Accepted Date : 15-Feb-2016

Article type : Systematic Review

# Efficacy, effectiveness, and safety of fumaric acid esters in the treatment of psoriasis: a systematic review of randomized and observational studies

**Running head:**

Fumarates for psoriasis: a systematic review

**Authors:**

D.M.W. Balak[1], S. Fallah Arani[1], E. Hajdarbegovic[1], C.A.F. Hagemans[1], W.M. Bramer[2], H.B. Thio[1], H.A.M. Neumann[1]

**Affiliations:**

[1]Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands; [2]Medical Library, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.

**Conflicts of interest:**

There are no conflicts of interest.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.14500

**Funding sources:**

None

**Conflict of interest:**

None declared

**Key-words:** fumarates, Fumaderm, psoriasis area and severity index, systemic treatment, adverse events.

**Corresponding author:**

Deepak M.W. Balak

Department of Dermatology, Erasmus MC

Burg. s' Jacobsplein 51, 3015 CA, Rotterdam, the Netherlands

Tel: +31 10 7032063. Fax: +31 10 7035609.

Email address: d.balak@erasmusmc.nl or balak.dmw@gmail.com

**ABSTRACT**

**Background:** Fumaric acid esters (FAEs) are increasingly used as a systemic treatment for psoriasis, but there are still uncertainties on their suitability.

**Objectives:** to assess the evidence on efficacy and safety of FAEs in psoriasis treatment.

**Methods:** A systematic literature search in 7 databases up to August, 17th 2015. Inclusion criteria were studies reporting clinical effects of FAEs in psoriasis patients without restrictions in study design, language, or publication date. Methodological quality of randomized controlled trials (RCTs) and overall level of quality were assessed using the Cochrane risk of bias tool and the Grades of Recommendation, Assessment, Development and Evaluation approach, respectively.

**Results:** Sixty-eight articles were included. There were 7 RCTs (total 449 patients) that had an unclear risk of bias and were too clinically heterogeneous to allow a meta-analysis. Overall, mean psoriasis area and severity index decreased with 42-65% following 12-16 weeks of treatment. There were 37 observational studies (total 3457 patients) that supported the RCT findings, but most were uncontrolled with a high risk of bias. Commonly reported adverse events were gastro-intestinal complaints and flushing, leading to treatment withdrawal in 6-40%. Rare adverse events were renal Fanconi syndrome and progressive multifocal leukoencephalopathy. There was a lack of studies on long-term and comparisons to other treatments.

**Conclusions:** There is low-quality evidence to recommend the use of oral FAEs as treatment for plaque psoriasis in adult patients. Studies focusing on long-term safety and comparison to systemic psoriasis treatments could lead to a better positioning of FAEs as psoriasis treatment.

**What's already known about this topic?**

- The introduction of fumaric acid esters as psoriasis treatment has not been based on high-quality evidence stemming from well-performed randomized controlled trials.
- Fumaric acid esters are licensed in Germany. Outside of Germany, the use of fumaric acid esters in psoriasis has been unlicensed and limited.

**What does this study add?**

- This systemic review provides a comprehensive summary and appraisal of available studies that reported clinical effects of fumaric acid esters in psoriasis patients.
- There was low-quality evidence with unclear and high-risk studies reporting favourable efficacy and tolerability of FAEs; long-term and comparative studies were lacking.

## INTRODUCTION

Fumaric acid esters (FAEs) are small molecules that have immunomodulating properties.[1] Oral FAEs have been used to treat psoriasis for 5 decades. There is a long-standing tradition in Germany and the Netherlands to treat psoriasis patients with FAEs as a first-line systemic treatment.[2,3] In other countries such as the U.K., FAEs are increasingly reported as treatment for psoriasis.[4,5] Globally, FAEs are limited in

availability and unlicensed for the treatment of psoriasis, primarily due to a lack of a high-quality evidence-based development with well-performed randomized controlled trials. The development of FAEs was mostly done empirical.

FAEs were introduced in 1959 as potential anti-psoriatic drugs by the German chemist Schweckendiek, who in several self-experiments reported improvement of psoriasis using different FAEs.[6] In the following two decades, FAEs were empirically developed further with favourable treatment effects.[7-10] However, initial dermatology-based observations on FAEs treatment showed variable improvements and concerns on safety.[11-13] Hence, for a long time FAEs were regarded as a controversial psoriasis treatment.[14]

In the mid-1980s, there was a revival of interest in FAEs as potential psoriasis drug, which was partly driven by requests from patients associations.[15-17] The first randomized, double-blind, placebo-controlled trials were published in the early 1990s.[18,19] Subsequently, FAEs became approved by German regulatory agencies in 1994 for the treatment of severe psoriasis and in 2011 for moderate psoriasis. The licensed FAE-formulation (Fumaderm) is a mixture of dimethylfumarate (DMF) and lesser concentrations of monoethylfumarate (MEF)-salts.[20]

The mechanisms of action of FAEs are not completely understood. DMF is considered the most active FAE and thought to improve psoriasis via various immunomodulating, antiproliferative, and anti-angiogenic effects.[21-24] Of importance, DMF is a pro-drug. The metabolites monomethylfumarate (MMF) and S-(1,2-dimethoxycarbonylethyl)glutathione (GS-DMS) are the in vivo moieties; MMF is the bioactive metabolite.[25,26]

Currently, FAEs are one of the most commonly prescribed treatments for psoriasis in Germany.[27] In other European countries, such as the Netherlands and the U.K, FAEs are increasingly in use for psoriasis treatment albeit as a unlicensed drug. In the U.K., FAEs are considered a second-line systemic therapy for psoriasis.[28] The 2009 European S3-guidelines recommended FAEs as systemic treatment for plaque psoriasis, but no consensus was reached for a recommendation as a maintenance treatment.[29] In the 2015 update of the European S3-guidelines, FAEs are recommended for the long-term treatment of psoriasis, but the recommendation is based on expert opinion only.[30] Hence, there are uncertainties on the suitability of FAEs as a psoriasis treatment.

In this systematic review, we aimed to comprehensively summarize and critically appraise the evidence on the efficacy, effectiveness, and safety of oral FAEs treatment in patients with psoriasis.

## METHODS

### Literature search strategy

The databases Embase.com, Medline (Ovid), Cochrane central registry of trials (CENTRAL), Web-of-Science, Scopus, PubMed (the subset as supplied by publisher, containing non-indexed citations), and Google scholar were searched from inception to August, 17th 2015. The searches, conducted by an experienced biomedical information specialist (WB), combined multiple thesaurus terms and words in title/abstract for FAEs with terms for psoriasis. Details of the search strategy are summarized in Appendix 1.

**Selection criteria**

Articles were screened for relevance according to the title and abstract. Remaining articles were assessed full text. Eligible for inclusion were articles describing clinical effects (i.e. efficacy, effectiveness, and/or safety outcomes) of oral FAEs in psoriasis treatment. To obtain a complete overview as much as possible, we did not apply restrictions for publication date, study design, or publication language.

**Data extraction**

Using a pre-defined data form, we extracted data on study design, study setting, sample size, study analyses, FAE formulation and dosage, efficacy or effectiveness outcomes, and safety outcomes.

**Quality assessment**

The methodological quality of RCTs and observational studies was assessed using the Cochrane risk of bias tool and the risk of bias assessment tool for nonrandomized studies (RoBANS), respectively.[31,32] Overall level of quality of evidence was assessed according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[33]

**Outcomes and data analysis**

We aimed to compare treatment effects of FAEs versus placebo, FAEs versus other systemic treatments, different FAEs formulations, and different FAEs dosage levels. In addition, we looked at treatment effects of FAEs in combination with other psoriasis treatments.

