, Outcome 5 PASI 90.

Study or subgroup	FAE n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah Arani 2011	1/26	2/25		0.48[0.05,4.98]



Analysis 2.6. Comparison 2 FAE vs MTX, Outcome 6 Common nuisance AEs (not leading to treatment discontinuation).

Study or subgroup	FAE n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah Arani 2011	24/27	27/27		0.89[0.77,1.03]



ADDITIONAL TABLES

Table 1. Glossary

Term	Description
Adaptive immune system	Immune cells that recognise specific infectious agents and secrete inflammatory cytokines in response
Alkaline phosphatase	An enzyme made mostly in the liver and bones, which may indicate liver damage or bone disease if raised in the blood
Angiogenic	Promoting new blood vessel formation
Apoptosis	Death of a cell
Arthralgia	Joint pain

Table 1. Glossary *(Continued)*

Atherosclerosis	Build up of fibrous and fatty material inside the arteries
Axial skeleton	The group of bones found along the central axis of the human body, such as the spine
Bilirubin	A yellow-orange compound produced by the breakdown of haemoglobin from red blood cells
Biologic treatment	A type of drug engineered to alter a specific element of the inflammatory cascade
Chemokines	Small protein molecules secreted by cells that attract other inflammatory cells to the area
Contraindication	A situation that serves as a reason to withhold a certain treatment or procedure because it may be harmful to a patient
Creatinine	A chemical waste product that comes from diet and normal breakdown of muscles and is excreted by the kidneys. It may indicate impaired kidney function if raised in the blood
Cytokines	Small protein molecules secreted by cells to communicate with neighbouring cells
Dendritic cells	A type of immune cell that act as a messenger between the innate and adaptive immune systems
Eosinophil	A cell of the immune system that combats parasite infections and is also involved in reactions to some drugs
Eosinophilia	Increased number of eosinophils in the blood
Erythrocytes	Red blood cells
Fumarates	Organic compounds widely found in nature that play a role in citric acid (Krebs) cycle
Gamma glutamyltransferase	An enzyme produced by many tissues, mainly the liver; if raised, it may indicate liver disease
Immunosuppressive	Reduction in the activity of the immune system
Inflammation	A protective response to injury mediated by cells of the immune system, characterised in the skin by redness, heat, swelling, and pain or itch
Innate immune system	Immune cells and proteins, such as complement, that fight infectious agents in a non-specific way
Leucocytes	White blood cells that are part of the immune system
Leukocytopenia	Decreased number of white blood cells
Locus	The position of a gene on a chromosome
Lymphocyte	A type of white blood cell involved in the adaptive immune system, which can be subdivided into T cells and B cells
Lymphocytopenia or lymphopenia	Decreased number of lymphocytes in the blood
Major histocompatibility complex	Cell surface molecules involved in recognition of pathogens and tolerance to an individual's own proteins
Platelet	A type of circulating blood cell that helps to form blood clots and stop bleeding (also called thrombocytes)

Table 1. Glossary *(Continued)*

Proteinuria	The presence of abnormal quantities of protein in the urine
Psoriasis Area and Severity Index (PASI)	A measure of psoriasis severity that includes the extent of body surface area involvement and the maximum thickness, redness, and scaliness of the plaques. Scores range from 0 to 72, and a higher score indicates more severe disease
Scaly	Silvery-white flakes of skin
Serum creatinine	The level of creatinine in the blood plasma
T (helper) cell	A type of white blood cell involved in the adaptive immune system
Thrombocytosis	Increased number of platelets in the blood
Transaminases	Enzymes normally found in the liver and heart, which may indicate liver or heart disease if raised in the blood
Triglycerides	A type of fat in the blood
Urinalysis	Urine analysis

APPENDICES

Appendix 1. Skin Group Specialised Register (CRS) search strategy

#1 ((psoriasis:MH OR psoria*) and (fumar* or dimethyl fumarate or fae or dmf or fumaderm)) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 2. CENTRAL (the Cochrane Library) search strategy

