OPTIMISING PSORIASIS CARE PATHWAY

Doctor of Medicine (MD)

Department of Dermatology

August 2018

Dr Ausama Abou Atwan

(ID: 0636554)

SUMMARY OF THESIS: POSTGRADUATE RESEARCH DEGREES

Please return the completed form to:
School Research Office

Please TYPE or write in BLACK ink and use BLOCK capitals

SECTION A: TO BE COMPLETED BY THE CANDIDATE AND SUBMITTED WITH THE THESIS

Student ID Number:	**0636554**
Title:	**Dr**
Surname:	**ABOU ATWAN**
First Names:	**AUSAMA**
School:	**MEDICINE**
Title of Degree:	**DOCTOR OF MEDICINE (MD)**
Full Title of Thesis	**OPTIMISING PSORIASIS CARE PATHWAY**

Student ID Number:	**0636554**

Summary of Thesis:

Optimising the psoriasis care pathway is a multifaceted process that requires input from all healthcare professionals involved in psoriasis patient care. At the primary healthcare level GPs should be more aware of the impact of psoriasis on patients' lives and use a validated quality of life instrument to measure this impact and ideally to improve the triage of psoriasis referrals to secondary care. One of the studies presented in this thesis shows a potential benefit of utilizing the Dermatology Life Quality Index (DLQI) as a triage tool to identify those individuals experiencing the greatest impact on their quality of life. Systemic therapies for psoriasis should be selected on a case by case basis according to guidelines, patients' comorbidities and their personal preferences. It is important that patients are fully aware of the available evidence to enable them to make informed decisions. Fumarates are one of the recognised systemic therapies for psoriasis. The Cochrane systemic review presented in this thesis demonstrates its superiority over placebo and possibly similar efficacy to methotrexate; however these findings were based on low-quality evidence. Following the Cochrane review publication, dimethylfumarate was licensed by the European Medicines Agency (EMA) based on new trial evidence and approved by the National Institute for Health and Care Excellence (NICE) as a third line systemic therapy for moderate-to-severe psoriasis. There is growing evidence that continued improvement on fumarates occurs after the usual 12 – 16 week endpoints commonly used in psoriasis trials. Therefore, long-term randomised clinical trials are needed to measure their true effect and safety in direct head-to-head comparisons with other systemic treatments. Inclusion of fumarates in pharmacovigilance databases will be important to assess rare, delayed adverse effects such as progressive multifocal leukoencephalopathy.

Acknowledgement

I express my sincere thanks and gratitude to my supervisor, Dr John Ingram, for his invaluable support and guidance throughout my research. I also thank Professor Vincent Piguet for giving me the opportunity to undertake this research project. I would like to take this opportunity to thank the patients who very kindly participated in my studies, the co-authors for their contributions in the publications of my research papers, and the Cochrane Skin Group for their guidance in the Cochrane systematic review. I am most grateful to the GPs and staff in the University Hospital of Wales who helped with participants' recruitment. Last but not least, I thank the Dermatology Forum for Wales and the Psoriasis and Psoriatic Arthritis Alliance for their grants to support the conduction of the research studies.

Dedication

I dedicate this work to my beloved mother and late father, my role-models who supported me through my life and encouraged me to embark this project. I also dedicate it to my son, Karam, who just turned six and was constantly asking me about my word count, wanting me to finish to give him more time. I finally dedicate it to my loving brothers and sisters whom I am very grateful to have in my life.

List of Figures

List of Tables

Abbreviations

AAD	American Academy of Dermatology
AE	Adverse effects
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AMP	Antimicrobial peptide
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BMI	Body Mass Index
BSA	Body surface area
Ca	Calcium
CVD	Cardiovascular disease
CNS	Clinical Nurse Specialist
CSG	Cochrane Skin Group
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPD	Continuing professional development
COMET	Core Outcome Measures in Effectiveness Trials
COSs	Core Outcome Sets
CSF	Cerebrospinal fluid
DC	Dendritic cells
DLQI	Dermatology Life Quality Index
DEF	Diethyl fumarate
DMF	Dimethyl fumarate
EADV	European Academy of Dermatology and Venereology
EMA	European Medicines Agency
ESDR	European Society for Dermatological Research
ESR	Erythrocyte sedimentation rate
EQ-5D	EuroQoL five dimensions
FDA	Food and Drug Administration
FA	Fumaric acid
FACT	Fumaric Acid Compound Therapy
FAE	Fumaric acid esters
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
GSTs	Glutathione S-transferases
HCP	Health care professionals
HO-1	Hemeoxygenase 1
HCA2	Hydroxy-caroxylic acid receptor 2
HIF-1α	Hypoxia-inducible factor 1-alpha
HT	Hypertension
IRIS	Immune reconstitution inflammatory syndrome
INF	Interferon
IL	Interleukin
IDEOM	International Dermatology Outcome Measures
IID	International Investigative Dermatology
IQR	Interquartile range
JCV	John Cunningham virus
Kg	Kilogram

Mg	Magnesium
MD	Mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
METC	Medical ethics review committee
MTX	Methotrexate
mg	Milligram
MCID	Minimal clinically important difference
MEF	Monoethyl fumarate
MMF	Monomethyl fumarate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPF	National Psoriasis Foundation
NB-UVB	Narrow-band ultraviolet B
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NICE-CKS	NICE Clinical Knowledge Summaries
Nrf2	Nuclear factor (erythroid-derived 2)-like 2;
NNTB	Number needed to treat to benefit
OR	Odds ratio
PILs	Patient Information Leaflets
PTX	Pentoxifylline
PCR	Polymerase chain reaction
PGA	Physician global assessment
PCDS	Primary Care Dermatology Society
PI	Principal Investigator
PML	Progressive multifocal leukoencephalopathy
PsA	Psoriatic arthritis
PAPAA	Psoriasis and Psoriatic Arthritis Alliance
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
PSS	Psoriasis Severity Score
PUVA	Psoralen and ultraviolet A
QoL	Quality of life
RCTs	Randomised controlled trials
REC	Research Ethics Committee
RD	Risk difference
RR	Risk ratio
SF-36	Short Form 36
SID	Society for Investigative Dermatology
SD	Standard deviation
STAT	Signal transducers and activators of transcription
SoF	Summary of findings
SmPC	Summary of Product Characteristics
Th	T helper
UK	The United Kingdom
TNF	Tumour necrosis factor
USA	United States of America
UHW	University Hospital of Wales
WHO	World Health Organisation
Zn	Zinc

Table of Contents

CHAPTER 1

Introduction

Background

The United Kingdom (UK) population in 2015 was estimated to be 65,110,000 and only 4.76% of those live in Wales (1). The Office for National Statistics reported an annual increase in the population by 0.8% a year for the past decade. This, along with the fact that people live longer, will eventually lead to further strains on public services, including the National Health Service (NHS).

Skin complaints are amongst the most common medical problems in the UK population. Population-based surveys have shown that around 54% of the population experience a skin condition each year (2). Interestingly, only 14% of those seek medical advice whereas the majority opt for self-medication. Despite this, skin conditions remain the top reason for General Practitioner (GP) new appointments with nearly 13 million consultations in 2006 of which 6.1% of these were referred to specialists. This demand is stretching available healthcare resources. The total number of doctors on the GP register in November 2016 was 61,140 representing one GP per 1,065 population (3) compared to approximately one dermatologist per 100,000 population (4). In comparison with other countries, the density of dermatologists in the UK remains lower than in the United States of America (USA) (3.4 dermatologists per 100,000 population) (5); Saudi Arabia (3.76 dermatologists per 100,000 population) (6); Australia (2.1 dermatologists per 100,000 population) (7)

What is more, the health care service model in the UK is different from other countries. Whereas patients can access a specialist directly in other countries, in the UK they need to be referred by GPs, who are the first-line contact and represent the gate-keepers to secondary care access. Yet, dermatology training is not compulsory in postgraduate GP training, and very minimal in undergraduate studies. As a result, the quality of dermatology services provided in primary care may not be ideal which can influence the appropriateness of referrals to secondary care. For instance, patients who require a specialist input may not be referred in a timely fashion and so endure severe skin disease whereas others with mild or benign conditions are referred which results in increased pressure and waiting times in

secondary care. There is a lack of robust studies to measure the quality of dermatology services in primary care.

The choice of systemic therapies provided in secondary care can be a challenge to patients and clinicians. Patients should be informed of the pros and cons of available treatment options to be able to make an informed decision in partnership with the treating clinician. Therefore, high quality evidence data is needed to facilitate the process of decision making, especially as health economics is becoming increasingly influential in dermatology commissioning and funding decisions (8).

Psoriasis: An overview

Psoriasis is a chronic inflammatory skin disease. It was thought to be a form of leprosy for hundreds of years until 1809 when Dr Robert Willan first recognised psoriasis as a distinct entity and described it accurately (9). Ferdinand Hebra (1816-1880) eliminated the term 'lepra' (10). Since then our knowledge about psoriasis has come along way mainly due to advancements in translational research in the past few decades.

Psoriasis can be divided into a number of clinical subtypes. The most common subtype is chronic plaque psoriasis, which presents as well-defined erythematous, scaly plaques typically on the elbows, knees, and scalp **(Figure 1)**. Other subtypes include flexural (inverse) psoriasis, in which erythematous patches are located in the skin creases **(Figure 2)**; guttate psoriasis, in which there are multiple small plaques, particularly on the trunk **(Figure 3)**; generalised pustular psoriasis, involving multiple skin pustules **(Figure 4)**; and erythrodermic psoriasis covering nearly all of the skin surface **(Figure 5)** (11). Palmoplantar pustulosis, characterised by inflammation and sterile pustules on the palms of the hands and the soles of the feet, is still debatable whether it is a varient of psoriasis or a separate entity. Psoriasis is usually diagnosed based on typical clinical features; a skin biopsy can also be helpful if there is diagnostic uncertainty. Psoriatic nail changes, including onycholysis and nail pitting, are observed in about 40% of people with psoriasis (12). Psoriatic arthritis (PsA) is a recognised comobidity of psoriasis, observed in 6% - 42% of cases in population based studies, depending on the definitions used (13).

Figure 1: Chronic plaque psoriasis *(from Griffiths and Barker (14)).*

Figure 2: Inverse psoriasis *(from Griffiths and Barker (14)).*

Figure 3: Guttate psoriasis *(from Lebwohl (11)).*

Figure4: Generalised pustular psoriasis *(from Lebwohl (11)).*

Figure 5: Erythrodermic psoriasis *(from Lebwohl (11)).*

Epidemiology:

Psoriasis occurs worldwide and has a higher prevalence in countries further from the equator (15). In the UK, it affects about 1.5-2% of the population (16, 17). 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 (18). Data from the General Practice Research Database (GPRD) on 114,521 patients with psoriasis showed the prevalence in children under 10 years of age to be less common, at 0.55% (17). This study showed the prevalence rates increased with age in a linear fashion. A similar trend of prevalence has been reported in a German study based on health insurance data (19). Psoriasis appears to affect men and women about equally (14, 17).

Pathogenesis:

The pathogenesis of psoriasis is complex and has attracted a great amount of research in the past few decades. It is now believed that a combination of genetic, immunological and environmental factors contribute to the phenotype of psoriasis (20).

Genetic factors:

Studies have indicated genetic contributions to psoriasis. A family history of psoriasis increases the risk of developing the condition. It has been observed that about a third of psoriasis patients have an affected first degree relative (21). The risk of psorasis in monozygotic twins is two to three times greater than in dizygotics twins (22). However, psoriasis in one identical twin does not always predict psoriasis in the other (23). The mode of inheritence is complex and appears polygenic (21). Mendelian pattern of inheritence is only observed in a small minority of families, whereas most of the posriasis population have multiple genetic risk factors interacting with each other and with environmental triggers leading to disease development (24). Genetic studies have identified several chromosomal loci *(PSORS1-9)* linked to the development of psoriasis (25). The major one is *PSORS1* gene, located on chromosome 6, which accounts for 35-50% of the disease heritability (26). Genetic heterogeneity has been demonstrated in clinical varients of psoriasis. For example guttate psoriasis is strongly associated with PSROS1 whereas this association was lacking in palmoplantar pustulosis and in psoriasis starting in persons over 50 years of age (27, 28).

Environmental factors:

Environmental exposures can precipitate psoriasis in some cases, such as *Streptococcus pyogenes* throat infections leading to guttate psoriasis (29), and medications, including beta-blockers, lithium and synthetic antimalarial drugs, may trigger or aggravate chronic plaque

psoriasis (30). Skin trauma (e.g. due to surgery) can trigger psoriasis at the surgical site, an observation known as the Koebner phenomenon (14). In a prospective cohort study based on the GPRD, smoking has been reported as independent risk factor for psoriasis (odds ratio (OR) 1.4 [95% confidence interval (95%CI) 1.3 to 1.6]) (31).

Keratinocytes and the innate immune system:

Until the early 1980's, psoriasis was thought to be a disease of epidermal keratinocyte proliferation. In 1984, Baker et al (32) proposed that psoriasis results from interaction between T helper (Th) cells with antigen-presenting cells in the epidermis. This theory was supported by reports of psoriasis clearance after allogenic bone marrow transplantation (33) and immune supression by cyclosporin A (34-36). It has been suggested that psoriasis evolves due to interplay between cells and mediators of the innate and adaptive immune system (37). Dysregulation of the innate immune system has been shown in psoriasis (38). Plasmacytoid dendritic cells, which are producers of interferon-α, are increased and activated in psoriatic lesions. Keratinocytes in psoriatic lesions are rich of antimicrobial peptides (AMP) which can have a chemotactic role and shape the function of dendritic cells and T cells (39).

Dendritic cells and cytokines:

Dendritic cells (DC) are key players in the pathogenesis of psoriasis; DC activated by various stimuli secrete tumour necrosis factor-α (TNF-α), interleukin (IL)-23 and IL-12. IL-23 induces differentiation of *naive* T cells into Th17 which in turn produce IL-17 and IL-22. TNF-α and IL-17 activate keratinocytes, promote epidermal hyperplasia, recruit inflammatory cells, such as neutrophils, and induce AMP production. IL-12 produced by DC also induces Th1, which then produces cytokines, including INF-γ. This immune cascade continues as TNF-α activates dendritic cells **(Figure 6)**. Understanding this pathway has led to the development of targeted therapies that inhibit specific steps in the inflammatory cascade, such as TNF-α, IL-12/23, and recently, IL-17 (40).

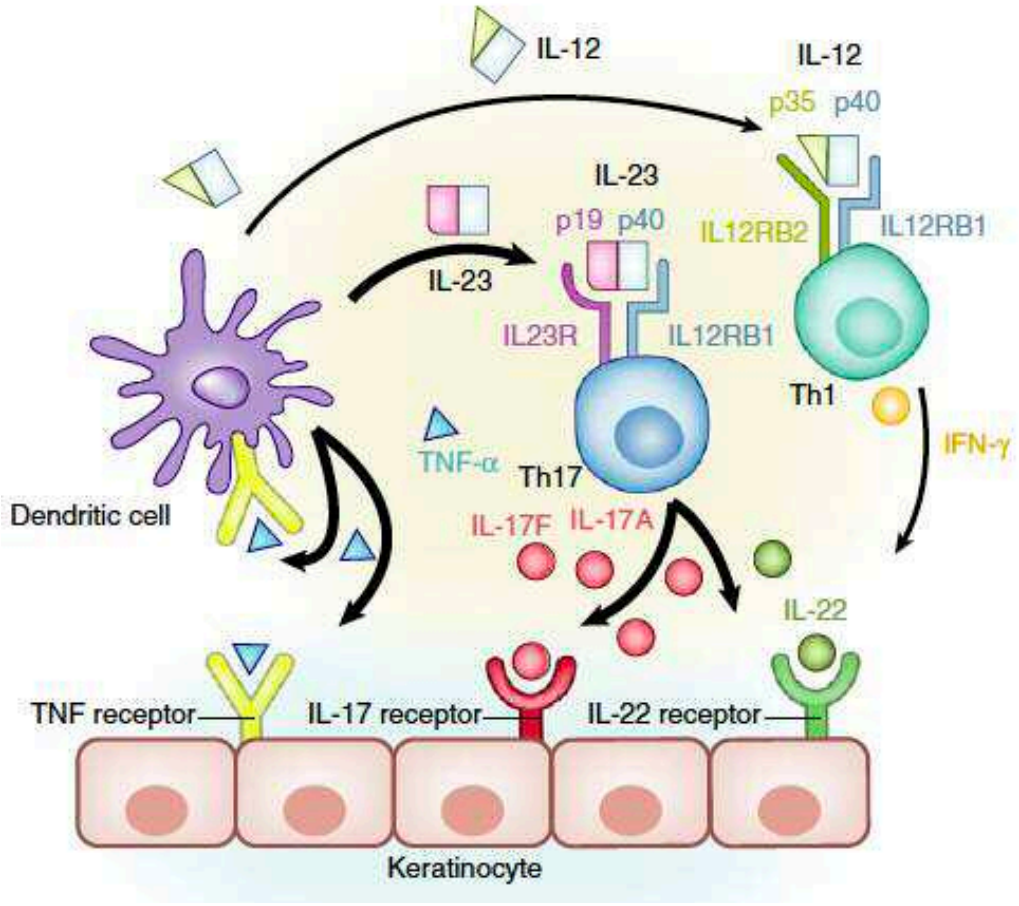


Figure 6: Main immunologic pathway in the pathogenesis of psoriasis. *IFN: interferon; IL: interleukin; TNF: tumour necrosis factor* (from Ogawa et al, 2017 (40)).

T-cells:

For a number of years psoriasis was believed a Th1 mediated disease as the expression of Th1 cytokines, such as γ-interferon (INF-γ), TNF-α and IL-12, were observed in psoriatic lesions while there was no such increase of Th2 cytokines (41-43). However, other factors are thought to play a role in the disease development as epidermal keratinocyte proliferation is not induced by these cytokines (44, 45). The aforementioned roles of Th-17 released cytokines, namely IL-17 and IL-22, have led to the believe that Th-17 is a key element in psoriasis development (20). This was further supported by the reduction of Th-17 during successful anti-TNF treatment (46).

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 (47).

Psoriasis severity assessment:

In 2013, the International Dermatology Outcome Measures (IDEOM) group was established to address the need for standardised patient-centred clinical outcome measures to assess disease course and response to treatment in clinical trials and clinical practice (48). This has led to the development of Core Outcome Sets (COSs); a consensus-driven minimum set of outcomes of a specific condition that must be measured and reported in a clinical trial (49). This is aimed to enable comparison and combination of results across trials, attempt to reduce selective outcome reporting bias and increase clinical interpretability (50).

Callis Duffin and colleagues (51) have recently published the results of an iterative Delphi process to identify a core domain set to assess psoriasis in clinical trials. The Delphi process stakeholders involved patients or advocates of patients with psoriasis and health care professionals (HCP) with expertise in psoriasis, including physicians, scientists, advocacy organisation representatives, and regulators. Most HCP were dermatologists (67%) from North America (57%) and Europe (32%). A domain was considered 'core' if a threshold consensus of at least 70% was met in both patient and HCP whereas domains meeting consensus in only one group were considered to be important but not required to be measured in all trials. Six core domains were identified, including: skin manifestations, psoriasis and psoriatic arthritis symptoms, health-related quality of life, investigator global assessment, patient global assessment, and treatment satisfaction **(Figure 7)**.

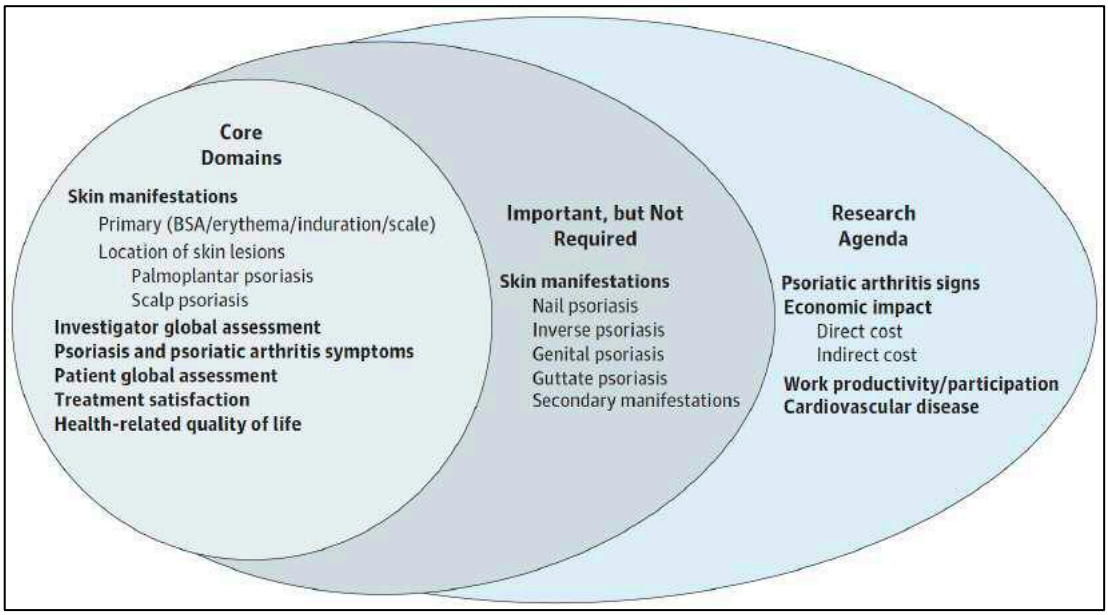


Figure 7: Onion model of core domains for psoriasis clinical trials. The inner (left ring) includes the 6 core domains that are considered required to measure in every psoriasis clinical trial. The middle ring includes 1 domain (skin manifestations) with 5 subdomains that are not required but may be important depending on the study objectives. The outer ring (right) includes 4 domains that are considered the "research agenda," or items that may be important but need further study. *BSA: body surface area* (From Callis Duffin et al (51)).

Assessment of psoriasis severity is important to determine appropriate treatment for individual patients and for assessment of response to treatment. Disease severity can be assessed by physical findings, such as body surface area (BSA) involved, distribution, and degrees of erythema and scaling. These parameters can be measured by using the Psoriasis Area and Severity Index (PASI), which is the current gold standard for the physical signs domain of psoriasis severity (52). Nevertheless, this does not indicate the effect of disease on a patient's social life, self-perception and physical discomfort.

There are different ways of obtaining information regarding patients' QoL, including face to face interviews, telephone interviews, focus groups and questionnaires. Interviews and focus groups, although valuable in providing rich data, are time consuming, expensive and are less likely to be practical in a clinical setting. On the other hand, a more common and practical approach to measuring QoL is by the use of questionnaires. Standardised questionnaires for self-rating by the respondents are very useful for recording QoL not only because of their ease of use but also being quicker and allowing data recording independent of the investigator thus avoiding the influence of the questioner on the respondent (53).

A number of validated dermatology-specific QoL questionnaires exist. Some of these are disease-specific, such as:

- Cardiff Acne Disability Index (54)
- Psoriasis Disability Index (PDI) (55). This is a self-adminstered 15 item psoriasis specific questionnaire with five subscales: daily activities, work, personal relations, leisure and treatment.

Other tools are not disease-specific and can be used in different skin conditions. These include:

- Dermatology-Specific Quality of Life Instrument (56); a self-completed 52-item questionnaire with domains on physical discomfort and symptoms, psychological well-being, social functioniong, self-care activities, performance at work or school, and self-perceptions.
- Skindex-29 (57, 58); a self-adminstered 29-item questionnaire with three domains: functioning, emotions and symptoms.
- Dermatology Life Quality Index (DLQI) (59); a self-completed 10-item questionnaire which covers symptoms and feelings, daily activities, leisure, work and school, personal relationship, and treatment.

Another tool, Medical Outcome Study Short Form 36 (SF-36) (60), is not a dermatology-specific, self-administered questionnaire of 36 items in eight subscales groups in two domains, physical and mental. Similarly, EuroQoL five dimensions (EQ-5D) is a nonspecific self-reported instrument used to measure health outcomes or general health status which is validated for use across a wide range of conditions (61). This tool covers five dimensions of the responder's perceived problems including mobility, salf-care, usual activities, pain/discomfort, and anxiety. Each dimension contains five descriptors and the patient selects the one which best describes the extent of their problem. The descriptors are converted into numerical values resulting a five-digit health profile. Each profile is associated with a single utility index value ranging from 0 (= dead) to 1 (= full health) (61).

A recent systematic review by Ali et al (62) examined the use of QoL instruments in ranomised controlled trials (RCTs) for psoriasis. This demonstrated that the DLQI was the most widely used instrument (83%), followed by SF-36 (31%), EuroQoL-5D (15%), PDI (14%) and Skindex (5%). The DLQI is the main QoL assessment tool used in forming the British Association of Dermatologists (BAD) guidelines (63, 64) and the National Institute for Health and Care Excellence (NICE) guidance (65). It is also widely recommended in Amercian and European guidelines (66, 67).

The DLQI questionnaire aims to measure the impact of skin disease on various aspects of the respondant's life over last 7 days, primarily to measure the current disease impact and to minimise the risk of recall bias. This can be considered as a limitation as a 'snapshot' view does not necessarily reflect on the overall impact of the disease. On the other hand, taking repeated measures and comparing scores between two time points (e.g. before and after treatment) can be helpful to evaluate the trend of changes.

There was a concept that psoriasis affecting < 2% BSA is mild; 3%-10% is moderate; > 10 is severe. However, this concept was challanged and later omitted as studies have shown that BSA involvement does not correlate to the impact on quality of life (68-70). For instance those with genital or facial psoriasis can suffer major QoL impairment despite limited disease. Therefore, the three assessment tools (BSA, PASI and DLQI) should used together to evaluate disease severity. The 'Rule of Tens' was then introduced to describe severe psoriasis as BSA >10; PASI >10 or DLQI >10 (71). These three parameters are now implemented is several quidelines and commonly used in clinical trials and routine clinical practice.

Disease implications:

Impact on Quality of Life:

Psoriasis is a stigmatising condition. It can have a major impact on quality of life, equivalent to conditions such as cancer, heart disease, and diabetes (72). Møller et al (61) conducted a systematic review to compare QoL impairment caused by psoriasis to other chronic disease using the EuroQoL five dimension (EQ-5D) tool. In this review 12 studies met the inclusion criteria. The mean EQ-5D index scores for psoriasis ranged from 0.52 (standard deviation (SD = 0.39)) to 0.9 (SD = 0.1), which were within the range of those reported for other diseases like type 2 diabetes (range from 0.2 to 0.88); liver disease (range from 0.66 to 0.79); cancers (range from 0.33 to 0.93); cardiovascular disease (range from 0.24 to 0.9) and end-stage renal disease (range from 0.44 to 0.86).

The impact of psoriasis on appearance and function can greatly affect occupational, psychological and social elements of life (73). The condition may profoundly restrict personal life choices (74). 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 and regular hospital appointments (75). The impact of psoriasis extends beyond individuals as it may also detrimentally affect other members of the family (76).

About two-thirds of patients have a chronic course of psoriasis that requires continuous control (77). A systematic review on health economic analyses of psoriasis management identified several relevant studies with heterogeneity in models so drawing conclusions was not possible (78). The included studies also failed to factor patients' loss of productivity. Another important factor to take into account is psoriasis-associated comorbidities and adverse effects from interventions.

Psoriasis associated comorbidities:

Optimising the psoriasis care pathway aims to place the patient at the centre of the management plan. Comorbidities associated with psoriasis should be recognised and managed appropriately in a timely fashion to avoid long-term complications. Psoriatic arthropathy is one example where early intervention is prudent to prevent irreversible joint damage. Screening for psoriatic arthritis (PsA) in all patients with psoriasis has been recommended by the Primary Care Dermatology Society (PCDS) and also highlighted in the

British Association of Dermatologists (BAD) guidance (64, 79). The prevalence of PsA has been reported variably in the literature, ranging from 6% to 42% (13). This variation could be due to various definitions used for PsA and whether point or period prevalence was measured.

There is growing evidence that psoriasis is not solely a skin disease but rather a systemic inflammatory condition. Large population-based cohort studies in the UK demonstrated that severe psoriasis was an independent risk factor for myocardial infarction and cardiovascular mortality (80, 81). Moreover, emerging data shows an association between psoriasis and kidney disease, inflammatory bowel disease, infections, certain malignancies and mood disorders (13). Metabolic syndrome, defined as the combination of central obesity, hypertension, insulin resistance and dyslipidaemia (82), is an entity that has attracted interest in psoriasis research. A meta-analysis from a systematic review has shown that patients with psoriasis have more than double the risk of associated metabolic syndrome compared to the general population (OR 2.26 (95% CI 1.70 to 3.01)) (83). Although the exact pathogenesis is not fully understood, shared inflammatory pathways, genetic susceptability and common risk factors are hypothesised contributing factors. Moreover, it is controversial whether these comorbidites are secondary sequelae to psoriasis rather than a primary cause.

Cardiovascular disease (CVD) risk factors (e.g. obesity, diabetes and hyperlipidaemia) were observed in those with psoriasis over three decades ago and it was believed that, while PsA was independent CVD risk factor, psoriatic skin disease was not (84). In a Dutch study by Dowlatshahi et al (85), 262 patients with psoriasis and 8,009 controls were followed up for 11 years and there was no increased risk of CVD in psoriasis (adjusted hazard ration 0.73; 95%CI 0.50 to 1.06). It was noted however that psoriasis patients were more likely to smoke and had higher diastolic blood pressure and BMI than those without psoriasis. This study involved mostly patients with mild psoriasis and so the results cannot be generalised to the whole psoriasis population. A pivotal study by Gelfand and co-workers using UK data (81) convincingly linked severe psoriasis as an independent risk factor with myocardial infarction, particularly in young patients. This was a large cohort study based on data collected from the General Practice Research Database (GPRD) between 1987 and 2002, comparing nearly 127,000 patients with mild psoriasis and 3,837 patients with severe psoriasis to over 500,000 controls, with adjustment for variables such as hypertension, diabetes, hyperlipdaemia, smoking, age, sex and BMI. The adjusted relative risk (RR) for myocardial infarction in a 30-year old patient with mild psoriasis was 1.29 (95%CI 1.14 to 1.46) and 3.10 (95% CI 1.98 to 4.86) for the same age patient with severe psoriasis.

Another UK-based cohort study (86), also based on data from the GPRD, included 44,164 patients with psoriasis and 219,784 matching controls, showed higher hazard ratio (HR) for several comorbidities in psoriasis than in matching control. These include diabetes (HR 1.33; 95%CI 1.25 to 1.42); hypertension (HR 1.09; 95% CI 1.05-1.14), obesity (HR 1.18; 95% CI 1.14-1.23) and hyperlipidaemia (HR 1.17; 95% CI 1.11 to 1.23); myocardial infarction (HR 1.21; 95% CI 1.10 to 1.32), angina (HR 1.20; 95% CI 1.12 to 1.29), atherosclerosis (HR 1.28; 95% CI 1.10 to 1.48), peripheral vascular disease (HR 1.29; 95% CI 1.13 to 1.47) and stroke (HR 1.12; 95% CI 1.00 to 1.25). Increased inflammatory markers such as C-reactive protein, leptin, osteopontin and other noted in psoriasis seem to play a role in both disease and comorbidities development (87). Moreover, a recent observational study (88) has highlighted the detrimental effect of psoriasis duration on vascular inflammation and major adverse cardiovascular events **(Figure 8)**. The risk appeared to be greatest in those who had psoriasis for ≥ 10 years (n=29,220) followed by patients with psoriasis for < 10 years (n=57,941) in comparison to general population (n=4,234,793).

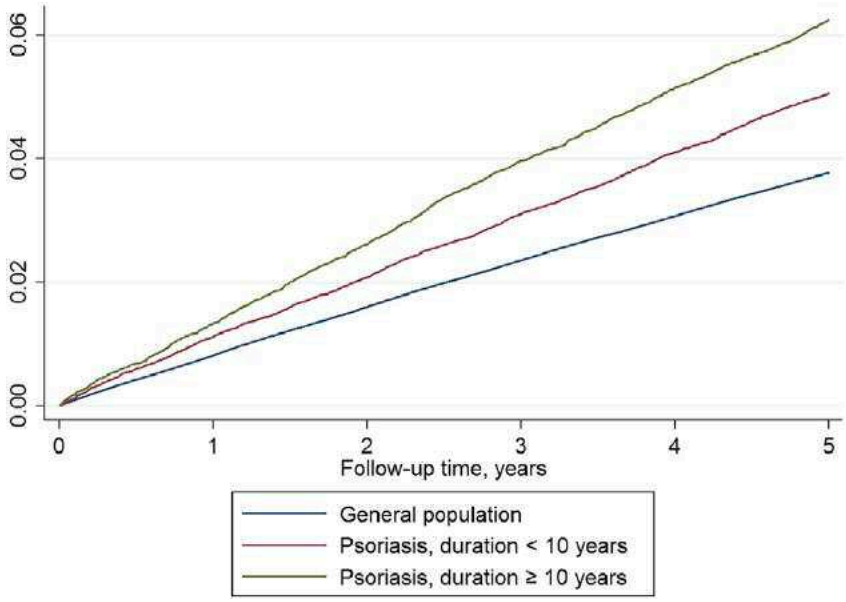


Figure 8: Nelson-Aalen cumulative hazards graph of the population cohort showing major adverse cardiovascular event risk in patients with psoriasis stratified on the basis of disease duration *(from Egeberg et al, 2017 (88))*.

The importance of recognising and treating these psoriasis-related comorbidities is highlighted in data reported from registries that patients treated with TNF-α inhibitors have reduced risks of CVD (89). This is an additional benefit of systemic therapy to patients which is used by the pharmaceutical industry to market new expensive drugs for psoriasis.

Although most of this data is derived from registries of rheumatoid arthritis patients, a recent retrospective cohort study showed a significant reduction of myocardial infarction in patients with psoriasis treated with TNF-α antagonists (HR 0.26; 95%CI 0.12 to 0.56) (90). Theoretically, supressing the inflammatory mediators with active treatments is likely to be responsible for this reduction. However, there has to be other important inflammatory pathways in the development of CVD other than TNF-α, and one question that remains to be answered is whether conventional systemic therapies can provide the same benefits as TNF-α inhibitors. Long-term prospective cohort studies are ideal to answer this question and the British Association of Dermatologists Biologic Interventions Register (BADBIR) is an ideal model to study this outcome.

These data collectively point towards the necessity of a holistic approach in the management and treatment of psoriasis patients, with the aim of preventing / treating comorbidities rather than simply aiming to clear the skin plaques. Early intervention to detect and manage comorbidities is prudent to minimise complications and improve the long-term outcome of patients. Therefore, clinicians in both primary and secondary care should be proactive in patient-education (e.g. advise on body weight reduction, smoking cessation, healthy diet) and aim to refer patients with moderate to severe disease in a timely fashion to be treated in secondary care with systemic treatment to reduce the overall inflammatory process, and subsequently the long-term sequelae.

Therapeutic choices for moderate to severe psoriasis:

Psoriasis is one of the chronic skin conditions that is evidenced to affect individuals functioning and psychosocial wellbeing (91). It has been extensively studied in the past few decades, yielding better understanding of the complexity of its pathogenesis and developments in its therapeutic interventions. Until recently, oral therapies were established as the most effective treatment for severe psoriasis cases. Since then several biological treatments have emerged to offer better disease control, although at a much higher drug cost on the health services. Nevertheless, surveys from different countries showed that a large proportion of psoriasis patients are under-treated and remain on ineffective treatments for a long duration (92).