The efficacy and effectiveness outcomes of interest were changes in psoriasis disease activity as measured by psoriasis area and severity index (PASI), body surface affected (BSA), or global psoriasis assessments. Additional outcomes included changes in arthritis, nail symptoms, and health-related quality of life.

The safety outcomes included proportions of patients reported with serious adverse events, subjective adverse events, laboratory abnormalities, and adverse events requiring withdrawal of treatment.

We classified observational studies that assessed FAEs treatment 12 months or longer into long-term studies.

Two researchers (DB and CH) independently assessed articles for eligibility for inclusion, extracted data, and evaluated methodological quality. Any disagreements were resolved by consensus.

Descriptive statistics were used to analyse data. Reporting of findings was in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[34] A pre-defined review protocol was used, but not registered beforehand.

## RESULTS

### Literature search

The literature search yielded 2515 hits, of which 275 articles were assessed full-text. Sixty-eight articles were included (See Figure 1).

### RCTs on FAEs treatment for psoriasis

*Characteristics of RCTs*

There were 7 RCTs found, published in the period 1990-2014.[18,19,35-38] Of these, three trials compared FAEs to placebo, one trial compared two different FAEs-formulations to placebo, one trial compared FAEs to methotrexate, one trial compared the combination of FAEs with topical calcipotriol to FAEs monotherapy, and the most recent trial compared FAEs plus an oral histamine antagonist to FAEs monotherapy. Two RCTs from the Netherlands were published additionally in an extended version in a Dutch journal.[39,40] The characteristics of study design and study population of each RCT are summarized in Table 1 and Supplement Table 1.

The sample sizes of the RCTs were relatively small, ranging from 27 to 134 patients. Overall, 449 patients were included. The majority of the RCTs included patients with chronic plaque psoriasis. One RCT enrolled patients with psoriatic arthritis.[41] All included patients were aged 18 years or older. There was considerable clinical heterogeneity among the RCTs in the efficacy outcomes, time of efficacy assessment, and used FAE formulations. Frequently used efficacy outcomes were changes in PASI or in BSA. The treatment duration was relatively short, ranging from 2.8 to 4 months. There were differences in the evaluated FAEs-formulations. Most

RCT's applied the standardized incremental dosage regimen up to FAEs 215 mg six times a day (equals 720 mg DMF). The study of Nieboer[18] used a different dosage regimen up to FAEs 215 mg four times a day (equals 480 mg DMF).

*Methodological quality assessment of RCTs*

Assessment of the methodological quality of the RCTs using the Cochrane risk of bias tool yielded an unclear risk of bias, often due to insufficient reporting (See Supplement Table 2). The overall level of quality of the included RCTs in the GRADE approach was therefore downgraded to moderate.

*Efficacy outcomes reported in RCTs*

Due to significant clinical heterogeneity and the small number of RCTs available (n = 7), we decided not to pool the efficacy data in a meta-analysis. All RCTs reported statistically significant efficacy results for FAEs. Overall, mean PASI decreased with 42-65% following 12-16 weeks of treatment. The efficacy results are summarized in Table 1 (See also Supplement Table 3).

All placebo-controlled RCTs reported statistically significant improvement in psoriasis severity by FAEs compared to placebo.[19,35] The placebo-controlled RCT in psoriatic arthritis found significant improvement in skin lesions, but only modest improvement in arthritis.[41] Only one RCT reported improvements in health-related quality of life following FAEs-treatment.[38]

The only head-to-head RCT compared FAEs to methotrexate and reported similar efficacy results following 16 weeks of treatment.[36] A RCT directly comparing a FAEs-formulation containing DMF and MEF to a DMF-formulation reported equal short-term efficacy.[18]

Addition of a topical vitamin D analogue calcipotriol resulted in greater and faster improvement of psoriasis severity compared to FAEs-treatment alone.[37] In contrast, addition of an oral histamine-1 receptor antagonist cetirizine did not increase the efficacy of FAEs.[38]

*Safety outcomes in RCTs*

FAEs treatment was not associated with an increased risk of serious or severe adverse events. There was only one serious adverse event reported: adnexitis in a subject that received FAEs and calcipotriol, which was rated as unlikely related to study medication.[37] The proportion of patients with AEs was relatively high, ranging from 69% to 92% (See Table 1). The most commonly reported AEs were gastrointestinal complaints (up to 100%) and flushing (up to 92%) (See Supplement Table 3). Common reported laboratory abnormalities included elevated liver enzymes (up to 62%), eosinophilia (up to 46%), and lymphocytopenia (up to 38%), but rarely resulted in treatment discontinuation. Definitions and grading of laboratory abnormalities were not reported in the individual studies. There was one case of reversible renal insufficiency reported.[39] Eight to 39% of patients discontinued FAEs treatment due to adverse events, mostly due to intolerable gastrointestinal or flushing complaints.

## Observational studies on FAEs treatment for psoriasis

*Characteristics of observational studies*

There were 37 observational studies included from the period 1987-2015 with a total of 3457 patients. There was considerable clinical heterogeneity in FAEs formulations and treatment duration. The characteristics of the included observational studies are summarized in Table 2 and Supplement Table 4. The majority (73%) of these studies were open-label, single-centre, cohort studies that were often uncontrolled. There were 2 cross-sectional studies[42,43], the rest of the observational studies were case series (n=8). The majority of studies included patients with moderate to severe plaque psoriasis. Two studies evaluated FAEs in mild cases of plaque psoriasis. In some studies small number of patients with subtypes other than plaque psoriasis were included, such as guttate or palmoplantar pustular psoriasis. Almost all studies involved adult patients, except for 2 studies that included paediatric psoriasis patients.[44,45] Sample sizes ranged from 6 to 984. The treatment duration ranged from 1 month to 14 years. There were 18 studies which described long-term FAEs treatment from 1 year up to 14 years. Most studies assessed Fumaderm with the recommended dosage schedule. There was variation in the used effectiveness outcomes. PASI, PGA, and global psoriasis severity assessments were used.

*Quality assessment of observational studies*

Most of the observational studies were retrospective and uncontrolled single-centre studies with a high or unclear risk of bias (See Supplement Table 5). Following the GRADE approach, there were insufficient grounds to upgrade the quality of evidence. Hence, the overall level of quality using GRADE was evaluated as a very low quality of evidence.

*Effectiveness in observational studies*

The effectiveness data are summarized in Table 2 and Supplement Table 6. There was a wide range in reported effectiveness outcomes. Overall, mean reductions in PASI ranged from 13% to 86% following 3-4 months of treatment. Reported PASI-75 responses ranged from 8% to 33%. One retrospective, single-centre cohort study reported a drug survival of FAEs of 60% after 4 years of treatment.[46] Several studies reported improvements in patient-reported quality of life.[47-49] There were anecdotal data on combination treatment with other systemic treatments.[50,51] One registry-study from Austria found similar effectiveness of FAEs and methotrexate.[52]

Two small retrospective case series from the Netherlands and Germany assessed the effects of FAEs in children with psoriasis.[44,45] The effectiveness results of FAEs were in line with results reported in adult patients.

*Safety outcomes in observational studies*

No deaths or serious adverse events were reported in the observational studies. The adverse events profile was in general similar among the studies. The most commonly reported adverse events were gastrointestinal complaints and flushing (See Table 3 and Supplement Table 6). Commonly reported laboratory abnormalities included lymphocytopenia, elevated liver enzymes, and eosinophilia.

Forty-five to 87% of patients had experienced an adverse event. The proportion of patients discontinuing FAEs treatment due to adverse events ranged from 6% to 47%. The most common cause for early treatment discontinuation was intolerable gastrointestinal symptoms and, to a lesser extent, severe flushing symptoms. There were few reported treatment discontinuations due to laboratory abnormalities.