#1 MeSH descriptor: [Psoriasis] explode all trees
#2 psoria*
#3 #1 or #2
#4 MeSH descriptor: [Fumarates] explode all trees
#5 fumar* and esters
#6 dimethyl fumarate
#7 fae
#8 dmf
#9 fumarate*
#10 fumaderm
#11 {or #4-#10}
#12 #3 and #11

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Psoriasis/ or psoria$.mp.
2. exp Fumarates/
3. (fumar$ and esters).mp.
4. dimethylfumarate.mp.
5. fae.ti,ab.
6. dmf.ti,ab.
7. fumarate$1.ti,ab.
8. fumaderm.mp.
9. or/2-8
10. randomised controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.

14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animals/ not humans.sh.
19. 17 not 18
20. 1 and 9 and 19

Appendix 4. EMBASE (Ovid) search strategy

1. exp psoriasis vulgaris/ or exp guttate psoriasis/ or exp erythrodermic psoriasis/ or exp psoriasis/ or exp pustular psoriasis/
2. psoria$.ti,ab.
3. 1 or 2
4. exp fumaric acid derivative/ or exp fumaderm/ or exp fumaric acid ethyl ester/ or exp fumaric acid dimethyl ester/
5. (fumar$ and esters).mp.
6. dimethylfumarate.mp.
7. fae.ti,ab.
8. dmf.ti,ab.
9. fumarate$1.ti,ab.
10. or/4-9
11. crossover procedure.sh.
12. double-blind procedure.sh.
13. single-blind procedure.sh.
14. (crossover$ or cross over$).tw.
15. placebo$.tw.
16. (doubl$ adj blind$).tw.
17. allocat$.tw.
18. trial.ti.
19. randomised controlled trial.sh.
20. random$.tw.
21. or/11-20
22. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
23. human/ or normal human/
24. 22 and 23
25. 22 not 24
26. 21 not 25
27. 3 and 10 and 26

Appendix 5. LILACS search strategy

(fumar$ or dimethyl fumarate or fae or dmf or fumaderm) and psoria$

WHAT'S NEW

Date	Event	Description
3 February 2017	Amended	Published note added about oral fumaric acid esters for psoriasis and the risk of progressive multifocal leukoencephalopathy.

HISTORY

Protocol first published: Issue 4, 2013
Review first published: Issue 7, 2015

Date	Event	Description
16 November 2016	Amended	A search of MEDLINE and Embase in October 2016 found some studies, which would not change the conclusion of the review.

Date	Event	Description
		A relevant trial has been finished but not reported. Thus, an update has not been considered necessary at this time. Our Information Specialist will run a new search in November 2017 to reassess whether an update is needed.

CONTRIBUTIONS OF AUTHORS

JRI was the contact person with the editorial base.
AA co-ordinated contributions from the co-authors and wrote the final draft of the review.
AA and JRI screened papers against eligibility criteria.
AA obtained data on ongoing and unpublished studies.
AA, RA, and JRI appraised the quality of papers.
AA, RA, and JRI extracted data for the review and sought additional information about papers.
AA entered data into RevMan.
AA, MJK, TP, and JRI analysed and interpreted data.
JRI, AA, MJK, and TP worked on the methods sections.
JRI, AA, VP, and AB drafted the clinical sections of the background and responded to the clinical comments of the referees.
AA, MJK, TP, and JRI responded to the methodology and statistics comments of the referees.
JRI is the guarantor of the update.

Disclaimer

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Skin Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DECLARATIONS OF INTEREST

Ausama Atwan: nothing to declare.
John R Ingram: nothing to declare.
Rachel Abbott: nothing to declare.
Mark J Kelson: nothing to declare.
Timothy Pickles: nothing to declare.
Andrea Bauer: nothing to declare.
Vincent Piguet has received departmental support from AbbVie, Johnson & Johnson, Pfizer, GSK, Novartis, and CEO. He has received honoraria from Johnson & Johnson, Novartis, and AbbVie. None of these companies produce any of the interventions listed in this review. His department benefits financially from the Dermatology Life Quality Index.
Ben Carter, who was the statistics referee for this review, is based at the same institution as the lead author and contributed to their MSc basic statistics teaching programme.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Psoriasis and Psoriatic Arthritis Alliance (PAPAA), UK.