Although psoriasis is incurable, there are several treatment options to achieve better disease control and improve patients' quality of life (QoL). In the early days of Hippocrates, tar and topical arsenic were the treatments of choice for psoriasis. However, due to the lack of

knowledge combined with superstitious beliefs, traditional remedies have been used ranging from cat dung, goose semen, urine-onion-sea salt mix to the more toxic mercury, nitrate and sulphur containing applications (93). With the advancements in clinical and basic-science research, more treatments options have been developed. These range from topical therapies to phototherapy and systemic therapies **(Figure 9)**.

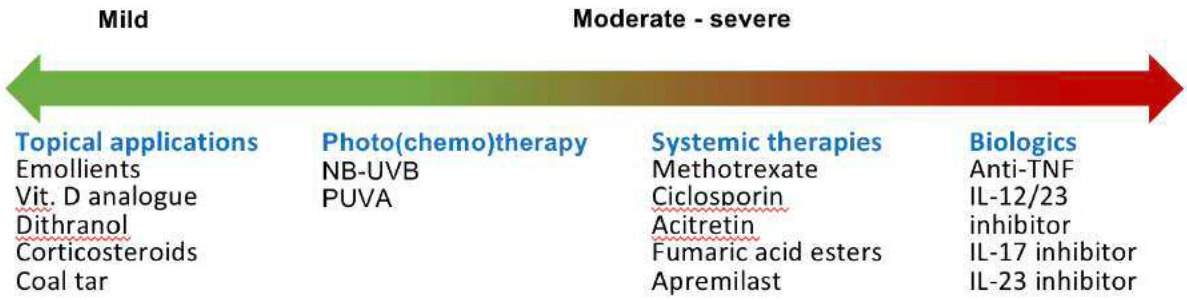


Figure 9: Range of therapeutic options in psoriasis in relation to disease severity. *IL: interleukin; NB-UVB: narrow-band ultraviolet B; PUVA: psoralen and ultraviolet A; TNF: tumour necrosis factor.*

Most patients with milder psoriasis can be managed with topical therapies in the community. However, 25%-30% of patients have moderate-to-severe disease that requires secondary care intervention (94). Phototherapy is a recognised treatment option for psoriasis and it can be offered to patients with psoriasis that cannot be controlled with topical treatment alone (95). However, regular hospital visits (2-3 times weekly) for several weeks can be inconvenient. For example, patients may live far or are unable to take regular time off work. Some patients may also be excluded due to frail status or having contraindications to phototherapy. Moreover, duration of remission after phototherapy is variable and it is often not a solution for long-term control. Systemic therapies on the other hand may provide enhanced long-term control and, apart from monitoring appointments, patients are not required to attend frequent hospital visits.

Systemic therapies for psoriasis:

There are a number of systemic therapies for psoriasis and the choice of treatment needs to be decided on a case-by-case basis. Several factors play part in the decision-making process, including individual factors (psoriasis severity, age, comorbidities, personal preferences) and organisational factors (guidelines, clinicians experience, resources, funding and facilities). For a consent to be valid, it must be voluntary and informed, and the person consenting must have the capacity to make the decision (96). Being informed implies that patients must be provided with all the information needed to make a decision, including what the treatment involves, benefits and risks, and reasonable alternative treatments. The

information provided to patients about intended benefits and potential risks must be based on evidence so they can be as informed as possible. Although Patient Information Leaflets (PILs) about individual treatments are accessible via the BAD website and commonly provided to patients in clinics, making a decision can be an overwhelming and confusing process for patients. A treatment grid summarising and comparing therapies side by side can be a valuable aid. The National Psoriasis Foundation (NPF) has put forward a similar chart (97). The BAD provides PILs on treatments for moderate or severe psoriasis (98) but does not provide head-to-head comparisons of possible adverse effects and other factors influencing choice of treatment.

Methotrexate (MTX) was approved in 1958 as the first systemic therapy for psoriasis (99). This was around the same time fumaric acid esters (FAE) were discovered as a treatment option for psoriasis (100). However, FAE did not have the approval in Germany until 1994, around the same time retinoids and ciclosporin were licensed, in 1992 and 1993 respectively (99). The vast development in understanding psoriasis pathogenesis in the past two decades has led to the development of more effective targeted therapies, such as biologics. Since the approval of the first biologic interventions for psoriasis 14 years ago, several others have emerged. These have shown greater efficacy in clearing psoriasis than conventional systemic therapies. However, in the current era of evidence-based medicine and economic pressure, effective, safe and affordable treatments are prioritised.

Methotrexate:

Methotrexate (MTX) is the most commonly used systemic treatment for moderate to severe plaque psoriasis, especially in cases with joint involvement (101). It competitively inhibits the enzyme dihydrofolate reductase and other folate-dependent enzymes. Inhibition of nucleic acid synthesis in activated T cells and keratinocytes resulting in the immunomodulatory and antiproliferative effects, respectively, are believed to be the main therapeutic effect of MTX in the treatment of psoriasis (99). It is administered once weekly orally or subcutaneously. The initial dose should be 5 to 10mg followed by gradual dose increments, up to 30mg a week, depending on response and tolerance (99). The addition of folic acid has been shown to reduce MTX-associated gastrointestinal adverse effects and hepatic dysfunction (102).

A recent study by West et al (103) reported the long-term efficacy and tolerability of MTX under real-word conditions. The study included 333 psoriasis patients treated with MTX for a median duration of 33 months. It was noted that the majority of treatment failures occurred during the first year of treatment and patients were likely to remain on treatment long term beyond this point. Interestingly, the most frequent reason for treatment discontinuation was

adverse effects rather than lack of efficacy; the latter was reported in approximately 10% of patients.

Ciclosporin:

Ciclosporin exerts a rapid immunosuppressive effect and so can be used in cases where quick response is desired. It acts by inhibition of CD4+ T cells, which leads to reduced synthesis of interleukin-2 and prevents T cell proliferation (104). The standard dose is 2.5 to 3mg/kg/day which can be increased slightly if needed and monitoring parameters are satisfactory (99). Nephrotoxicity is a major drawback of this treatment, which increases with higher doses (e.g. 5mg/kg/day) (105). Therefore, it is used as a short-term intervention. Another major limitation of long-term use of ciclosporin is its carcinogenic effect. In a five-year prospective cohort study by Paul and colleagues (106) including 1252 psoriasis patients treated with ciclosporin, the incidence of skin cancer, mostly squamous cell carcinoma, was six-fold higher in the treated group compared with the general population. This risk was greater in those who received the treatment for more than two years. However, the incidence of non-skin malignancy was not significantly different.

Acitretin:

Acitretin, a vitamin A analogue, is another systemic therapy used in psoriasis. It has the advantage of non-immunosuppressive effects. Retinoids bind to nuclear receptors from the steroid hormone receptors family (107), resulting in antiproliferative and immunomodulatory effects. They reduce the proliferation and regulate the differentitation of epidermal keratinocytes, reduce intraepidermal migration of neutrophils and inhibit IL-6-driven induction of Th17 cells. The dose ranges from 0.3 to 0.8 mg/kg/day, adjusted based on response and tolerance (99). A higher dose of acitretin is more effective but xerosis and chilitis are more encountered. Three RCTs from the 1980s ((108-110) demonstrated that acitretin 50–75 mg daily was significantly better than placebo and a lower acitretin dose (10–25 mg daily) in treating psoriasis, but no PASI scores were reported and the dropout rate due to adverse effects was unclear. As a teratogenic agent, it is usually avoided in females of childbearing age, as contraception for three years following treatment discontinuation is necessary (107).

Apremilast:

The phosphodiesterase 4 inhibitor, apremilast, is a small molecule drug which gained NICE approval for the treatment of moderate to severe plaque psoriasis in adults in 2016 (111). It reduces the production of proinflammatory TNFα and IFNγ in psoriasis. The dose is administered orally at 30mg twice daily (112). In the ESTEEM 1 study published by Papp et al (113), 75% reduction in PASI score (PASI75) was achieved in 33.1% of those received

Apremilast (n=562) 30mg twice daily for 16 weeks, compared to 5.3% of those received placebo (n=282) (P <0.0001). However, the majority of Apremilast-treated patients experienced diarrhoea (72.4%) and nausea (77.4%) within two weeks after first dose. A warning was issued by the Medicines and Healthcare products Regulatory Agency a year after Apremilast NICE approval to highlight increased risk of psychiatric symptoms with the medication, including depression, suicidal thoughts and suicidal behaviours(114).

Fumaric acid esters:

Although FAE are licensed and widely used in Germany for the treatment of psoriasis since 1994, it was evident from the literature that they have also been used, as an off-label drug, in other countries such as the Netherlands (115-117), the United Kingdom (118, 119) and Italy (120, 121). Studies have shown that dimethyl fumarate (DMF) is the active ingredient of FAE (see Chapter 3). In September 2017 (after the publication of our Cochrane systematic review), a DMF alone preparation has gained the European Medicines Agency (EMA) (122) and National Institute for Health and Care Excellence (NICE) (123) approval for the treatment of moderate-to-severe psoriasis.

The treatment regimen starts with DMF 30mg tablets once daily, increased gradually to three times daily in the first 3 weeks of treatment then followed by DMF 120mg tablets once daily from week 4 to a maximum of six tablets daily (720mg) in week 9. This gradual dose increments has been proposed to improve tolerability, mainly gastrointestinal adverse effects. Lymphopaenia is a recognised potential side effect of DMF and hence blood monitoring, and treatment discontinuation if necessary, are essential safety measures.

Aims of this thesis:

The psoriasis care pathway has been summarised in NICE guidelines **(Figure 10)** and includes primary care management, referral to secondary care when required, and selection of appropriate phototherapy, systemic and biologic therapies in secondary care (124). The objective of this research project is to generate data relevant to clinical practice to improve the care psoriasis patients receive through their journey in the healthcare system.

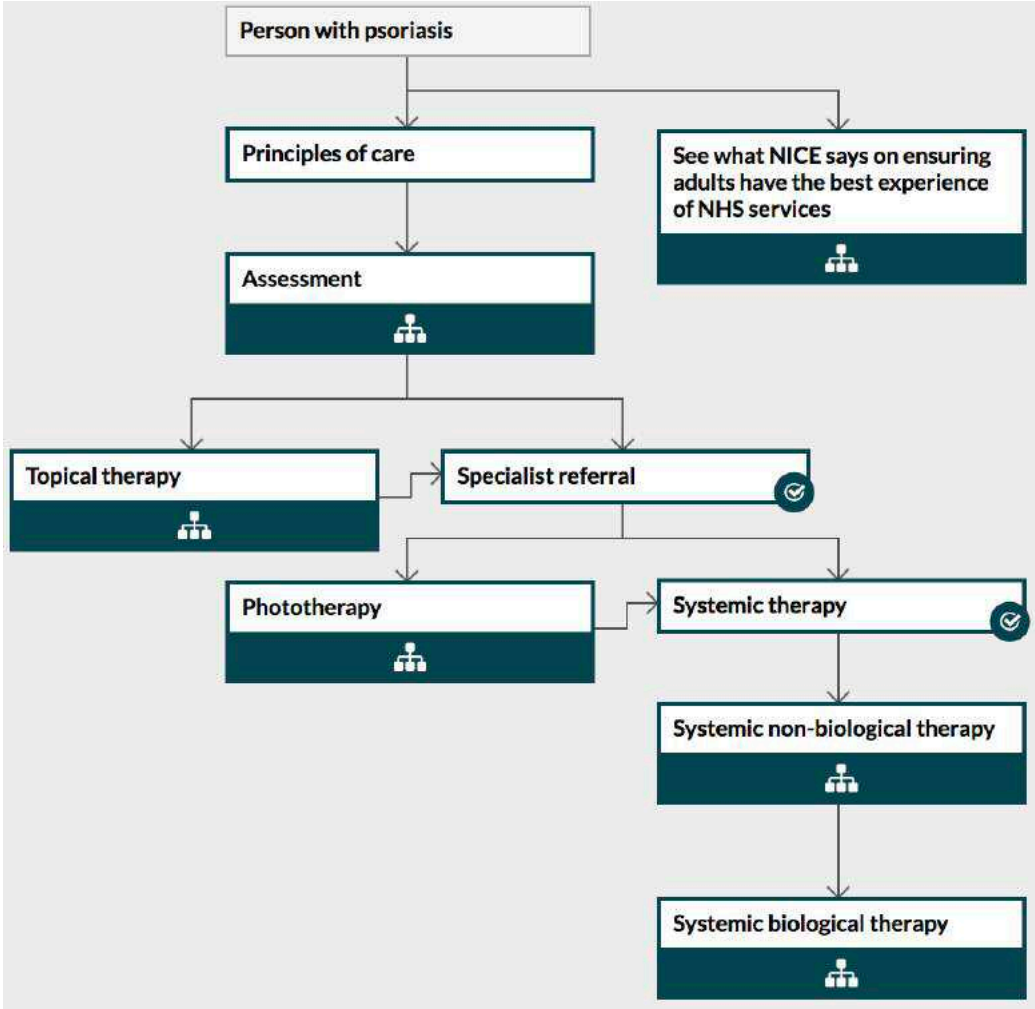


Figure 10: An overview of psoriasis care pathway (from NICE pathways (124)).

Access to care 'In the right place, at the right time, by the right people' has been prioritised by the Welsh Assembly Government in their 2005 policy 'Designed for Life: Creating world class health and social care for Wales in the 21st century' (125). As psoriasis is a life-long condition with intermittent remissions and flares, and causes a significant impairment of patients' quality of life, patients' care should be more streamlined to be enable those with significant disease to be seen by a specialist in secondary care at the right time. This stimulated our thoughts to perform the first of the two projects that comprise this thesis to address the issue of timely referral from primary care.

When patients with moderate-to-severe psoriasis are seen in secondary care, systemic therapies are often considered to achieve long-term disease control. The choice of the systemic therapy can be influenced by different factors, as previously discussed. At the time of starting the MD project, FAE were unlicensed for psoriasis in the UK. As a result, FAE were omitted from guidelines and standard sources of patient information, leaving clinicians

and patients unsupported in considering FAE treatment. This is particularly important in the context that, as an unlicensed intervention, clincians were more exposed medicolegally in prescribing FAE. As a result, there was considerable variation in FAE prescribing for psoriasis across the UK, depending on individual clinicians' familiarity with the intervention. Thus, there was a need to provide a robust evidence on the use of FAE for psoriasis. The project involved conducting a Cochrane systematic review of FAE for psoriasis because the Cochrane Collaboration provides a framework to conduct the highest quality systematic review that is most accessible to patients as well.

CHAPTER 2

Optimising psoriasis referrals from primary care: Dermatology Life Quality Index (DLQI) as a triage tool

---

There is substantial evidence indicating that psoriasis patients are under-treated. A German survey including 1511 psoriasis follow-up patients in dermatology clinics revealed an average PASI score of 12 and DLQI score of 8.6, indicating moderate-to-severe disease, and only 45.4% of those with PASI > 20 had been prescribed systemic therapies (126). However, the cross-sectional study design does not provide the clinical outcomes for these patients. Further surveys from the US National Psoriasis Foundation (127), including 1657 patients, and Canada (128, 129) showed 37% and 18% of patients, respectively, received systemic and/or phototherapy. The Canadian surveys found that only 24% of participants were satisfied with their treatment at the time of the survey and demonstrated patients' lack of awareness of available treatment options.

There are several possible reasons to explain insufficient treatment of psoriasis patients. Potential reasons include lack of local resources, insufficient patient education regarding available therapies or concerns about treatment-related adverse effects, lack of access to specialist care or reluctance from clinicians to initiate therapies that require long-term visits and monitoring in the current era of meeting targets. Another possible explanation of under-treatment is the lack of utilising quality of life measures that play a central role in treatment goal and management plan. Although assessment of psoriasis impact on patients' psychosocial wellbeing is part of NICE Clinical Knowledge Summaries (NICE-CKS) guidance (130), guidance from the Primary Care Dermatology Society (PCDS) (79) lacks a recommendations regarding QoL measurement in psoriasis. Correction of this omission may help encourage QoL measurement by GPs to assist their management of psoriasis.

Currently, almost all written primary care psoriasis referrals are triaged as 'Routine'. In part this is because of the prioritisation of skin cancer. The length of routine waiting times when this study was carried out was 9-10 months; this means that many patients with severe psoriasis wait several months to be seen, enduring a preventable reduction in quality of life. Furthermore, due to the relapsing/remitting nature of psoriasis, some patients have spontaneously recovered from their psoriasis flare by the time they are reviewed by a

specialist and so the appointment is unnecessary at that time. This results in a frustrating situation for patients, GPs and dermatologists.

It is challenging for GPs to undertake a physical signs based measure of psoriasis severity with limited training and insufficient consulting time to fully expose a patient. In the context that quality of life scores are now used by NICE and other guideline producers, the hypothesis of the project is that patient self-assessed QoL may be an efficient and helpful tool to allow GPs to select those psoriasis patients requiring referral to secondary care. It may also support effective triage of the referrals by secondary care.

Dermatology Life Quality Index (DLQI) is the most validated and widely used dermatology-specific quality of life measure in current use (62, 131). It is self-completed by patients in 1-2 minutes (59). The questionnaire includes 10 items, answered by selecting relevant level of impact (very much, a lot, a little, not at all), yielding a total score ranging from zero to 30 (Appendix 1). A DLQI cut-off score of greater than 10 indicates a very large effect on a patient's quality of life, whereas scores of 10 or less reflect a moderate or small effect (59, 132). It can be completed by the patient before or after the GP consultation, to ensure that consultation duration is unaffected.

A previous longitudinal study by Basra et al (133) demonstrated that a 4-point difference in DLQI scores represents minimal clinically important difference (MCID). The MCID has been defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient's management" (134).

In order to optimise the care provided to psoriasis patients the present study has been proposed to evaluate the usefulness of the DLQI questionnaire in triaging patients referred to dermatology secondary health care services.

Study Aims:

- **Primary aim:** to assess whether DLQI questionnaire can be a useful triage tool when patients with psoriasis are referred from primary to secondary health care.
- **Secondary aims:**
    - To assess the average DLQI score in newly-referred psoriasis patients.
    - To determine the difference between DLQI scores at GP referral and on review by a specialist.
    - To investigate the degree of patient satisfaction with the referral waiting time.

- To assess the correlation between PASI and DLQI scores when patients are seen in secondary care.
- To assess the effect of psoriasis duration on DLQI scores.

Study Design:

A single-site questionnaire-based controlled study on newly-referred patients with psoriasis to the department of dermatology at University Hospital of Wales (UHW).

Methods:

Local GPs were provided with DLQI questionnaires to use when referring patients with psoriasis. The Principal Investigator (PI) screened all referral letters received from GPs with a stated diagnosis of psoriasis. DLQI questionnaires were sent to the referring GPs requesting these to be filled in by referred patients. Completed forms then were returned to the PI via the GP. This ensures the communication occured between the PI and referring GPs only.

In agreement with the Cardiff consultant dermatologists based at the University Hospital of Wales (UHW), the PI triaged referred patients with a DLQI score greater than 10 as 'Urgent' (10-12 weeks wait) while those with no DLQI scores, either from participating or non-participating GPs, were triaged as 'Routine' (9-10 months wait) as a control group **(Figure 11)**. This produced two groups for comparison: 1- a group with DLQI score more than 10, and a group with no DLQI score.

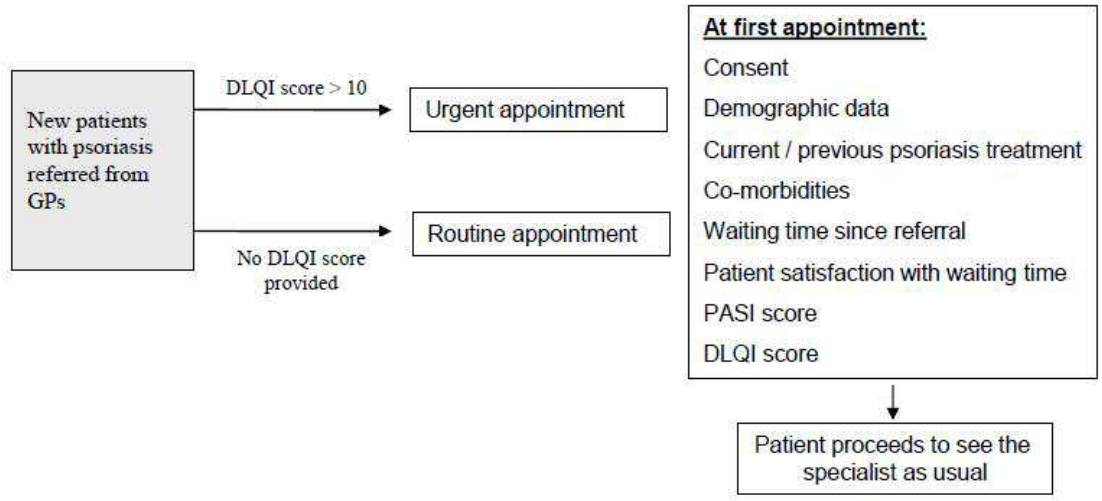


Figure 11: Outline of the study flowchart.

In the first version of the protocol, a third group with DLQI scores of 10 or lower was planned to be included. However, a protocol amendement was submitted to exclude this group from the study as no referrals had been made for these patients. It is assumed that they were managed in primary care as their psoriasis had no major impact on their quality of life.

Referred patients received the study information sheet (Appendix 2) when they arrived for their first appointment at the dermatology department. Patients had time to read the information in the waiting area before they were invited to take part by the study PI. Potential participants were either recruited on the day or allowed up to two days to decide whether they wished to take part. Patients were allowed to ask any questions related to the study before they were requested to sign a written informed consent (Appendix 3). If they preferred not to take part, their data were not included in the study and they were reviewed in the clinic in the usual way. If they agreed to participate, the researcher invited the patient for a 20-30 minute consultation. The researcher recorded on a data collection sheet (Appendix 4) demographic information, current and previous psoriasis treatment, co-morbidities, DLQI scores (currently and at the point of referral if applicable), the waiting time from the GP referral to their secondary care appointment and patient satisfaction with the waiting time on a five-point Likert scale. PASI score (Appendix 5) was also measured. Participants then saw the Consultant's outpatient team in the usual way, who had access to the collected data to aid the consultation.

Study Population:

Patients with psoriasis referred from primary care to the department of dermatology at the UHW (study site) were recruited.

Inclusion Criteria:

- New referrals with a clinical diagnosis of psoriasis, confirmed by a dermatologist
- Adults aged at least 18 years
- Able to understand and write English
- Able to give informed written consent

Exclusion Criteria:

- Patients unable or unwilling to sign the consent form.

Sample Size:

A power calculation demonstrated that 20 patients were required in each group to give 80% power to detect a five point difference in PASI score for an alpha significance level of 0.05.

Number of Visits:

Participants were assessed once for around 20 minutes prior to the first consultation with the specialists. No further visits were required for the sake of the study but those who required follow-up for their psoriasis management were reviewed in clinics as needed.

Data Recording and Retention of Documents:

Research data were entered onto data collection sheets (Appendix 4). All the research documents were kept securely in the Department of Dermatology of UHW. Only the study investigators could access these data.

Study Outcomes and Data Analysis:

The primary outcome for the study was the PASI score at the time of outpatient review in the two groups: DLQI score greater than 10 and no DLQI score in referral letter. Patient satisfaction with the waiting time was also measured on a five-point Likert scale. The data generated from the study was reported using descriptive statistics.

Ethical and Legal Consideration:

Ethical Approval from the South East Wales Local Research Ethics Committee (Appendix 6) was obtained on 19 July 2012 (REC reference: 12/WA/0212). Amendments were submitted to the committee and no changes were made to the conduct of the study until approval was granted.

All participants were required to give their written consent after the nature of the study had been fully explained. The researcher informed the GPs if their referred patients participated in the study. All original consent forms and study data were kept in a secure location. Three consent forms were signed, one for the subject, one for the patient notes and one to be stored securely in the Trials Unit, Department of Dermatology at UHW. The participants were informed that they could withdraw their consent at any stage without being required to state a reason and without prejudice to any future care. Study documentation was available for examination by regulatory authorities for monitoring the quality of the research during the course of the study. The data could be identified only by the date of birth and a unique study number.

Funding:
Funding was approved by the Dermatology Forum for Wales (Appendix 7). This was utilised to fund staff time.

Sponsorship:
This study was sponsored by Cardiff University (Appendix 8).

Project Management:
Dr John Ingram supervised and monitored the project. The Trial Management Group (Dr John R Ingram and Dr Ausama Abou Atwan) met frequently to discuss the study progress and to ensure adherence to study protocol. A Clinical Trials Nurse helped in printing and posting DLQI forms to referring GPs, and in storing the study documents.

Results:
The 40 recruited patients, 20 in each group, had no significant difference in demographics and disease characteristics **(Table 1)**. The median waiting time for the 'urgent' group was 88 days (interquartile range (IQR) 66-99 days) whereas patients triaged as 'routine' waited 256 days (IQR 228–295 days).

	Routine (no DLQI at referral)	**Urgent (DLQI > 10 at referral)**
Number	20	20
Gender	M=9; F=11	M=11; F=9
Age median (years) (IQR)	34 (28-51)	40 (33–52)
Psoriasis duration median (years) (IQR)	13 (8.5-20)	8.5 (4-20)
Body Mass Index (BMI) (median kg/m2) (IQR)	27.1 (23.4–31.2)	29.2 (26–33.5)
Family history of psoriasis	10	9
Co-morbidities	11 (HT=5; hypercholesterolaemia=2; depression=8)	8 (HT=4; DM=1; hypercholesterolaemia=2; depression=2; PsA=2)
Waiting time median (days) (IQR)	256 days (228–295)	88 days (66–99)

Table 1: Participants' characteristics. *HT: hypertension; IQR: interquartile range; PsA: Psoriatic arthritis.*

Of those patients seen urgently, 60% were 'happy' or 'very happy' with the waiting time. In contrast, in the routine group no patients were 'happy' or 'very happy'. The median PASI score in the urgent group was 6.2 (IQR 3.5–10.6) compared to 3.85 (IQR 2.8–6.3) in the routine group (P = 0.0968) **(Figure 12)**.

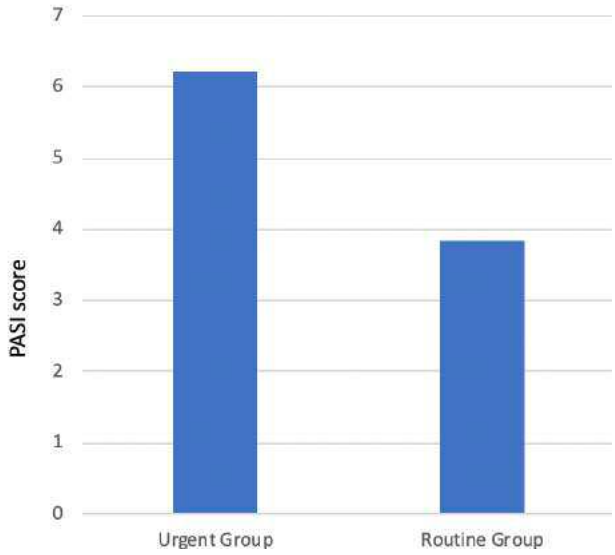


Figure 12: The median PASI scores in the urgent and routine groups.

The median DLQI score in the urgent group when seen in secondary care was four points higher compared to the routine group (urgent=16, IQR 12-20, vs. routine=12, IQR 8.5–17) (P = 0.097) **(Figure 13)**, reflecting higher disease impact as shown by the difference reaching the level of the MCID for the DLQI instrument (133). In those triaged as urgent, the median DLQI score at the time of secondary care assessment was not significantly different compared to their baseline scores at the time of referral (17.5; IQR 13.5–23) (P = 0.15625)

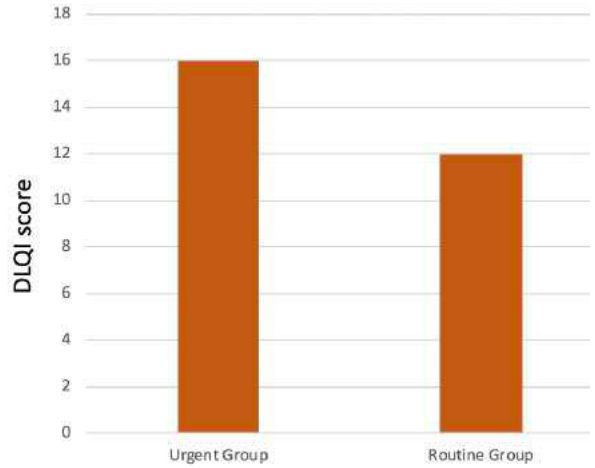


Figure 13: The median DLQI scores in the urgent and routine groups.

Pearson correlation coefficient calculation showed no significant correlation between PASI and DLQI scores in both urgent (R=0.3207) and routine (R= 0.3809) groups. Similarly, no significant correlation was noted between the duration of participants' psoriasis and their DLQI scores when presented in secondary care (R= - 0.1921).

Discussion:

Pressures on dermatology secondary care services in the UK and a requirement to meet skin cancer waiting time targets results in patients with inflammatory dermatoses having long waiting times. Triaging GP referrals accurately is difficult if information is incomplete and disease severity scores are not given. Asking GPs to perform a severity score involving complete skin examination, such as PASI, is not practical because of lack of time and insufficient training. However, a QoL questionnaire can easily be completed by patients while the GP documents the consultation. Patients seen urgently due to a baseline DLQI score > 10 at referral had a DLQI score four points higher than those referred without a DLQI and seen 'routinely'. As the minimal clinically important difference (MCID) for DLQI is four points (133), using a baseline DLQI score greater than 10 does identify those patients whose psoriasis has a particularly high impact on QoL, compared to an unselected group of psoriasis referrals.

Cardiff's long waiting time of 256 days for routine referrals reflects pressures on dermatology secondary care services in Wales. While we chose a DLQI cut off score of 10 points, as it indicates major impairment of QoL, a different cut off score could be selected depending on the attitude and resources of the referral centre. The Scottish (135) and Malaysian (136) guidelines recommend referral for DLQI scores >5 in psoriasis patients unresponsive to topical therapy. However, in keeping with our study experience, 65.5% of eligible patients in Scotland were not seen by a specialist (137).

This study, although small in size, demonstrated the associations with comorbidities in line with reports in the literature. Obesity, defined by the World Health Organisation (WHO) as Body Mass Index (BMI) of 30 or greater (138), was the most common association, noted in 17 (42.5%) of our cohort. This was followed by depression (n=10; 25%), hypertension (n=9; 22.5%), and dylipidaemia (n=4; 10%). Therefore, a holistic management approach is prudent in psoriasis patients to improve their overall health status, not just the visible skin disease.

One limitation of the study is the lack of a separate group of psoriasis referrals with a DLQI score ≤10. Although this was initially planned in the first version of the study protocol, we found that almost no patients were referred with scores in this range, perhaps because GPs chose not to refer less severely affected patients. Another potential limitation is the possibility that patients or GPs might inflate DLQI scores to reduce waiting time delays, however we mitigated for this in our study by not specifying the DLQI score triage cut-off for urgent appointments.

The course of psoriasis severity can fluctuate unpredictably. When patients are referred routinely from their GP their psoriasis can be milder by the time they see the specialist several months later. As a result, the outcome may be advice on topical therapies and discharge from further follow up. This common clinical scenario can be frustrating to patients who need to see the GP to be referred again when their condition flares and wait more months to be seen again in secondary care. To break this vicious circle, and to implement the NICE guidance which indicates that patients with psoriasis should have a single point of contact to access information or advice (95), a more responsive healthcare model is needed.

Such a model was established by the department of dermatology at the Aneurin Bevan University Health Board in 2013 and given the name “Psoriasis Direct Service” (139). This was specifically designed for psoriasis patients seen in secondary care and not requiring phototherapy, systemic treatment or regular monitoring. The aim was to empower these patients to self-refer when needing advice and/or review by a Clinical Nurse Specialist (CNS), who in turn triaged patients according to their needs. This ‘open-access’ model has no time cut-offs after the initial clinic consultation. This service was audited two years after its launch (139). It was found that 645 psoriasis patients were provided with written information on the service, including the phone number of the CNSs. Of those, 203 patients (31.5%) contacted the service of whom 166 (81.8%) were then reviewed in person by the CNS after an average period of 27 days (range 0 to 148 days). This represents a timely review as opposed to the routine outpatient waiting time if re-referred to secondary care by the GP. The mean time for contacting the service after the initial clinic consultation was 7.2 months (range 0 to 34 months). This means a fixed three- or six-month follow-up appointment would have been unnecessary for these patients and the appointment slots were used more effectively. Importantly, the majority of patients (91%) rated this service as good/excellent. These findings suggest that several models, including DLQI measurement, can streamline referrals, free up appointments and improve patient care at the interface between primary and secondary services. The positive rating from patients indicates their satisfaction and reassurance from having access to a specialist service when needed.

In summary, we have demonstrated that a QoL instrument such as the DLQI can be used as a triage tool. Its use may help GPs quantify psoriasis severity, and ensure that patients whose psoriasis is causing greatest impact on QoL are prioritised for referral and seen in secondary care in a timely manner. A much larger randomised study is needed to evaluate the usefulness of DLQI as a triage tool in dermatology services.

Dissemination of Study Findings:

The study was published as a research letter in the British Journal of Dermatology (140) (Appendix 9).

CHAPTER 3

Fumaric acid esters in the treatment of psoriasis: A Cochrane Systematic Review

---

Historical Background:

Fumaric acid esters (FAE) are chemical compounds derived from fumaric acid (FA); they have a combination of methyl and ethyl groups added to fumaric acid backbone (141). Schweckendiek, a German chemist who had psoriasis, proposed that psoriasis develops due to disturance in the citric acid cycle where fumaric acid (FA) was lacking. Because of the poor oral absorption of FA and its high irritancy (e.g. induction of gastric ulceration), Schweckendiek esterified it into monoethyl fumarate (MEF), monomethyl fumarate (MMF), diethyl fumarate (DEF) and dimethyl fumarate (DMF) in enteric coated tablets which had increased efficacy and bioavailability (141-143). In 1959, he reported successful treatment of psoriasis with FAE after self- experimentation (100).

Several combinations of the components were tried following Schweckendiek's report until the treatment was standaridised by Schafer in 1982 (144). A couple of years later, it was known as Fumaric Acid Compound Therapy, or FACT (145). This consisted of DMF, mixtures of FA and several MEF salts (calcium, cupric, ferrous, potassium, lithium, magnesium, manganase and zinc) (146). This compound was used along with topical MEF 1-3% ointment or bathing oil and strict diet (avoiving spices, etheric oils, nuts and wine) and so it was inconvenient (145). Therefore, a simplified version of the treatment was developed, consisting of low and high dose of DMF tablets including only three MEF salts (calcium (Ca), zinc (Zn) and magnesium (Mg)). This formula was then approved in Germany in 1994 and given the brand name Fumaderm®. The dietary restrictions were dropped because no added benefit was noted.

Fumaderm® (Biogen Idec Inc) is available in two strengths (147):

- Fumaderm® Initial, containing 30mg of DMF per tablet plus MEF-Ca 67mg, MEF-Zn 3mg, and MEF-Mg 5mg
- Fumaderm®, containing 120mg of DMF per tablet plus MEF-Ca 87mg, MEF-Zn 3mg, and MEF-Mg 5mg.

Dimethyl fumarate (DMF) is believed to be the active ingredient that exerts clinical effects in psoriasis. This was first elucidated by Nieboer et al in 1989 (146) in a publication of a series of five open-label and controlled studies. It was concluded that MEF monotherapy was not superior to placebo, assessed by a Psoriasis Severity Score (PSS), whereas DMF 240mg daily as monotherapy was superior to placebo and induced considerable improvement in 22% of patients at 4 months and in 33% of patients at 9 months. This study also reported a statistically significant correlation between treatment-induced lymphopaenia, occurring in 60% of those who received DMF, and considerable psoriasis improvement (≥ 50% improvement in PSS). This observation however was based on a small number of patients.