There were few studies that specifically evaluated long-term treatment with FAEs. The available data indicated no increased risk for infections, malignancies, or other serious adverse events associated with long-term FAE treatment. In a small, retrospective single centre study among patients treated with FAE continuously for up to 10 to 14 years, no serious adverse events or malignancies were observed.[53] Similar safety results were reported in a large, German study among nearly 1000 patients treated with FAE for a mean duration of 3.5 years.[42]

*Case reports on adverse events of FAEs*

Twenty-four case reports described adverse events associated with FAEs treatment (See Table 6). Of these, several involved immunosuppressive events linked to FAEs-induced lymphocytopenia: Kaposi sarcoma[54], organizing pneumonia[55], tuberculous lymphadenitis[56], squamous cell carcinoma[57], melanoma[58], and progressive multifocal leukoencephalopathy (PML).[59-65] There have been 7 cases published of PML. In most cases the development of PML was linked to exposure to severe low lymphocyte counts for prolonged periods of time. However, there was one case of PML linked to moderate lymphocytopenia.[65]

Furthermore, there were several renal adverse events reported: six cases of a drug-induced Fanconi syndrome linked to FAEs.[66-71] Fanconi syndrome is characterized by proximal renal tubular dysfunction and can lead to proteinuria, glycosuria, and low serum levels of phosphate. Furthermore, there were 9 cases of acute renal insufficiency linked to FAEs. These cases of acute renal insufficiency were all reported in the 1990s and involved uncontrolled use of oral and topical FAEs.

Lastly, there was one case reported of collagenous colitis during FAEs treatment, which may be associated with a FAE-induced T helper 2 immune response.[72]

## DISCUSSION

FAEs have a long history as a systemic psoriasis treatment, but their development was not based on high-quality evidence. Here, we assessed studies on efficacy and safety of FAEs in psoriasis treatment. The available evidence was limited with 7 RCTs with relatively small sample sizes and an unclear risk of bias. Overall, mean PASI decreased

with 42-65% following 12-16 weeks of treatment. The number of observational studies (n=37) was much larger, but the majority were uncontrolled and with a high risk of bias. The safety profile of FAEs was well-characterized. Intolerable gastrointestinal complaints and flushing led to early treatment withdrawal in 6-40%. Lymphocytopenia, eosinophilia, increased liver enzymes, and proteinuria were commonly observed, but rarely resulted in FAEs discontinuation. Studies with long-term data were lacking.

To appreciate our results, several aspects of this systematic review need to be considered. Strengths of our study include the extensive literature search involving multiple bibliographic databases and the fact that we did not exclude specific study types or publication dates, making this the largest systematic review on FAEs in psoriasis to date. In addition, we included articles written in languages other than English, thereby decreasing language bias. Furthermore, quality of the included studies was critically evaluated using the GRADE approach. A limitation was that most included studies were open-label and uncontrolled studies with a low level of evidence. Moreover, due to considerable clinical heterogeneity among the studies, a meta-analysis was not possible. Furthermore, the majority of the RCTs from the 1990s did not adhere to reporting guidelines that are now considered standard (e.g. CONSORT guidelines).[73] Moreover, there was a lack of standardization of efficacy outcomes across the RCTs.

A recent Cochrane review of the effects of FAEs in psoriasis could not perform a meta-analysis because of incomplete and heterogeneous reporting of outcomes.[74] Several previous studies did apply a meta-analysis on a limited number of studies. These meta-analyses reported similar efficacy of FAEs to methotrexate[75], superior

efficacy of FAEs compared to the biologic efalizumab[76], and significant differences of FAEs compared to placebo.[77]

Most studies assessed the FAE-formulation Fumaderm that has had German marketing authorisation since 1994. The choice of the components of Fumaderm (i.e. DMF and MEF-salts) was not based on rational pharmacological studies. Recent preclinical studies suggest that DMF is the most active FAEs with anti-psoriatic effects.[78,79] In particular, DMF is a pro-drug for which MMF is the bioactive metabolite.[20] Two small studies from the 1990s compared a FAEs-formulation containing DMF plus MEF to a DMF-formulation and found no statistically significant differences.[18,80] However, these studies applied different dosage schedules and did not use validated efficacy outcomes. Consequently, clear conclusions cannot be made on the results of these results. A novel DMF-formulation BG-12 was assessed in several psoriasis RCTs[81], but these studies have yet to be published. The BG12-formulation later became approved for treatment of multiple sclerosis by the FDA in 2013.[82,83] Several novel FAEs-formulations are now in development, e.g. a MMF-linker formulation and a DMF-formulation (Clinicaltrials.gov, numbers NCT02173301 and NCT01230138, respectively).

Since the mid-1990s, FAEs are increasingly being used and regarded as a systemic treatment with a favourable risk-benefit ratio. FAEs have several advantages. FAEs seem suitable for psoriasis patients with co-morbidity. Also, there are no known drug-interactions. Also, FAEs appear to have no increased risk of significant immunosuppressive adverse events, in contrast to other systemic classical treatments.[84] Although lymphocytopenia is relatively frequently observed during FAEs

treatment in about 50% of patients, in most cases the lymphocyte reductions are mild.[30] A small proportion of patients of circa 3% has a severe lymphocytopenia during FAEs treatment.[30] FAEs-induced lymphocytopenia does not seem to cause significant immunosuppression as long as lymphocyte-counts are closely monitored according to the guidelines.[85] FAE dosage reduction is recommended in case of lymphocyte-counts below 700 per cubic mm and direct FAE discontinuation is recommended in case of lymphocyte-counts below 500 per cubic mm.[29,30] The occurrence of opportunistic infections during FAEs treatment was linked to exposure to prolonged severe lymphocytopenia or to other known risk factors.

It is noted that the experience of FAEs as psoriasis treatment is larger than the published data.[86] It is interesting to compare the level of evidence of FAEs to that of methotrexate. Methotrexate is globally the most commonly used classical systemic treatment for psoriasis.[87] The available evidence, however, is limited even though methotrexate is in use since 1958.[29] Results from a RCT and a registry-based observational study indicated that methotrexate and FAEs have similar clinical improvements in short-term treatment.[36,52] Excluding methotrexate, FAEs have not been compared head-to-head to other systemic psoriasis treatments. Such comparative studies are needed to better define the position of FAEs as psoriasis treatment.[4]

In conclusion, FAEs are considered to be suitable as a systemic treatment for moderate to severe plaque psoriasis, but the quality of the available evidence is low. Future studies could focus to optimize FAEs-formulations and to compare FAEs to other systemic treatments in order to better define the position of FAEs in the landscape of psoriasis treatment.

## REFERENCES


1 Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends Mol Med* 2005; 11: 43-8.

2 Mrowietz U, Rostami-Yazdi M, Neureither M et al. [15 years of fumaderm: fumaric acid esters for the systemic treatment of moderately severe and severe psoriasis vulgaris] 15 Jahre Fumaderm: Fumarsaureester fur die systemische Behandlung der mittelschweren und schweren Psoriasis vulgaris. *J Dtsch Dermatol Ges* 2009; 7 Suppl 2: S3-16.

3 Fallah Arani S, Balak DM, Neumann HA et al. Treatment of psoriasis with non-registered fumaric acid esters in The Netherlands: a nationwide survey among Dutch dermatologists. *J Eur Acad Dermatol Venereol* 2014; 28: 972-5.

4 Anstey AV. Fumaric acid esters in the treatment of psoriasis. *Br J Dermatol* 2010; 162: 237-8.

5 Iskandar IY, Ashcroft DM, Warren RB et al. Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. *Br J Dermatol* 2015;Aug;173(2):510-8

6 Schweckendiek W. [Treatment of psoriasis vulgaris] Heilung von Psoriasis vulgaris. *Med Monatsschr* 1959; 13: 103-4.

7 Schweckendiek W. Behandlung von Psoriasis mit lipoidloslichen Fumarsaureverbindungen. *Medizin Heute* 1966; 15: 219-20.