  Grant award
- The National Institute for Health Research (NIHR), UK.

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We had not planned to include 'Summary of findings' ('SoF') tables in our review at the time the protocol was published. However, following the Cochrane Skin Group's recommendations, we added these tables to summarise the outcomes of the two identified comparisons.

- Types of outcome measures: we "planned to undertake a priori subgroup analysis to investigate the influence of duration of treatment"; however, we were unable to do this because all of the included studies had medium duration.
- Measures of treatment effect: we changed our planned use of mean differences to either standardised or unstandardised mean differences to capture different scales used in the included studies. Also, we planned to analyse ordinal data from short outcome scales using the methods for dichotomous data, by combining relevant adjacent categories to form a dichotomy. We planned to treat longer outcome scales as continuous data. We were unable to carry out these plans because the included studies did not report short or long ordinal scales.
- Unit of analysis issues: we planned to permit the first phase of cross-over trials and pool the results with those from equivalent parallel group randomised controlled trials. For cluster randomised trials, we planned to deflate the sample size using the design effect reported. However, we were unable to carry out these plans because none of the included studies were cluster randomised trials or had a cross-over design.
- Dealing with missing data: we planned to explore the impact of missing data through sensitivity analyses. For missing dichotomous outcome data, we planned to conduct two sensitivity analyses in which we would assume all missing data to be either events or non-events. However, we were unable to carry out these plans because of the lack of original data.
- Assessment of heterogeneity: an I^2 statistic of between 40% and 75% may represent substantial heterogeneity (Higgins 2011), and we planned to explore the potential causes where possible for the primary outcome measures. However, we were unable to carry out these plans because there were no I^2 statistic values between 40% and 75%.
- Assessment of reporting biases: we planned to perform funnel plots and Egger's test for publication bias (Egger 1997) if 10 or more studies contributed data. However, we were unable to carry out these plans because of the low number of studies.
- Data synthesis: we did not plan in the protocol to deal with the Psoriasis Area and Severity Index (PASI) score as a continuous outcome but decided in the review that this was the best way to deal with this outcome.
- Subgroup analysis and investigation of heterogeneity: we planned to perform subgroup analyses on the variables listed but identified insufficient studies.
- Sensitivity analysis: we planned to perform sensitivity analysis for studies at higher risk of bias, determined by allocation concealment and blinding of outcome assessment. We planned to conduct two sensitivity analyses in which we assumed all missing data were to be either events or non-events. However, we were unable to carry out these plans because of an insufficient number of included studies where risk of bias was mostly unclear.

NOTES

A recent review has summarised seven cases of progressive multifocal leukoencephalopathy (PML) in psoriasis patients receiving oral fumaric acid esters (FAEs) to treat psoriasis (Balak 2016). PML is a brain infection caused by the John Cunningham virus. It causes symptoms such as weakness, difficulty with speech or co-ordination, or visual problems, and can be fatal. Most, but not all, cases were associated with prolonged low levels of one of the white blood cell types that fight infection, called lymphocytes. The risk of PML is very low in the context of the many thousands of psoriasis patients treated with oral FAE preparations. However, new recommendations require patients and their clinicians to check for any relevant symptoms and more frequent monitoring of lymphocyte counts.

A search of MEDLINE and Embase in October 2016 found some studies, which would not change the conclusion of the review. A relevant trial has been finished but not reported. Thus, an update has not been considered necessary at this time. Our Information Specialist will run a new search in November 2017 to re-assess whether an update is needed.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Arthritis, Psoriatic [drug therapy]; Dermatologic Agents [adverse effects] [therapeutic use]; Fumarates [*administration & dosage] [adverse effects]; Methotrexate [therapeutic use]; Psoriasis [*drug therapy]; Randomized Controlled Trials as Topic; Severity of Illness Index

MeSH check words

Humans