A year later, the same study group conducted a double-blind, head-to-head trial to compare FAE compound therapy (DMF plus salts of MEF) with DMF monotherapy (148). In this study they demonstrated >50% improvement of PSS in 55% of those who received DMF (n=22) and 80% in the combined FAE group (n=23) but the difference was not statistically significant at the study endpoint at 4 months. Four patients (18%) in the DMF group discontinued treatment due to therapy-related adverse effects in comparison to 7 (30.4%) in the FAE mixure group; yet this difference was not reported whether statistically significant. As a result, the authors concluded that FAE mixure did not have additional therapeutic benefit over DMF monotherapy.

A DMF monotherapy preparation manufactured in the Netherlands called Psorinovo® (GMP Apotheek Mierlo-Hout) is available and used for psoriasis treatment for over 2 decades, although it is not registered through the Dutch Medicines Evaluation Board (149). In addition, a delayed-release oral formuation of DMF, Tecfidera® (120mg and 240mg) (Biogen Idec Inc) is licensed for the treatement of relapsing-remitting multiple sclerosis. It was approved for this indication by the Food and Drug Administration (FDA) (150) and EMA (151).

Tolerability:

Gastrointestinal (GI) adverse effects are common with FAE but in the majority of patients they are mild in severity and ease with time. Severe symptoms however can lead to treatment discontinuation. A gradual dose-increment schedule of Fumaderm® is well established in the European S3 guidelines (99) **(Table 2)** and is meant to improve tolerability. The same dosing schedule is advised for the recently approved DMF-only product, Skilarence®.

	30 mg dimethyl fumarate (Fumaderm® initial) – No. of tablets per day	120 mg dimethyl fumarate (Fumaderm®) – No. of tablets per day
Week 1	0-0-1	–
Week 2	1-0-1	–
Week 3	1-1-1	–
Week 4	–	0-0-1
Week 5	–	1-0-1
Week 6	–	1-1-1
Week 7	–	1-1-2
Week 8	–	2-1-2
Week 9	–	2-2-2

Table 2: Dosing schedule for FAE *(from Pathirana et al (99)).*

One strategy to improve the tolerability of FAE is gradual dose increments on starting therapy according to the recommended dosing schedule (99). It is common in routine practice to be even more cautious with dose increments if patients still develop the common adverse effects of GI symptoms and flushing. Another strategy that was recommended in the Dutch guidelines (152) and in an expert panel recommendation for patients receiving DMF for multiple sclerosis (153) is prescribing antihistamines for those experiencing these adverse effects. This is based on the hypothesis that GI symptoms and flushing are similar to histamine-mediated symptoms (154). However, Balak et al (155) tested this theory by conducting a randomised placebo-controlled trial to assess if antihistamine addition to FAE would reduce the adverse effects. This trial included 50 participants with a median age of 44 years and PASI score ≥ 10. All participants received the FAE according to the standard dose increment schedule for 12 weeks, and half of the participants were randomised to receive cetirizine 10mg once daily whereas the other half received additional placebo tablets. At the study end-point it was observed that the addition of cetirizine did not reduce the incidence of adverse effects compared with placebo (84% in each group, P = 1.00) and the proportion of participants who dropped out due adverse effects did not statistically differ (24% vs. 32%, P = 0.53). This study however included a relatively small sample size and so may have been under-powered to detect a difference.

Pharmacokinetics:

After oral intake, DMF is rapidly hydrolysed by esterases in the gut to monomethyl fumarate (MMF). This rapid conversion is believed to be the cause of lack of detectable DMF in the blood circulation (141, 156). There is growing evidence to show that MMF is the prinicple active molecule *in vivo* after FAE oral administration (157). MMF reaches peak plasma concentration after 3.5 – 5 hours where it is metablised via the citric acid cycle to fumaric

acid, water (H_2O) and carbon dioxide (CO_2) (158). So, the majority of DMF metabolites (89%) are excreted by CO_2 exhalation (141, 159). A small proportion (11%) may enter the systemic circulation where it forms cysteine and N-acetyl cysteine conjugates of mono- and dimethyl succinate, excreted in urine (160). As urinary excretion plays a minor role in DMF metabolism, dose adjustment is not usually required for patients with renal impairment (159).

Mechanism of action:

The mode of action of FAEs is complex and appear to be multi-faceted. The different mechanisms of actions have been recently reviewed by Brück et al (159) and are summarised below **(Table 3)**. Yet, the full pharmacokinetic profiles of DMF and MMF remain unclear and to be elucidated.

Author	Mechanism of action	Effect
Ghoreschi et al (161) Lehmann et al (162) Dibbert et al (163) Rostami-Yazdi et al (164) Schmidt et al (165) Peterson et al (166) Schmidt & Dringen (167)	Influencing intracellular glutathione levels via binding of DMF/MMF to thiol groups of glutathione	Regulation of cellular responses to oxidative stress
Wilms et al (168) Linker et al (169) Gold et al (170) Helwa et al (171)	Activation of Nrf2 by DMF/MMF	Regulation of cellular antioxidant responses and stimulation of cytoprotective and anti-inflammatory factors such as HO-1
Ghoreschi et al (161) Vandermeeren et al (172) Loewe et al (173) Litjens et al (174) Mrowietz & Asadullah (160) Gerdes et al (175) Moharregh-Khiabani et al (176) Peng et al (177)	Indirect and/or direct inhibition of NF-κB activity by DMF	Influencing cytokine production by antigen-presenting cells, inhibition of Th1/Th17 responses, promotion of Th2 responses
Ghoreschi et al (161) Zhao et al (178) Li et al (179) Kang et al (180)	Modulation of oxidative stress-sensitive transcription factors HIF-1α and STATs by DMF	Inhibition of genes regulated by HIF-1α and STAT3/STAT1
Tang et al (181) Hanson et al (182, 183) Chen et al (184)	Agonism of HCA2 by MMF	Formation of COX-1 and PGE2, inhibition of neutrophil recruitment

Table 3: Summary of the main mechanisms of action of DMF/MMF. DMF: dimetyl fumarate; HCA2: hydroxy-caroxylic acid receptor 2; HIF-1α: hypoxia-inducible factor 1-alpha; HO-1: hemeoxygenase 1; MMF: monomethyl fumarate; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2: nuclear factor (erythroid-derived 2)-like 2; STAT: signal transducers and activators of transcription. *(adapted from Brück et al (159))*

To date, at least five mechanisms for DMF/MMF have been described in the treatment of psoriasis (159).

- After cellular uptake, the α, β unsaturated carboxylic acid easter DMF reacts with thiol groups of glutathione and lowers its levels. This as a result impacts cellular responses to oxidative stress
- Activation of nuclear factor-like 2 (Nrf2) dependent antioxidant response pathway leads to stimulation of cytoprotective and anti-inflammatory genes
- Inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activity affects cytokine production and the phenotype of APCs, which shifts Th1/Th17 immune response to a Th2 phenotype, resulting in anti-inflammatory response
- Inhibition of hydroxy-caroxylic acid receptor 2 (HCA2) which influences neutrophil adhesion, migration and recruitment, and
- Modulation of oxidative stress-sensitive transcription factors such as hypoxia-inducible factor 1-alpha (HIF-1α) and signal transducers and signal transducers and activators of transcription (STAT).

Biological Effects in Psoriasis:

Most of the data describing the actions of FAE are derived from *in vitro* studies. The complexity of FAE ingredients and pharmacokinetics also add to the challenge of understanding the biological effects they exert in psoriasis. However, data indicate multiple effects of fumarates on different cell types relevant to psoriasis pathogenesis as summarised below.

LYMPHOCYTES:

It has been shown that resident T lymphocytes, macrophages and neutrophils infiltrate psoriatic lesions before the development of significant epidermal changes (185, 186). T lymphocytes play a role in the development of psoriasis in three stages: activation, migration into the skin and release of cytokines (187). FAE interfer in this process, through the inhibition of NF-kB, by inducing immune cells apoptosis and preventing the release of inflammatory cytokines. *In vitro* studies have indeed demostrated the potent apoptotic effect of DMF (188) and their ability to impair the release of T-cell cytokines (189). A study in six patients treated with DMF for 16 weeks showed a significant reduction of lesional T-cell subset and normalised epidermal proliferation (190).

KERATINOCYTES:

Dimethyl fumarate has been shown to strongly suppress chemokine expression by keratinocytes (191) and inhibit keratonocyte cell proliferation and differentiation *in vitro* in a dose-dependent manner (188). The anti-proliferative effect of DMF and MMF is believed to occur as a result of transient increase of intracellular calcium in human keratinocytes (192). Another *in vitro* study using human keratinocyte cell line showed that DMF could also downregulate the expression of cell surface molecules such as the intercellular adhesion molecule 1 (ICAM-1) (193).

ENDOTHELIAL CELLS:

Angiogenesis is a key driver of psoriasis pathogenesis, evident by hyperproliferation of small dermal vessels in psoriasis skin (47). DMF has been shown to inhibit the expression of adhesion molecules such as E-selectin and vascular cell adhesion molecule-1 (VCAM-1) (194). DMF also causes a decrease in the formation of capillary-like structures in vascular endothelial growth factor (VEGF)-stimulated human endothelial cells, associated with a reduced expression of VEGF receptor 2 (195).

Study rationale:

Current oral systemic therapies, namely methotrexate, acitretin, and ciclosporin, are not effective in all of those with moderate to severe psoriasis and may cause adverse effects that require discontinuation of treatment. The next licensed step in treatment are expensive biologic treatments and more recently apremilast. Oral FAE are a cheaper alternative systemic therapy that are licensed in Germany, and recommended as first-line systemic agents for moderate to severe psoriasis in the European S3 guidelines (196). However, when we conducted our review, FAE were unlicensed in many other countries, which limited their clinical use and restricted the production of guidelines to assist patients and clinicians. For example, FAE are used to treat many individuals with psoriasis in the UK (118, 119), but when our review was conducted, no guidance existed from NICE or the BAD (NICE approval was issued in September 2017 (123), after publication of our review). This meant that there was no standardisation of prescribing schedules for oral fumaric acid esters, and many dermatologists chose not to consider their use for psoriasis because of the lack of guidance. Other factors that probably influenced prescribing FAE as an off-label medication were the cost of FAE in comparison to other systemic therapies such as methotrexate and acitretin, and physicians' lack of experience with FAE and managing resulting adverse effects. As a result, inequalities existed in psoriasis care due to patient location. This review intended to assist in decision-making between patients and clinicians regarding choice of systemic therapy for psoriasis.

The study was registered with the Cochrane Skin Group (CSG). The plans for this review were published in the Cochrane Library as a protocol 'Oral fumaric acid esters for psoriasis' (197).

Funding sources:

A grant was awarded by the Psoriasis and Psoriatic Arthritis Alliance (PAPAA) (Appendix 10).

Methods:

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 FAE, with or without another systemic or topical active treatment, with placebo or another active treatment:

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

We included studies that used any form of FAE, including Fumaderm®, the main commercially available preparation.

Types of outcome measures:

The study outcomes were specified in line with the Cochrane handbook for systematic reviews of interventions (198), which recommends no more than three primary outcomes. These should include at least one desirable and at least one undesirable outcome. A patient research partner was involved in selecting the outcomes at the protocol writing stage.

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.

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 nuisance adverse effects of treatment, i.e., non-serious side-effects that do not lead to treatment discontinuation.
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 included studies of any duration, but we planned to undertake a priori subgroup analysis to investigate the influence of duration of treatment. Studies were divided into short-term treatment duration (less than 12 weeks), medium-term duration (from 12 weeks to less than 6 months), and long-term duration (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 11;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 4, 2015) using the strategy in Appendix 11;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 11;
- EMBASE via Ovid (from 1974) using the strategy in Appendix 11; and

- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 11.

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.controlledtrials.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, two authors (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:

The first author (AA) contacted by email the corresponding authors of included and excluded FAE clinical trials to check for further unpublished RCTs. I 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 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 (198).

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. The full texts of studies that potentially met the criteria were examined, 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. The reasons for exclusion of studies were recorded in the 'Characteristics of excluded studies' tables **(Table 4)**.

Study	Reason for exclusion
Balak, 2015 (155)	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 (199)	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 (200)	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 (146)	The paper reported observations from 5 studies of which study 3 might have been eligible, but there was no evidence of randomisation
Nieboer, 1990 (148)	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

Table 4: Characteristics of excluded studies. AE: adverse effects; DMF: dimethyl fumarate; FAE: fumaric acid esters; MEF: monoethyl fumarate; PTX: pentoxifylline (from Atwan et al (201).

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 (198). The following information from the reports of included studies were sought: 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. The information collected was entered into the 'Characteristics of included studies' tables **(Table 5)**.

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 (198). They graded the risk of bias as 'low', 'high', or 'unclear' for each of the following domains:

- **random sequence generation** (biased allocation to interventions due to inadequate generation of a randomised sequence);
- **allocation concealment** (biased allocation to interventions due to inadequate concealment of allocations prior to assignment);
- **blinding of participants and personnel** (performance bias due to knowledge of the allocated interventions by participants and personnel during the study);
- **blinding of outcome assessment** (detection bias due to knowledge of the allocated interventions by outcome assessors);
- **incomplete outcome data** (attrition bias due to amount, nature or handling of incomplete outcome data);

- **selective outcome reporting** (reporting bias due to selective outcome reporting). For this Cochrane review, trial databases were checked to ensure that reported outcomes matched those prospectively listed; and
- **other sources of bias** (sources of bias that are relevant only in certain circumstances (e.g. recruitment bias in cluster-randomised trials) or particular clinical setting).

Measures of treatment effect:

For dichotomous outcomes, risk ratios with 95% confidence intervals (CIs) were pooled. 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. Follow-up scores rather than change from baseline were used as recommended by The Cochrane Collaboration (198). 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 (198). However, we did not include any cross-over or cluster-randomised trials.

Dealing with missing data:

Whenever possible, AA 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:

Statistical heterogeneity was assessed 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 (202). An I^2 statistic of between 40% and 75% may represent substantial heterogeneity (198), 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 (203) 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% CI 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 (FAE versus placebo, FAE 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:

Results of the search

The database searches identified a total of 80 records. Six additional records were identified by handsearching and 8 by searching the trials registers **(Figure 14)**, giving a total of 78 records after the removal of duplicates and ongoing studies. Two authors independently screened the titles and abstracts yielding 11 potentially eligible reports of studies. After obtaining the full texts of these reports, five studies were excluded **(Table 4)**, and the remaining six were eligible for inclusion in the review. Two of the included studies were published in full reports (115, 204), one in a brief communication (205), one in a letter (206), and two as abstracts (207, 208). Full reports of published abstracts were not obtained by contacting the authors *(see 'notes' for Langner 2004 and Mrowietz 2006; Characteristics of included studies Table 5).*

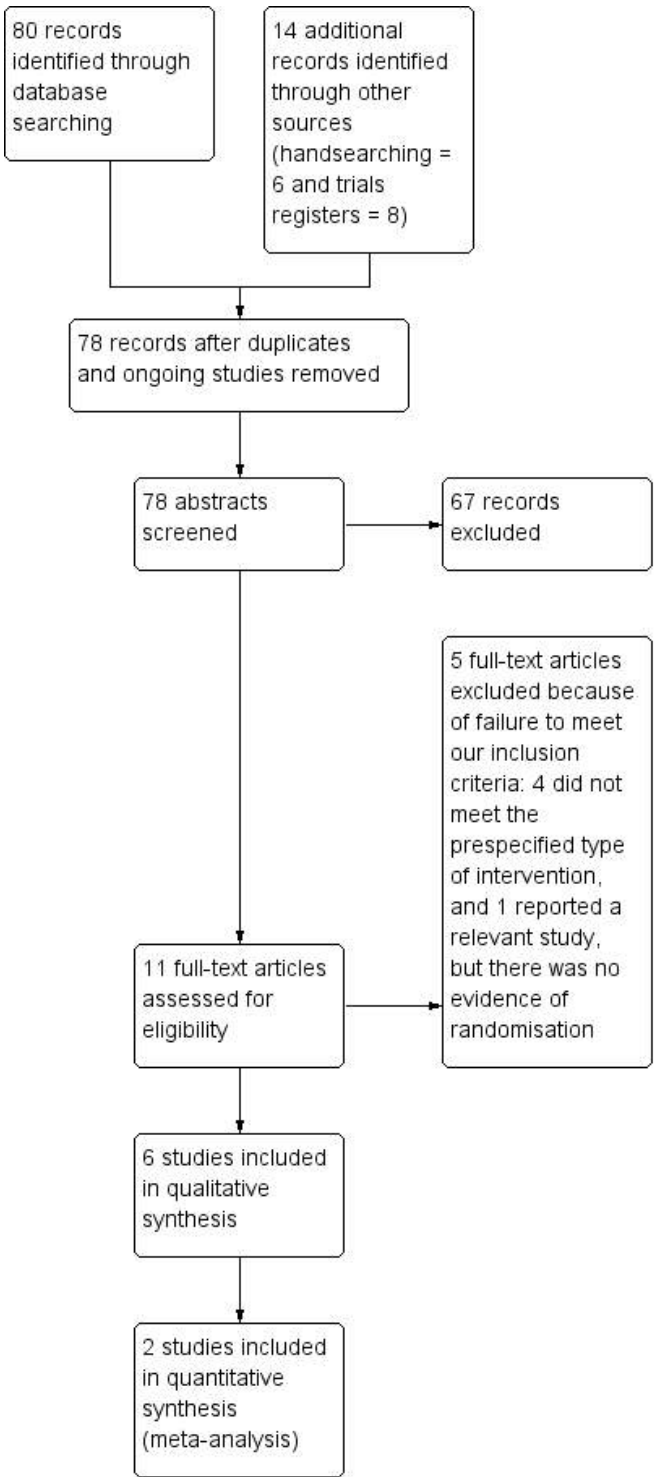


Figure 14: Study flow diagram *(from Atwan et al (201))*.

Included studies:

Six studies (115, 204-208) with a total of 544 participants met the inclusion criteria **(Table 5)**.

Table 5: Characteristics of included srudies *(from Atwan et al (201).*

Study author: Altmeyer 1994 (204)

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
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

Study author: Fallah Arani 2011 (115)

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** 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 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

Study author: Langner 2004 (207)

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) 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 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

Study author: Mrowietz 2006 (208)

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 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

Study author: Nugteren-Huying 1990 (205)

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** 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
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

Study author: Peeters 1992 (206)

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 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

***AE:** adverse effects**; BSA:** body surface area; **FAE:** 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.*

Setting:

Three of the included studies were carried out in the Netherlands (115, 205, 206), one in Poland (207), and two were international multicenter studies, all conducted in secondary care settings (204, 208).

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 (206). 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 in Langner et al (207), which did not mention the age range of the participants. Two studies included only participants with chronic plaque psoriasis (115, 208); two included chronic plaque, guttate, pustular, and erythrodermic types (204, 207), but two studies did not report the type (205, 206). For participants to be eligible, 1 study (115) required them to have a Psoriasis Area and Severity Index (PASI) score ≥ 10 at baseline; 1 study (208) ≥ 12; and 1 study (207) 16 to 24. Two studies used body surface area (BSA) to assess severity for eligibility, being at least 10% in 1 study, (205), and more than 10% in another (204). One study, which was specifically designed for PsA, did not include psoriasis severity for eligibility assessment (206). Fallah Arani et al (115) 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 (204, 206, 208), and one compared FAE with methotrexate (115). One study had a four-group dose-finding placebo-controlled design (207), and one compared FAE versus octylhydrogen fumarate plus magnesium and zinc monoethyl fumarate (MEF) versus placebo (205).

Interventions:

There were some variations in the dose increments between studies. Four studies (115, 204-206) 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 were BG-12 (207) and Panaclar™, formerly BG00012, which contained 120 mg DMF (208). Low-strength tablets (containing 30 mg DMF) were

given in the first 2 weeks of the intervention in Altmeyer et al (204) and the first 3 weeks in Fallah Arani et al (115) whereas the other studies did not mention treatment initiation with low-strength tablets (205-208). In Altmeyer et al (204) the 120 mg DMF tablets dose increased 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 et al (115) to a maximum of 6 tablets daily at week 9. Mrowietz et al (208) the dose was titrated over 7 days to the maximum dose of 720mg DMF (6 tablets). Two studies reported a gradual increase from one to six tablets daily with no further information (205, 206). Finally, Langner et al (207) 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 (115), 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 (115, 207) or week 16 (204-206, 208). Not all trials reported on all outcomes prespecified in our review. The included studies reported the following outcomes: PASI score (115, 204, 207, 208); proportion of participants who discontinued treatment because of adverse effects (115, 206); quality of life score (208); proportion of participants attaining PASI 50, PASI 75 (115, 208), and PASI 90 (115); proportion of participants experiencing any AEs (115, 204); and proportion of participants experiencing serious AEs (115). None of the included studies reported data on economic evaluations.

Risk of bias in included studies:

Details of the ’Risk of bias’ assessment are provided in the ’Risk of bias’ tables in **Table 5**. Overall, there was insufficient reporting in most of the included studies to permit judgement of ’low risk’ or ’high risk’ **(Figure 15; Figure 16)**. One reason is the publication type of some included studies, which included two abstracts (207, 208), one letter (206), and one brief communication (205). The fact that some studies were about 20 years old may also have influenced their incomplete reporting (204, 206).

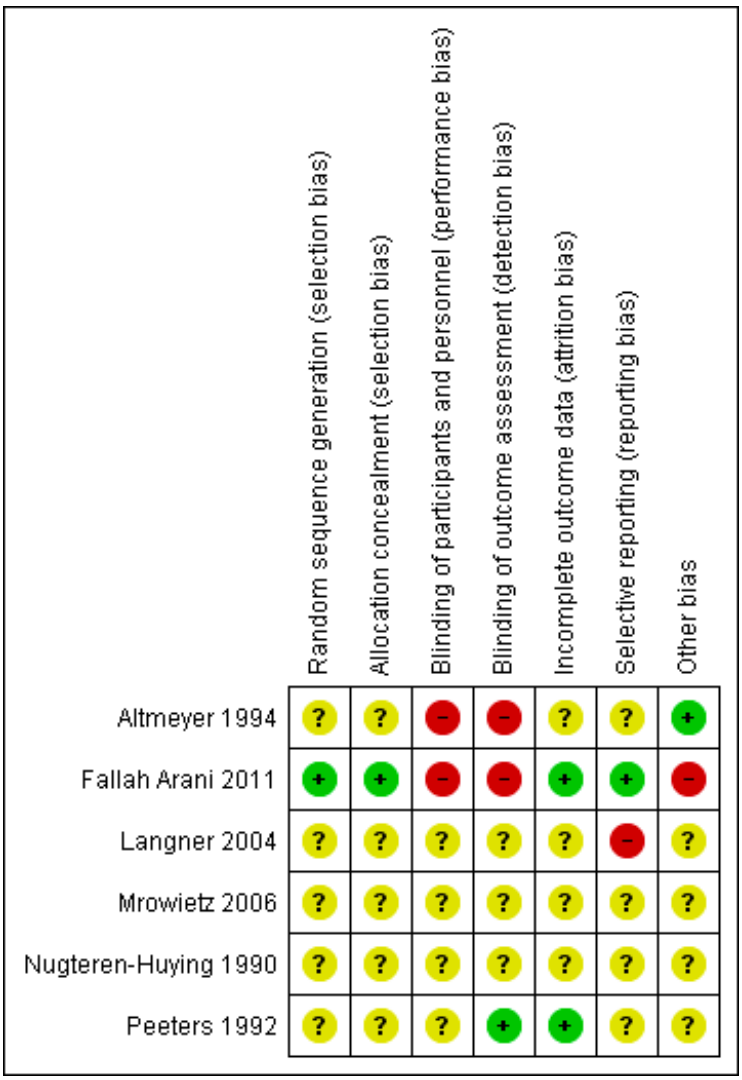


Figure 15: 'Risk of bias' summary: review authors' judgement about each 'Risk of bias' item for each included study *(from Atwan et al (201)).*

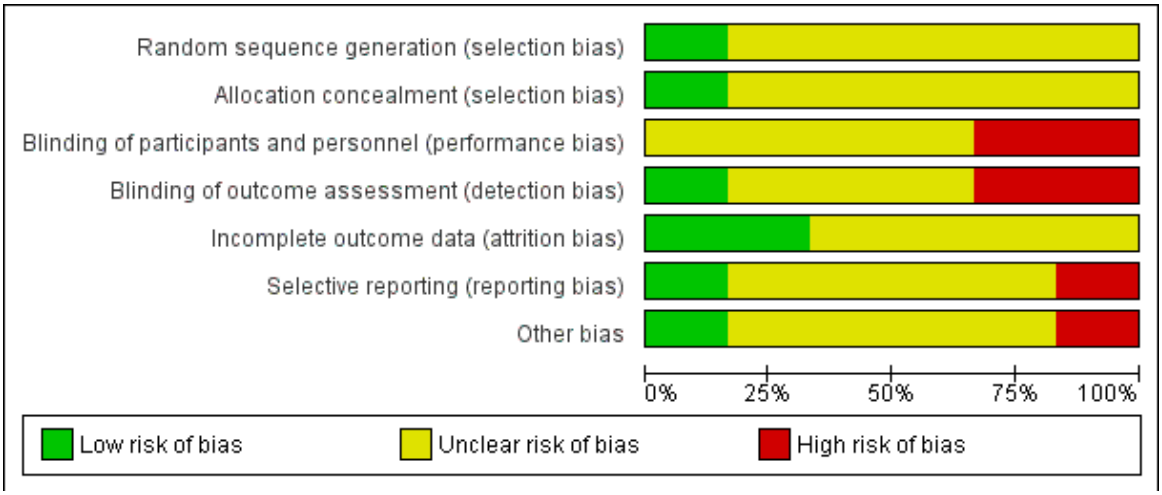


Figure 16: 'Risk of bias' graph: review authors' judgement about each 'Risk of bias' item presented as percentages across all included studies *(from Atwan et al (201)).*

Allocation:

Only one study (115) 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 (204-208). Blinding of participants and personnel (performance bias) was of unclear risk in four of these studies and high risk in one (204). Blinding of outcome assessment (detection bias) was of low risk in one study (206), high risk in one (204), and unclear risk in the remaining three double-blinded studies (205, 207, 208). The sixth study included in our review by Fallah Arani et al (115) 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 (115, 206). This risk was unclear in the remaining four studies (204, 205, 207, 208).

Selective reporting:

The protocol of one study was prospectively registered (115). Slight variations between the registered protocol and published report was noted, but contact with the author confirmed that the relevant ethics committee had approved some minor changes after registering the protocol. High risk of selective reporting was observed 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 (207). The risk was unclear in other studies (204-206, 208). Funnel plots and Egger's test were not performed 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 (204), unclear in four studies (205-208), and high in one study (115), in which the dosing schedule of the comparator intervention (methotrexate) may have influenced the true efficacy results.

Effects of interventions:

All of the included studies had a medium duration (12 – 16 weeks), so subgroup analysis for different treatment durations was not performed. Sensitivity analysis also was not performed because the risk of bias in the included studies was mostly unclear. Five studies compared FAE with placebo **(Table 6)**, and one study compared FAE with methotrexate **(Table 7)**. The two comparisons are displayed in separate 'Summary of findings' ('SoF') tables.

A narrative approach was adopted to present the effects of FAE in the treatment of psoriasis because of a lack of opportunities for meta-analysis. Data from two reports comparing FAE with placebo were combined 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 (204-208), one of which was designed to measure the treatment effect in psoriatic arthritis (PsA) where all participants also had psoriasis (206). Three studies used a mixture of dimethyl fumarate (DMF) plus monoethyl fumarate (MEF) in enteric-coated tablets as an intervention (204-206) whereas the other two studies used DMF alone (207, 208). The prespecified outcomes were reported in some of the studies:

- PASI score (204, 207, 208);
- proportion of participants discontinued treatment because of adverse effects (206);
- quality of life (QoL) score (208);
- proportion of participants attaining PASI 50 and PASI 75 (207, 208); and
- proportion of participants experiencing common nuisance adverse effects (204).

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 **(Table 6)**.

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, only the PASI 50 meta-analysis results are reported because of significant heterogeneity for the PASI 75 data. Meta-analyses were not possible for all other outcomes, so these were reported in a narrative manner.

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)[b]	Comments
	Risk with placebo	Risk with FAEs				
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, $P < 0·001$); median reduction of 71% (FAE) and 6% (placebo) (1 study, 144 participants, $P < 0·001$); median reduction of 67·8% (FAE) and 10·2% (placebo) (1 study, 175 participants, $P < 0·001$)			418 (3 RCTs)	⊕⊕◯◯; LOW[c,d]	All three studies reported significant benefit with FAEs, at week 12 (one study) and week 16 (two studies), but data could not be pooled in a meta-analysis due to different ways of PASI score reporting
AEs leading to treatment discontinuation	Two participants withdrew from the FAE group (n = 13) compared with no dropouts in the placebo group (n = 14) (RR 5·36, 95% CI 0·28–102·12)			27 (1 RCT)	⊕◯◯◯; VERY LOW[e,f]	Outcome reported at week 16. Unclear whether any of the reported AEs were 'serious'
QoL assessed with Skindex-29 (range 0–100; higher scores indicate lower level of QoL)	Mean scores reduced from 54·7 at baseline to 27·0 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[c,g]	The reporting abstract did not provide the statistical values needed to calculate the mean difference with 95% CI
Common nuisance AEs (not leading to treatment discontinuation)	Moderate 16 per 100	76 per 100 (39–100)	RR 4·72 (2·45–9·08)	99 (1 RCT)	⊕⊕⊕◯; MODERATE[c]	Most commonly stomach ache or cramps, diarrhoea and flushing
PASI 50	Moderate 14 per 100	64 per 100 (39–100)	RR 4·55 (2·80–7·40)	247 (2 RCTs)	⊕⊕◯◯; LOW[c,g]	The meta-analysis included participants who received dimethylfumarate 720 mg
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[c,g]	Reported to be a statistically significant difference but data not pooled because of significant heterogeneity ($I^2 = 77\%$)
PASI 90 (not measured)	See comment	See comment	Not estimable	–	–	Not measured in the included studies

AE, adverse effect; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI 50, ≥ 50% improvement in PASI; QoL, quality of Life; RCT, randomized controlled trial; RR, risk ratio. [a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [b]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 the effect. [c]Downgraded one level due limitations in design; high risk of performance and detection bias. [d]Downgraded one level due to risk of publication bias; data obtained from abstract(s), full report(s) not available. [e]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. [f]Downgraded two levels for imprecision; small sample size and very wide CIs that included the possibility of an effect in either direction (crosses line of no effect). [g]Downgraded one level due to risk of bias; insufficient reporting.

Table 6: Summary of findings: fumaric acid esters (FAEs) vs. placebo (from Atwan et al 2016 (188)).

Primary outcomes:

PASI score:

Altmeyer et al (204) 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 and colleagues (207) compared 3 doses of FAE (120mg, 360mg, 720mg) with placebo and 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 360mg and 720mg dose groups compared with placebo (P<0.001). The paper did not report mean PASI scores at baseline and follow-up. Similarly, Mrowietz et al (208) 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%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 (205, 206), “scoring the degree of infiltration and scaling of the plaques from 0 (no infiltration or scaling) to 8 (very severe infiltration or scaling)” (205), or scoring the degree of erythema and scaling on a scale range from 0 to 8 (206).

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) (206). 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) **(Figure 17)**. However, these findings were uncertain because of indirectness and a very wide confidence interval.

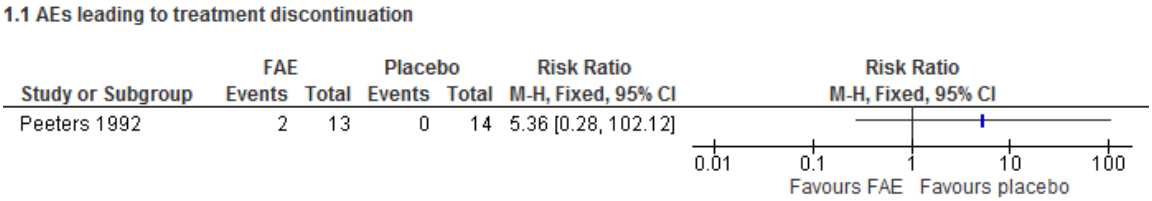


Figure 17: Comparison: FAE vs placebo; Outcome: AEs leading to treatment discontinuation *(from Atwan et al (201)).*

Nugteren-Huying et al (205) 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 one experienced renal insufficiency.

In another study by Altmeyer et al (204), 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 (207, 208) 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 (208) 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 points (P<0.001).

Proportion of participants attaining PASI 50, 75, and 90:

The included studies reported PASI 50 and PASI 75 (207, 208). 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) **(Figure 18)**. More participants on FAE therapy also attained PASI 75, but the results were not combined in meta-analysis due to substantial heterogeneity between these 2 studies (I^2 statistic = 77%).

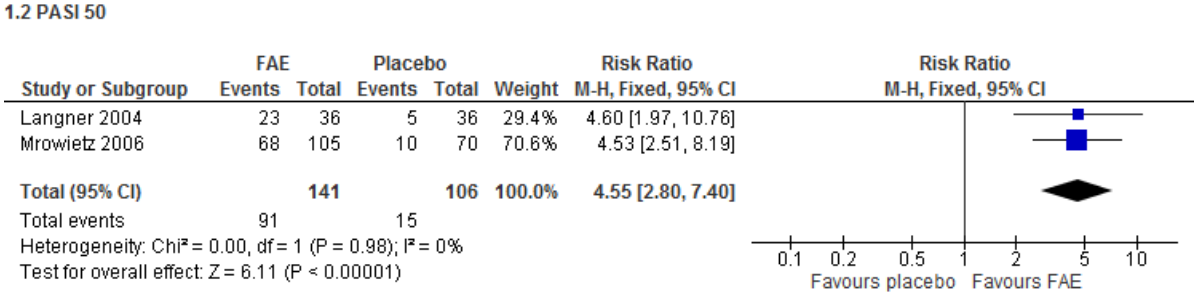


Figure 18: Comparison: FAE vs placebo; Outcome: PASI 50 *(from Atwan et al (201)).*

Altmeyer et al (204) 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 - 95%, 30 - 69%, < 30%, 0%, and < 0%; hence, we could not integrate these into the above calculations. The remaining two studies (205, 206) did not use PASI for severity assessment.

Proportion of participants experiencing any adverse effects of treatment:

Based on one study (204), 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) **(Figure 19)**. 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.

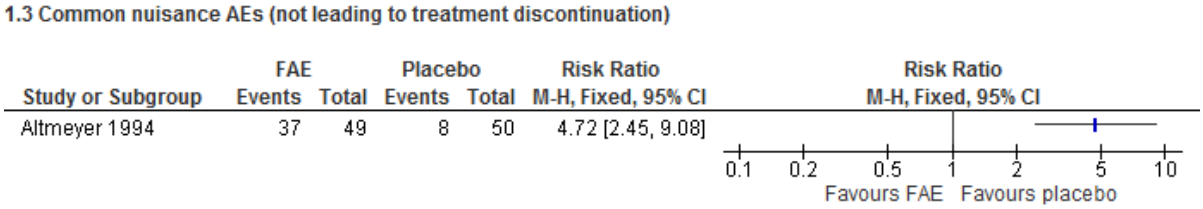


Figure 19: Comparison: FAE vs placebo; Outcome: common nuisance AEs (i.e. not leading to treatment discontinuation *(from Atwan et al (201)).*

One study (206) 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 skin psoriasis alone.