8 Schäfer G, Schweckendiek W. Dem Problem Psoriasis auf der Spur. *Arztl. Prax.* 1971; 18: 1034.

9 Kunst L. Psoriasis behandeling. *Ned Tijdschr Int Geneesknd* 1985; 7: 24-9.

10 Schafer G. Fumarsaure lindert die schuppenflechte. *Selecta* 1984; 15: 1260-1.

11 Vonkennel J, Zingsheim M. [Is a therapy of psoriasis through intermediate metabolism possible?]. *Med Welt* 1961; 34: 1697-701.

12 Dubiel W, Happle R. [Experimental treatment with fumaric acid monoethylester in psoriasis vulgaris] Behandlungsversuch mit Fumarsauremonoathylester bei Psoriasis vulgaris. *Z Haut Geschlechtskr* 1972; 47: 545-50.

13 Roodnat JI, Christiaans MHL, Nugteren-Huying WM et al. Acute renal failure in patients treated for psoriasis with fumaric acid esters. *NED TIJDSCHR GENEESKD* 1989; 133: 2623-6.

14 Raab W. [Psoriasis therapy with fumaric acid and fumaric acid esters] Psoriasis-Behandlung mit Fumarsaure und Fumarsaureestern. *Z Hautkr* 1984; 59: 671-9.

15 van Dijk E. [Fumaric acid in the treatment of patients with psoriasis] Fumaarzuur voor de behandeling van patienten met psoriasis. *Ned Tijdschr Geneeskd* 1985; 129: 485-6.

16 Bayard W, Hunziker T, Krebs A et al. [Peroral long-term treatment of psoriasis using fumaric acid derivatives] Perorale Langzeitbehandlung der Psoriasis mit Fumarsaurederivaten. *Hautarzt* 1987; 38: 279-85.

17 Nieboer C, de Hoop D, van Loenen AC et al. Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. *J Am Acad Dermatol* 1989; 20: 601-8.

18 Nieboer C, de Hoop D, Langendijk PN et al. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. *Dermatologica* 1990; 181: 33-7.

19 Altmeyer PJ, Matthes U, Pawlak F et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 1994; 30: 977-81.

20 Rostami Yazdi M, Mrowietz U. Fumaric acid esters. *Clin Dermatol* 2008; 26: 522-6.
21 Ghoreschi K, Bruck J, Kellerer C et al. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. *J Exp Med* 2011; 208: 2291-303.
22 Onderdijk AJ, Balak DM, Baerveldt EM et al. Regulated genes in psoriatic skin during treatment with fumaric acid esters. *Br J Dermatol* 2014; 171: 732-41.
23 Helwa I, Patel R, Karempelis P et al. The antipsoriatic agent monomethylfumarate has antiproliferative, prodifferentiative, and anti-inflammatory effects on keratinocytes. *J Pharmacol Exp Ther* 2015; 352: 90-7.
24 Garcia-Caballero M, Mari-Beffa M, Medina MA et al. Dimethylfumarate inhibits angiogenesis in vitro and in vivo: a possible role for its antipsoriatic effect? *J Invest Dermatol* 2011; 131: 1347-55.
25 Litjens NH, van Strijen E, van Gulpen C et al. In vitro pharmacokinetics of anti-psoriatic fumaric acid esters. *BMC Pharmacol* 2004; 4: 22.
26 Rostami-Yazdi M, Clement B, Mrowietz U. Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. *Arch Dermatol Res* 2010; 302: 531-8.
27 Augustin M, Spehr C, Radtke MA et al. German psoriasis registry PsoBest: Objectives, methodology and baseline data. *JDDG J German Soc Dermatol* 2014; 12: 48-57.
28 Jabbar-Lopez ZK, Wu KC, Reynolds NJ. Newer agents for psoriasis in adults. *BMJ* 2014; 349: g4026.
29 Pathirana D, Ormerod AD, Saiag P et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; 23 Suppl 2: 1-70.
30 Nast A, Gisondi P, Ormerod AD et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris - Update 2015 - Short version - EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015; 29: 2277-94.
31 Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org* 2011.
32 Kim SY, Park JE, Lee YJ et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 2013; 66: 408-14.
33 Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924-6.
34 Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
35 Nugteren-Huying WM, Van der Schroeff JG, Hermans J et al. Fumaric acid therapy for psoriasis: A randomized, double-blind, placebo-controlled study. *J AM ACAD DERMATOL* 1990; 22: 311-2.
36 Fallah Arani S, Neumann H, Hop WCJ et al. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: A multicentre prospective randomized controlled clinical trial. *Br J Dermatol* 2011; 164: 855-61.
37 Gollnick H, Altmeyer P, Kaufmann R et al. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. *Dermatology* 2002; 205: 46-53.
38 Balak DM, Fallah-Arani S, Venema CM et al. Addition of an oral histamine antagonist to reduce adverse events associated with fumaric acid esters in the treatment of psoriasis: A randomized double-blind placebo-controlled trial. *Br J Dermatol* 2014; Mar;172(3):754-9
39 Nugteren-Huying WM, Schroeff JG, Hermans J et al. [Fumaric acid therapy in psoriasis; a double-blind, placebo-controlled study]. *Nederlands tijdschrift voor geneeskunde* 1990; 134: 2387-91.

40 Peeters AJ, Dijkmans BAC, Van Der Schroeff JG. Favourable effect of fumaric acid treatment in psoriatic arthritis: A double-blind placebo-controlled study. *NED TIJDSCHR GENEESKD* 1992; 136: 2428-31.

41 Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. *Br J Rheumatol* 1992; 31: 502-4.

42 Reich K, Thaci D, Mrowietz U et al. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis - A retrospective study (FUTURE). *JDDG J German Soc Dermatol* 2009; 7: 603-11.

43 Thaci D, Weisenseel P, Philipp S et al. Efficacy and safety of fumaric acid esters in patients with psoriasis on medication for comorbid conditions - A retrospective evaluation (FACTS). *JDDG J German Soc Dermatol* 2013; 11: 429-36.

44 Balak DMW, Oostveen AM, Bousema MT et al. Effectiveness and safety of fumaric acid esters in children with psoriasis: A retrospective analysis of 14 patients from the Netherlands. *Br J Dermatol* 2013; 168: 1343-7.

45 Steinz K, Gerdes S, Domm S et al. Systemic Treatment with Fumaric Acid Esters in Six Paediatric Patients with Psoriasis in a Psoriasis Centre. *Dermatology* 2014.

46 Ismail N, Collins P, Rogers S et al. Drug survival of fumaric acid esters for psoriasis: A retrospective study. *Br J Dermatol* 2014; 171: 397-402.

47 Wain EM, Darling MI, Pleass RD et al. Treatment of severe, recalcitrant, chronic plaque psoriasis with fumaric acid esters: A prospective study. *Br J Dermatol* 2010; 162: 427-34.

48 Walker F, Adamczyk A, Kellerer C et al. Fumaderm in daily practice for psoriasis: dosing, efficacy and quality of life. *Br J Dermatol* 2014.

49 Schmieder A, Poppe M, Hametner C et al. Impact of fumaric acid esters on cardiovascular risk factors and depression in psoriasis: a prospective pilot study. *Arch Dermatol Res* 2015; 307: 413-24.

50 Balasubramaniam P, Stevenson O, Berth-Jones J. Fumaric acid esters in severe psoriasis, including experience of use in combination with other systemic modalities. *Br J Dermatol* 2004; 150: 741-6.

51 Wilsmann-Theis D, Frambach Y, Philipp S et al. Systemic antipsoriatic combination therapy with fumaric acid esters for plaque-type psoriasis: report on 17 cases. *Dermatology* 2015; 230: 119-27.

52 Inzinger M, Weger W, Heschl B et al. Methotrexate vs. fumaric acid esters in moderate-to-severe chronic plaque psoriasis: Data registry report on the efficacy under daily life conditions. *J Eur Acad Dermatol Venereol* 2013; 27: 861-6.

53 Hoefnagel JJ, Thio HB, Willemze R et al. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; 149: 363-9.

54 Philipp S, Kokolakis G, Hund M et al. Immunological changes in psoriasis patients under long-term treatment with fumaric acid esters: Risk of Kaposi sarcoma occurrence? *Eur J Dermatol* 2013; 23: 339-43.

55 Deegan AP, Kirby B, Rogers S et al. Organising pneumonia associated with fumaric acid ester treatment for psoriasis. *Clin Respir J* 2010; 4: 248-51.

56 Ahmad K, McDonnell TJ, Rogers S. Does prior treatment with fumaric acid esters predispose to tuberculosis in patients on etanercept? [8]. *Clin Exp Dermatol* 2007; 32: 329.

57 Jennings L, Murphy GM. Squamous cell carcinoma as a complication of fumaric acid ester immunosuppression. *J Eur Acad Dermatol Venereol* 2009; 23: 1451.

58 Barth D, Simon JC, Wetzig T. Malignant melanoma during treatment with fumaric acid esters - Coincidence or treatment-related? *JDDG J German Soc Dermatol* 2011; 9: 223-5.

59 Ermis U, Weis J, Schulz JB. PML in a patient treated with fumaric acid. *New Engl J Med* 2013; 368: 1657-8.

60 Van Oosten BW, Killestein J, Barkhof F et al. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. *New Engl J Med* 2013; 368: 1658-9.

61 Stoppe M, Thoma E, Liebert UG et al. Cerebellar manifestation of PML under fumarate and after efalizumab treatment of psoriasis. *J Neurol* 2014; 261: 1021-4.

62 Bartsch T, Rempe T, Wrede A et al. Progressive neurologic dysfunction in a psoriasis patient treated with dimethyl fumarate. *Ann Neurol* 2015; Oct;78(4):501-14

63 Dammeier N, Schubert V, Hauser TK et al. Case report of a patient with progressive multifocal leukoencephalopathy under treatment with dimethyl fumarate. *BMC Neurol* 2015.

64 Hoepner R, Faissner S, Klasing A et al. Progressive multifocal leukoencephalopathy during fumarate monotherapy of psoriasis. *Neurol Neuroimmunol Neuroinflamm* 2015; 2: e85.

65 Nieuwkamp DJ, Murk JL, Van Oosten BW. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. *New Engl J Med* 2015; 372: 1474-6.

66 Fliegner L, Spiegel P. Osteomalacia as an obviously rare secondary effect of oral fumaric acid therapy. *HAUTARZT* 1992; 43: 554-60.

67 Haviv YS, Zimmerman M, Berkman N et al. Fumaric acid ester-induced diffuse renal tubular injury presenting as Fanconi syndrome and osteomalacia. *Clin Drug Invest* 1999; 17: 333-5.

68 Raschka C, Koch HJ. Longterm treatment of psoriasis using fumaric acid preparations can be associated with severe proximal tubular damage. *Hum Exp Toxicol* 1999; 18: 738-9.

69 Schilling F, Schopf RE. Adult Debre-de Toni-Fanconi syndrome with osteomalacia, acquired through long-term psoriasis therapy with fumaric acid ester - And a contribution to malacic osteoarthropathy. *Aktuel Rheumatol* 1999; 24: 174-9.

70 Warzecha J, Runck A, Priepke E et al. Multiple pathological fractures in acquired Fanconi's syndrome after treatment of psoriasis with fumaric acid. *Unfallchirurg* 2001; 104: 448-51.

71 Reid C, Holian J, Kane D et al. De Toni-Fanconi syndrome secondary to fumaric acid esters. *Br J Dermatol* 2013; 169: 24.

72 Hoffmann K, Casetti F, Venzke T et al. Collagenous colitis during treatment with fumaric acid esters. *J Dtsch Dermatol Ges* 2014; 12: 1138-40.

73 Schulz KF, Altman DG, Moher D et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340: c332.

74 Atwan A, Ingram JR, Abbott R et al. Oral fumaric acid esters for psoriasis. *Cochrane Database Syst Rev* 2015; 8: CD010497.

75 Schmitt J, Zhang Z, Wozel G et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol* 2008; 159: 513-26.

76 Schmitt J, Rosumeck S, Thomaschewski G et al. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol* 2014; 170: 274-303.

77 Griffiths CE, Clark CM, Chalmers RJ et al. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; 4: 1-125.

78 Treumer F, Zhu K, Glaser R et al. Dimethylfumarate is a potent inducer of apoptosis in human T cells. *J Invest Dermatol* 2003; 121: 1383-8.

79 Lehmann JC, Listopad JJ, Rentzsch CU et al. Dimethylfumarate induces immunosuppression via glutathione depletion and subsequent induction of heme oxygenase 1. *J Invest Dermatol* 2007; 127: 835-45.

80 Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: Results and side effects of 2 years of treatment. *J AM ACAD DERMATOL* 1992; 27: 769-71.

81 **BG 12: BG 00012, BG 12/Oral Fumarate, FAG-201, second-generation fumarate derivative--Fumapharm/Biogen Idec. *Drugs R D* 2005; 6: 229-30.**

82 **Gold R, Kappos L, Arnold DL et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; 367: 1098-107.**

83 **Fox RJ, Miller DH, Phillips JT et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; 367: 1087-97.**

84 **Naldi L, Griffiths CE. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. *Br J Dermatol* 2005; 152: 597-615.**

85 **Mrowietz U, Reich K. Case reports of PML in patients treated for psoriasis. *N Engl J Med* 2013; 369: 1080-1.**

86 **Nast A, Boehncke WH, Mrowietz U et al. German S3-guidelines on the treatment of psoriasis vulgaris (short version). *Arch Dermatol Res* 2012; 304: 87-113.**

87 **Dogra S, Mahajan R. Systemic methotrexate therapy for psoriasis: past, present and future. *Clin Exp Dermatol* 2013; 38: 573-88.**

88 **Lijnen R, Otters E, Balak D et al. Long-term safety and effectiveness of high-dose dimethylfumarate in the treatment of moderate to severe psoriasis: a prospective single-blinded follow-up study. *J Dermatolog Treat* 2015: 1-6.**

89 **Brewer L, Rogers S. Fumaric acid esters in the management of severe psoriasis. *Clin Exp Dermatol* 2007; 32: 246-9.**

90 **Carboni I, De Felice C, De Simoni I et al. Fumaric acid esters in the treatment of psoriasis: An Italian experience. *J Dermatol Treat* 2004; 15: 23-6.**

91 **Litjens NHR, Nibbering PH, Barrois AJ et al. Beneficial effects of fumarate therapy in psoriasis vulgaris patients coincide with downregulation of type 1 cytokines. *Br J Dermatol* 2003; 148: 444-51.**

92 **Boesken WH, Oser B, Roth J et al. Nephrotoxic effects of fumaric acid therapy of psoriasis. *Nieren- Hochdruckkr* 1998; 27: 145-50.**

93 **Thio HB, Van Der Schroeff JG, Nugteren-Huying WM et al. Long-term systemic therapy with dimethylfumarate and monoethylfumarate (Fumaderm) in psoriasis. *J EUR ACAD DERMATOL VENEREOL* 1995; 4: 35-40.**