In Nugteren-Huying et al (205), 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=8) and group two (n=4) 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 et al (208) 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 AEs to be generally mild to moderate in severity and transient.

Finally, Langner et al (207) 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 (no numerical values provided 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 oral fumaric acid esters with methotrexate

Only one study with an open label design compared FAE with methotrexate (MTX) (115). Reported outcomes included PASI score; proportion of participants who discontinued treatment because of AEs; proportion of participants who achieved PASI 50, 75, and 90; and proportion of participants experiencing common nuisance and serious AEs. The quality of the evidence for these outcomes was graded as 'very low' **(Table 7)**.

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)[b]	Comments
	Risk with MTX	Risk with FAE				
PASI score; scale range from 0 to 72 (higher score indicates more severe psoriasis)	Mean PASI score was 6·7	Mean PASI score in the intervention group was 3·8 more (0·68–6·92 more)	–	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	PASI score was measured at week 12. The study reported no significant difference between FAEs and MTX based on mean change from baseline
AEs leading to treatment discontinuation	Moderate 20 per 100	4 per 100 (0–31)	RR 0·19 (0·02–1·53)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (FAE 26, MTX 25). The main reasons were elevated liver enzymes with MTX and diarrhoea with FAEs. No serious AEs occurred in either group
Quality of life: not measured	See comment	See comment	Not estimable	–	–	Quality of life was not assessed
Common nuisance AEs (not leading to treatment discontinuation)	Moderate 100 per 100	89 per 100 (77–100)	RR 0·89 (0·77–1·03)	54 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Only flushing was significantly more reported with FAEs. Occurrences of other AEs including laboratory findings were not significantly different
PASI 50	Moderate 60 per 100	43 per 100 (25–73)	RR 0·71 (0·41–1·22)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (MTX 25, FAE 26)
PASI 75	Moderate 24 per 100	19 per 100 (7–55)	RR 0·80 (0·28–2·29)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (MTX 25, FAE 26)
PASI 90	Moderate 8 per 100	4 per 100 (0–40)	RR 0·48 (0·05–4·98)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (MTX 25, FAE 26)

AE, adverse effect; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI 50, ≥ 50% improvement in PASI; RCT, randomized controlled trial; RR, risk ratio. [a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [b]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 the effect. [c]Downgraded one level due to limitations in design; highest dose of MTX given was 15 mg per week while the maximum dose of FAEs was given. [d]Downgraded one level due to limitations in design; open-label design (high risk of performance and detection bias). [e]Downgraded one level due to imprecision; small sample size.

Table 7: Summary of findings: fumaric acid esters (FAE) vs. methotrexate (MTX). Patient or population: psoriasis in adults (from Atwan et al 2016 (188)).

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). However, this comparison does not take into account the baseline difference and so is unreliable.

Proportion of participants who discontinued treatment due to adverse effects (AEs):

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) **(Figure 20)**. The study reported the elevated liver enzymes to be transient and normalised four to eight weeks after treatment cessation.

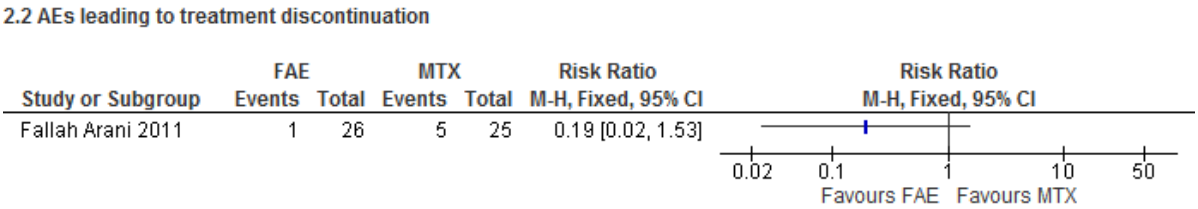


Figure 20: Comparison: FAE vs methotrexate (MTX); Outcome: Adverse effects (AEs) leading to treatment discontinuation *(from Atwan et al (201)).*

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, 75, and 90 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) **(Figure 21)**. 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) **(Figure 22)**, 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) **(Figure 23)**.

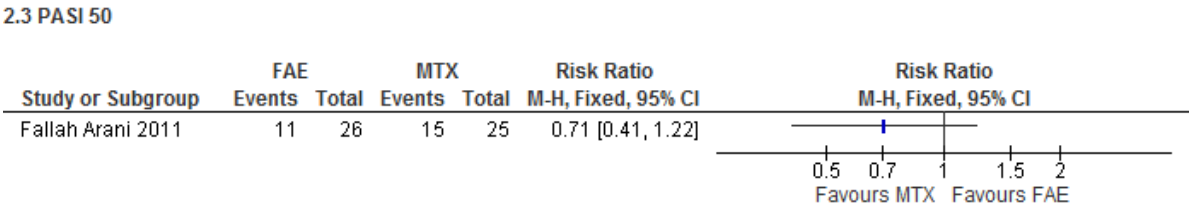


Figure 21: Comparison: FAE vs methotrexate (MTX); Outcome: PASI 50 *(from Atwan et al (201)).*

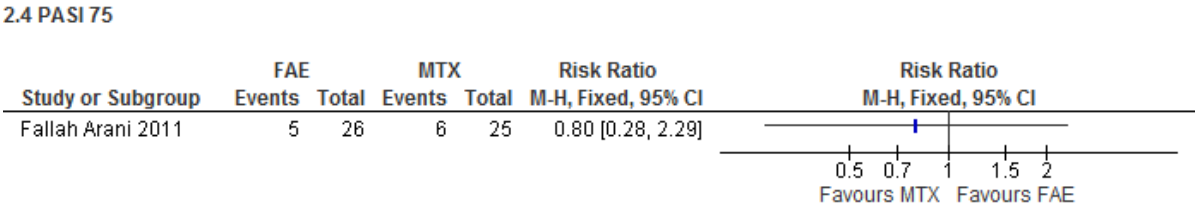


Figure 22: Comparison: FAE vs methotrexate (MTX); Outcome: PASI 75 *(from Atwan et al (201)).*

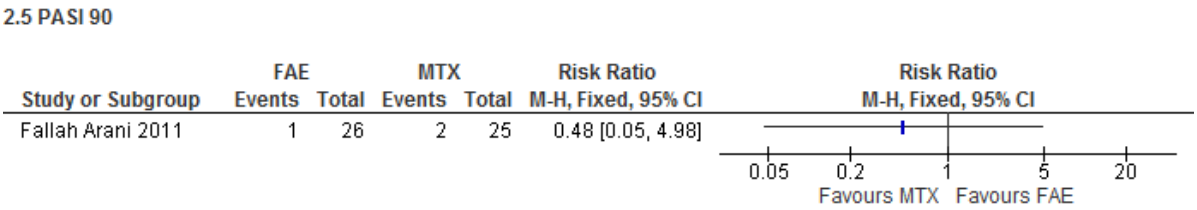


Figure 23: Comparison: FAE vs methotrexate (MTX); Outcome: PASI 90 *(from Atwan et al (201)).*

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) **(Figure 24)**. 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).

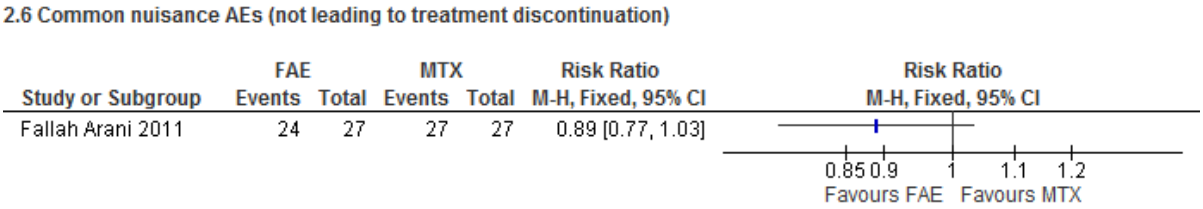


Figure 24: Comparison: FAE vs methotrexate (MTX); Outcome: common nuisance AEs (i.e. not leading to treatment discontinuation *(from Atwan et al (201)).*

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) 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) 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) 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:

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. Six randomised controlled trials (RCTs), with a total of 544 participants, were included in this review. Five of these studies compared FAE with placebo. Data from these studies could not be pooled in meta-analyses because of variations in reported outcomes and insufficient reporting; the only

exception was for 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 (64), and some have argued that in the era of biologic therapies, PASI 90 should be the treatment goal (209). Unfortunately, PASI 75 data in our review showed significant heterogeneity (I^2 statistic = 77%), so we did not combine these studies.

Three of the studies reported statistically significant reduction of PASI scores with FAE when compared with placebo, but the mean difference could not be evaluated. The dropout rate due to adverse effects (AEs) was obtained from one study with uncertain findings due to indirectness, as designed for psoriatic arthritis, and a very wide confidence interval. 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 abdominal pain, 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.

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. It was not possible to draw conclusions regarding whether the variations in dose increments had an impact on the magnitude of treatment effect or risk of AEs. 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 (15mg weekly) may have been suboptimal as higher doses are often 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 percentage 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, the long-term efficacy and safety of FAE could not be established from the included trials. Also, none of the included studies reported data on economic evaluations, so this was not possible to assess in our review.

Data presented in this review was obtained from six reports, including two abstracts, one brief communication, and one letter. Incompletely reported studies present challenges for data extraction; however, we felt it was important to include them in this review because of the overall lack of eligible RCTs. Four studies presented PASI score as a primary outcome 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. 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.

To our knowledge, all of the studies related to this review were identified. 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 Table 5). In some cases, no replies received, in part due to the length of time that had elapsed since the studies were performed. Advice was regularly sought from the Cochrane Skin Group (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 the update of this review (planned for 2020) 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 from two reports (207, 208), although we concede that this is a somewhat arbitrary threshold for assessing heterogeneity, which may depend on several factors (section 9.5.2 – Cochrane Handbook for Systematic Reviews of Interventions (198)).

Efficacy and safety data from non-Cochrane systematic reviews:

Other non-Cochrane systematic reviews examining FAE for psoriasis were identified in the literature. Griffiths et al (94) conducted a review for treatments of severe psoriasis that included FAE. This review included five studies, two of which we excluded from our review (146, 148) (please see Table 2 for the reasons for exclusion). On the other hand, the Griffiths et al review (94) excluded Peeters et al study (206) 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 et al review (94) 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 concluded that FAE was superior to placebo with a pooled RD value of 0.47 (95%CI 0.33 to 0.61) (combined results of Altmeyer et al (204) and Nugteren-Huying et al (205)). This review performed no meta-analyses regarding adverse effects or other outcomes specified in our review.

Mustafa and Al-Hoqail (210) performed a systematic review that included 21 RCTs reporting efficacy of systemic treatments for moderate to severe psoriasis. This 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 this review mentioned *"Rates of withdrawals due to adverse events were highest for methotrexate and oral fumaric acid esters"*, but the paper provided no relevant details. 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 and colleagues (8) 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 et al included two studies (Altmeyer et al (204) and Fallah Arani et al (115)). The review found that FAE is superior to placebo based on mean PASI change and has similar efficacy to MTX (absolute risk difference 0.05, 95% CI -0.18 to 0.27) based on Fallah Arani et al report (115)), in agreement with the findings of our Cochrane review which calculated risk ratios. In keeping with our review, Schmitt et al review (8) reported that the rates of adverse effects and withdrawals did not differ between FAE and MTX but no statistical analysis was undertaken.

Another systematic review by Ceglowska et al (211) in a conference proceeding reported clinical effectiveness of FAE for psoriasis and psoriatic arthritis. This review included three of our included studies (Altmeyer et al (204); Fallah Arani et al (115); and Peeters et al (206)), 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 et al review (211) did not examine the safety of FAE to compare with our findings. The quality of included studies in their review 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"* (99). 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 et al (212) examined the effectiveness, dosing, and adverse effects of Fumaderm® 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 DLQI scores in the study population decreased by 66.6% and 67.2% at 12 months, respectively. In comparison, one of our included studies (208) reported 47% improvement in mean Skindex-29 score at 16 weeks, a much earlier endpoint. The Walker et al study (212) 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 et al (206) and Fallah Arani et al (115) 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.

Recent evidence for DMF in psoriasis:

Following the publication of our Cochrane systematic review, Mrowietz et al (213) published the BRIDGE study, a three-arm randomised double-blind placebo-controlled non-inferiority trial including 671 participants with moderate to severe psoriasis. In this study, participants received either DMF (n=267), Fumaderm® (n=273) or placebo (n=131). The primary outcomes were the proportion of participants achieving PASI 75 and a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at week 16. It was found that 37.5% of those received DMF and 40.3% of participants on Fumaderm® achieved PASI 75 (non-inferiority: P<0.001) but both interventions were superior to placebo (P<0.001). Both DMF and Fumaderm® had a similar occurrences of treatment-related AEs, commonly diarrhoea (DMF = 38.7%; Fumaderm® = 39.9%), upper abdominal pain (DMF = 20.1%; Fumaderm® = 22.6%) and flushing (DMF = 18.3%; Fumaderm® = 16.3%). The noninferiority margin between DMF and Fumaderm® in this study was set at 15%, so the results must be

interpreted with caution especially because of the lack of established MCID for PASI score. This study was funded by Almirall S.A., the manufacturer of the now approved DMF preparation, Skilarence®.

Based on this study, DMF gained European Medicines Agency (EMA) (122) and NICE (123) approval for the treatment of moderate to severe psoriasis in adults. The NICE guidance recommends DMF as an option in those with severe psoriasis (PASI score of 10 or more) who have not responded to other systemic treatments including methotrexate, ciclosporin and PUVA, or if these are contraindicated or not tolerated (123). This implies that DMF is not a first-line systemic treatment and the eligibility criteria are comparable to biologic therapies. In part these recommendations were based on the available evidence from the BRIDGE study (213) in which PASI >10 and DLQI > 10 were eligibility criteria.

Lymphopaenia and the risk of progressive multifocal leukoencephalopathy:

Long-term safety of systemic therapies is an important factor to be considered by patients and clinicians. This could not be analysed from our Cochrane systematic review which included only short-term studies. One of the concerns with FAE treatment is the risk of prolonged lymphopaenia. The occurrence of this adverse effect cannot be estimated reliably from studies with small sample sizes. Also, in older studies lymphopaenia was measured according to different definitions (e.g. < 20% of the total leucocyte count (116); or > 50% reduction compared with baseline count (214)). The FUTURE study by Reich et al (215) examined the long-term efficacy and safety of FAE in 984 patients who received the treatment for a mean duration of 44 months in a retrospective fashion. Some of these (71%) received continuous treatment for at least 2 years whereas others had temporary interruptions for no longer than 6 months. Lymphopaenia was noted in 32% of patients after 3 months of treatment, increasing to 41% in studied population after 24 months **(Figure 25)**.

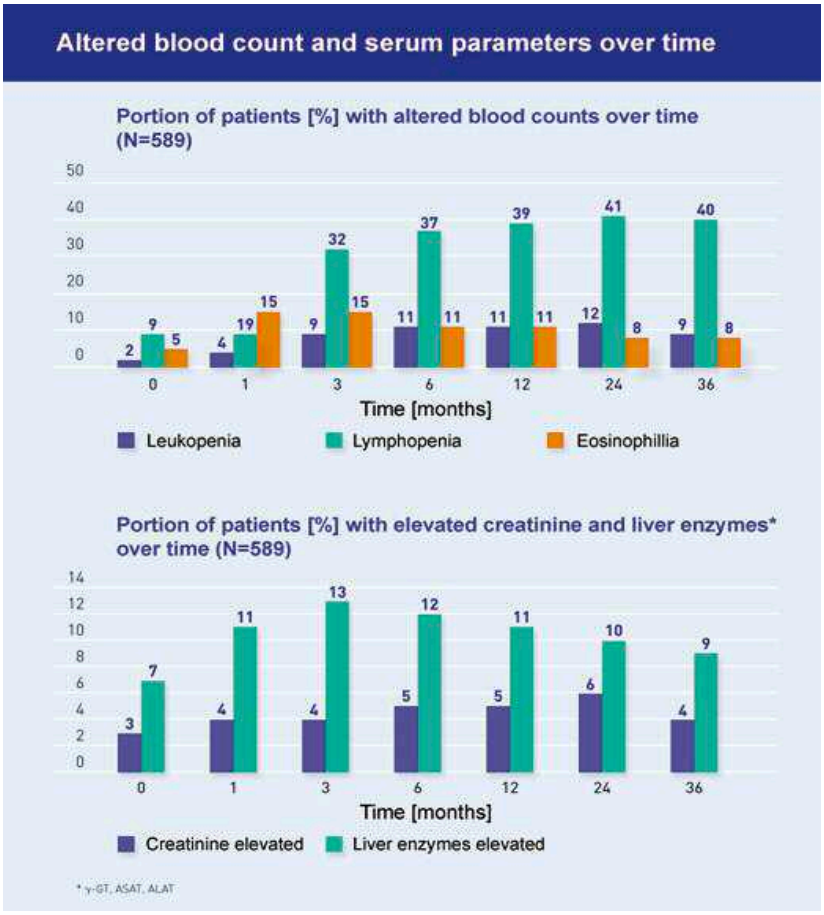


Figure 25: Percent of patients with change in blood count and other serum parameters during long-term treatment (*from Reich et al (215)*).

Further data is provided by the BRIDGE study, an RCT involving 671 participants, showed lymphopaenia occurrence in 20.6% of patients who had FAE (n= 562) at week 16 (213). The lymphopaenia is not necessarily associated with leucopoenia, which was observed in 9% of patients at 3 months and maximally in 12% after 2 years (215). Interestingly, the status of certain genotypes of glutathione S-transferases (GSTs), a group of enzymes involved in xenobiotic detoxification, appeared to serve as a predictor for the occurrence of marked lymphopaenia in a study where 106 psoriasis patients were treated with Fumaderm® (216). Long-term FAE treatment did not appear to affect hepatic or renal function in the majority of patients where 96.1% of patients continued the treatment with no need for dose adjustments or treatment discontinuation (215).

Before the approval of dimethyl fumarate (DMF) (Skilarence®) for the treatment of moderate to severe psoriasis in the UK and Europe in 2017, guidance on blood count monitoring was available for Fumaderm® (combined DMF plus MEF) via the Fumaderm Summary of Product Characteristics (SmPC) and the European S3-guidelines on the systemic treatment for psoriasis vulgaris (67, 99, 196). These recommendations indicated that blood test monitoring

should be performed at baseline and then every 4 – 8 weeks (weak consensus on frequency) (67). FAE should be withdrawn if leucocyte count drops below 3.0 $x10^9$ /L or if total lymphocyte counts is less than 0.5 $x10^9$ /L, whereas dose reduction is necessary if lymphocyte count is between 0.5 and 0.7 $x10^9$ /L. Guidance produced for Tecfidera® (DMF alone preparation licensed for the treatment of relapsing-remitting multiple sclerosis) recommended measuring leucocyte count at baseline and then annually, or as clinically indicated, and treatment should be withheld in patients with severe infections, but there was no guidance on managing leuco – or lymphopaenia (217). More recently, approval of Skilarence® came with clear guidance on blood count monitoring in patients receiving this treatment for moderate-to-severe psoriasis (218, 219), recommending treatment discontuation if lymphocyte level drops below 0.7 $x10^9$ /L **(Table 8)**.

	Monitoring during treatment	
	Action to take in the following circumstances:	
Lymphocytes	≥1.0x10⁹ cells/L	**Every 3 months**
	<1.0 x 10⁹ cells/L and ≥0.7 x 10⁹ cells/L	**Monthly** monitoring until values return to ≥1.0x10⁹ cells/L for 2 consecutive tests
	<0.7 x 10⁹ cells/L	Blood test must be **repeated** and if levels are confirmed then **discontinue** treatment
Leukocytes	<3.0 x 10⁹ cells/L	**Discontinue** treatment

Table 8: Blood test monitoring during dimethyl fumarate treatment (from Skilarence® Summary of Product Characterises (219))

Blood monitoring in patients receiving FAE is particularly important as longstanding lymphopaenia, especially reduction in CD4+ T cells, may promote opportunistic infections and activation of latent infections (220). One such condition is progressive multifocal leukoencephalopathy (PML), a severe demyelinating disease of the nervous system caused by endogenous reactivation of John Cunningham virus (JCV). This polyoma virus typically causes an asymptomatic infection in childhood, usually in the first decade of life, resulting in circulating antibodies in 86% of healthy adults (219, 221). The virus remains latent in the kidneys and lymphoid organs but reactivation and spread to the brain can occur in the event of profound cellular immunosuppression (222). This infection develops almost exclusively in immunocompromised individuals. Patients with acquired immunodeficiency syndrome (AIDS) and idiopathic lymphopaenia for example have been observed to have higher incidence of PML (220). PML has also been reported in patients treated with certain

medications with immunosuppressive properties such as rituximab, natalizumab, efalizumab, and glucocorticoids (149). However, in some of these cases these therapies were used in combination with other immunosuppressants (e.g. cyclophosphamide, leflunomide and methotrexate) and others had underlying haematologic malignancy or collagen vascular disease (222). Drug-induced PML was noted to be less aggressive and usually not fatal, in comparison to HIV-associated PML (220). There is no specific treatment for PML but the main approach is to restore the host adaptive immune response (223). In HIV-related case, initiating or optimising antiretroviral therapy should be considered whereas stopping culprit immunosuppressive drugs is usually needed in drug-related PML. Treatment withdrawal may result in immune reconstitution inflammatory syndrome (IRIS) which may require methylprednisolone for a few days (149, 223). Mefloquine and mirtazapine are usually prescribed in those experiencing PML (149, 220, 223).

The risk of PML with the use of FAE for psoriasis emerged in 2013 when three separate cases were reported in the *New England Journal of Medicine*. Two of these cases received Fumaderm® for 3 years (224, 225), while the third case had Psorinovo® (DMF alone preparation) for 5 years (226). Subsequently, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a warning when a multiple sclerosis (MS) patient in Germany died due to PML following the use of Tecfidera® for 4.5 years with severe lymphopaenia for more than 3.5 years (227). These reports have increased clinicians' awareness and several other reports were published in 2014-2015, describing PML in patients receiving FAE for either psoriasis or MS.

In 2017, Balak et al (228) reviewed the literature with respect to PML in psoriasis and a total of 8 reported cases were identified **(Table 9)**. The median age was 64 years (range 42 – 74 years) and the median duration of FAE treatment (Fumaderm® in 6 cases and Psorinovo® in 2 cases) was 3 years (range 1.5 – 5 years). All cases were linked to reduction of absolute lymphocyte counts, with nadirs ranging from 0.2 – 0.79 $x10^9$ /L for a median duration of 2 years (range 1 – 5 years). Also, some of the reported cases had previously had immunosuppressive therapies such as steroids, methotrexate and efalizumab, or had other known risk factors for PML including malignancies. The most commonly reported neurological symptoms were aphasia (n=3), hemiparesis (n=3) and dysarthria (n=2). Other symptoms included hemiataxia, dysphagia, confusion, headache, apraxia and dysesthesia. All patients were managed by FAE discontinuation and started mefloquine and mirtazapine, leading to improvement in three patients and three patients had residual PML symptoms.

Five patients developed IRIS following FAE withdrawal, of whom one died due to complications.

No	Author (year) (Reference)	Sex	Age (yrs)	FAE time (yrs)	FAE dose / day	FAE formula	PML symptoms	Diagnosis of PML	IRIS	Treatment	Outcome	Known risk factors for PML	Previous psoriasis treatments
1	Ermis (2013) (224)	M	74	3	430 mg	Fumaderm	Sensory aphasia	MRI findings, brain biopsy, PCR JCV in CSF	Yes	Mefloquine, mirtazapine	Improvement, persistence of sensory aphasia	-	Topical steroids, acitretin, methotrexate
2	Van Oosten (2013) (226)	F	42	5	420 mg	Psorinovo	Right-sided hemiparesis	MRI findings, PCR JCV in CSF	Yes	Mefloquine, mirtazapine, methyl-prednisolone	Improvement	-	NR
3	Buttmann (2013) (225)	F	57	3	860 mg	Fumaderm	NR	NR	NR	NR	Residual symptoms	Pulmonary sarcoidosis	Methotrexate, steroids
4	Stoppe (2014) (229)	M	NR	3	NR	Fumaderm	Left-sided hemiataxia, dysarthria	MRI findings, PCR JCV in CSF	No	Immune-globulin, mirtazapine, mefloquine	Improvement	Melanoma	Topical steroids, topical vitamin D analogue, steroids, UVB, acitretin, efalizumab
5	Metz (2015) (230)	M	68	2.5	1075 mg	Fumaderm	Left-sided hemi-hypesthesia, dysesthesia, left-sided weakness, dysphagia, dysarthria, focal motor seizures	MRI findings, brain biopsy, PCR JCV in CSF	Yes	Mirtazapine, mefloquine	Stable	Rectum adeno-carcinoma	Topical steroids, PUVA
6	Dammmeier (2015) (231)	F	53	1.5	360 mg	Fumaderm	Transient confusion, sensory aphasia, headache	MRI findings, brain biopsy, PCR JCV in brain tissue	No	Mirtazapine, mefloquine	Stable	-	Topical treatments
7	Hoepner (2015) (232)	M	69	5	1290 mg	Fumaderm	Right-sided hemiparesis, aphasia	MRI findings, brain biopsy, PCR JCV in CSF	Yes	Mirtazapine, mefloquine, levetiracetam, glucocorticoids	Improvement	Monoclonal gammopathy	-
8	Nieuwkamp (2015) (233)	F	64	2	NR	Psorinovo	Apraxia, hemiparesis, somnolence	MRI findings, brain biopsy, PCR JCV in CSF and brain tissue	Yes	Mefloquine, mirtazapine, glucocorticoids	Died due to PML-IRIS	-	-

Table 9: A summary of the reported PML cases associated with FAE treatment in patients with psoriasis. CSF: cerebrospinal fluid; IROS: immune reconstitution inflammatory syndrome; JCV: John Cunningham virus; NR: not reported; PML: progressive multifocal leukoencephalopathy; PCR: polymerase chain reaction. (adapted from Balak et al (2017) (228)

In conclusion, regular monitoring blood tests are crucial to detect lymphopaenia at an early stage and it is important to follow the recommendations regarding treatment withdrawal in such cases to prevent the occurrence of PML in patients receiving FAE.

Other systemic therapies:

There are other systemic therapies for psoriasis and patients may have various factors influencing their treatment preference (e.g. safety profile, likely efficacy, speed of response). Bansback et al (234) reported in meta-analyses a RR of PASI 50 response of 4.74 with methotrexate 15-22.5mg weekly (95% CI 3.52 to 5.73), with an NNTB of 2; and 4.06 with ciclosporin 3 mg/kg per day (95% CI 2.54 to 5.73), with an NNTB of 2. These are comparable with our findings of FAE efficacy with a PASI 50 RR of 4.55 compared with placebo (95% CI 2.80 to 7.40) and an NNTB of 2. However, the dropout rates and risk of adverse effects were not reported by Bansback et al.

Some of the best available evidence comparing efficacy and safety of conventional systemic agents (acitretin, ciclosporin, fumaric acid esters (FAE), methotrexate (MTX)), small molecules (apremilast, tofacitinib, ponesimod), anti-TNFα (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab), anti-IL23 (guselkumab, tildrakizumab), and other biologics (alefacept, itolizumab) for patients with moderate to severe psoriasis has been recently reported in a Cochrane systematic review with network meta-analysis by Sbidian and co-workers (235). This review included 109 studies involving 39,882 randomised participants. The primary outcomes were the proportion of participants achieving PASI 90 and experiencing serious adverse effects (SAE), while PASI 75, PGA 0 or 1, QoL measure, AE were all secondary outcomes.

Endpoints from all trials included in the network meta-analysis were assessed 12 to 16 weeks after randomisation. This review concluded that all interventions were significantly superior to placebo in terms of efficacy and not significantly different from placebo in terms of SAE. Anti-IL17, anti-IL12/23, anti-IL23 and anti-TNFα were significantly more effective than small molecules and conventional systemic therapies. The risk ratio (RR) for attaining PASI 90 with FAE compared with placebo was 4.09 (95%CI 1.88 to 8.88). This was comparable to MTX (RR 3.91 (95%CI 2.16 to 7.08)) and ciclosporin (RR 3.99 (95%CI 1.81 to 8.78)). Acitretin on the other hand did not appear to be better than placebo for PASI 90 (RR 0.98 (95%CI 0.06 to 17.24)). The chances of achieving PASI90 with apremilast was higher than all the conventional systemic agents (RR 7.66 (95%CI 4.30 to 13.66)).

With respect to PASI 75 in this network meta-analysis, FAE was ranked lower than other systemics when compared with placebo (RR for FAE= 2.64 (95%CI 1.64 to 4.25)); MTX= 3.64 (95%CI 2.53 to 5.24); acitretin= 3.98 (95%CI 1.86 to 8.49); ciclosporin= 4.79 (95%CI 2.84 to 8.09) the latter being similar to the small molecule apremilast (RR 4.85 (95%CI 3.60 to 6.52)). It is worth noting that FAE data in this review was derived from a study where outcomes were measured at week 16, which may be too soon to evaluate the maximum treatment effect.

The Sbidian et al Cochrane review has also shown that AE were more commonly noted with fumarates (RR 1.23 (95%CI 1.07 to 1.41) compared with ciclosporin (RR 1.16 (95%CI 0.93 to 1.44) and MTX (RR 1.06 (95%CI 0.96 to 1.17). Again, these findings were on the basis of short-term treatment durations and as maintenance treatment is usually required for psoriasis, long-term safety should not be ignored. Although ciclosporin is a rapidly acting therapy in comparison to other conventional agents, long-term treatment is not recommended due to risks of nephrotoxicity and reduced renal function (236), and carcinogenicity (106). Also, both efficacy and nephrotoxicity have been demonstrated to be dose-dependent (5mg/kg/day vs. 2.5mg/kg/day) (105). Methotrexate on the other hand is hepatotoxic and long-term monitoring of liver function is needed. Occasionally, further investigations for liver fibrosis / cirrhosis are also needed. On the other hand, acitretin is a potent vitamin A analogue associated with dose-dependent xerosis and cheilitis, and is generally avoided in females of childbearing age due to long-lasting teratogenic effect after treatment discontinuation(107)

Conclusion:

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 RCTs and lack of meta-analyses due to outcome measure heterogeneity in the pre-PASI era when some studies were conducted. The limited data obtained from this review provide evidence that FAE are superior to placebo and may be similar in efficacy to MTX. Because of the different ways of reporting changes in PASI scores in studies comparing FAE with placebo, the magnitude of benefit could only be established for PASI 50. This was 4.5 times more likely to be achieved with FAE after 12 to 16 weeks, with a NNTB 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. 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.

The included RCTs have not fully established the timescale in which FAE produce benefit in psoriasis. There is now consensus regarding gradual dose increments for FAE following treatment initiation (99), 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.consortstatement.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 (49). 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 (63).

Dissemination of study results:

Our full Cochrane review was published in the Cochrane Library (201) (Appendix 12) and co-published in the British Journal of Dermatology (237) (Appendix 13).

CHAPTER 4

Discussion and conclusion

Two studies have been conducted in this research project with the aim of providing further evidence on improving psoriasis care through patients' journeys from GP referrals to systemic therapy choices in secondary care. The first study explored the usefulness of quality of life (QoL) assessment when psoriasis patients are being referred from their GP to secondary care.

Recognition of quality of life assessment is needed in psoriasis care:

Quality of life is defined by the World Health Organisation (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (238). Although there are different ways of measuring disease severity, such as disease extent and physical findings, these measurement domains do not quantify the extent to which the disease affects the patient's wellbeing (239-241). Health is defined as "a state of complete physical, mental, and social well-being not merely the absence of disease". Therefore, patient reported outcomes are integral part of measuring disease severity, and response to interventions.

In our study we used the Dermatology Life Quality Index (DLQI) because it is the most widely used QoL instrument in psoriasis-related clinical trials (62) and clinical guidelines (64). It is accessible via the British Association of Dermatologists (BAD) and Cardiff University department of dermatology websites (242). There is no need to seek permission and there is no charge when using the instrument for routine clinical purposes (242). Another advantage of the DLQI questionnaire is that it is short, consisting of 10 tick-box questions and can be self-completed by patients in an average completion time of 2 minutes (59, 243).

One of the challenges faced when conducting the study was difficulty engaging referring GPs to have the forms completed by their patients. This could be attributed to the fact that GPs have restricted consultation time and so with the time pressure forget or have insufficient time to give the questionnaire to patients. Another possibility is that lack of familiarity with the DLQI instrument led to concerns about additional consultation time. To mitigate for these potential concerns a DLQI teaching session was delivered to local GPs, as part of a regional cluster GP education meeting, including psoriasis severity assessment.

GPs have many questionnaires they are required to use in their routine practice and hence promoting the use of a new one was challenging. However, reassuring GPs that DLQI can be completed by patients before, after or during the consultation while they complete their own notes proved a helpful approach. Continuing professional development (CPD) sessions for practicing GPs could make use of the 'Rule of Tens' proposed by Finlay in 2005 (BSA > 10; PASI > 10; DLQI > 10) (71), providing a simple and practical method that can be taught to GPs when assessing disease severity in patients with psoriasis.

Psoriasis is a potentially stigmatizing condition with evidence of significant psychological impact including anxiety, depression and suicidal ideation (241, 244, 245). Despite this evidence, the psychological impact on patients is rarely addressed by clinicians (246). Studies have shown that psoriasis patients can be dissatisfied with their management and have unmet expectations (247-249). Nelson et al (250) conducted a qualitative study based on semi-structured interviews with 29 psoriasis patients. They concluded that patients felt their disease is complex with physical and psychosocial impacts which were largely unacknowledged by clinicians during consultations, both in primary and secondary care. Although the study included patients from different ethnic groups and ages, they were recruited from the community by direct advertising which raises the possibility of selection bias, as those with frustrating experiences may have been more likely to participate in the study. Still, these findings indicate that clinicians need to recognise and manage psoriasis as a complex long-term disease with physical, psychological and social impacts. So, using patient-reported outcome measure instruments, such as DLQI, is important at both primary and secondary care levels.

Fumarates for psoriasis:

When this research project was conducted, fumarates were used for the treatment of psoriasis in the UK as an unlicensed drug. Although a PIL was available on the BAD website, there was no clinical guidance on use of fumarates due to the lack of an EMA licence, arising in part from production issues and not being able to adhere to Good Manufacturing Practice in terms of the exact ratio of fumaric acid esters in the formulation. Therefore, we conducted a Cochrane systematic review to summarise the evidence for their efficacy and safety. Although non-Cochrane systematic reviews had been conducted to address this research area, a Cochrane systematic review was chosen to present the best available evidence. This is achieved because the process of conducting a Cochrane review is more robust and involves multiple levels of quality checks at protocol stage and when

results are generated. Statisticians, methodologists and clinical experts are involved in the peer-review of the study.

This Cochrane review demonstrated a low number of RCTs investigating fumarates for psoriasis and found that most of the studies were old with unclear risk of bias and low-quality evidence. Our review concluded that fumarates were superior to placebo based on five RCTs. Only one study compared fumarates to an active comparator, methotrexate, in a head-to-head trial (115). This study concluded that both interventions were comparable in efficacy and safety but the study had a non-blinded design, producing high risk of performance and detection bias that resulted in the evidence being of very low quality (201). So, there is a need for well-designed double-blind trials comparing fumarates directly with methotrexate and other active standard interventions.