94 **Gambichler T, Kreuter A, Susok L et al. Glutathione-S-transferase T1 genotyping and phenotyping in psoriasis patients receiving treatment with oral fumaric acid esters. *J Eur Acad Dermatol Venereol* 2014; 28: 574-80.**

95 **Heelan K, Markham T. Fumaric acid esters as a suitable first-line treatment for severe psoriasis: An Irish experience. *Clin Exp Dermatol* 2012; 37: 793-5.**

96 **Gambichler T, Bechara FG, Scola N et al. Serum levels of antimicrobial peptides and proteins do not correlate with psoriasis severity and are increased after treatment with fumaric acid esters. *Arch Dermatol Res* 2012; 304: 471-4.**

97 **Gambichler T, Scola N, Rotterdam S et al. Monitoring peripheral blood CD4+ intracellular adenosine triphosphate concentration in patients with psoriasis treated with fumaric acid esters. *Acta Derm -Venereol* 2012; 92: 364-6.**

98 **Boehncke S, Fichtlscherer S, Salgo R et al. Systemic therapy of plaque-type psoriasis ameliorates endothelial cell function: Results of a prospective longitudinal pilot trial. *Arch Dermatol Res* 2011; 303: 381-8.**

99 **Haring N, Mahr HS, Mundle M et al. Early detection of renal damage caused by fumaric acid ester therapy by determination of urinary (beta)2-microglobulin. *Br J Dermatol* 2011; 164: 648-51.**

100 **Kokelj F, Plozzer C, Avian A et al. Fumaric acid and its derivatives in the treatment of psoriasis vulgaris: Our experience in forty-one patients. *Acta Dermatovenerol Croat* 2009; 17: 170-5.**

**101** **Sladden MJ, Osborne JE, Hutchinson PE. Fumaric acid esters for severe psoriasis: The Leicestershire experience [3]. *Br J Dermatol* 2006; 155: 843-4.**

**102** **Fika Z, Williams REA, Williamson DJ. Fumaric acid esters in psoriasis [12]. *Br J Dermatol* 2006; 154: 567-8.**

**103** **Harries MJ, Chalmers RJG, Griffiths CEM. Fumaric acid esters for severe psoriasis: A retrospective review of 58 cases. *Br J Dermatol* 2005; 153: 549-51.**

**104** **Stander H, Stadelmann A, Luger T et al. Efficacy of fumaric acid ester monotherapy in psoriasis pustulosa palmoplantaris [17]. *Br J Dermatol* 2003; 149: 220-2.**

**105** **Friedrich M, Sterry W, Klein A et al. Addition of pentoxifylline could reduce the side effects of fumaric acid esters in the treatment of psoriasis [2]. *Acta Derm -Venereol* 2001; 81: 429-30.**

**106** **Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: Results of a prospective multicentre study. *Br J Dermatol* 1998; 138: 456-60.**

**107** **Hoxtermann S, Nuchel C, Altmeyer P. Fumaric acid esters suppress peripheral CD4- and CD8-positive lymphocytes in psoriasis. *Dermatology* 1998; 196: 223-30.**

**108** **Altmeyer P, Hartwig R, Matthes U. Efficacy and safety profile of fumaric acid esters in oral long-term therapy of severe psoriasis vulgaris. An investigation of 83 patients. *HAUTARZT* 1996; 47: 190-6.**

**109** **Altmeyer P, Hoxtermann S, Auer T. Long term observations of lymphocyte subsets in psoriatic patients treated with fumaric acid esters. *AKTUEL DERMATOL* 1996; 22: 272-7.**

**110** **Dalhoff K, Faerber P, Arnholdt H et al. Acute renal failure during treatment of psoriasis with fumaric acid derivatives. *DTSCH MED WOCHENSCHR* 1990; 115: 1014-7.**

**111** **Stuhlinger W, Innerebner M, Aberer W. Nephrotoxic effects of fumaric acid ester during treatment of psoriasis. *DTSCH MED WOCHENSCHR* 1990; 115: 1712-5.**

**112** **Ogilvie S, Lewis Jones S, Dawe R et al. Proteinuria with fumaric acid ester treatment for psoriasis. *Clin Exp Dermatol* 2011; 36: 632-4.**

**113** **Dammeier N, Schubert V, Hauser TK et al. Case report of a patient with progressive multifocal leukoencephalopathy under treatment with dimethyl fumarate. *BMC Neurol* 2015; 15: 108.**

**114** **Nieuwkamp DJ, Murk JL, van Oosten BW et al. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. *N Engl J Med* 2015; 372: 1474-6.**

**115** **Philipp S, Sabat R, Sterry W et al. Kaposi-sarcoma during therapy with fumaric acid esters. *Eur J Immunol* 2009; 39: S213.**

## TABLES AND FIGURES

**Figure 1:** Overview of literature search and selection

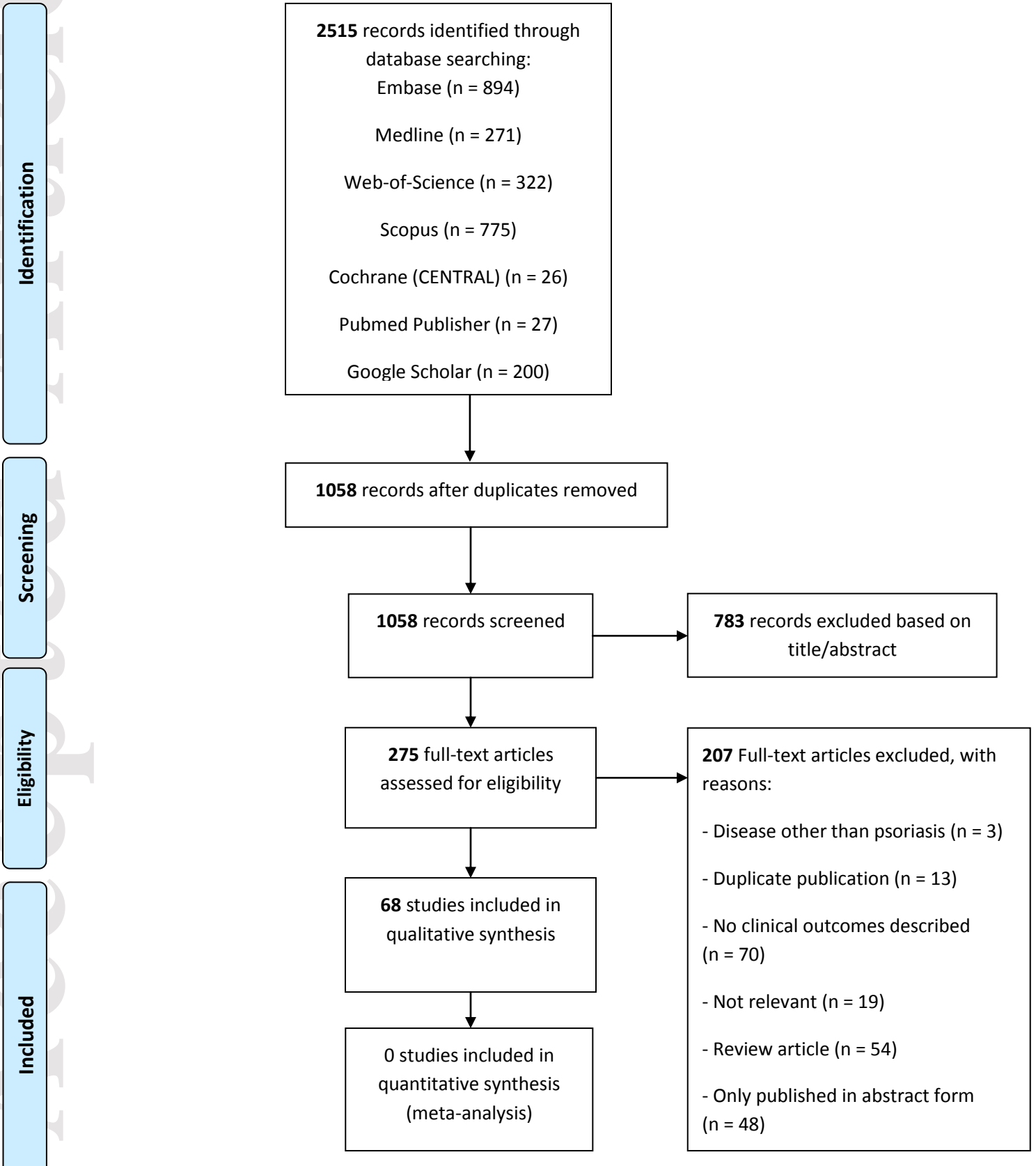

**Table 1:** Summary of characteristics and outcomes from RCTs on FAEs treatment in psoriasis

| No. | Study (year) | Sample size | Treatment duration in weeks | Risk of bias | Treatment arm | FAEs dosage per day in mg | PASI-75 response | Mean change in PASI | Proportion with AEs | Withdrawal rate due to AEs |
|---|---|---|---|---|---|---|---|---|---|---|
| ***FAEs in combination with other treatments compared to FAEs alone:*** | | | | | | | | | | |
| 1 | Balak et al. (2014)[38] | 50 | 12 | Low | FAEs + placebo | 720 mg DMF + 570 mg MEF | 20% | - 65% | 84% | 32% |
| | | | | | FAEs + cetirizine | 720 mg DMF + 570 mg MEF | 20% | - 66% | 84% | 24% |
| 2 | Gollnick et al. (2002)[37] | 134 | 13 | Low | FAEs + placebo ointment | 720 mg DMF + 570 mg MEF | NR | - 52% | 79% | 30% |
| | | | | | FAEs + calcipotriol ointment | 720 mg DMF + 570 mg MEF | NR | - 76% | 82% | 21% |
| ***FAEs compared to other systemic psoriasis treatments:*** | | | | | | | | | | |
| 3 | Fallah Arani et al. (2011)[36] | 54 | 16 | Unclear | FAEs | 720 mg DMF + 570 mg MEF | 19% | - 42% | 92% | 8% |
| | | | | | MTX | NA | 24% | - 54% | 100% | 16% |
| ***FAEs compared to placebo:*** | | | | | | | | | | |
| 4 | Altmeyer et al. (1994)[19] | 100 | 16 | Unclear | FAEs | 720 mg DMF + 570 mg MEF | NR | - 50% | 76% | 39% |
| | | | | | Placebo | | NR | NR | 16% | 2% |
| 5 | Peeters et al. (1992)[41] | 27 | 16 | Unclear | FAEs | 720 mg DMF + 570 mg MEF | NR | NR | 69% | 15% |
| | | | | | Placebo | NA | NR | NR | NR | 0% |
| 6 | Nieboer et al. (1990)[18] | 45 | 16 | Unclear | FAEs | 480 mg DMF + 380 mg MEF | NR | NR | 87% | 35% |
| | | | | | FAEs (DMF) | 480 mg DMF | NR | NR | 86% | 18% |
| 7 | Nugteren-Huying et al. (1990)[35] | 39 | 16 | Unclear | FAEs | 720 mg DMF + 570 mg MEF | NR | NR | NR | 8% |
| | | | | | FAEs (OF) | 1704 mg OF + 48 mg MEF | NR | NR | NR | 23% |

Abbreviations: AEs, adverse events; DMF, dimethylfumarate; FAEs, fumaric acid esters; MEF, monoethylfumarate; MTX, methotrexate; NA, not applicable; NR, not reported; OF, octylfumarate; PASI, psoriasis area and severity index;

**Table 2:** Summary of characteristics and outcomes from observational studies on FAEs treatment in psoriasis

| No. | Study (year) | Study design | Sample size | Treatment duration in months | FAEs treatment | Maximum FAEs dosage per day in mg | PASI-75 response | Mean change in PASI | Proportion with AEs | Withdrawal rate due to AEs |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Long-term studies (treatment duration > 12 months):*** | | | | | | | | | | |
| 1 | Wilsmann-Theis et al. (2015)[51] | Retrospective, multicentre case series | 17 | Mean 21 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | 82% | 12% |
| 2 | Lijnen et al. (2015)[88] | Prospective, singlecentre cohort study | 176 | Median 28 | DMF | 1680 mg DMF | NR | NR | 86% | 25% |
| 3 | Steinz et al. (2014)[45] | Retrospective, singlecentre case series in children with psoriasis | 6 | Mean 18 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | 33% | NR | 80% | 0% |
| 4 | Walker et al. (2014)[48] | Prospective, multicentre cohort study | 249 | 12 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | 67% | NR | 44% |
| 5 | Ismail et al. (2014)[46] | Retrospective, singlecentre cohort study | 249 | Mean 28 | FAEs | 720 mg DMF + 570 mg MEF | NR | NR | NR | 47% |
| 6 | Balak et al. (2013)[44] | Retrospective multicentre case series in children with psoriasis | 14 | Median 10 | DMF + MEF (Dutch formulations) | 720 mg DMF + 570 mg MEF | NR | NR | 64% | 14% |
| 7 | Thaci et al. (2013)[43] | Retrospective multicentre cross-sectional study | 69 | Mean 27 | DMF + MEF (Fumaderm) | NR | NR | NR | 64% | 6% |
| 8 | Wain et al. (2010)[47] | Prospective, single centre cohort study | 80 | 3 – 60 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | 8% | 19% | 74% | 36% |
| 9 | Reich et al. (2009)[42] | Retrospective multicentre, cross-sectional study | 984 | Mean 44 | DMF + MEF (Fumaderm) | NR | NR | 79% | NR | 2% |
| 10 | Brewer et al. (2007)[89] | Retrospective single centre case series | 31 | Mean 8 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | 87% | 26% |
| 11 | Balasubramani et al. (2004)[50] | Retrospective single centre case series | 12 | Mean 10 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | 83% | 8% |
| 12 | Carboni et al. (2004)[90] | Prospective, single centre cohort study | 40 | Mean 15 | DMF + MEF (Fumaderm) | 360 mg DMF + 285 MEF | NR | 80% | 27% | 10% |
| 13 | Hoefnagel et al. (2003)[53] | Retrospective single centre cohort study | 66 | 0 – 168 | FAEs | 720 mg DMF + 570 mg MEF | NR | NR | 73% | 40% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 14 | Litjens et al. (2003)[91] | Prospective, single centre cohort study | 12 | 24 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | NR | 42% |
| 15 | Boesken et al. (1998)[92] | Prospective, single centre cohort study | 47 | Mean 17 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | 45% | NR |
| 16 | Thio et al. (1995)[93] | Retrospective single centre cohort study | 83 | 1 – 36 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | NR | 11% |
| 17 | Kolbach et al. (1992)[80] | Prospective, single centre cohort study | 129 | 1 – 24 | DMF + MEF (Fumaderm) | 480 mg DMF + 380 mg MEF | NR | NR | NR | 18% |
| | | | 67 | | DMF | 240 mg DMF | NR | NR | NR | 26% |
| 18 | Bayard et al. (1987)[16] | Prospective, single centre cohort study | 30 | 12 – 14 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | NR | 17% |
| | | | 18 | 3 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | NR | 11% |
| **Short-term studies (study duration < 12 months)** | | | | | | | | | | |
| 19 | Schmieder et al. (2015)[49] | Prospective, multicentre cohort study | 39 | 4 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | 27% | 59% | 77% | 13% |
| 20 | Gambichler et al. (2014)[94] | Prospective, single centre cohort study | 106 | 6 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | 28% | 71% | NR | 16% |
| 21 | Inzinger et al. (2013)[52] | Retrospective single centre cohort study | 200 | 3 – 12 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | 27% | 13% | NR | 31% |
| 22 | Heelan et al. (2012)[95] | Retrospective single centre cohort study | 45 | Median 10 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | 66% | 33% |
| 23 | Gambichler et al. (2012)[96] | Prospective, single centre cohort study | 32 | 3 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | 54% | NR | 13% |
| 24 | Gambichler et al. (2012)[97] | Prospective, single centre cohort study | 21 | 4 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | 67% | NR | NR |
| 25 | Boehncke et al. (2011)[98] | Prospective, single centre cohort study | 13 | 6 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | 31% | 71% | NR | 8% |
| 26 | Häring et al. (2011)[99] | Prospective, single centre case series | 23 | NR | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | NR | NR |
| 27 | Kokelj et al. (2009)[100] | Prospective, single centre cohort study | 41 | 4 | DMF + MEF (Fumaderm) | 216 mg DMF + 126 mg MEF | NR | 32% | NR | 7% |
| 28 | Sladden et al. (2006)[101] | Retrospective single centre cohort study | 30 | NR | DMF + MEF | 720 mg DMF + 570 mg MEF | NR | NR | NR | 30% |
| 29 | Fika et al. (2006)[102] | Retrospective single centre case series | 11 | NR | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | NR | 18% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 30 | Harries et al. (2005)[103] | Retrospective single centre case series | 58 | NR | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | 66% | 26% |
| 31 | Ständer et al.(2003)[104] | Prospective, single centre cohort study | 13 | 6 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | 75% | NR | 15% |
| 32 | Friedrich et al. (2001)[105] | Prospective, single centre randomized cohort study | 21 | 2 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | 76% | 19% |
| | | | 23 | | DMF + MEF (Fumaderm) + pentoxifylline | 720 mg DMF + 570 mg MEF | NR | NR | 52% | 17% |
| 33 | Mrowietz et al. (1998)[106] | Prospective, multicentre cohort study | 101 | 4 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | 80% | 69% | 7% |
| 34 | Höxtermann et al. (1998)[107] | Prospective single centre cohort study | 10 | 12 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | 86% | NR | 0% |
| 35 | Altmeyer et al. (1996)[108] | Prospective, single centre cohort study | 83 | 12 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | 76% | 62% | 13% |
| 36 | Altmeyer et al. (1996)[109] | Prospective, single centre cohort study | 16 | 3 | DMF + MEF (Fumaderm) | 720 mg DMF + 570 mg MEF | NR | NR | NR | NR |
| 37 | Nieboer et al. (1989)[17] | Prospective, single centre cohort study | 36 | Mean 10 | DMF + MEF | 720 mg DMF + 570 mg MEF | NR | NR | NR | 8% |
| | | | 38 | 4 | MEF | 240 mg MEF | NR | NR | NR | 5% |
| | | | 42 | 4 | DMF | 240 mg DMF | NR | NR | NR | 27% |
| | | | 20 | 3 | MEF | 240 - 720 mg MEF | NR | NR | NR | 0% |
| | | | 56 | 4 – 9 | DMF | 240 mg DMF | NR | NR | NR | 27% |