Psoriatic nail changes and arthropathy are common findings in psoriasis patients but to date there is lack of evidence to support the role of FAE in their treatment. In a double-blinded placebo-controlled trial by Peeters et al (206), which was designed for PsA, those who received FAE (n=13) showed reduction in some parameters measuring arthritis compared to the placebo group (n=14) but the difference was not statistically significant. Roll and colleagues (143) recommend FAE for patients with psoriasis and mild PsA but those with more severe joint disease should be considered for other treatments, such as methotrexate or anti-TNFα. Long-term FAE treatment may result in some improvement in psoriatic nail disease after 4 months of treatment (214), but this was not assessed in controlled trials.

A combined use of FAE with other anti-psoriatic treatments has been documented. The addition of topical calcipotriol resulted in increased FAE efficacy and quicker resolution of psoriatic plaques compared to FAE monotherapy (200). A report of 10 patients treated with FAE in combination with other systemic agents including ciclosporin, acitretin, methotrexate and hydroxyurea showed a reduction of the dose or treatment duration of the other drugs used (251). The exact duration of the combination therapy was not clearly stated. In contrast, a recent randomised exploratory study comparing etanercept monotherapy (n=14) vs. a combination of etanercept and fumarates (n=18) showed no statistically significant difference in terms of achieving PASI 75 effect after 24 weeks (252). Concomitant use of systemic therapies with FAE is not recommended in routine practice due to lack of safety data. The recently approved DMF preparation for psoriasis (Skilarence®) joined the BADBIR small molecules arm in March 2018 (253) so long-term efficacy and safety data from a large number of patients will be available in the future.

Real-world data about FAE for psoriasis:

A prospective observational study by Walker et al (212) monitored 249 patients starting FAE in an outpatients setting at baseline, 3, 6 and 12 months and highlighted that PASI and DLQI scores continued to improve at 6 and 12 months, especially in those with severe and moderate-to-severe psoriasis **(Figure 26)**.

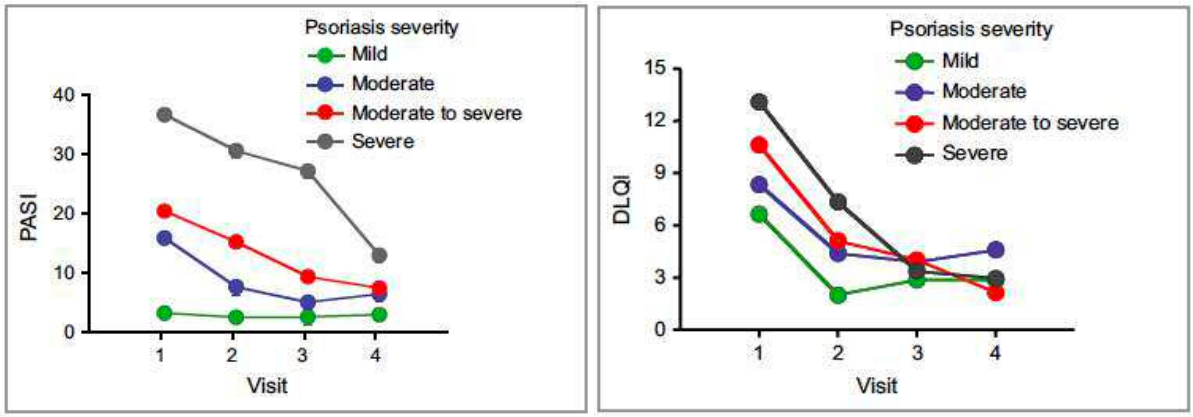


Figure 26: Reduction in PASI (left) and DLQI (right) scores in the study population from baseline (visit 1) at 3 months (visit 2), 6 months (visit 3) and 12 months (visit 4) *(from Walker et al 2014 (212))*.

Similar long-term efficacy data was reported by Reich et al (215) in a retrospective study including 984 patients who received FAE continuously for a mean duration of 44 months. PGA assessment showed that after 3 months of therapy 30.8% of patients were “markedly improved” or “clear” and an additional 50% of patients “slightly improved”. After 6 months of therapy 67% of patients were “markedly improved” or “clear”; after one year this degree of improvement was documented in 76 % of patients and after 24 months 80% of patients were markedly improved or clear. In the subgroup of patients with recorded PASI score (n=107), the mean PASI score dropped from 22.7 at baseline to 4.8 after 36 months of treatment, representing 79% reduction **(Figure 27)**. The retrospective design and the funding by Biogen Idec GmbH, the manufacturer of Fumaderm®, are potential sources of bias for this study. From the abovementioned long-term studies, it can be concluded that maximum efficacy of FAE should not be judged before 6 months of treatment.

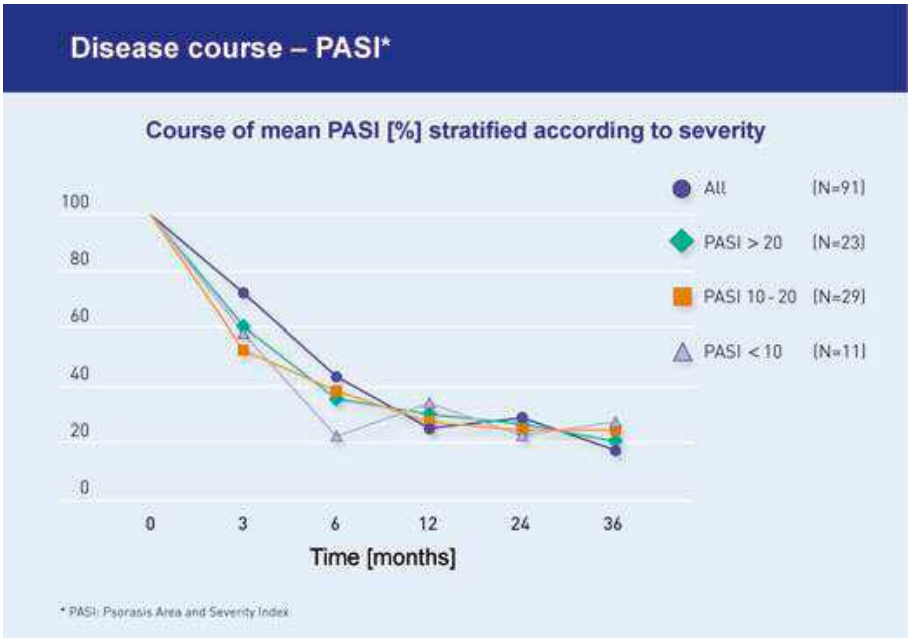


Figure 27: Mean percent change in PASI score stratified according to baseline values *(from Reich et al 2009 (215)).*

There are some pitfalls with FAE therapy. The fact that patients are required to take multiple tablets daily can lead to suboptimal treatment due to lack of adherence (214), which may be less of a problem with other conventional systemic therapies taken once or twice daily (e.g. acitretin and ciclosporin) or once weekly (e.g. methotrexate). However, it has been shown that the most patients on FAE therapy (70%) only require 2 to 3 tablets daily for long-term maintenance (212, 215). The gastrointestinal (GI) symptoms associated with FAE are common nuisance adverse effects; reported in 56% - 63.3% of patients (204, 213, 214). Although these are mild and transient in most patients, they can lead to treatment discontinuation in 3.8% - 7.7% of those starting treatment (115, 206, 214). Flushing is another adverse effect of FAE, reported variably in the literature in 34.6% - 55% of patients (116, 201, 213, 214). Eosinophila has been noted, also variably, in 15% - 38% of patients on FAE (116, 201, 213). This is mostly observed between the first and third month of treatment and no dose adjustment is needed (214, 215).

A few published reports highlighted the use of FAE in children with psoriasis. In 2014, Steinz and colleagues (254) reported the efficacy of FAE in six paediatric patients treated at Kiel Psoriasis Centre. In this retrospective report, five girls and one boy with a median age of 11.5 years (range 6 to 17 years) with moderate to severe psoriasis refractory to topical treatment or UVB were treated with Fumaderm®. The treatment duration ranged from 3 months to 4 years and the dose was escalated in the same manner as in adults, following the German guidelines (196). The authors reported substantial response in all participants

after 12 weeks, achieving PASI75 (n=2), PASI90 (n=1) or PASI100 (n=3). However, these results in a small cohort need to be interpreted with caution; three of the treated children had guttate type psoriasis where PASI assessment is not reliable and spontaneous resolution is expected. Also, all patients were allowed concomitant use of topical steroids or vitamin D analogues if necessary, and four of the six children had tonsillectomy either one month after starting FAE (n=1) or at least 2 months before treatment initiation.

Another retrospective paediatric case series from the Netherlands by Balak et al (255) reported the efficacy of FAE in 14 children and young people. The median age was 15 years (range 8 to 17) and all patients had chronic plaque psoriasis. The majority of participants (93%) had received prior phototherapy and / or systemic treatment. The standardised Dutch formulation of FAE was provided for a median duration of 10 months (range 1 to 80 months) with dose increments as in adults based on efficacy and tolerability. Five patients discontinued treatment after a median duration of 8 months (range 2 to 17 months) due to lack of response. Complete clearance was reported in 5 of the 14 patients (36%), one patient had had 82% reduction in PASI score after 4 months, and three patients had partial response after 6 months of treatment. Some of those remaining on the treatment experienced adverse effects included abdominal cramps (n=5), diarrhoea (n=4) and flushes (n=2) which were described as tolerable and transient in most cases but led to treatment discontinuation in two children after having treatment for 1 and 4 months because of abdominal complaints in one and severe flushing in the other.

Overall, there is lack of high quality evidence for systemic options including FAE in refractory moderate-to-severe psoriasis in children and comparative studies in this age group are needed.

Conclusion:

Optimising the psoriasis care pathway is a multifaceted process that requires input from all healthcare professionals involved in psoriasis patient care. At the primary healthcare level GPs should be more aware of the impact of psoriasis on patients' lives and use a validated quality of life instrument to measure this impact and ideally to improve the triage of psoriasis referrals to secondary care. One of the studies presented in this thesis shows a potential benefit of utilizing the DLQI as a triage tool to identify those individuals experiencing the greatest impact on their quality of life. In providing holistic care, healthcare providers are also expected to identify those with psoriatic arthritis or at risk of cardiovascular and metabolic

diseases so that early treatment can be initiated as primary or secondary prevention to improve the long-term health of patients.

Systemic therapies for psoriasis should be selected on a case by case basis according to guidelines, patients' comorbidities and their personal preferences. It is important that patients are fully aware of the available evidence to enable them to make informed decisions. Fumarates are one of the recognised systemic therapies for psoriasis. The Cochrane systemic review presented in this thesis demonstrates its superiority over placebo and possibly similar efficacy to methotrexate; however these findings were based on low-quality evidence. Following the Cochrane review publication, dimethylfumarate was licensed by the EMA based on new trial evidence and approved by NICE as a third line systemic therapy for moderate-to-severe psoriasis. There is growing evidence that continued improvement on FAE occurs after the usual 12 – 16 week endpoints commonly used in trials. Therefore, long-term randomised clinical trials are needed to measure the true effect of FAE and its safety in direct head-to-head comparisons with other systemic treatments. Inclusion of FAE in pharmacovigilance databases will be important to assess rare, delayed adverse effects such as PML.

Now, more than ever, psoriasis patients should be empowered to make decisions about their care in partnership with their clinicians, in the context of the increasing number of interventions available to treat psoriasis. Optimising the psoriasis care pathway includes ensuring that people with psoriasis are seen by dermatology secondary care services at the right time. In addition, people with psoriasis and their doctors need access to summaries of evidence for the different treatment options, a good source of which is provided by Cochrane reviews which combine a comprehensive meta-analysis with a plain language summary.

References:

1. Population estimates. Office for National Statistics. Available at: http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates. Access date: 15 November 2016.
2. Schofield J, Grindlay D, Williams H. Skin Conditions in the UK: a Health Care Needs Assessment. Centre of Evidence Based Dermatology, University of Nottingham, UK; 2009.
3. List of Registered Medical Practitioners-statistics. Available at http://www.gmc-uk.org/doctors/register/search_stats.asp Accessed November 2016.
4. Eedy D. The crisis in dermatology. BMJ Careers; 9 June 2015.
5. Glazer AM, Rigel DS. Analysis of Trends in Geographic Distribution of US Dermatology Workforce Density. JAMA Dermatol. 2017;153(5):472-3.
6. Bin Saif GA, Al-Haddab M. The Dermatology workforce in Saudi Arabia: Current trends, challenges and future directions. Int J Health Sci (Qassim). 2010;4(2):178-93.
7. Australia's Future Health Workforce - Dermatology. Department of Health. May 2017. Available at http://www.health.gov.au/internet/main/publishing.nsf/Content/2353661782F117E3CA258145001D7617/$File/AFHW%20-%20Dermatology%20Final_May2017.pdf Access date June 2018.
8. Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2014;170(2):274-303.
9. Seiden E. The History of psoriasis. 1996-2004. Accessed June 2018, Available at: http://www.psoriasis.org/publications/psoriasis-advance-magazine/2011/spring/psoriasis-uncovered.
10. Burg G, Geiges M. Lepra vulgaris. History of psoriasis.: J Turk Acad Dermatol; 2014. p. 1483r1.
11. Lebwohl M. Psoriasis. Lancet. 2003;361(9364):1197-204.
12. Augustin M, Ogilvie A. Methods of outcomes measurement in nail psoriasis. Dermatology. 2010;221 Suppl 1:23-8.
13. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017;76(3):377-90.
14. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370(9583):263-71.
15. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, team IaMoPaACIp. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-85.
16. Smith CH, Barker JN. Psoriasis and its management. BMJ. 2006;333(7564):380-4.
17. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Arch Dermatol. 2005;141(12):1537-41.
18. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64 Suppl 2:ii18-23; discussion ii4-5.
19. Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schäfer I. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol. 2010;162(3):633-6.
20. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496-509.
21. Andressen C, Henseler T. [Inheritance of psoriasis. Analysis of 2035 family histories]. Hautarzt. 1982;33(4):214-7.
22. Farber EM, Nall ML, Watson W. Natural history of psoriasis in 61 twin pairs. Arch Dermatol. 1974;109(2):207-11.
23. Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. J Am Acad Dermatol. 1993;29(3):428-34.
24. Barker JN. The pathophysiology of psoriasis. Lancet. 1991;338(8761):227-30.

25. Capon F, Trembath RC, Barker JN. An update on the genetics of psoriasis. Dermatol Clin. 2004;22(4):339-47, vii.
26. Trembath RC, Clough RL, Rosbotham JL, Jones AB, Camp RD, Frodsham A, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet. 1997;6(5):813-20.
27. Asumalahti K, Ameen M, Suomela S, Hagforsen E, Michaëlsson G, Evans J, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. J Invest Dermatol. 2003;120(4):627-32.
28. Allen MH, Ameen H, Veal C, Evans J, Ramrakha-Jones VS, Marsland AM, et al. The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. J Invest Dermatol. 2005;124(1):103-6.
29. Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. Arch Dermatol. 1992;128(1):39-42.
30. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. Int J Dermatol. 2010;49(12):1351-61.
31. Huerta C, Rivero E, Rodríguez LA. Incidence and risk factors for psoriasis in the general population. Arch Dermatol. 2007;143(12):1559-65.
32. Baker BS, Swain AF, Fry L, Valdimarsson H. Epidermal T lymphocytes and HLA-DR expression in psoriasis. Br J Dermatol. 1984;110(5):555-64.
33. Eedy DJ, Burrows D, Bridges JM, Jones FG. Clearance of severe psoriasis after allogenic bone marrow transplantation. BMJ. 1990;300(6729):908.
34. Mueller W, Herrmann B. Cyclosporin A for psoriasis. N Engl J Med. 1979;301(10):555.
35. Griffiths CE, Powles AV, Leonard JN, Fry L, Baker BS, Valdimarsson H. Clearance of psoriasis with low dose cyclosporin. Br Med J (Clin Res Ed). 1986;293(6549):731-2.
36. Meffert H, Brautigam M, Farber L, Weidinger G. Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile. Acta Derm Venereol. 1997;77(2):137-41.
37. Schön MP, Boehncke WH. Psoriasis. N Engl J Med. 2005;352(18):1899-912.
38. Nickoloff BJ. Skin innate immune system in psoriasis: friend or foe? J Clin Invest. 1999;104(9):1161-4.
39. Büchau AS, Gallo RL. Innate immunity and antimicrobial defense systems in psoriasis. Clin Dermatol. 2007;25(6):616-24.
40. Ogawa E, Sato Y, Minagawa A, Okuyama R. Pathogenesis of psoriasis and development of treatment. J Dermatol. 2018;45(3):264-72.
41. Nestle FO, Turka LA, Nickoloff BJ. Characterization of dermal dendritic cells in psoriasis. Autostimulation of T lymphocytes and induction of Th1 type cytokines. J Clin Invest. 1994;94(1):202-9.
42. Schlaak JF, Buslau M, Jochum W, Hermann E, Girndt M, Gallati H, et al. T cells involved in psoriasis vulgaris belong to the Th1 subset. J Invest Dermatol. 1994;102(2):145-9.
43. Austin LM, Ozawa M, Kikuchi T, Walters IB, Krueger JG. The majority of epidermal T cells in Psoriasis vulgaris lesions can produce type 1 cytokines, interferon-gamma, interleukin-2, and tumor necrosis factor-alpha, defining TC1 (cytotoxic T lymphocyte) and TH1 effector populations: a type 1 differentiation bias is also measured in circulating blood T cells in psoriatic patients. J Invest Dermatol. 1999;113(5):752-9.
44. Hancock GE, Kaplan G, Cohn ZA. Keratinocyte growth regulation by the products of immune cells. J Exp Med. 1988;168(4):1395-402.
45. Detmar M, Orfanos CE. Tumor necrosis factor-alpha inhibits cell proliferation and induces class II antigens and cell adhesion molecules in cultured normal human keratinocytes in vitro. Arch Dermatol Res. 1990;282(4):238-45.

46. Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suárez-Fariñas M, Suárez Fariñas M, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med. 2007;204(13):3183-94.
47. Heidenreich R, Röcken M, Ghoreschi K. Angiogenesis drives psoriasis pathogenesis. Int J Exp Pathol. 2009;90(3):232-48.
48. Gottlieb AB, Armstrong AW, Christensen R, Garg A, Duffin KC, Boehncke WH, et al. The International Dermatology Outcome Measures initiative as applied to psoriatic disease outcomes: a report from the GRAPPA 2013 meeting. J Rheumatol. 2014;41(6):1227-9.
49. Williamson P, Altman D, Bagley H, Barnes K, Blazeby J, Brookes S, et al. COMET Handbook: version 1.0. 2017;18(Suppl 3):280.
50. Kirkham JJ, Gargon E, Clarke M, Williamson PR. Can a core outcome set improve the quality of systematic reviews?--a survey of the Co-ordinating Editors of Cochrane Review Groups. Trials. 2013;14:21.
51. Callis Duffin K, Merola JF, Christensen R, Latella J, Garg A, Gottlieb AB, et al. Identifying a Core Domain Set to Assess Psoriasis in Clinical Trials. JAMA Dermatol. 2018.
52. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.
53. Augsutin M, Amon U, Bullinger M, Gieler U. Recommendations for the Assesment of Quality of Life in Dermatology. Dermatology Psychosom2000. p. 84-7.
54. Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. Clin Exp Dermatol. 1992;17(1):1-3.
55. Finlay AY, Kelly SE. Psoriasis--an index of disability. Clin Exp Dermatol. 1987;12(1):8-11.
56. Anderson RT, Rajagopalan R. Development and validation of a quality of life instrument for cutaneous diseases. J Am Acad Dermatol. 1997;37(1):41-50.
57. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. J Invest Dermatol. 1996;107(5):707-13.
58. Chren MM, Lasek RJ, Flocke SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. Arch Dermatol. 1997;133(11):1433-40.
59. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.
60. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
61. Møller AH, Erntoft S, Vinding GR, Jemec GB. A systematic literature review to compare quality of life in psoriasis with other chronic diseases using EQ-5D-derived utility values. Patient Relat Outcome Meas. 2015;6:167-77.
62. Ali FM, Cueva AC, Vyas J, Atwan AA, Salek MS, Finlay AY, et al. A systematic review of the use of quality-of-life instruments in randomized controlled trials for psoriasis. Br J Dermatol. 2017;176(3):577-93.
63. Burden AD, Warren RB, Kleyn CE, McElhone K, Smith CH, Reynolds NJ, et al. The British Association of Dermatologists' Biologic Interventions Register (BADBIR): design, methodology and objectives. Br J Dermatol. 2012;166(3):545-54.
64. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, Bale T, Burden AD, Coates LC, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. Br J Dermatol. 2017;177(3):628-36.
65. National Clinical Guideline C. National Institute for Health and Care Excellence : Guidance. Psoriasis: Assessment and Management of Psoriasis. London: Royal College of Physicians (UK)

Copyright (c) National Clinical Guideline Centre - October 2012.; 2012.
66. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of

psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826-50.
67. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, 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(12):2277-94.
68. Krueger GG, Feldman SR, Camisa C, Duvic M, Elder JT, Gottlieb AB, et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? J Am Acad Dermatol. 2000;43(2 Pt 1):281-5.
69. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol. 2001;137(3):280-4.
70. Fortune DG, Main CJ, O'Sullivan TM, Griffiths CE. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. Br J Dermatol. 1997;137(5):755-60.
71. Finlay AY. Current severe psoriasis and the rule of tens. Br J Dermatol. 2005;152(5):861-7.
72. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41(3 Pt 1):401-7.
73. Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. Am J Clin Dermatol. 2005;6(6):383-92.
74. Warren RB, Kleyn CE, Gulliver WP. Cumulative life course impairment in psoriasis: patient perception of disease-related impairment throughout the life course. Br J Dermatol. 2011;164 Suppl 1:1-14.
75. Menter A, Griffiths CE. Current and future management of psoriasis. Lancet. 2007;370(9583):272-84.
76. Eghlileb AM, Davies EE, Finlay AY. Psoriasis has a major secondary impact on the lives of family members and partners. Br J Dermatol. 2007;156(6):1245-50.
77. Reich K, Mrowietz U. Treatment goals in psoriasis. J Dtsch Dermatol Ges. 2007;5(7):566-74.
78. Gutknecht M, Krensel M, Augustin M. Health economic analyses of psoriasis management: a systematic literature search. Arch Dermatol Res. 2016;308(9):601-16.
79. Primary care Dermatology Society (PCDS). Psoriasis: An overview and chronic plaque psoriasis. Available at http://www.pcds.org.uk/clinical-guidance/psoriasis-an-overview#management Access date May 2018.
80. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J. 2010;31(8):1000-6.
81. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735-41.
82. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med. 2011;9:48.
83. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. J Am Acad Dermatol. 2013;68(4):654-62.
84. Török L, Tóth E, Bruncsák A. [Correlation between psoriasis and cardiovascular diseases (author's transl)]. Z Hautkr. 1982;57(10):734-9.
85. Dowlatshahi EA, Kavousi M, Nijsten T, Ikram MA, Hofman A, Franco OH, et al. Psoriasis is not associated with atherosclerosis and incident cardiovascular events: the Rotterdam Study. J Invest Dermatol. 2013;133(10):2347-54.
86. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol. 2008;159(4):895-902.
87. Gisondi P, Girolomoni G. Psoriasis and atherothrombotic diseases: disease-specific and non-disease-specific risk factors. Semin Thromb Hemost. 2009;35(3):313-24.

88. Egeberg A, Skov L, Joshi AA, Mallbris L, Gislason GH, Wu JJ, et al. The relationship between duration of psoriasis, vascular inflammation, and cardiovascular events. J Am Acad Dermatol. 2017;77(4):650-6.e3.
89. Lebwohl M. Does Treatment of Psoriasis Reduce Cardiovascular Comorbidities? J Invest Dermatol. 2017;137(8):1612-3.
90. Wu JJ, Poon KY. Tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis, psoriatic arthritis, or both. J Drugs Dermatol. 2014;13(8):932-4.
91. Fortune DG, Richards HL, Griffiths CE. Psychologic factors in psoriasis: consequences, mechanisms, and interventions. Dermatol Clin. 2005;23(4):681-94.
92. Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. J Eur Acad Dermatol Venereol. 2012;26 Suppl 2:12-20.
93. Kazandjieva J, Grozdev I, Darlenski R, Tsankov N. Climatotherapy of psoriasis. Clin Dermatol. 2008;26(5):477-85.
94. Griffiths CE, Clark CM, Chalmers RJ, Li Wan Po A, Williams HC. A systematic review of treatments for severe psoriasis. Health Technol Assess. 2000;4(40):1-125.
95. Psoriasis: assessment and management. National Institute for Health and Care Excellence (NICE). Updated September 2017; Clinical guideline [CG153]. Available at https://www.nice.org.uk/guidance/cg153/chapter/1-Guidance access date 7 June 2018.
96. Consent to treatment. NHS Choices available at https://www.nhs.uk/conditions/consent-to-treatment/#defining-consent Accessed May 2018.
97. Treating psoriasis: Overview of systemic medication for psoriasis. National Psoriasis Foundation. Available at https://www.psoriasis.org/about-psoriasis/treatments/systemics Access date May 2018.
98. Treatments for moderate or severe psoriasis. The British Association of Dermatologists. Available at http://www.bad.org.uk/shared/get-file.ashx?id=124&itemtype=document Access date May 2018.
99. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009;23 Suppl 2:1-70.
100. Schweckendiek W. Treatment of psoriasis vulgaris. Med Monatsschr. 1959;13(2):103-4.
101. Smith KC. Systemic therapy of psoriasis using methotrexate. Skin Therapy Lett. 2000;6(3):1-2; 5.
102. Shea B, Swinden MV, Tanjong Ghogomu E, Ortiz Z, Katchamart W, Rader T, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev. 2013(5):CD000951.
103. West J, Ogston S, Palmer C, Fleming C, Dawe R, Kumar V, et al. Methotrexate in psoriasis under real-world conditions: long-term efficacy and tolerability. Br J Dermatol. 2016;174(6):1407-10.
104. Ho S, Clipstone N, Timmermann L, Northrop J, Graef I, Fiorentino D, et al. The mechanism of action of cyclosporin A and FK506. Clin Immunol Immunopathol. 1996;80(3 Pt 2):S40-5.
105. Christophers E, Mrowietz U, Henneicke HH, Färber L, Welzel D. Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. The German Multicenter Study. J Am Acad Dermatol. 1992;26(1):86-90.
106. Paul CF, Ho VC, McGeown C, Christophers E, Schmidtmann B, Guillaume JC, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J Invest Dermatol. 2003;120(2):211-6.
107. Sbidian E, Maza A, Montaudié H, Gallini A, Aractingi S, Aubin F, et al. Efficacy and safety of oral retinoids in different psoriasis subtypes: a systematic literature review. J Eur Acad Dermatol Venereol. 2011;25 Suppl 2:28-33.
108. Goldfarb MT, Ellis CN, Gupta AK, Tincoff T, Hamilton TA, Voorhees JJ. Acitretin improves psoriasis in a dose-dependent fashion. J Am Acad Dermatol. 1988;18(4 Pt 1):655-62.
109. Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. J Am Acad Dermatol. 1989;20(6):1088-93.

110. Olsen EA, Weed WW, Meyer CJ, Cobo LM. A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. J Am Acad Dermatol. 1989;21(4 Pt 1):681-6.
111. Apremilast for treating moderate to severe plaque psoriasis. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance [TA419]. Published 23 November 2016. Available at https://www.nice.org.uk/guidance/ta419 access date June 2018.
112. Torres T, Filipe P. Small Molecules in the Treatment of Psoriasis. Drug Dev Res. 2015;76(5):215-27.
113. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37-49.
114. Medicines and Healthcare products Regulatory Agency. Apremilast (Otezla ▼): risk of suicidal thoughts and behaviour. Published 19 January 2017. Available at: https://www.gov.uk/drug-safety-update/apremilast-otezla-risk-of-suicidal-thoughts-and-behaviour (Access date January 2019).
115. Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol. 2011;164(4):855-61.
116. Hoefnagel JJ, Thio HB, Willemze R, Bouwes Bavinck JN. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. Br J Dermatol. 2003;149(2):363-9.
117. Onderdijk AJ, Balak DM, Baerveldt EM, Florencia EF, Kant M, Laman JD, et al. Regulated genes in psoriatic skin during treatment with fumaric acid esters. Br J Dermatol. 2014;171(4):732-41.
118. Harries MJ, Chalmers RJ, Griffiths CE. Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. Br J Dermatol. 2005;153(3):549-51.
119. Sladden MJ, Osborne JE, Hutchinson PE. Fumaric acid esters for severe psoriasis: the Leicestershire experience. Br J Dermatol. 2006;155(4):843-4.
120. Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S. Fumaric acid esters in the treatment of psoriasis: an Italian experience. J Dermatolog Treat. 2004;15(1):23-6.
121. Kokelj F, Plozzer C, Avian A, Trevisan G. Fumaric acid and its derivatives in the treatment of psoriasis vulgaris: our experience in forty-one patients. Acta Dermatovenerol Croat. 2009;17(3):170-5.
122. European Medicines Agency. Skilarence (dimethyl fumarate) Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002157/human_med_002118.jsp&mid=WC0b01ac058001d124 Accessed May 2018.
123. Dimethyl fumarate for treating moderate to severe plaque psoriasis. National Institute for Health and Care Excellence (NICE). 06 September 2017; Technology appraisal guidance [TA475]. Available at: https://www.nice.org.uk/guidance/ta475.
124. Psoriasis overview. National Institute for Health and Care Excellence (NICE) pathways. Available at https://pathways.nice.org.uk/pathways/psoriasis Access date June 2018.
125. Designed for Life: Creating world class health and social care for Wales in the 21st century. Welsh Assembly Government. [URL:http://www.wales.nhs.uk/documents/designed-for-life-e.pdf]. Accessed 16 April 2012. .
126. Augustin M, Krüger K, Radtke MA, Schwippl I, Reich K. Disease severity, quality of life and health care in plaque-type psoriasis: a multicenter cross-sectional study in Germany. Dermatology. 2008;216(4):366-72.
127. Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. J Am Acad Dermatol. 2007;57(6):957-62.
128. Poulin Y, Papp KA, Wasel NR, Andrew R, Fraquelli E, Bernstein G, et al. A Canadian online survey to evaluate awareness and treatment satisfaction in individuals with moderate to severe plaque psoriasis. Int J Dermatol. 2010;49(12):1368-75.

129. Wasel N, Poulin Y, Andrew R, Chan D, Fraquelli E, Papp K. A Canadian self-administered online survey to evaluate the impact of moderate-to-severe psoriasis among patients. J Cutan Med Surg. 2009;13(6):294-302.
130. National Institute for Health and Care Excellence Clinical Knowledge Summaries (CKS). Psoriasis. Available at https://cks.nice.org.uk/psoriasis#!nicequalitystandards Access date May 2018.
131. Bronsard V, Paul C, Prey S, Puzenat E, Gourraud PA, Aractingi S, et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. J Eur Acad Dermatol Venereol. 2010;24 Suppl 2:17-22.
132. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005;125(4):659-64.
133. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27-33.
134. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-15.
135. Scottish Intercollegiate Guidelines Network (SIGN): 121-Diagnosis and management of psoriasis and psoriatic arthritis in adults - A national clinical guideline; October 2010. Available at: www.sign.ac.uk/guidelines/fulltext/121/recommendations.html.
136. Choon S, Chan L, Choon SE, Jamil A, Chin CL, Cheng CH, et al. Malaysian Clinical Practice Guideline for the Management of Psoriasis Vulgaris: Summary of recommendations for management in primary healthcare setting. Malays Fam Physician. 2014;9(1):16-21.
137. Wade AG, Crawford GM, Young D, Leman J, Pumford N. Severity and management of psoriasis within primary care. BMC Fam Pract. 2016;17(1):145.
138. WHO. Obesity and overweight. http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight (accessed 27 April 2018).
139. Ormerod E, Bale T, Stone N. Psoriasis Direct Service: An Audit and Review. Dermatological Nursing2017. p. 45-9.
140. Atwan A, Piguet V, Finlay AY, Francis NA, Ingram JR. Dermatology Life Quality Index (DLQI) as a psoriasis referral triage tool. Br J Dermatol. 2017;177(4):e136-e7.
141. Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. Br J Dermatol. 1999;141(3):424-9.
142. Rostami Yazdi M, Mrowietz U. Fumaric acid esters. Clin Dermatol. 2008;26(5):522-6.
143. Roll A, Reich K, Boer A. Use of fumaric acid esters in psoriasis. Indian J Dermatol Venereol Leprol. 2007;73(2):133-7.
144. Schafer GN. Psoriasis mit Fumarsaure beherrschbar. Selecta. 1982;17:1868-72.
145. Schafer GN. Fumarsaure lindert die Schuppenflechte. Selecta. 1984;15:1260-1.
146. Nieboer C, de Hoop D, van Loenen AC, Langendijk PN, van Dijk E. Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. J Am Acad Dermatol. 1989;20(4):601-8.
147. Biogen Inc (2016) Fachinformation. Fumaderm. initial Fumaderm. Biogen. https://www.wuensche.synology.me/Wordpress/wp-content/uploads/Fumarderm.pdf Accessed April 2018.
148. Nieboer C, de Hoop D, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica. 1990;181(1):33-7.
149. Netherlands pharmacovigilance centre (2015) Dimethyl fumarate and progressive multifocal leucoencephalopathy
(PML). http://databankws.lareb.nl/Downloads/KWB_2015_1_Dimethylfum.pdf Accessed April 2018.

150. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=204063 Accessed April 2018.
151. European Medicines Agency (2017) Tecfidera: dimethyl fumarate. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002601/human_med_001657.jsp&mid=WC0b01ac058001d124 Accessed April 2018.
152. Zweegers J, de Jong EM, Nijsten TE, de Bes J, te Booij M, Borgonjen RJ, et al. Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. Dermatol Online J. 2014;20(3).
153. Phillips JT, Hutchinson M, Fox R, Gold R, Havrdova E. Managing flushing and gastrointestinal events associated with delayed-release dimethyl fumarate: Experiences of an international panel. Mult Scler Relat Disord. 2014;3(4):513-9.
154. Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr. 2007;85(5):1185-96.
155. Balak DM, Fallah-Arani S, Venema CM, Neumann HA, Thio HB. 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. 2015;172(3):754-9.
156. Werdenberg D, Joshi R, Wolffram S, Merkle HP, Langguth P. Presystemic metabolism and intestinal absorption of antipsoriatic fumaric acid esters. Biopharm Drug Dispos. 2003;24(6):259-73.
157. Mrowietz U, Morrison PJ, Suhrkamp I, Kumanova M, Clement B. The Pharmacokinetics of Fumaric Acid Esters Reveal Their In Vivo Effects. Trends Pharmacol Sci. 2018;39(1):1-12.
158. Rostami-Yazdi M, Clement B, Mrowietz U. Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. Arch Dermatol Res. 2010;302(7):531-8.
159. Brück J, Dringen R, Amasuno A, Pau-Charles I, Ghoreschi K. A review of the mechanisms of action of dimethylfumarate in the treatment of psoriasis. Exp Dermatol. 2018.
160. Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. Trends Mol Med. 2005;11(1):43-8.
161. Ghoreschi K, Brück J, Kellerer C, Deng C, Peng H, Rothfuss O, et al. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. J Exp Med. 2011;208(11):2291-303.
162. Lehmann JC, Listopad JJ, Rentzsch CU, Igney FH, von Bonin A, Hennekes HH, et al. Dimethylfumarate induces immunosuppression via glutathione depletion and subsequent induction of heme oxygenase 1. J Invest Dermatol. 2007;127(4):835-45.
163. Dibbert S, Clement B, Skak-Nielsen T, Mrowietz U, Rostami-Yazdi M. Detection of fumarate-glutathione adducts in the portal vein blood of rats: evidence for rapid dimethylfumarate metabolism. Arch Dermatol Res. 2013;305(5):447-51.
164. Rostami-Yazdi M, Clement B, Schmidt TJ, Schinor D, Mrowietz U. Detection of metabolites of fumaric acid esters in human urine: implications for their mode of action. J Invest Dermatol. 2009;129(1):231-4.
165. Schmidt TJ, Ak M, Mrowietz U. Reactivity of dimethyl fumarate and methylhydrogen fumarate towards glutathione and N-acetyl-L-cysteine--preparation of S-substituted thiosuccinic acid esters. Bioorg Med Chem. 2007;15(1):333-42.
166. Peterson JD, Herzenberg LA, Vasquez K, Waltenbaugh C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. Proc Natl Acad Sci U S A. 1998;95(6):3071-6.
167. Schmidt MM, Dringen R. Fumaric acid diesters deprive cultured primary astrocytes rapidly of glutathione. Neurochem Int. 2010;57(4):460-7.
168. Wilms H, Sievers J, Rickert U, Rostami-Yazdi M, Mrowietz U, Lucius R. Dimethylfumarate inhibits microglial and astrocytic inflammation by suppressing the synthesis of nitric oxide, IL-1beta, TNF-alpha and IL-6 in an in-vitro model of brain inflammation. J Neuroinflammation. 2010;7:30.

169. Linker RA, Lee DH, Ryan S, van Dam AM, Conrad R, Bista P, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain. 2011;134(Pt 3):678-92.
170. Gold R, Linker RA, Stangel M. Fumaric acid and its esters: an emerging treatment for multiple sclerosis with antioxidative mechanism of action. Clin Immunol. 2012;142(1):44-8.
171. Helwa I, Choudhary V, Chen X, Kaddour-Djebbar I, Bollag WB. Anti-Psoriatic Drug Monomethylfumarate Increases Nuclear Factor Erythroid 2-Related Factor 2 Levels and Induces Aquaporin-3 mRNA and Protein Expression. J Pharmacol Exp Ther. 2017;362(2):243-53.
172. Vandermeeren M, Janssens S, Wouters H, Borghmans I, Borgers M, Beyaert R, et al. Dimethylfumarate is an inhibitor of cytokine-induced nuclear translocation of NF-kappa B1, but not RelA in normal human dermal fibroblast cells. J Invest Dermatol. 2001;116(1):124-30.
173. Loewe R, Pillinger M, de Martin R, Mrowietz U, Gröger M, Holnthoner W, et al. Dimethylfumarate inhibits tumor-necrosis-factor-induced CD62E expression in an NF-kappa B-dependent manner. J Invest Dermatol. 2001;117(6):1363-8.
174. Litjens NH, Rademaker M, Ravensbergen B, Rea D, van der Plas MJ, Thio B, et al. Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses. Eur J Immunol. 2004;34(2):565-75.
175. Gerdes S, Shakery K, Mrowietz U. Dimethylfumarate inhibits nuclear binding of nuclear factor kappaB but not of nuclear factor of activated T cells and CCAAT/enhancer binding protein beta in activated human T cells. Br J Dermatol. 2007;156(5):838-42.
176. Moharregh-Khiabani D, Linker RA, Gold R, Stangel M. Fumaric Acid and its esters: an emerging treatment for multiple sclerosis. Curr Neuropharmacol. 2009;7(1):60-4.
177. Peng H, Guerau-de-Arellano M, Mehta VB, Yang Y, Huss DJ, Papenfuss TL, et al. Dimethyl fumarate inhibits dendritic cell maturation via nuclear factor κB (NF-κB) and extracellular signal-regulated kinase 1 and 2 (ERK1/2) and mitogen stress-activated kinase 1 (MSK1) signaling. J Biol Chem. 2012;287(33):28017-26.
178. Zhao G, Liu Y, Fang J, Chen Y, Li H, Gao K. Dimethyl fumarate inhibits the expression and function of hypoxia-inducible factor-1α (HIF-1α). Biochem Biophys Res Commun. 2014;448(3):303-7.
179. Li Y, Tang J, Hu Y. Dimethyl fumarate protection against collagen II degradation. Biochem Biophys Res Commun. 2014;454(2):257-61.
180. Kang HJ, Seo HA, Go Y, Oh CJ, Jeoung NH, Park KG, et al. Dimethylfumarate suppresses adipogenic differentiation in 3T3-L1 preadipocytes through inhibition of STAT3 activity. PLoS One. 2013;8(4):e61411.
181. Tang H, Lu JY, Zheng X, Yang Y, Reagan JD. The psoriasis drug monomethylfumarate is a potent nicotinic acid receptor agonist. Biochem Biophys Res Commun. 2008;375(4):562-5.
182. Hanson J, Gille A, Zwykiel S, Lukasova M, Clausen BE, Ahmed K, et al. Nicotinic acid- and monomethyl fumarate-induced flushing involves GPR109A expressed by keratinocytes and COX-2-dependent prostanoid formation in mice. J Clin Invest. 2010;120(8):2910-9.
183. Hanson J, Gille A, Offermanns S. Role of HCA_2 (GPR109A) in nicotinic acid and fumaric acid ester-induced effects on the skin. Pharmacol Ther. 2012;136(1):1-7.
184. Chen H, Assmann JC, Krenz A, Rahman M, Grimm M, Karsten CM, et al. Hydroxycarboxylic acid receptor 2 mediates dimethyl fumarate's protective effect in EAE. J Clin Invest. 2014;124(5):2188-92.
185. Bjerke JR, Krogh HK, Matre R. Characterization of mononuclear cell infiltrates in psoriatic lesions. J Invest Dermatol. 1978;71(5):340-3.
186. Christophers E, Metzler G, Röcken M. Bimodal immune activation in psoriasis. Br J Dermatol. 2014;170(1):59-65.
187. Krueger G, Ellis CN. Psoriasis--recent advances in understanding its pathogenesis and treatment. J Am Acad Dermatol. 2005;53(1 Suppl 1):S94-100.
188. Sebök B, Bonnekoh B, Geisel J, Mahrle G. Antiproliferative and cytotoxic profiles of antipsoriatic fumaric acid derivatives in keratinocyte cultures. Eur J Pharmacol. 1994;270(1):79-87.

189. Ockenfels HM, Schultewolter T, Ockenfels G, Funk R, Goos M. The antipsoriatic agent dimethylfumarate immunomodulates T-cell cytokine secretion and inhibits cytokines of the psoriatic cytokine network. Br J Dermatol. 1998;139(3):390-5.
190. Bovenschen HJ, Langewouters AM, van de Kerkhof PC. Dimethylfumarate for psoriasis: Pronounced effects on lesional T-cell subsets, epidermal proliferation and differentiation, but not on natural killer T cells in immunohistochemical study. Am J Clin Dermatol. 2010;11(5):343-50.
191. Stoof TJ, Flier J, Sampat S, Nieboer C, Tensen CP, Boorsma DM. The antipsoriatic drug dimethylfumarate strongly suppresses chemokine production in human keratinocytes and peripheral blood mononuclear cells. Br J Dermatol. 2001;144(6):1114-20.
192. Thio HB, Zomerdijk TP, Oudshoorn C, Kempenaar J, Nibbering PH, van der Schroeff JG, et al. Fumaric acid derivatives evoke a transient increase in intracellular free calcium concentration and inhibit the proliferation of human keratinocytes. Br J Dermatol. 1994;131(6):856-61.
193. Sebok B, Bonnekoh B, Vetter R, Schneider I, Gollnick H, Mahrle G. The antipsoriatic dimethyl-fumarate suppresses interferon-gamma -induced ICAM-1 and HLA-DR expression on hyperproliferative keratinocytes. Quantification by a culture plate-directed APAAP-ELISA technique. Eur J Dermatol. 1998;8(1):29-32.
194. Vandermeeren M, Janssens S, Borgers M, Geysen J. Dimethylfumarate is an inhibitor of cytokine-induced E-selectin, VCAM-1, and ICAM-1 expression in human endothelial cells. Biochem Biophys Res Commun. 1997;234(1):19-23.
195. Meissner M, Doll M, Hrgovic I, Reichenbach G, König V, Hailemariam-Jahn T, et al. Suppression of VEGFR2 expression in human endothelial cells by dimethylfumarate treatment: evidence for anti-angiogenic action. J Invest Dermatol. 2011;131(6):1356-64.
196. Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, et al. S3 - Guidelines on the treatment of psoriasis vulgaris (English version). Update. J Dtsch Dermatol Ges. 2012;10 Suppl 2:S1-95.
197. Atwan A, Abbott R, Kelly M, Pickles T, Bauer A, Taylor C, et al. Oral fumaric acid esters for psoriasis. Cochrane Database of Systematic Reviews. 2013(4).
198. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[updated March 2011]. Available from: www.cochrane-handbook.org.
199. Friedrich M, Sterry W, Klein A, Ruckert R, Docke WD, Asadullah K. Addition of pentoxifylline could reduce the side effects of fumaric acid esters in the treatment of psoriasis. Acta Derm Venereol. 2001;81(6):429-30.
200. Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, 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(1):46-53.
201. Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, et al. Oral fumaric acid esters for psoriasis. Cochrane Database Syst Rev. 2015;8:CD010497.
202. O'Rourke K, Detsky AS. Meta-analysis in medical research: strong encouragement for higher quality in individual research efforts. J Clin Epidemiol. 1989;42(10):1021-4.
203. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
204. Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. J Am Acad Dermatol. 1994;30(6):977-81.
205. Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 1990;22(2 Pt 1):311-2.
206. 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(7):502-4.

207. Langner A, Roszkiewicz J, Baran E, Placek W. Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis (Abstract P075). European Congress on Psoriasis 2004. Journal of the European Academy of Dermatology & Venereology. 2004;18(6):798.
208. Mrowietz U, Reich K, Spellman M. Efficacy, safety, and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis: Results of a phase 3 study. Journal of the American Academy of Dermatology. 2006;54(Suppl):AB202.
209. Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. J Eur Acad Dermatol Venereol. 2015;29(4):645-8.
210. Mustafa A, Al-Hoqail I. Biologic systemic therapy for moderate-to-severe psoriasis: A review. Journal of Taibah University Medical Sciences. 2013;8(3):142-50.
211. Ceglowska U, Wlodarczyk A, Slomka M. Clinical effectiveness of fumaric acid esters (Fumaderm) in psoriasis: A systematic review of literature. ISPOR 17th Annual European Congress. Amsterdam, The Netherlands, Nov 2014:PSS6.
212. Walker F, Adamczyk A, Kellerer C, Belge K, Brück J, Berner T, et al. Fumaderm® in daily practice for psoriasis: dosing, efficacy and quality of life. Br J Dermatol. 2014;171(5):1197-205.
213. Mrowietz U, Szepietowski JC, Loewe R, van de Kerkhof P, Lamarca R, Ocker WG, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm. Br J Dermatol. 2017;176(3):615-23.
214. Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. Br J Dermatol. 1998;138(3):456-60.
215. Reich K, Thaci D, Mrowietz U, Kamps A, Neureither M, Luger T. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis--a retrospective study (FUTURE). J Dtsch Dermatol Ges. 2009;7(7):603-11.
216. Gambichler T, Kreuter A, Susok L, Skrygan M, Rotterdam S, Höxtermann S, 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(5):574-80.
217. The US Food and Drug Administration. FDA Approved Drug Product: Tecfidera, approval 27/03/2013. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204063lbl.pdf Access date April 2018.
218. The Electronic Medicines Compendium (EMC). Skilarence 30mg Gastro-resistant Tablets. Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/752/smpc Access date May 2018.
219. Healthcare Professional Guideline - Important safety information for Skilarence (dimethyl fumarate). Available at https://www.medicines.org.uk/emc/rmm/1012/Document Access date 27 May 2018.
220. Mrowietz U, Reich K. Dear-Doctor-Letter Fumaderm® - What are the facts? J Dtsch Dermatol Ges. 2013;11(10):1016-7.
221. Weber T, Trebst C, Frye S, Cinque P, Vago L, Sindic CJ, et al. Analysis of the systemic and intrathecal humoral immune response in progressive multifocal leukoencephalopathy. J Infect Dis. 1997;176(1):250-4.
222. Koralnik I. Progressive multifocal leukoencephalopathy: Epidemiology, clinical manifestations, and diagnosis. UpToDate. Available at https://www.uptodate.com/contents/progressive-multifocal-leukoencephalopathy-epidemiology-clinical-manifestations-and-diagnosis?search=progressive-multifocal-leukoencephalopathy-epidemiology-clinical-&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H13 Access date 26 May 2018.
223. Koralnik I. Progressive multifocal leukoencephalopathy: Treatment and prognosis. UpToDate. Available at https://www.uptodate.com/contents/progressive-multifocal-

leukoencephalopathy-treatment-and-prognosis?topicRef=1694&source=see_link Access date 27 May 2018.
224. Ermis U, Weis J, Schulz JB. PML in a patient treated with fumaric acid. N Engl J Med. 2013;368(17):1657-8.
225. Buttmann M, Stoll G. Case reports of PML in patients treated for psoriasis. N Engl J Med. 2013;369(11):1081.
226. van Oosten BW, Killestein J, Barkhof F, Polman CH, Wattjes MP. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. N Engl J Med. 2013;368(17):1658-9.
227. Dimethyl fumarate (Tecfidera): fatal PML in an MS patient with severe, prolonged lymphopenia. Medicines and Healthcare products Regulatory Agency (MHRA). Published 30 March 2015. Available at https://www.gov.uk/drug-safety-update/dimethyl-fumarate-tecfidera-fatal-pml-in-a-ms-patient-with-severe-prolonged-lymphopenia Access date April 2018.
228. Balak DMW, Hajdarbegovic E, Bramer WM, Neumann HAM, Thio HB. Progressive multifocal leukoencephalopathy associated with fumaric acid esters treatment in psoriasis patients. J Eur Acad Dermatol Venereol. 2017;31(9):1475-82.
229. Stoppe M, Thomä E, Liebert UG, Major EO, Hoffmann KT, Claßen J, et al. Cerebellar manifestation of PML under fumarate and after efalizumab treatment of psoriasis. J Neurol. 2014;261(5):1021-4.
230. Metz I, Traffehn S, Straßburger-Krogias K, Keyvani K, Bergmann M, Nolte K, et al. Glial cells express nuclear nrf2 after fumarate treatment for multiple sclerosis and psoriasis. Neurol Neuroimmunol Neuroinflamm. 2015;2(3):e99.
231. Dammeier N, Schubert V, Hauser TK, Bornemann A, Bischof F. Case report of a patient with progressive multifocal leukoencephalopathy under treatment with dimethyl fumarate. BMC Neurol. 2015;15:108.
232. Hoepner R, Faissner S, Klasing A, Schneider R, Metz I, Bellenberg B, et al. Progressive multifocal leukoencephalopathy during fumarate monotherapy of psoriasis. Neurol Neuroimmunol Neuroinflamm. 2015;2(3):e85.
233. Nieuwkamp DJ, Murk JL, van Oosten BW, Cremers CH, Killestein J, Viveen MC, et al. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. N Engl J Med. 2015;372(15):1474-6.
234. Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18.
235. Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2017;12:CD011535.
236. Maza A, Montaudié H, Sbidian E, Gallini A, Aractingi S, Aubin F, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol. 2011;25 Suppl 2:19-27.
237. Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, et al. Oral fumaric acid esters for psoriasis: Abridged Cochrane systematic review including GRADE assessments. Br J Dermatol. 2016.
238. World Health Organization. WHOQOL: Measuring Quality of Life. Available at http://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/ Accessed May 2018.
239. Mckenna KE, Stern RS. The outcomes movement and new measures of the severity of psoriasis. J Am Acad Dermatol. 1996;34(3):534-8.
240. Jayaprakasam A, Darvay A, Osborne G, McGibbon D. Comparison of assessments of severity and quality of life in cutaneous disease. Clin Exp Dermatol. 2002;27(4):306-8.
241. Russo PA, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: a review. Australas J Dermatol. 2004;45(3):155-9; quiz 60-1.

242. Quality of Life Questionnaires. Department of Dermatology Cardiff University. Available at http://sites.cardiff.ac.uk/dermatology/quality-of-life/ Accessed May 2018.
243. Loo WJ, Diba V, Chawla M, Finlay AY. Dermatology Life Quality Index: influence of an illustrated version. Br J Dermatol. 2003;148(2):279-84.
244. Fortune DG, Richards HL, Main CJ, Griffiths CE. What patients with psoriasis believe about their condition. J Am Acad Dermatol. 1998;39(2 Pt 1):196-201.
245. Leibovici V, Canetti L, Yahalomi S, Cooper-Kazaz R, Bonne O, Ingber A, et al. Well being, psychopathology and coping strategies in psoriasis compared with atopic dermatitis: a controlled study. J Eur Acad Dermatol Venereol. 2010;24(8):897-903.
246. Richards HL, Fortune DG, Weidmann A, Sweeney SK, Griffiths CE. Detection of psychological distress in patients with psoriasis: low consensus between dermatologist and patient. Br J Dermatol. 2004;151(6):1227-33.
247. Uhlenhake EE, Kurkowski D, Feldman SR. Conversations on psoriasis--what patients want and what physicians can provide: a qualitative look at patient and physician expectations. J Dermatolog Treat. 2010;21(1):6-12.
248. Jobling RG. Psoriasis -- a preliminary questionnaire study of sufferers' subjective experience. Clin Exp Dermatol. 1976;1(3):233-6.
249. Renzi C, Abeni D, Picardi A, Agostini E, Melchi CF, Pasquini P, et al. Factors associated with patient satisfaction with care among dermatological outpatients. Br J Dermatol. 2001;145(4):617-23.
250. Nelson PA, Chew-Graham CA, Griffiths CE, Cordingley L, Team I. Recognition of need in health care consultations: a qualitative study of people with psoriasis. Br J Dermatol. 2013;168(2):354-61.
251. 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(4):741-6.
252. van Bezooijen JS, Balak DM, van Doorn MB, Looman CW, Schreurs MW, Koch BC, et al. Combination Therapy of Etanercept and Fumarates versus Etanercept Monotherapy in Psoriasis: A Randomized Exploratory Study. Dermatology. 2016;232(4):407-14.
253. The British Association of Dermatologists' Biologic Interventions Register. News. Available at http://www.badbir.org/News/ Access date April 2018.
254. Steinz K, Gerdes S, Domm S, Mrowietz U. Systemic treatment with fumaric acid esters in six paediatric patients with psoriasis in a psoriasis centre. Dermatology. 2014;229(3):199-204.
255. Balak DM, Oostveen AM, Bousema MT, Venema AW, Arnold WP, Seyger MM, 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(6):1343-7.

Appendices

APPENDIX 1

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Patient code: ..... Date: / / Score: **DLQI**

Initials: .....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes No A lot A little Not at all	❒ ❒ ❒ ❒ ❒	 Not relevant ❒
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

Please check you have answered EVERY question. Thank you.

APPENDIX 2:

Participant Information Sheet

(Version 1.0 – 27.04.2012)

Study Title:
Optimising psoriasis referrals from primary care: Dermatology Life Quality Index (DLQI) as a triage tool

Invitation:
You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take your time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of this study?
It is well known that psoriasis can cause a major impact on a patient's quality of life in terms of physical discomfort, psychological distress and social problems. Currently, almost all GP psoriasis referrals to the hospital are prioritised as 'Routine' which results in several months of waiting, regardless of the effect of psoriasis on patients' quality of life. This study has been put forward to assess whether a short questionnaire called "Dermatology Life Quality Index (DLQI)" would be a useful aid to help prioritise patients with psoriasis when they are referred to the specialist.

Why I have been invited?
You have been diagnosed with psoriasis and newly referred to the dermatology department at the University Hospital of Wales. This makes you eligible to participate in this study. We need 60 people like yourself to take part in this study.

Do I have to take part?
Participation is entirely voluntary; it is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to read and also be asked to sign a consent form. You still can withdraw from the study at anytime without giving any reasons, this will not affect the care provided to you. Also if you decide not to participate in the study the standard of care you receive will not be affected.

What will happen to me if I take part?
If you are willing to participate in this study, a member of the research team (investigator or clinical studies nurse) will spend 20-30 minutes with you in private. You will be allowed to ask any questions you may have in relation to this study then you will be requested to sign a consent form and to complete a simple questionnaire about the effect of your psoriasis on your life. This is called Dermatology Life Quality Index (DLQI) questionnaire, which is a short "tick boxes" questionnaire that normally takes around 2 minutes to complete.

After completing the questionnaire, the researcher will ask you questions about your condition and medications, as in a normal doctor consultation. These questions will

include the duration of the psoriasis, current and previous psoriasis treatment(s), any other medical conditions, family history of psoriasis, etc. Following this you will be asked to indicate how happy you are with waiting time for your referral.

The researcher then will examine your skin to evaluate the distribution, degrees of redness and scaling of your psoriasis. There will be no tests (e.g. blood tests or X-rays) and you will not be required to make any extra visits to the hospital for the sake of this study. Also, this study will not include trying any medication. The collected data will then pass with your medical notes to the doctor who will see you to aid the consultation.

How long will it take?
For this study you will need to be seen by a member of the research team only once for 20-30 minutes. This can take place on the same day you attend your first appointment in dermatology prior to seeing the specialist. Nonetheless, you have up to 2 days from receiving this information to decide whether you would like to participate.

What if I do not wish to take part in the study?
Taking part is entirely voluntary. If you do not want to take part in the study then there is no need to do so.

What are the possible benefits of taking part in the study?
Your participation will help us to decide whether using the DLQI questionnaire is useful when patients with psoriasis are referred to the hospital. The ultimate aim is to improve the care provided to psoriasis patients.

What are the possible risks of taking part?
The study involves filling in a questionnaire; so there are no risks associated with it.

What will happen to the results of the research?
The collective results of this study will be published in a scientific journal. All information generated from this study will be anonymous meaning that your name or any identifier will not appear anywhere. You can be provided with a copy of this publication, if you are interested.

Will my taking part in this study be kept confidential?
We will follow ethical and legal practice and all information about you will be handled in confidence. The researcher will inform your GP that you have participated in this study. However, all the information collected about you during the course of study will be kept strictly confidential. Each person participating in the research will be given a code number to maintain confidentiality. Only the investigators will have access to the participant's details that link with the code number. These details will be kept in secure place within the dermatology department of the hospital. Only the collective study results will be published, without giving individual participant details.

Who is organising and funding the study?
A group of Cardiff doctors including dermatologists and a GP are organising this study. It has been funded by the Dermatology Forum for Wales.

Who has reviewed the study?
This study has been reviewed by the Dermatology Forum for Wales, the Research and Commercial Division (RACD) of Cardiff University, Research and Development Department and the South East Wales Local Research Ethics Committee.

What should I do if I have a complaint about the conduct of the study?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions

Dr Ausama Abou Atwan	Tel: 02920745870
Dr John Ingram	Tel: 02920746357

If you remain unhappy and wish to complain formally, you can do this by contacting Research Governance officer, Cardiff University

Helen Falconer	Tel: 02920879277

Thank you for taking time to read this information sheet and for your help with this study.

APPENDIX 3

PATIENT CONSENT FORM

Study Title:

Optimising psoriasis referrals from primary care: Dermatology Life Quality Index (DLQI) as a triage tool

Please initial each box to indicate that you have read and agree to each statement.

1. I confirm that I have read and understand the information sheet, (version 1.0, dated 27.04.2012) for this study, that I have had the opportunity to ask questions and that I have received satisfactory answers to the questions I have asked. ☐
2. I understand that my participation is voluntary and that I am free to withdraw consent at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at for the purposes of this study and by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to these records. ☐
4. I understand that anonymous data about me, as collected for this study, including information about my health may be used in publications about the study. ☐
5. I am happy for you to inform my GP that I shall be participating in this study. ☐
6. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	**Date**	**Signature**

(Please print your name and date your own signature)

_____	_____	_____
Name of person taking consent	**Date**	**Signature**

(Investigator)

APPENDIX 4

Optimising psoriasis referral from primary care: DLQI as a triage tool
Department of Dermatology

Data Collection Sheet

Date: _ _ / _ _ _ / _ _ _ _

Study Title: Optimising psoriasis referrals from primary care: Dermatology Life Quality Index (DLQI) as a triage tool

Code Number	_ _ _
Initials	_ _ _
Age (years)	_ _ _ years
Gender	□ Male □ Female
Marital status	□ Single □ Married □ Divorced □ Widowed
Occupation	
Duration of psoriasis	_ _ _ _ Years _ _ _ _ Months
Specific sites affected?	□ Scalp □ Nails □ Face □ Hands □ Armpits □ Groin
Current Psoriasis Treatments *(Dose / Frequency / Duration)*	- - -
Previous Psoriasis Treatment *(Dose / Frequency / Duration)*	- - -
Any proven health problems?	□ Heart Disease (Including high blood pressure) □ Diabetes □ High Cholesterol □ Depression □ Psoriatic arthritis □ Other Please specify……

1

Data Collection Sheet V 2.0 *19 Sept 2012*
SPON 1115-12 *REC: 12/WA/0212*

Optimising psoriasis referral from primary care: DLQI as a triage tool
Department of Dermatology

Any Family Members With Psoriasis?	□ Yes □ No □ Uncertain If you tick "Yes", please state the relation(s) ……
Referral Date	_ _ / _ _ / _ _ _ _
Date seen	_ _ / _ _ / _ _ _ _
Waiting time (days)	…… days
Weight (Kg), Height (m), BMI	Weight = …….. Kg Height = ……m BMI = $\frac{\text{Weight (kg)}}{\text{Height (m)}^2}$ = ---------- = ……
How satisfied are you with the waiting time since your referral?	**1** □ Not at all Happy **2** □ Not very Happy **3** □ Neutral **4** □ Happy **5** □ Very Happy
DLQI score at referral *(if applicable)*	…….
DLQI score today	…….
How is your psoriasis today compared to when your referral was made?	□ A lot worse □ Slightly worse □ The same □ Slightly better □ A lot better □ Not sure
PASI score	…….

Data Collected by:

Name (Please Print): ……..

Signature: ……

APPENDIX 5

Appendix 5 - PSORIASIS AREA AND SEVERITY INDEX (PASI)[1]

Patient code number: _ _ _ Initials: _ _ _ _ Date: _ _ / _ _ / _ _ _ _

SEVERITY OF PSORIATIC LESIONS

Circle one number in each of the categories below:

0 = None **1 =** Slight **2 =** Moderate **3 =** Severe **4 =** Very Severe

		Head	Upper Limbs	Trunk	Lower Limbs
1	**Erythema**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
2	**Thickness**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
3	**Scaling**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
4	**Total each column**	☐☐	☐☐	☐☐	☐☐

AREA OF PSORIASIS INVOLVEMENT

5	**Degree of Involvement**	**0=** None **4=** 50 to < 70%	**1=** <10% **5=** 70 to < 90%	**2=** 10 to < 30% **6=** 90 to < 100%	**3=** 30 to < 50%
6	Insert degree of involvement from **Row 5**	☐	☐	☐	☐
7	Multiply **Row 4** by **Row 6**	☐☐	☐☐	☐☐	☐☐
8		**X 0.1**	**X 0.2**	**X 0.3**	**X 0.4**
9	Multiply **Row 7** by **Row 8**	☐☐.☐	☐☐.☐	☐☐.☐	☐☐.☐
ADD TOGETHER EACH COLUMN IN ROW 9		☐☐.☐ **= TOTAL PASI SCORE**			
Assessor (print name please): ……					

1. Fredrickson T and Pettersson U. Dermatologica 1978; 157: 238-244

APPENDIX 6

Part of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Government.
Yn rhan o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cymru

NISCHR
Gwasanaeth Moeseg Ymchwil | RES | Research Ethics Service

South East Wales Research Ethics Committee, Panel B
Sixth Floor, Churchill House
17 Churchill Way
Cardiff CF10 2TW
Telephone : 029 2037 6823

E-mail : carl.phillips@wales.nhs.uk
Website : www.nres.nhs.uk

19 July 2012

Dr John R Ingram
Clinical Lecturer
Cardiff University in Dermatology
3rd Floor, Glamorgan House
Dept of Dermatology
Heath Park, Cardiff University
CF14 4XN

Dear Dr Ingram

Study title:	**Optimising psoriasis referrals from primary care: Dermatology Life Quality Index (DLQI) as a triage tool**
REC reference:	**12/WA/0212**
Protocol number:	**SPON 1115-12**

The Research Ethics Committee reviewed the above application at the meeting held on the 18 July 2012.

The Committee was most grateful to both you and Dr A Atwan for kindly taking the time to attend the meeting. The additional information and clarification that you were able to provide was much appreciated and most helpful.

The Committee also wished me to congratulate you on the very high standard of the application submitted for ethical review. The Committee commented that the project was an excellent one and members were delighted to have the opportunity to support it.

Ethical opinion

The Committee noted that this was a single site study which involved administering questionnaires for quantitative analysis, or using mixed quantitative/qualitative methodology, and which aimed to determine if the Dermatology Life Quality Index (DLQI) questionnaire was a valuable tool to triage referrals of psoriasis patients from General Practitioners to dermatologists.

The Committee in noting that the study was sponsored by Cardiff University also noted that evidence of indemnity to cover any potential liability arising from the research had been provided as required by *Section 1.45* of the *Standard Operating Procedures for Research Ethics Committees version 5.1 dated March 2012,* issued by the *National Research Ethics Service (NRES).*

GIG NHS Bwrdd Iechyd Addysgu Powys Powys Teaching Health Board

Cynhelir Cydweithrediad Gwyddor Iechyd Academaidd y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd gan Fwrdd Addysgu Iechyd Powys

The National Institute for Social Care and Health Research Academic Health Science Collaboration is hosted by Powys Teaching Health Board

Ariennir gan Lywodraeth Cymru funded by Welsh Government

The Committee noted that the study was being undertaken as part of an educational qualification, namely a Medical Doctorate and members further noted that the '*Declaration for student projects by academic supervisor*' had been signed as part of the application for ethical review.

The Committee wished to draw attention to the fact that the National Research Ethics Service (NRES) advised applicants that where a project was being undertaken as part of a PhD or other doctorate, the student should normally be named as the Chief Investigator (CI). However this was principally a matter for the study sponsor.

The Committee noted that the sponsor's representative had declared that an appropriate process of scientific critique had demonstrated that this research proposal was worthwhile and of high scientific quality and confirmation had been provided that scientific review had been undertaken by The Dermatology Forum for Wales, who had also agreed to fund the project.

The Committee noted that the study would involve a total of 60 participants aged 18 years of age and over whose involvement in the study would total approximately 30 minutes. The Committee also noted the confirmation that you kindly provided that potential participants would be identified and approached by clinical medical and nursing staff involved in their care.

The Committee questioned whether the proposed recruitment figure would be sufficient bearing in mind likely withdrawals, and members noted the response provided that you had allowed for a 20% drop-out and that you were satisfied that the overall figure would be sufficient.

The Committee noted that potential participants would be provided with written information about the purpose of the study, why they had been invited to participate, who was conducting the research, how the data would be used and what participation would be required of them. They would also be given the opportunity to ask any questions about the study. Written consent would be obtained prior to participation in the study and it was made clear that participation was entirely voluntary and that those taking part could withdraw at any point for any reason.

The Committee noted that participants would have up to two days in which to decide whether or not to take part in the study.

The Committee noted that General Practitioners would be informed of their patients' involvement in this study. Members further noted that potential participants were advised of this within the proposed information sheet and that an appropriate section seeking consent had been included within the proposed consent form.

The Committee noted from *section A43* of the *application form* that personal data would be stored for between 6 - 12 months after the study had ended and pointed out that it was the responsibility of the Chief Investigator to be up to date and to comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

- Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.
- Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.
- Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.
- Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.
- For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.
- Sponsors are not required to notify the Committee of approvals from host organisations
- It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter	J Ingram	25 June 2012
Evidence of insurance or indemnity	Cardiff University	06 July 2011
GP/Consultant Information Sheets	1.0	27 April 2012
Investigator CV	JR Ingram	14 June 2012
Letter from Sponsor	Cardiff University	30 May 2012
Other: CV	Professor V Piguet	01 September 2011
Other: CV	Dr AA Atwan	12 June 2012
Other: Letter re funding	Dermatology Forum for Wales	06 February 2012
Other: Letter to GP	1.0	27 April 2012
Participant Consent Form	1.0	27 April 2012
Participant Information Sheet	1.0	27 April 2012
Protocol	1.0	27 April 2012

Questionnaire: Dermatology Life Quality Index		
Questionnaire: Psoriasis Area and Severity Index		
REC application	3.4	25 June 2012

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/WA/0212 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Mrs A Dowden
Chair, Panel B
South East Wales Research Ethics Committees

4

APPENDIX 7

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

Ysbyty Athrofaol Cymru
University Hospital of Wales

Heath Park,
Cardiff, CF14 4XW
Phone 029 2074 7747
Fax 029 2074 3838
Minicom 029 2074 3632

Parc Y Mynydd Bychan,
Caerdydd, CF14 4XW
Ffôn 029 2074 7747
Ffacs 029 2074 3838
Minicom 029 2074 3632

Eich cyf/Your ref
Ein cyf/Our ref
Welsh Health Telephone Network 1872
Direct line/Llinell uniongyrchol

DERMATOLOGY FORUM FOR WALES
GRANT APPLICAION

Dr John Ingram
Clinical Lecturer
Department of Dermatology and Wound Healing
3rd Floor, Glamorgan House
University Hospital of Wales
Heath Park
Cardiff CF14 4XN

6th February 2012

Dear Dr Ingram,

Title: Optimising psoriasis referrals from primary care: Dermatology Quality of Life Index as a triage tool.

Grant amount: £ 2000.00

It gives me great pleasure to inform you that your application for the Dermatology Forum for Wales grant has been successful.

The grant can be claimed either as a single invoice or serial invoices by a named individual or institute. I would be grateful if you could kindly inform me of this individual or institute as soon as possible.

The funds must be claimed by 31st January 2013. Any unclaimed funds by this date will be re-deposited back in the DFW reserves.

Please note that the grant amount quoted above is **maximum final** and cannot be increased for whatever reason. Applications for further funds in subsequent years will be considered in the same manner as a first time applicant.

The Dermatology Forum for Wales should be duly credited in any presentations or publications resulting from the above project. The Forum also requires a written scientific report upon completion of the utilization of the grant.

Congratulations on your successful grant application.

Yours sincerely

Dr Ru Katugampola
Consultant Dermatologist and secretary to the Dermatology Forum for Wales

Chairman: Dr Richard Williams Chairman elect: Dr Richard Motley

APPENDIX 8

Research and Commercial Division
Director Geraint W Jones
Adran Ymchwil a Masnach
Cyfarwyddwr Geraint W Jones

Cardiff University
7th Floor
30 - 36 Newport Road
Cardiff CF24 0DE
Wales UK
Tel *Ffôn* +44(0)29 2087 5834
Fax *Ffacs* +44(0)29 2087 4189
Prifysgol Caerdydd
Llawr 7
30 - 36 Heol Casnewydd
Caerdydd CF24 0DE
Cymru Y Deyrnas Gyfunol

30 May 2012

Dr John R Ingram
Department of Dermatology and Wound Healing
School of Medicine
Cardiff University
Heath Park
Cardiff, CF14 4XN

Dear Dr Ingram,

Optimising psoriasis referrals from primary care: Dermatology Life Quality Index (DQLI) as a triage tool.