**Table 3:** Adverse events associated with FAEs in psoriasis treatment reported in ≥ 5 patients in randomized and observational studies

| Adverse event | Combined total number of patients |
|---|---|
| Lymphocytopenia* | 1115 |
| Gastrointestinal complaints | 670 |
| Flushing | 626 |
| Increase in liver enzymes* | 341 |
| Eosinophilia* | 254 |
| Proteinuria* | 242 |
| Leukocytopenia* | 218 |
| Increase in creatinine* | 79 |
| Pruritus | 55 |
| Fatigue | 55 |
| Headache | 34 |
| Malaise | 33 |
| Increase in urea* | 19 |
| Dizziness | 15 |
| Increase in cholesterol* | 12 |
| Hypertension | 10 |
| Dermatitis/rash | 9 |
| Hyperkalaemia* | 8 |

*Of note, the definitions and grading of laboratory abnormalities were not reported in the individual studies.



This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.14500

**Table 4:** Summary of safety outcomes of FAEs in psoriasis treatment reported in case reports

| Adverse event | No. of cases | References |
|---|---|---|
| ***Related to renal events:*** | | |
| Acute renal insufficiency | 7 | Roodnat (1989)[13], Dalhoff (1990)[110], Stuhlinger (1990)[111] |
| Renal Fanconi syndrome | 6 | Fliegner (1992)[66], Haviv (1999)[67], Raschka (1999)[68],Schilling (1999)[69], Warzecha (2001)[70], Reid (2013)[71] |
| Proteinuria | 3 | Ogilvie (2011)[112] |
| ***Potentially related to immunosuppression:*** | | |
| Progressive multifocal leukoencephalopathy (PML) | 7 | Ermis (2013)[59], van Oosten (2013)[60],Stoppe (2014)[61], Bartsch (2015)[62], Dammeier (2015)[113], Hoepner (2015)[64], Nieuwkamp (2015)[114] |
| Malignant melanoma | 2 | Barth (2011)[58] |
| Tuberculous lymphadenitis | 1 | Ahmad (2007)[56] |
| Organizing pneumonia | 1 | Deegan (2010)[55] |
| Squamous cell carcinoma | 1 | Jennings (2009)[57] |
| Kaposi sarcoma | 1 | Phillips (2009, 2013)[54,115] |
| ***Other adverse events:*** | | |
| Collagenous colitis | 1 | Hoffmann (2014)[72] |

## **Appendix 1:** Electronic literature search strategy

**Embase.com:**

('fumaric acid'/exp OR 'fumaric acid derivative'/exp OR 'fumaric acid dimethyl ester'/exp OR 'fumaric acid ethyl ester'/exp OR 'fumaric acid methyl ester'/exp OR 'fumaric acid octyl ester'/exp OR fumaderm/exp OR (fumarat* OR dimethylfumarat* OR monomethylfumarat* OR 'fumaric acid' OR fumaderm)) AND (psoriasis/exp OR 'psoriatic arthritis'/de OR 'antipsoriasis agent'/de OR (psoria* OR antipsoria*))

**Medline (OvidSP):**

(fumarates/ OR (fumarat* OR dimethylfumarat* OR monomethylfumarat* OR fumaric acid OR fumaderm)) AND (exp psoriasis/ OR (psoria* OR antipsoria*))

**Cochrane (CENTRAL):**

((fumarat* OR dimethylfumarat* OR monomethylfumarat* OR 'fumaric acid' OR fumaderm)) AND ((psoria* OR antipsoria*))

**Web-of-science:**

TS=(((fumarat* OR dimethylfumarat* OR monomethylfumarat* OR "fumaric acid" OR fumaderm)) AND ((psoria* OR antipsoria*)))

**Scopus:**

TITLE-ABS-KEY(((fumarat* OR dimethylfumarat* OR monomethylfumarat* OR "fumaric acid" OR fumaderm)) AND ((psoria* OR antipsoria*)))

**PubMed publisher:**

((fumarat*[tiab] OR dimethylfumarat*[tiab] OR monomethylfumarat*[tiab] OR fumaric acid*[tiab] OR fumaderm*[tiab])) AND ((psoria*[tiab] OR antipsoria*[tiab])) AND publisher[sb]

**Google scholar:**

Fumarate|Fumarates|dimethylfumarate|dimethylfumarates|monomethylfumarate|monomethylfumarates|"fumaric acid"|fumaderm psoriasis|psoriatic|antipsoriasis|antipsoriatic