I understand that you are acting as Academic Supervisor for the above MD project to be conducted by Dr Ausama Abou Atwan. I confirm that Cardiff University agrees in principle to act as Sponsor for the above project, as required by the Research Governance Framework for Health and Social Care.

Scientific Review
I can also confirm that Scientific Review has been obtained from The Dermatology Forum for Wales.

Insurance
The necessary insurance provisions will be in place prior to the project commencement. Cardiff University is insured with Zurich Municipal. Copies of the insurance certificate are attached to this letter.

Approvals
On completion of your IRAS form (for NHS REC and NHS R&D approvals), you will be required to obtain signature from the Sponsor ('Declaration by the Sponsor Representative').

Please then submit the project to the following organisations for approval:

- the appropriate Research Ethics Committee(s);
- National Institute for Social Care Health Research Permissions Coordinating Unit (NISCHR PCU- to arrange host organisation R&D approval);

Once RACD has received evidence of the above approvals, the University is considered to have accepted Sponsorship and your project may commence.

Roles and Responsibilities
As Chief Investigator you have signed a Declaration with the Sponsor to confirm that you will adhere to the standard responsibilities as set out by the Research Governance Framework for Health and Social Care/ Medicines for Human Use (Clinical Trials) Regulations. In accordance with the University's Research Governance Framework, the Chief Investigator is also responsible for ensuring that each research team member is qualified and experienced to fulfill his/her delegated roles including ensuring adequate supervision, support and training.

Roles and responsibilities are adequately detailed in the research protocol.

May I take this opportunity to remind you that, as Chief Investigator, you are required to:

- ensure you are familiar with your responsibilities under the Research Governance Framework for Health and Social Care;
- undertake the study in accordance with Cardiff University's Research Governance Framework and the principles of Good Clinical Practice;
- ensure the Research complies with the Data Protection Act 1998;
- inform the Research and Commercial Division (RACD) of any amendments to the protocol of study design, including changes to start /end dates;
- co-operate with any audit inspection of the project files or any requests from RACD for further information

You should quote the following unique reference number in any correspondence relating to sponsorship for the above project:

SPON 1115-12

This reference number should be quoted on all documentation associated with this project.

Yours sincerely

Dr K J Pittard Davies
Head of Research Policy & Management
Direct line: +44 (0) 29208 79274
Email: resgov@cardiff.ac.uk

cc Dr Ausama Abou Atwan

APPENDIX 9

Research letter

Dermatology Life Quality Index (DLQI) as a psoriasis referral triage tool

DOI: 10.1111/bjd.15446

Dear Editor, Most primary care psoriasis referrals in the U.K. are triaged as 'routine', in part because of the prioritization of skin cancer. As a result, patients with severe psoriasis may wait several months to be seen, enduring quality of life (QoL) impairment that could have been reduced. Furthermore, some patients may spontaneously improve by the time they are seen by a specialist, making the appointment unnecessary at that time. Therefore, following approval from the local ethics committee, we conducted a prospective study to evaluate the usefulness of Dermatology Life Quality Index (DLQI) scores in triaging patients with psoriasis referred to our dermatology secondary healthcare services.

Local general practitioners (GPs) were provided with DLQI questionnaires when referring patients with psoriasis. Referrals were triaged as 'urgent' if the DLQI score was > 10 because this represents a very large effect on a patient's life.[1] Those referred with no DLQI scores, either from participating or nonparticipating GPs, were triaged as routine, as a control group. When patients were seen in clinic, we measured their DLQI and Psoriasis Area and Severity Index (PASI) scores, and satisfaction with the waiting time (measured on a five-point Likert scale from 1, not at all happy to 5, very happy). A power calculation predicted that 20 patients were required in each group to give 80% power to detect a 5-point difference in PASI score for an alpha significance level of 0·05. The 40 recruited patients had no significant differences in demographics or disease characteristics (Table 1). The median waiting time for the 'urgent' group was 88 days [interquartile range (IQR) 66–99], whereas patients triaged as 'routine' waited a median 256 days (IQR 228–295).

As expected, of those patients seen urgently, 60% were 'happy' or 'very happy' with the waiting time. In contrast, in the routine group no patients were 'happy' or 'very happy'. The median PASI score in the urgent group was 6·2 (IQR 3·5–10·6), compared with 3·85 (IQR 2·8–6·3) in the routine group (no significant difference). The median DLQI score in the urgent group when seen in secondary care was 4 points higher than in the routine group (urgent 16, IQR 12–20 vs. routine 12, IQR 8·5–17). In those triaged as urgent, the median DLQI score was not significantly different from the baseline score at the time of referral (17·5, IQR 13·5–23).

Pressures on dermatology secondary care services in the U.K. and a requirement to meet skin cancer waiting time targets result in patients with inflammatory dermatoses having long waiting times. Triaging GP referrals accurately is difficult if information is incomplete and disease severity scores are not given. Asking GPs to determine a severity score involving complete skin examination, such as the PASI, is not practical because of lack of time and insufficient training. However, a QoL questionnaire can easily be completed by patients while the GP documents the consultation. The DLQI is the most commonly used QoL assessment tool in psoriasis trials[2] and takes 1–2 min to complete.[3] Patients seen urgently due to a baseline DLQI score > 10 at referral had a DLQI score 4 points higher than those referred without a DLQI and seen 'routinely'. As the minimal clinically important difference for the DLQI is 4 points,[4] using a baseline DLQI score > 10 does identify those patients whose psoriasis has a particularly high impact on QoL, compared with an unselected group of psoriasis referrals.

Table 1 Participants' characteristics

	Routine (no DLQI at referral)	Urgent (DLQI > 10 at referral)
Number	20	20
Sex	9 male, 11 female	11 male, 9 female
Age (years), median (IQR)	34 (28–51)	40 (33–52)
Psoriasis duration (years), median (IQR)	13 (9–20)	9 (4–20)
Body mass index (kg m^{-2}), median (IQR)	27·1 (23·4–31·2)	29·2 (26–33·5)
Family history of psoriasis	10	9
Comorbidities	11 (5 hypertension, 2 hypercholesterolaemia, 8 depression)	8 (4 hypertension, 1 diabetes mellitus, 2 hypercholesterolaemia, 2 depression, 2 psoriatic arthritis)
Waiting time (days), median (IQR)	256 (228–295)	88 (66–99)

DLQI, Dermatology Life Quality Index; IQR, interquartile range.

One limitation of this study is the lack of a separate group of psoriasis referrals with a DLQI score ≤ 10. However, we found that almost no patients were referred with scores in this range, perhaps because GPs chose not to refer less severely affected patients. The Scottish[5] and Malaysian[6] guidelines recommend referral for DLQI scores > 5 in patients with psoriasis unresponsive to topical therapy, and, in keeping with our study experience, 65·5% of eligible patients in Scotland were not seen by a specialist.[7] It is possible that patients or GPs might inflate DLQI scores to reduce waiting time delays; however, we mitigated this in our study by not specifying the DLQI score triage cut-off for urgent appointments.

Our long waiting time of 256 days for routine referrals reflects pressures on dermatology secondary care services in Wales. While we chose a DLQI cut-off score of 10 points, as it indicates major impairment of QoL, a different cut-off score could be selected depending on the attitude and resources of the referral centre.

In summary, we have demonstrated that a QoL instrument such as the DLQI can be used as a triage tool. Its use may help GPs quantify psoriasis severity, and ensure that patients whose psoriasis is causing the greatest impact on QoL are seen in a timely manner. A much larger randomized study is needed to evaluate the usefulness of DLQI as a triage tool in dermatology services.

Acknowledgments

We would like to thank Dr M.K. Basra and Professor A.V. Anstey for their contribution to the study protocol and comments on this letter, and we thank Dr Mark Kelson for his comments on the statistical data.

[1]Department of Dermatology and [2]Department of Primary Care and Public Health, Cardiff University School of Medicine, Cardiff, U.K.
E-mail: abouatwanaa@cardiff.ac.uk

A. Atwan[1]
V. Piguet[1]
A.Y. Finlay[1]
N.A. Francis[2]
J.R. Ingram[1]

References

1 Finlay AY. Current severe psoriasis and the rule of tens. Br J Dermatol 2005; **152**:861–7.
2 Ali FM, Cueva AC, Vyas J et al. A systematic review of the use of quality of life instruments in randomised controlled trials of psoriasis. Br J Dermatol 2017; **176**:577–93.
3 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; **19**:210–6.
4 Basra MK, Salek MS, Camilleri L et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology 2015; **230**:27–33.
5 Scottish Intercollegiate Guidelines Network (SIGN). Guideline 121. Diagnosis and management of psoriasis and psoriatic arthritis in adults. Available at: http://www.sign.ac.uk/assets/sign121.pdf (last accessed 20 July 2017).
6 Choon S, Chan L, Choon SE et al. Malaysian Clinical Practice Guideline for the Management of Psoriasis Vulgaris: summary of recommendations for management in primary healthcare setting. Malays Fam Physician 2014; **9**:16–21.
7 Wade AG, Crawford GM, Young D et al. Severity and management of psoriasis within primary care. BMC Fam Pract 2016; **17**:145.

Funding sources: a research grant from the Dermatology Forum for Wales.

Conflicts of interest: V.P. has received departmental support from AbbVie, Johnson & Johnson, Pfizer, GSK, Novartis and CEO. He has received honoraria from Johnson & Johnson, Novartis and AbbVie. His department benefits financially from the DLQI. A.Y.F. is joint copyright holder of the DLQI; Cardiff University and A.Y.F. receive royalties. A.Y.F. has received honoraria from Novartis, Eli Lilly, Sanofi, Napp and Galderma.

APPENDIX 10

papaa®
Charity no: 1118192

The Psoriasis and Psoriatic Arthritis Alliance
3 Horseshoe Business Park
Lye Lane
Bricket Wood
St Albans
Hertfordshire
AL2 3TA

Tel: 01923 672837
Fax: 01923 682606

Email: info@papaa.org
Website: www.papaa.org
eCommerce: www.psoriasis-shop.org

26 April 2012

Dr John Ingram
Dermatology Clinical Lecturer
3rd Floor Glamorgan House
University Hospital of Wales
Heath Park
Cardiff
CF14 4XN

Terms and conditions of grant award

Name of project: Cochrane Review: Fumeric acid esters for psoriasis
Amount awarded: £10,000

Dear Dr Ingram

We are please to inform you that your application for funding of the above project has been approved by the PAPAA Board of Trustees. The award is subject to following terms and conditions:

1. The project must be started and completed within the stated timescales.
2. PAPAA must be informed of any changes or slippage in time as soon as it becomes apparent.
3. PAPAA must be informed of any change in personnel or institutional structures, if it directly impacts on the completion of the project.
4. The funds can only be used for project that is the subject the application.
5. Any unused funds must be returned to PAPAA on completion of the project.
6. A brief interim report must be produced at 6 months following the start of the project, with a final report produced within 6 months of the completion date.
7. A brief lay report must be produced for inclusion on the PAPAA website and for inclusion in the organisation's journal.
8. Full acknowledgment of PAPAA's support should be included in any publication or reporting of the project as follows:
   "This project was funded by a grant from the Psoriasis and Psoriatic Arthritis Alliance"
9. VAT (if applicable) and other costs must be included in the total amount requested as no additional amounts will be paid over and above the awarded amount stated above

I would be grateful if you would complete the attached Registration Form to confirm your acceptance of the above and return to me at your earliest convenience.

Yours sincerely

David Chandler.

David Chandler
Chief Executive

c.c.
Dr David Ashton
PAPAA Senior Medical Advisor

APPENDIX 11

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]

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
#12 #3 and #11

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

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

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

APPENDIX 12

Cochrane Library

Cochrane Database of Systematic Reviews

Oral fumaric acid esters for psoriasis (Review)

Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, Piguet V

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.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Oral fumaric acid esters for psoriasis

Ausama Atwan[1], John R Ingram[1], Rachel Abbott[2], Mark J Kelson[3], Timothy Pickles[3], Andrea Bauer[4], Vincent Piguet[1]

[1]Department of Dermatology & Wound Healing, Cardiff Institute of Infection & Immunity, Cardiff University, Cardiff, UK. [2]Welsh Institute of Dermatology, University Hospital of Wales, Cardiff, UK. [3]South East Wales Trials Unit, Institute of Translation, Innovation, Methodology and Engagement, Cardiff University, Cardiff, UK. [4]Department of Dermatology, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

Contact address: John R Ingram, Department of Dermatology & Wound Healing, Cardiff Institute of Infection & Immunity, Cardiff University, 3rd Floor, Glamorgan House, Heath Park, Cardiff, CF14 4XN, UK. ingramjr@cardiff.ac.uk.

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 FOR THE MAIN COMPARISON *[Explanation]*

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
Common nuisance AEs (not leading to treatment discontinuation)	Moderate		RR 4.72 (2.45 to 9.08)	99 (1 RCT)	⊕⊕⊕◯ MODERATE[2]	Most commonly stomach-ache or cramps, diarrhoea, and flushing
	16 per 100	76 per 100 (39 to 100)				
PASI 50	Moderate		RR 4.55 (2.80 to 7.40)	247 (2 RCTs)	⊕⊕◯◯ LOW[1, 4]	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, 4]	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).

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

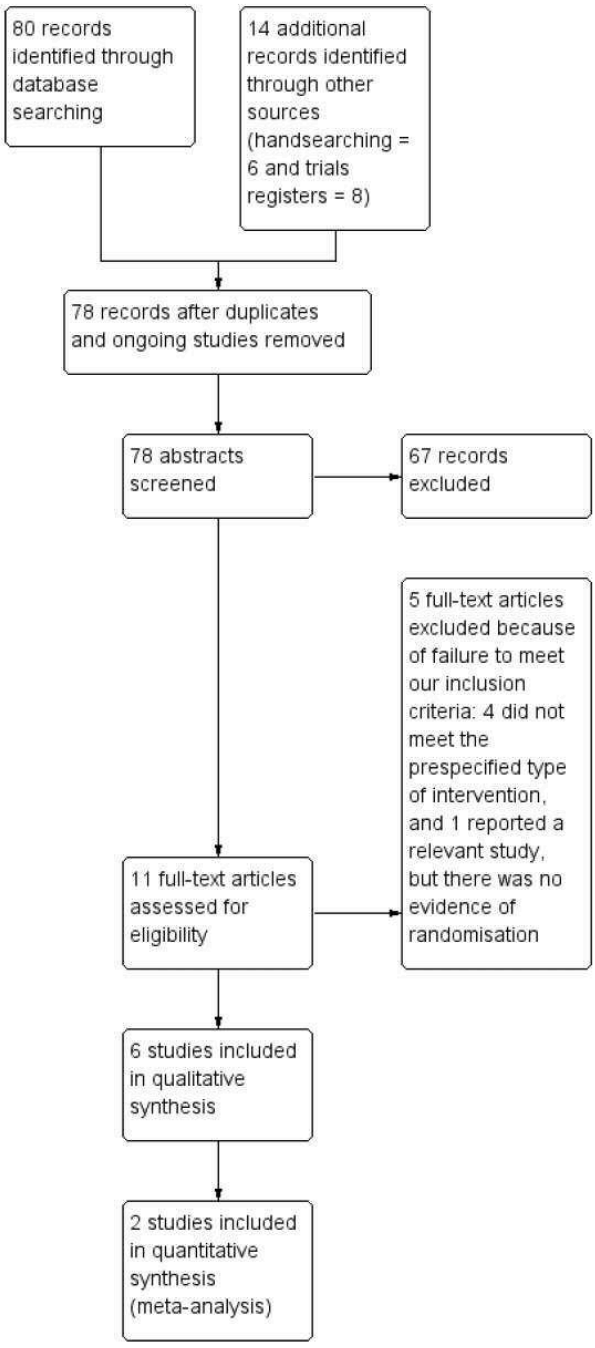
Description of studies

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 $\geq$ 10 at baseline; 1 study, Mrowietz 2006, $\geq$ 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.

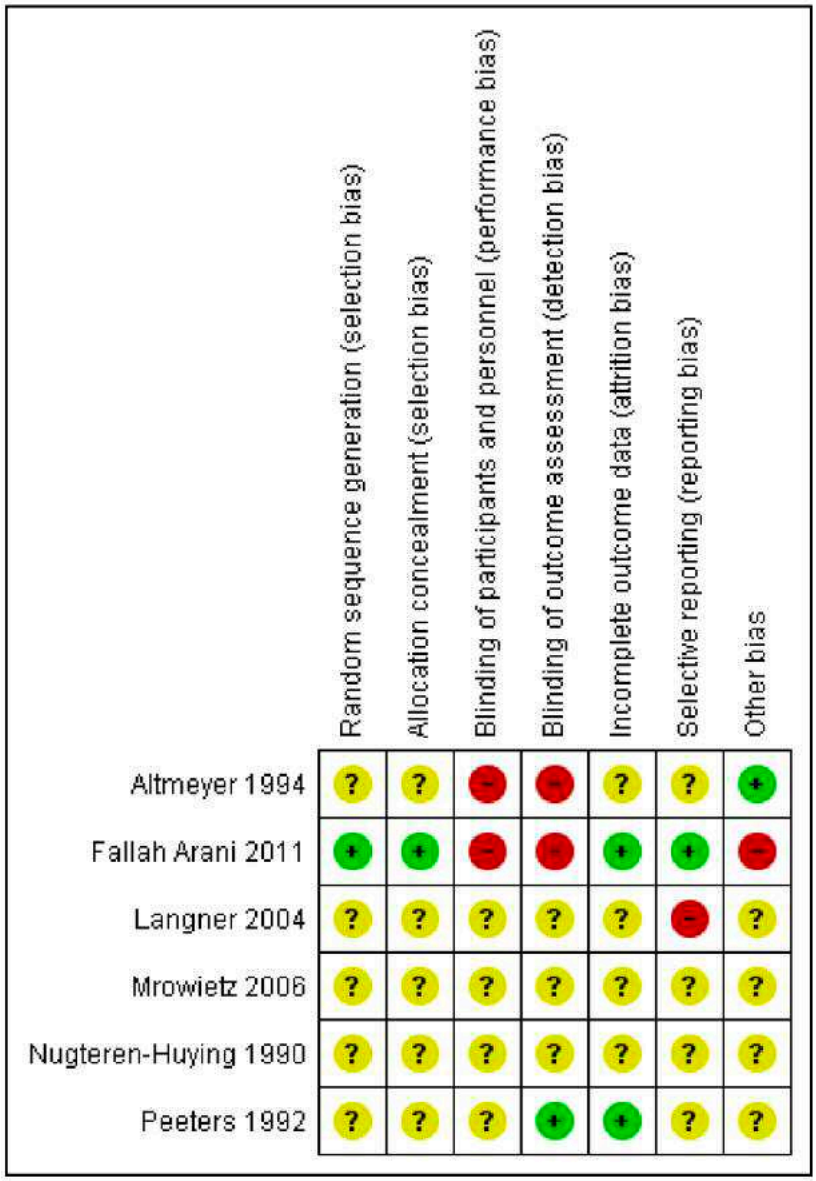
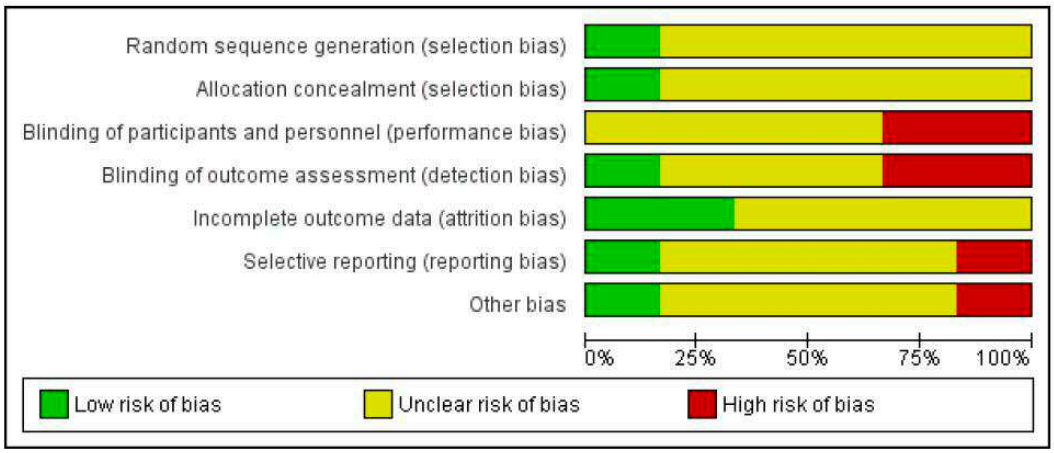


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.



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.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

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.

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.

REFERENCES

References to studies included in this review

Altmeyer 1994 ***{published data only (unpublished sought but not used)}***

Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. *Journal of the American Academy of Dermatology* 1994;**30**(6):977–81. ; PUBMED: 8188891

Fallah Arani 2011 ***{published data only (unpublished sought but not used)}***

Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. *British Journal of Dermatology* 2011; **164**(4):855–61. ; PUBMED: 21175564

Langner 2004 ***{published data only (unpublished sought but not used)}***

Langner A, Roszkiewicz J, Baran E, Placek W. Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis (Abstract P075). European Congress on Psoriasis 2004. *Journal of the European Academy of Dermatology & Venereology* 2004;**18**(6):798.

Mrowietz 2006 ***{published data only (unpublished sought but not used)}***

* Mrowietz U, Reich K, Spellman MC. Efficacy, safety, and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis: Results of a phase 3 study. *Journal of the American Academy of Dermatology* 2006;**54**(Suppl):AB202.

Mrowietz U, Spellman M. Dimethyl Fumarate (BG00012) as an Oral Therapy for Moderate to Severe Psoriasis: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial (Abstract 406). 35th Annual ESDR Meeting 22-24th September 2005, Tübingen, Germany. *Journal of Investigative Dermatology* 2005;**125**(3 Suppl): A69.

Mrowietz U, Spellman MC. Results of a phase III study of a novel oral formulation of dimethylfumarate in the treatment of moderate to severe plaque psoriasis: efficacy, safety, and quality of life effects (Abstract P06.97). The 14th Congress of the European Academy of Dermatology and Venereology, London,UK. 12-15th October 2005. *Journal of the European Academy of Dermatology & Venereology : JEADV* 2005;**19**(Suppl 2):187.

Ortonne JP, van de Kerkhof P, Mrowietz U. A novel oral agent improves quality of life (QOL) in patients with plaque psoriasis (Abstract P013). 4th European Association of Dermatology & Venereology (EADV) Spring Symposium. Saariselka, Lapland, Finland, Feb 9th-12th 2006. 2006: P–013.

Nugteren-Huying 1990 ***{published data only (unpublished sought but not used)}***

* Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy for psoriasis: A randomized, double-blind, placebo-controlled study. *Journal of the American Academy of Dermatology* 1990;**22**(2 Pt 1):311–312. ; PUBMED: 2312814

Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy in psoriasis; a double-blind, placebo-controlled study [Fumaarzuurtherapie tegen psoriasis; een dubbelblind, placebo–gecontroleerd onderzoek]. *Nederlands Tijdschrift Voor Geneeskunde* 1990; **134**(49):2387–91. ; PUBMED: 2263264

Peeters 1992 ***{published data only (unpublished sought but not used)}***

* Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. *British Journal of Rheumatology* 1992;**31**(7):502–4. ; PUBMED: 1628175

Peeters AJ, Dijmans BAC, van der Schroeff JG. Favourable effect of fumaric acid treatment in psoriatic arthritis: A double-blind placebo-controlled study [Gunstig effect van fumaarzuurtherapie bij arthritis psoriatica: een dubbelblind, placebo–gecontroleerd onderzoek]. *Nederlands Tijdschrift Voor Geneeskunde* 1992;**136**(49):2428–31. ; EMBASE: 1993004024

References to studies excluded from this review

Balak 2015 ***{published data only}***
Balak DM, Fallah-Arani S, Venema CM, Neumann HA, Thio HB. 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. *British Journal of Dermatology* 2015;**172**(3):754–9. ; PUBMED: 25041291

Friedrich 2001 ***{published data only}***
Friedrich M, Sterry W, Klein A, Rückert R, Döcke WD, Asadullah K. Addition of pentoxifylline could reduce the side effects of fumaric acid esters in the treatment of psoriasis. *Acta Dermato-Venereologica* 2001;**81**(6):429–30. ; PUBMED: 11859949

Gollnick 2002 ***{published data only}***
Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, 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**(1):46–53. ; PUBMED: 12145434

Nieboer 1989 ***{published data only (unpublished sought but not used)}***
Nieboer C, de Hoop D, van Loenen AC, Langendijk PNJ, van Dijk E. Systemic therapy with fumaric acid derivates: New possibilities in the treatment of psoriasis. *Journal of the American Academy of Dermatology* 1989;**20**(4):601–8. ; PUBMED: 2654206

Nieboer 1990 ***{published data only}***
Nieboer C, de Hoop D, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. *Dermatologica* 1990;**181**(1):33–7. ; PUBMED: 2394301

References to ongoing studies

DRKS00000716 ***{unpublished data only}***
DRKS00000716. Regulatory T-cell function in psoriasis vulgaris. apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00000716 (accessed 14 May 2015).

EudraCT Number 2012-000035-82 ***{unpublished data only}***
EudraCT Number: 2012-000035-82. A 2:1 randomized, 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). www.clinicaltrialsregister.eu/ctr-search/trial/2012-000035-82/DE (accessed 14 May 2015).

EudraCT Number 2012-000055-13 ***{unpublished data only}***
EudraCT Number: 2012-000055-13. A multi-center, randomized, 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. www.clinicaltrialsregister.eu/ctr-search/trial/2012-000055-13/AT (accessed 14 May 2015).

EudraCT Number 2012-005685-35 ***{unpublished data only}***
EudraCT Number: 2012-005685-35. 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. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number%3A2012-005685-35 (accessed 14 May 2015).

EudraCT Number 2014-005258-20 ***{unpublished data only}***
EudraCT Number: 2014-005258-20. A 24-week, randomized, 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. www.clinicaltrialsregister.eu/ctr-search/trial/2014-005258-20/DE (accessed 14 May 2015).

NCT00811005 ***{unpublished data only}***
NCT00811005. Fumaric Acid Ester-PUVA Therapy Versus Acitretin -PUVA Therapy in Pustular Palmoplantar Psoriasis (FVSA-PUVA). www.clinicaltrials.gov/show/NCT00811005 (accessed 14 May 2015).

NCT01088165 ***{unpublished data only}***
NCT01088165. The Influence of Adalimumab on Cardiovascular and Metabolic Risk in Psoriasis (CASTIP). www.clinicaltrials.gov/show/NCT01088165 (accessed 14 May 2015).

NCT01321164 ***{unpublished data only}***
NCT01321164. Fumaric Acid Versus Fumaric Acid Plus Narrow Band Type B Ultraviolet (UVB) for Psoriasis. www.clinicaltrials.gov/ct2/show/NCT01321164 (accessed 14 May 2015).

Additional references

Augustin 2010
Augustin M, Ogilvie A. Methods of outcomes measurement in nail psoriasis. *Dermatology* 2010;**221**(Suppl 1):23–8. MEDLINE: 20733312

Baker 1984
Baker BS, Swain AF, Fry L, Valdimarsson H. Epidermal T lymphocytes and HLA-DR expression in psoriasis. *British Journal of Dermatology* 1984;**110**(5):555–64. [PUBMED: 6232938]

Balak 2016
Balak DM, Fallah Arani S, Hajdarbegovic E. Efficacy, effectiveness and safety of fumaric acid esters in the treatment of psoriasis: a systematic review of randomized and observational studies. *British Journal of Dermatology* 2016;**175**:250–62. [PUBMED: 26919824]

Basavaraj 2010
Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. *International Journal of Dermatology* 2010;**49**(12):1351–61. MEDLINE: 21091671

Bovenschen 2010
Bovenschen HJ, Langewouters AM, van de Kerkhof PC. Dimethylfumarate for psoriasis: Pronounced effects on lesional T-cell subsets, epidermal proliferation and differentiation, but not on natural killer T cells in

immunohistochemical study. *American Journal of Clinical Dermatology* 2010;**11**(5):343–50. MEDLINE: 20553063

Burden 2012
Burden AD, Warren RB, Kleyn CE, McElhone K, Smith CH, Reynolds NJ, et al. The British Association of Dermatologists' Biologic Interventions Register (BADBIR): design, methodology and objectives. *British Journal of Dermatology* 2012;**166**(3):545–54. MEDLINE: 22356636

Carboni 2004
Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S. Fumaric acid esters in the treatment of psoriasis: an Italian experience. *Journal of Dermatological Treatment* 2004;**15**(1): 23–6. [PUBMED: 14754645]

Ceglowska 2014
Ceglowska U, Wlodarczyk A, Slomka M. Clinical effectiveness of fumaric acid esters (Fumaderm) in psoriasis: A systematic review of literature. ISPOR 17th Annual European Congress. Amsterdam, The Netherlands, Nov 2014:PSS6.

Duffy 1993
Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. *Journal of the American Academy of Dermatology* 1993;**29**(3):428–34. MEDLINE: 8349859

Eedy 1990
Eedy DJ, Burrows D, Bridges JM, Jones FG. Clearance of severe psoriasis after allogenic bone marrow transplantation. *BMJ* 1990;**300**(6729):908. MEDLINE: 2337714

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34. MEDLINE: 9310563

Eghlileb 2007
Eghlileb AM, Davies EE, Finlay AY. Psoriasis has a major secondary impact on the lives of family members and partners. *British Journal of Dermatology* 2007;**156**(6): 1245–50. MEDLINE: 17459044

García-Caballero 2011
García-Caballero M, Marí-Beffa M, Medina MÁ, Quesada AR. Dimethylfumarate inhibits angiogenesis in vitro and in vivo: a possible role for its antipsoriatic effect?. *Journal of Investigative Dermatology* 2011;**131**(6):1347–55. MEDLINE: 21289642

Ghoreschi 2011
Ghoreschi K, Brück J, Kellerer C, Deng C, Peng H, Rothfuss O, et al. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. *Journal of Experimental Medicine* 2011;**208**(11):2291–303. MEDLINE: 21987655

Griffiths 2000
Griffiths CE, Clark CM, Chalmers RJ, Li Wan Po A, Williams HC. A systematic review of treatments for severe psoriasis. *Health Technology Assessment* 2000;4(40):1–125. [DOI: 10.3310/hta4400; MEDLINE: 11207450

Griffiths 2007
Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;**370**(9583):263-71. MEDLINE: 17658397

Harries 2005
Harries MJ, Chalmers RJ, Griffiths CE. Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. *British Journal of Dermatology* 2005;**153**(3):549–51. [PUBMED: 16120141]

Heidenreich 2009
Heidenreich R, Rocken M, Ghoreschi K. Angiogenesis drives psoriasis pathogenesis. *International Journal of Experimental Pathology* 2009;**90**(3):232–48. MEDLINE: 19563608

Higgins 2011
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.

Hoefnagel 2003
Hoefnagel JJ, Thio HB, Willemze R, Bouwes Bavinck JN. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *British Journal of Dermatology* 2003;**149**(2):363–9. MEDLINE: 12932244

Huerta 2007
Huerta C, Rivero E, Rodriguez LA. Incidence and risk factors for psoriasis in the general population. *Archives of Dermatology* 2007;**143**(12):1559–65. MEDLINE: 18087008

Ingram 2012
Ingram JR, Desai N, Kai AC, Chua SL, Woo PN, Kerdel F, et al. Interventions for hidradenitis suppurativa. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD010081]

Kimball 2005
Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. *American Journal of Clinical Dermatology* 2005;**6**(6):383–92. MEDLINE: 16343026

Kokelj 2009
Kokelj F, Plozzer C, Avian A, Trevisan G. Fumaric acid and its derivatives in the treatment of psoriasis vulgaris: our experience in forty-one patients. *Acta Dermatovenerologica Croatica* 2009;**17**(3):170–5. [PUBMED: 19818215]

Langley 2005
Langley RGB, Krueger GG, Griffiths CEM. Psoriasis: epidemiology, clinical features, and quality of life. *Annals of the Rheumatic Diseases* 2005;**64**(Suppl II):18–23. MEDLINE: 15708928

Lebwohl 2003
Lebwohl M. Psoriasis. *Lancet* 2003;**361**(9364):1197–204. MEDLINE: 12686053

Mehta 2010
Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased

risk of cardiovascular mortality: cohort study using the General Practice Research Database. *European Heart Journal* 2010;**31**(8):1000-6. MEDLINE: 20037179

Meissner 2011
Meissner M, Doll M, Hrgovic I, Reichenbach G, König V, Hailemariam-Jahn T, et al. Suppression of VEGFR2 expression in human endothelial cells by dimethylfumarate treatment: evidence for anti-angiogenic action. *Journal of Investigative Dermatology* 2011;**131**(6):1356–64.

Menter 2007
Menter A, Griffiths CEM. Current and future management of psoriasis. *Lancet* 2007;**370**(9583):272–84. [PUBMED: 17658398]

Mrowietz 1999
Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. *British Journal of Dermatology* 1999;**141**(3):424–29. MEDLINE: 10584060

Mrowietz 2005
Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends in Molecular Medicine* 2005;**11**(1):43–8. [PUBMED: 15649822]

Mustafa 2013
Mustafa AA, Al-Hoqail IA. Biologic systemic therapy for moderate-to-severe psoriasis: A review. *Journal of Taibah University Medical Sciences* 2013;**8**(3):142–50. [DOI: 10.1016/j.jtumed.2013.09.001]

Nast 2012
Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, et al. S3 - Guidelines on the treatment of psoriasis vulgaris (English version). Update. *Journal der Deutschen Dermatologischen Gesellschaft* 2012;**10**(Suppl 2): S1–95. MEDLINE: 22386073

Nestle 2009
Nestle FO, Kaplan DH, Barker J. Psoriasis. *New England Journal of Medicine* 2009;**361**(5):496–509. MEDLINE: 19641206

O'Rourke 1989
O'Rourke K, Detsky AS. Meta-analysis in medical research: strong encouragement for higher quality in individual research efforts. *Journal of Clinical Epidemiology* 1989;**42** (10):1021–4. MEDLINE: 2809651

Onderdijk 2014
Onderdijk AJ, Balak DM, Baerveldt EM, Florencia EF, Kant M, Laman JD, et al. Regulated genes in psoriatic skin during treatment with fumaric acid esters. *British Journal of Dermatology* 2014;**171**(4):732–41. MEDLINE: 24852654

Parisi 2012
Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, on behalf of the Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *Journal of Investigative Dermatology* 2013;**133**(2):377–85. [DOI: 10.1038/jid.2012.339; MEDLINE: 23014338

Pathirana 2009
Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. *Journal of the European Academy of Dermatology & Venereology* 2009;**23**(Suppl 2): 1–70. MEDLINE: 19712190

Rapp 1999
Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *Journal of the American Academy of Dermatology* 1999;**41**(3 Pt 1):401–7. MEDLINE: 10459113

Rubant 2008
Rubant SA, Ludwig RJ, Diehl S, Hardt K, Kaufmann R, Pfeilschifter JM, et al. Dimethylfumarate reduces leukocyte rolling in vivo through modulation of adhesion molecule expression. *Journal of Investigative Dermatology* 2008;**128** (2):326–31. MEDLINE: 17671516

Schmitt 2014
Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *British Journal of Dermatology* 2014;**170**(2):274–303. MEDLINE: 24131260

Sladden 2006
Sladden MJ, Osborne JE, Hutchinson PE. Fumaric acid esters for severe psoriasis: the Leicestershire experience. *British Journal of Dermatology* 2006;**155**(4):843–4. [PUBMED: 16965442]

Smith 2006
Smith CH, Barker JN. Psoriasis and its management. *BMJ* 2006;**333**(7564):380–4. MEDLINE: 16916825

Smith 2009
Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *British Journal of Dermatology* 2009;**161**(5):987–1019. MEDLINE: 19857207

Taylor 2006
Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis & Rheumatology* 2006;**54**(8): 2665–73. [PUBMED: 16871531]

Telfer 1992
Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. *Archives of Dermatology* 1992;**128**(1):39–42. MEDLINE: 1739285

Trembath 1997
Trembath RC, Clough RL, Rosbotham JL, Jones AB, Camp RD, Frodsham A, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for

further disease loci revealed by a two stage genome-wide search in psoriasis. *Human Molecular Genetics* 1997;**6**(5): 813–20. [PUBMED: 9158158]

Walker 2014
Walker F, Adamczyk A, Kellerer C, Belge K, Bruck J, Berner T, et al. Fumaderm® in daily practice for psoriasis: dosing, efficacy and quality of life. *British Journal of Dermatology* 2014;**171**(5):1197–1205. MEDLINE: 24813676

Warren 2011
Warren RB, Kleyn CE, Gulliver WP. Cumulative life course impairment in psoriasis: patient perception of disease-related impairment throughout the life course. *British Journal of Dermatology* 2011;**164**(Suppl 1):1–14. MEDLINE: 21477010

References to other published versions of this review

Atwan 2013
Atwan A, Abbott R, Kelly MJ, Pickles T, Bauer A, Taylor C, Piguet V, Ingram JR. Oral fumaric acid esters for psoriasis. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD010497]

* *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

Altmeyer 1994 (*Continued*)

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
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** 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

Fallah Arani 2011 (*Continued*)

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 the protocol after registering the study at trialregister.nl. The protocol and the published paper are identical"

Fallah Arani 2011 (*Continued*)

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**

Langner 2004 (*Continued*)

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) 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 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 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

Mrowietz 2006 *(Continued)*

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** 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

Nugteren-Huying 1990 (*Continued*)

	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

Nugteren-Huying 1990 (*Continued*)

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
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

Peeters 1992 (*Continued*)

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 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

Peeters 1992 (*Continued*)

		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

DRKS00000716 (*Continued*)

Interventions	**Intervention 1** Adalimumab (Humira®) 80 mg initially and 40 mg every other week subcutaneously over a time period of 24 weeks **Intervention 2** 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 • Non-inferiority of LAS41008 compared with LASW1835 regarding PASI 75 after 16 weeks of treatment **Secondary outcomes**

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

	• 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** • 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

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

	○ 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 **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

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

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 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 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)

NCT01321164 *(Continued)*

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.

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

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

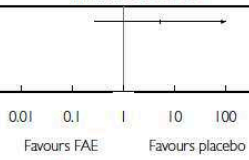
Analysis 1.1. Comparison 1 FAE vs placebo, Outcome 1 AEs leading to treatment discontinuation.

Review: Oral fumaric acid esters for psoriasis

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.

Review: Oral fumaric acid esters for psoriasis

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		29.4 %	4.60 [1.97, 10.76]
Mrowietz 2006	68/105	10/70		70.6 %	4.53 [2.51, 8.19]
Total (95% CI)	**141**	**106**		**100.0 %**	**4.55 [2.80, 7.40]**

Total events: 91 (FAE), 15 (Placebo)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 6.11 (P < 0.00001)

Test for subgroup differences: Not applicable

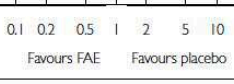
Analysis 1.3. Comparison 1 FAE vs placebo, Outcome 3 Common nuisance AEs (not leading to treatment discontinuation).

Review: Oral fumaric acid esters for psoriasis

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]

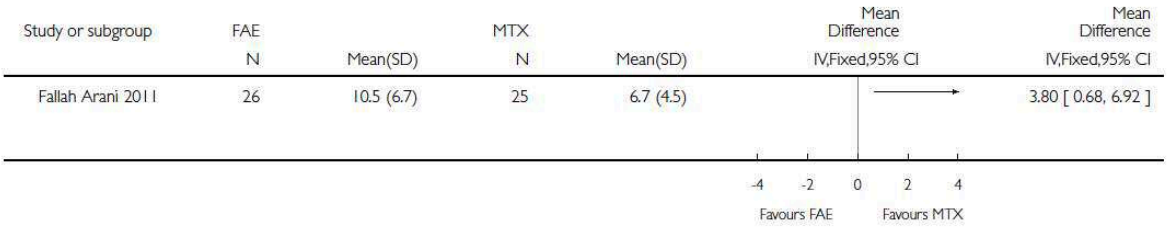


Analysis 2.1. Comparison 2 FAE vs MTX, Outcome 1 PASI score.

Review: Oral fumaric acid esters for psoriasis

Comparison: 2 FAE vs MTX

Outcome: 1 PASI score

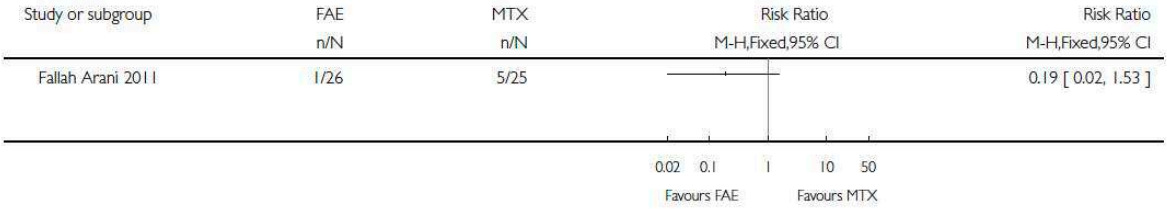


Analysis 2.2. Comparison 2 FAE vs MTX, Outcome 2 AEs leading to treatment discontinuation.

Review: Oral fumaric acid esters for psoriasis

Comparison: 2 FAE vs MTX

Outcome: 2 AEs leading to treatment discontinuation



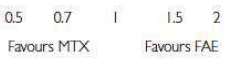
Analysis 2.3. Comparison 2 FAE vs MTX, Outcome 3 PASI 50.

Review: Oral fumaric acid esters for psoriasis

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]



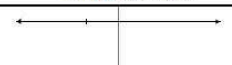
Analysis 2.4. Comparison 2 FAE vs MTX, Outcome 4 PASI 75.

Review: Oral fumaric acid esters for psoriasis

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		0.80 [0.28, 2.29]



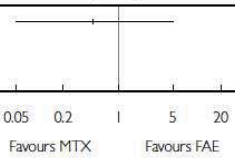
Analysis 2.5. Comparison 2 FAE vs MTX, Outcome 5 PASI 90.

Review: Oral fumaric acid esters for psoriasis

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]



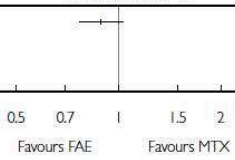
Analysis 2.6. Comparison 2 FAE vs MTX, Outcome 6 Common nuisance AEs (not leading to treatment discontinuation).

Review: Oral fumaric acid esters for psoriasis

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
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

Table 1. Glossary *(Continued)*

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)
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

Table 1. Glossary *(Continued)*

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

Last assessed as up-to-date: 7 May 2015.

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. 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

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

APEENDIX 13

SYSTEMATIC REVIEW

BJD
British Journal of Dermatology

Oral fumaric acid esters for psoriasis: abridged Cochrane systematic review including GRADE assessments

A. Atwan,[1] J.R. Ingram,[1] R. Abbott,[2] M.J. Kelson,[3] T. Pickles,[3] A. Bauer[4] and V. Piguet[1]

[1]Department of Dermatology & Wound Healing, Cardiff Institute of Infection & Immunity, Cardiff University, 3rd Floor Glamorgan House, Heath Park, Cardiff CF14 4XN, U.K.
[2]Welsh Institute of Dermatology, University Hospital of Wales, Cardiff, U.K.
[3]South East Wales Trials Unit, Institute of Translation, Innovation, Methodology and Engagement, Cardiff University, Cardiff, U.K.
[4]Department of Dermatology, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

Linked Comment: Egeberg. *Br J Dermatol* 2016; **175**:857

Summary

Fumaric acid esters (FAEs) are licensed for the treatment of moderate-to-severe psoriasis in Germany but are also used off-label in many other countries. We conducted this systematic review to synthesize the highest-quality evidence for the benefits and risks of FAEs for psoriasis. Our primary outcomes were change in Psoriasis Area and Severity Index score and dropout rates due to adverse effects. Randomized controlled trials (RCTs) of FAEs or dimethylfumarate were included, with no restriction on age or psoriasis subtype. We searched the Cochrane Skin Group Specialised Register, CENTRAL in the Cochrane Library, Medline, Embase, LILACS and five trials registers, and hand searched six conference proceedings. Six RCTs with a total of 544 participants were included, four of which were published only as abstracts or brief reports, limiting study reporting. Five RCTs compared FAEs with placebo, and all demonstrated benefit in favour of FAEs. However, meta-analysis was possible only for PASI 50 response after 12–16 weeks, which was achieved by 64% of participants on FAEs compared with 14% on placebo: risk ratio (RR) 4·55, 95% confidence interval (CI) 2·80–7·40; two studies; 247 participants; low-quality evidence). There was no difference in dropout rates due to adverse effects (RR 5·36, 95% CI 0·28–102·12; one study; 27 participants; very low-quality evidence and wide CI). More participants experienced nuisance adverse effects with FAEs (76%) than with placebo (16%) (RR 4·72, 95% CI 2·45–9·08; one study; 99 participants; moderate-quality evidence), mainly abdominal pain, diarrhoea and flushing. One head-to-head study of very low-quality evidence comparing FAEs with methotrexate reported comparable efficacy and dropout rates, although FAEs caused more flushing. The evidence in this review was limited and must be interpreted with caution; studies with better design and outcome reporting are needed.

Correspondence
John R. Ingram.
E-mail: ingramjr@cardiff.ac.uk

Accepted for publication
12 April 2016

Funding sources
Psoriasis and Psoriatic Arthritis Alliance (PAPAA), U.K. Grant award. The National Institute for Health Research (NIHR), U.K. The NIHR, U.K., is the largest single funder of the Cochrane Skin Group.

Conflicts of interest
V.P. 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 produces any of the interventions listed in this review. His department benefits financially from the Dermatology Life Quality Index.

This article is based on a Cochrane Review published in the Cochrane Database of Systematic Reviews 2015; 8:CD010497.

DOI 10.1111/bjd.14676

What's already known about this topic?

- Fumaric acid esters (FAEs) are licensed for the treatment of moderate-to-severe psoriasis in Germany, and are used off-label in many other countries.
- Non-Cochrane systematic reviews previously examined the effect of FAEs in psoriasis, but have not rigorously assessed the quality of the evidence.

What does this study add?

- Six randomized controlled trials with 544 participants were included, four of which were published only as abstracts or brief reports, resulting in low- or very low-quality evidence.

- Results suggest that FAEs are superior to placebo, but their efficacy in comparison with methotrexate is uncertain due to very low-quality evidence.
- The relative risk of nuisance adverse effects with FAEs is about five times greater than with placebo; however, there is insufficient evidence available to give an accurate figure for dropout rates due to adverse effects.

Psoriasis is a chronic inflammatory skin disease with various subtypes, of which chronic plaque psoriasis is the most common.[1] Fumaric acid esters (FAEs) were first used in the treatment of psoriasis in 1959 after successful self-experimentation by Schweckendiek, a German chemist who proposed that psoriasis was caused by a disturbance in the citric acid cycle in which fumaric acid was lacking.[2] FAEs contain dimethylfumarate (DMF), believed to be the active component, and salts of ethyl hydrogen fumarate.[3] Fumaderm® Initial (Biogen Idec, Cambridge, MA, U.S.A.), containing 30 mg of DMF per tablet, and Fumaderm®, containing 120 mg of DMF per tablet, are commercially available and have been licensed for the treatment of psoriasis in Germany since 1994.[4] They are also used for psoriasis treatment as off-label drugs in many other countries. The aim of this Cochrane review was to provide the best available evidence for the efficacy and safety of FAEs in the treatment of psoriasis. The results are summarized in this report, and the full review is available in the Cochrane Library.[5]

Material and methods

This systematic review was carried out according to a prespecified protocol[6] and incorporated Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[7]

Search strategies

An electronic search for relevant studies was carried out up to May 2015 using the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane library, Medline via Ovid from 1946, Embase via Ovid from 1974, and the Latin American and Caribbean Health Science Information (LILACS) database from 1982. We also searched the following trial registers up to May 2015 using the search terms 'fumaric acid', 'fumarate' and 'fumaderm': the metaRegister of Controlled Trials (http://www.isrctn.com/page/mrct), The US National Institute 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) and the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Abstracts of proceedings not included in electronic registries from the following dermatology conferences were hand searched by two authors independently (A.A. and R.A.): American Academy of Dermatology (2008/2009), British Association of Dermatologists (2008–2010) European Academy of Dermatology and Venereology (May 2006 to May 2013), European Society for Dermatological Research (2005–2009), International Investigative Dermatology (2003 to May 2013) and Society for Investigative Dermatology (2007–2009). The reference lists of included and excluded studies were checked for further references to relevant trials. We included all relevant randomized controlled trials (RCTs), with no language restrictions.

Inclusion criteria

We included RCTs that involved participants of either sex, and any age or ethnicity, with a clinical diagnosis of psoriasis of any subtype, where FAEs, as monotherapy or in combination, were compared with placebo or any other active treatment.

Types of outcome measures

The primary outcomes were Psoriasis Area and Severity Index (PASI) score and dropout rates due to adverse effects. Other outcomes of interest were quality-of-life scores measured with a validated scale; the proportion of participants achieving ≥ 50%, ≥ 75% and ≥ 90% improvement in PASI (PASI 50, 75 and 90); the proportion of participants experiencing serious adverse effects and those experiencing nonserious nuisance adverse effects.

Data extraction and synthesis

The titles and abstracts of retrieved studies were screened by two authors independently (A.A. and R.A.). The full texts of potentially eligible studies were examined by the same authors who extracted data from eligible studies using a data extraction form based on the 'checklists of items to consider in data extraction';[8] a third author (J.R.I.) adjudicated on disagreements.

Review Manager,[9] the software used for Cochrane reviews, was used for statistical analysis with a fixed-effects model. For dichotomous outcomes we pooled risk ratios (RRs) with 95% confidence intervals (CIs), while we combined the mean difference (MD) with 95% CI for continuous outcomes. We made contact with trial authors whenever possible to request relevant unreported data. Statistical heterogeneity was assessed using I^2 statistics; we took a narrative approach if the I^2 value exceeded 75%.[10] The quality of evidence for each outcome was ranked using GRADEpro software, from which we produced our 'summary of findings' tables.[7]

Results

Description of the included studies

In total, 94 records were identified through the initial search: database searching (n = 80), hand searching (n = 6) and trials registers (n = 8) (Fig. 1). These included eight ongoing studies and eight duplicate reports, which were excluded, giving a total of 78 records. Of these, 11 potentially eligible studies were identified after screening the titles and abstracts. After reading the full texts, five articles were excluded due to failure to meet our prespecified inclusion criteria[11–14] and lack of evidence of randomization.[15] As a result, six studies with a total of 544 participants were included in our review; five compared FAE with placebo[16–20] and one used methotrexate as an active comparator.[21]

The included studies were reported between 1990 and 2011. Only two of the six studies were published in full reports,[16,21] whereas the others were available in a brief communication,[19] a letter[20] and abstracts.[17,18] We were unable to obtain the full reports of published abstracts by contacting the authors. Despite the limitations of incompletely reported studies, we decided it was important to include them in our review because of the limited number of eligible RCTs.

Three of the included studies were carried out in the Netherlands,[19–21] one of which was designed to measure the effect of FAEs in the treatment of psoriatic arthritis.[20] However, contact with the authors confirmed that all participants had concomitant psoriasis, so we included this study to obtain safety data. All of the included studies involved adults aged > 18 years, except one study that did not report the participants' ages.[17] Participants in the included studies had chronic plaque psoriasis in two studies;[18,21] various psoriasis subtypes in two studies (chronic plaque, guttate, pustular and erythrodermic)[16,17] and unreported psoriasis subtype in two studies.[19,20]

PASI score at baseline was reported in only three studies, and was required to be ≥ 10 in one study,[21] ≥ 12 in one study[18] and 16–24 in one study.[17] Outcome reporting was at 12–16 weeks in all of the included studies, but not all of our prespecified outcomes were reported in every study. None of the included studies reported data on economic evaluations.

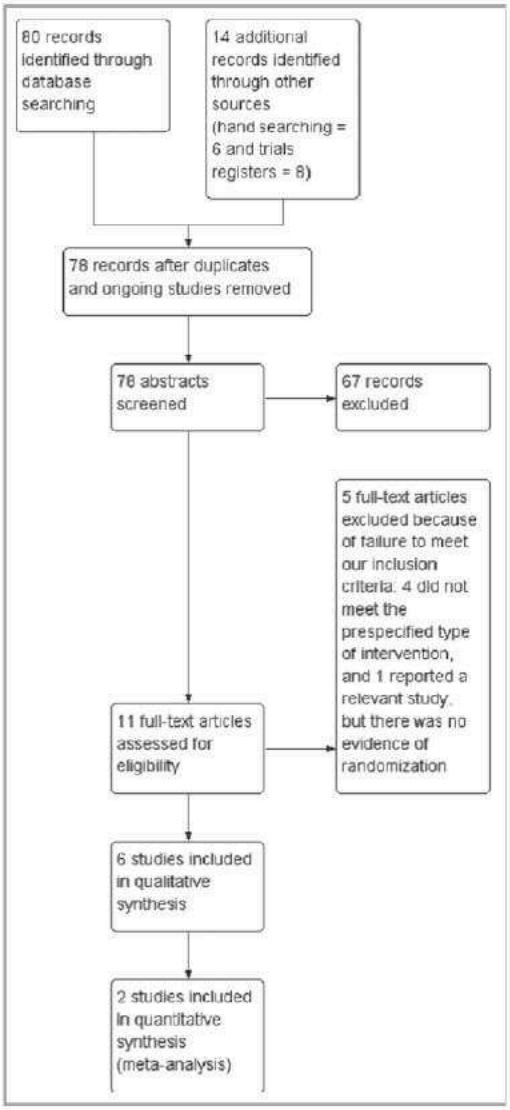


Fig 1. Study flow diagram.

Risk of bias in the included studies

Three of the included studies had 'high risk' of bias in at least one domain.[16,17,21] Insufficient reporting in most of the included studies, due to lack of full reports and old publications, rendered the risk of bias for most domains 'unclear' (Fig. 2).

Effects of interventions

Due to the lack of opportunities for meta-analyses, we used mainly a narrative approach to present the effects of FAEs in the treatment of psoriasis. The only exception was for the secondary outcome PASI 50 when FAEs were compared with placebo, where data from two studies were combined.

Comparison of fumaric acid esters with placebo

Three of the five studies comparing FAEs with placebo used a mixture of DMF plus monoethylfumarate as an intervention,[16,19,20] whereas DMF alone was used in the other two studies.[17,18] Two of the included studies[17,18] were reported in abstracts only; contact with the lead author[18] confirmed that the studies were not reported in full manuscripts and only the

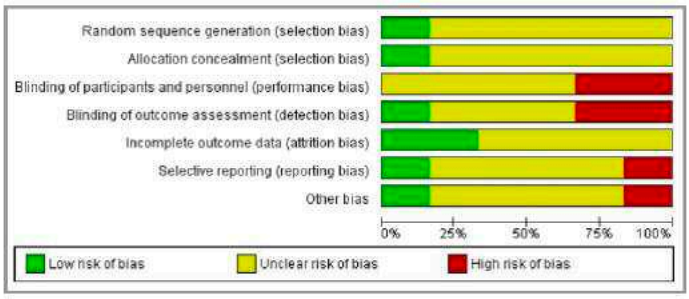


Fig 2. Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies.

data contained in the abstracts are available. In view of the limited number of eligible studies, and in agreement with the Cochrane Editorial Unit, we included these abstracts in our review. The quality of evidence for each outcome is presented in Table 1.

Altmeyer *et al.*[16] 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 the same ($P < 0·001$). Langner *et al.*[17] compared three doses of FAE (120 mg, 360 mg, 720 mg) with placebo, and reported statistically significant reductions in PASI score after 12 weeks, compared with baseline, of 31%, 52% and 71%, respectively ($P < 0·001$ compared with placebo for the 360-mg and 720-mg doses). Similarly, Mrowietz *et al.*[18] reported a median PASI score of 5·8 after 16 weeks of FAE treatment ($n = 105$), compared with a median of 14·2 in the placebo group ($n = 70$) ($P < 0·001$). This represented 67·8% and 10·2% reductions, respectively, and an effect size of 7·4 points (95% CI 5·40–9·40). It was not possible to compute the MD in these studies because of unreported mean PASI scores at baseline and follow-up.

In a meta-analysis from two studies[17,18] including a total of 247 participants, the number of participants who attained PASI 50 was greater with FAEs than with placebo (RR 4·55, 95% CI 2·80–7·40; $P < 0·001$; $I^2 = 0\%$; low-quality evidence) (Fig. 3). The combined PASI 50 was 64% with FAEs, compared with 14% for placebo, representing a number needed to treat to benefit (NNTB) of 2. The other studies comparing FAEs with placebo did not include a PASI score and instead measured the disease severity by estimating the body surface area involved.[19,20]

The dropout rate due to FAE adverse effects was reported clearly in only one study, which was designed for psoriatic arthritis.[20] In this study, two withdrawals occurred in the FAE group ($n = 13$) compared with no dropouts in the placebo arm ($n = 14$) (RR 5·36, 95% CI 0·28–102·12; 27 participants; very low-quality evidence). However, this finding is unreliable due to indirectness and very wide CIs. The reasons for dropout in the FAE group were diarrhoea (after 6 weeks) and proteinuria with raised serum creatinine (after 12 weeks). We could not establish the RR of dropouts due to adverse effects alone in the other studies because of unclear[16,19] or lack[17,18] of reporting. None of the included studies reported whether the adverse effects that led to treatment discontinuation were serious.

One study[16] reported a higher incidence of nuisance adverse effects (not leading to treatment discontinuation) with FAEs compared with placebo (RR 4·72, 95% CI 2·45–9·08; 99 participants; moderate-quality evidence), affecting 76% of participants given FAEs ($n = 49$) and 16% of the placebo group ($n = 50$), representing a number needed to treat to harm of 2. The most common were abdominal pain, diarrhoea and flushing (percentage and RR could not be computed).

A within-group comparison showed a statistically significant decrease of leucocytes with FAEs ($P = 0·016$), due to a reduction in lymphocyte count. The eosinophil count was unchanged in the placebo group, and increased in the FAE group from 2% at baseline to 3·4% at 4 weeks ($P < 0·05$), with a further insignificant increase to 4·7% at week 12. The maximum increase in eosinophil count was 28% (time point not stated). Another study[19] with a small number of participants in the FAE group ($n = 13$) reported diarrhoea (100% of participants), flushing (95%) and nausea (46%) as the most common adverse effects. Increased serum creatinine to 238 $\mu mol\ L^{-1}$ and reduced creatinine clearance rate by 51% were reported in one participant (8%) in the FAE group, but this was reversible (unknown whether treatment was stopped prior to improvement of the renal function).

Transient increase in liver enzymes (62%), eosinophilia (38%) and lymphopenia (31%) were also reported with FAEs, but it was not clear whether these occurrences were serious or caused treatment discontinuation. In the abstract published by Mrowietz *et al.*,[18] gastrointestinal adverse effects were observed in 58% of participants in the FAE group ($n = 105$), compared with 23% of those given placebo ($n = 70$) (RR 2·54, 95% CI 1·60–4·03). Adverse effect severity was described as moderate in 82% of cases (unclear whether any of the remaining 18% dropped out due to severe symptoms). In this abstract, more participants experienced flushing with FAEs in comparison with placebo (42% vs. 9%) (RR 4·67, 95% CI 2·09–10·39).

Quality of life was reported in only one abstract, using Skindex-29.[18] The mean score in the FAE group decreased from 54·7 at baseline to 27·0 at week 16, in comparison with

Table 1 Summary of findings: fumaric acid esters (FAEs) vs. placebo. Patient or population: psoriasis in adults. Setting: two reports from the Netherlands, one from Poland and two international multicentre studies. Intervention: FAE. Comparison: placebo

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)[b]	Comments
	Risk with placebo	Risk with FAEs				
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, $P < 0·001$); median reduction of 71% (FAE) and 6% (placebo) (1 study, 144 participants, $P < 0·001$); median reduction of 67·8% (FAE) and 10·2% (placebo) (1 study, 175 participants, $P < 0·001$)			418 (3 RCTs)	⊕⊕◯◯; LOW[c,d]	All three studies reported significant benefit with FAEs, at week 12 (one study) and week 16 (two studies), but data could not be pooled in a meta-analysis due to different ways of PASI score reporting
AEs leading to treatment discontinuation	Two participants withdrew from the FAE group (n = 13) compared with no dropouts in the placebo group (n = 14) (RR 5·36, 95% CI 0·28–102·12)			27 (1 RCT)	⊕◯◯◯; VERY LOW[e,f]	Outcome reported at week 16. Unclear whether any of the reported AEs were 'serious'
QoL assessed with Skindex-29 (range 0–100; higher scores indicate lower level of QoL)	Mean scores reduced from 54·7 at baseline to 27·0 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[e,g]	The reporting abstract did not provide the statistical values needed to calculate the mean difference with 95% CI
Common nuisance AEs (not leading to treatment discontinuation)	Moderate		RR 4·72 (2·45–9·08)	99 (1 RCT)	⊕⊕⊕◯; MODERATE[f]	Most commonly stomach ache or cramps, diarrhoea and flushing
PASI 50	16 per 100	76 per 100 (39–100)	RR 4·55 (2·80–7·40)	247 (2 RCTs)	⊕⊕◯◯; LOW[e,g]	The meta-analysis included participants who received dimethylfumarate 720 mg
	Moderate					
PASI 75	14 per 100	64 per 100 (39–100)		247 (2 RCTs)	⊕⊕◯◯; LOW[e,g]	Reported to be a statistically significant difference but data not pooled because of significant heterogeneity ($I^2 = 77\%$)
	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)					
PASI 90 (not measured)	See comment	See comment	Not estimable	–	–	Not measured in the included studies

AE, adverse effect; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI 50, ≥ 50% improvement in PASI; QoL, quality of life; RCT, randomized controlled trial; RR, risk ratio. [a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [b]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 the effect. [c]Downgraded one level due to risk of publication bias; data obtained from abstract(s), full report(s) not available. [d]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. [e]Downgraded two levels for imprecision; small sample size and very wide CIs that included the possibility of an effect in either direction (crosses line of no effect). [f]Downgraded one level due to risk of bias; insufficient reporting.

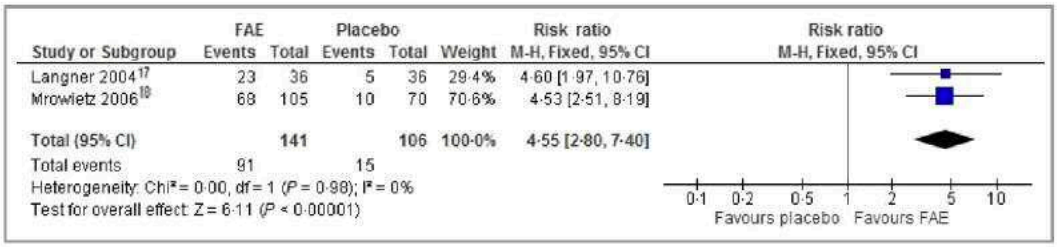


Fig 3. Comparison: fumaric acid esters (FAEs) vs. placebo. Outcome: ≥ 50% improvement in Psoriasis Area and Severity Index. CI, confidence interval.

a reduction from 54·0 to 51·1 in the placebo arm, a between-group difference of −19·3 points ($P < 0·001$).

Comparison of fumaric acid esters with methotrexate

Only one study, involving 60 randomized participants, compared FAEs with methotrexate in an open-label fashion.[21] Thirty participants were assigned to each group, of whom 26 of the FAE group and 25 in the methotrexate group were included in the primary analysis at week 12. The quality of evidence for each outcome is summarized in Table 2.

The study reported similar efficacy of FAE and methotrexate, with a mean PASI score reduction from 14·5 at baseline to 6·7 after 12 weeks in the methotrexate group ($n = 25$) in comparison with a reduction from 18·1 to 10·5 in the FAE group ($n = 26$). The reported absolute difference after adjustment for baseline values was 1·4 (95% CI −2·0 to 4·7; $P = 0·42$). However, when we compared the PASI scores at follow-up (week 12), as recommended by The Cochrane Collaboration, there was a significant difference in favour of methotrexate (MD 3·80, 95% CI 0·68–6·92; very low-quality evidence) (Fig. 4).

No significant difference was noted between the two groups in the numbers of participants who attained PASI 50 (RR 0·71, 95% CI 0·41–1·22; very low-quality evidence), PASI 75 (RR 0·80, 95% CI 0·28–2·29; very low-quality evidence) and PASI 90 (RR 0·48, 95% CI 0·05–4·98; very low-quality evidence). However, the maximum dose of methotrexate used in this study (15 mg per week) may have been suboptimal, as higher doses can be prescribed in routine clinical practice. Also, the time of assessment at 12 weeks might have been too early to evaluate true efficacy. Although the study reported no significant difference in the number of participants attaining PASI 75 and PASI 90 at week 16, it must be noted that the dose of methotrexate was reduced gradually from week 12, which may have reduced the effect size.

The dropout rate due to adverse effects in both groups was not significantly different (RR 0·19, 95% CI 0·02–1·53; very low-quality evidence) (Fig. 5). Four participants (16%) in the methotrexate group dropped out because of elevated liver enzymes; another patient dropped out due to recurrent angina unrelated to treatment. Raised liver enzymes were reported to be transient, and normalized 4–8 weeks after treatment discontinuation. Only one participant in the FAE group (4%) discontinued treatment, due to diarrhoea.

Overall, the number of participants experiencing nuisance adverse effects was not significantly different between the two groups (RR 0·89, 95% CI 0·77–1·03; very low-quality evidence). However, more participants experienced flushing in the FAE group (13 vs. two) (RR 6·50, 95% CI 1·62–26·09).

There was no significant difference in reported laboratory findings between the two groups, which may reflect the small study size. Transient increase of liver enzymes (up to double the baseline value) was observed in 11% of participants in the FAE group and 30% of participants given methotrexate (RR 0·38, 95% CI 0·11–1·26). There was transient eosinophilia (maximum measured level $1·55 \times 10^9$ cells L^{-1}) in five participants in the FAE group, compared with none of those on methotrexate (RR 11·00, 95% CI 0·64–189·65), and transient leucocytopenia ($2·1 \times 10^9$ cells L^{-1}) in one participant in the FAE group, compared with none in the methotrexate group (RR 3·00, 95% CI 0·13–70·53). An equal number of eight participants from each group (30%) showed transient proteinuria (RR 1·00, 95% CI 0·44–2·28).

Discussion

Limited evidence suggests that FAEs are superior to placebo in the treatment of psoriasis, and there is very low-quality evidence to determine the relative efficacy of FAEs compared with methotrexate. Commonly reported adverse effects associated with FAEs include gastrointestinal symptoms (58% of participants in one study), flushing (42%, 48% and 95% in three studies), eosinophilia (19% and 38% in two studies) and reversible proteinuria (30% in one study). However, the evidence provided by this review was limited due to a lack of full reports and inconsistencies of reporting. No long-term studies were identified to comment on the long-term efficacy and safety of FAEs in psoriasis.

The small number of included studies and insufficient reporting of outcomes were major limitations to address the objectives of our review. Some studies included participants with various types of psoriasis, but the outcomes reported did not indicate whether the response to FAEs varied between different subgroups. The majority of studies comparing FAEs with placebo did not report the number of participants who

Table 2 Summary of findings: fumaric acid esters (FAEs) vs. methotrexate (MTX). Patient or population: psoriasis in adults. Setting: departments of dermatology, Rotterdam and Eindhoven, the Netherlands. Intervention: FAE 720 mg (after week 9, following the standard progressive dosage regimen). Comparison: oral MTX 15 mg weekly (following gradual dose increments)

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)[b]	Comments
	Risk with MTX	Risk with FAE				
PASI score; scale range from 0 to 72 (higher score indicates more severe psoriasis)	Mean PASI score was 6·7	Mean PASI score in the intervention group was 3·8 more (0·68–6·92 more)	–	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	PASI score was measured at week 12. The study reported no significant difference between FAEs and MTX based on mean change from baseline
AEs leading to treatment discontinuation	Moderate 20 per 100	4 per 100 (0–31)	RR 0·19 (0·02–1·53)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (FAE 26, MTX 25). The main reasons were elevated liver enzymes with MTX and diarrhoea with FAEs. No serious AEs occurred in either group
Quality of life: not measured	See comment	See comment	Not estimable	–	–	Quality of life was not assessed
Common nuisance AEs (not leading to treatment discontinuation)	Moderate 100 per 100	89 per 100 (77–100)	RR 0·89 (0·77–1·03)	54 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Only flushing was significantly more reported with FAEs. Occurrences of other AEs including laboratory findings were not significantly different
PASI 50	Moderate 60 per 100	43 per 100 (25–73)	RR 0·71 (0·41–1·22)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (MTX 25, FAE 26)
PASI 75	Moderate 24 per 100	19 per 100 (7–55)	RR 0·80 (0·28–2·29)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (MTX 25, FAE 26)
PASI 90	Moderate 8 per 100	4 per 100 (0–40)	RR 0·48 (0·05–4·98)	51 (1 RCT)	⊕◯◯◯; VERY LOW[c,d,e]	Based on a small sample size (MTX 25, FAE 26)

AE, adverse effect; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI 50, ≥ 50% improvement in PASI; RCT, randomized controlled trial; RR, risk ratio. [a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [b]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 the effect. [c]Downgraded one level due to limitations in design; highest dose of MTX given was 15 mg per week while the maximum dose of FAEs was given. [d]Downgraded one level due to limitations in design; open-label design (high risk of performance and detection bias). [e]Downgraded one level due to imprecision; small sample size.

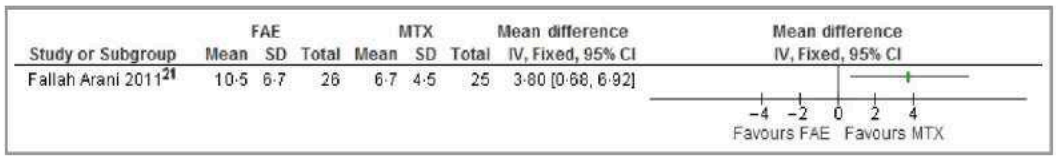


Fig 4. Comparison: fumaric acid esters (FAEs) vs. methotrexate (MTX). Outcome: Psoriasis Area and Severity Index score at follow-up. CI, confidence interval.

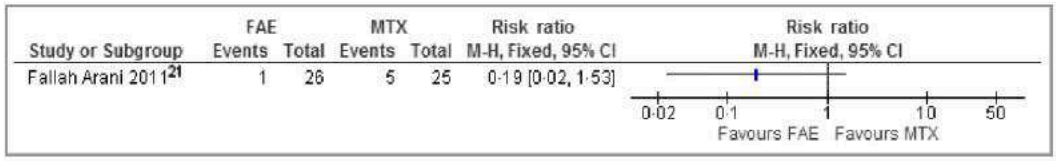


Fig 5. Comparison: fumaric acid esters (FAEs) vs. methotrexate (MTX). Outcome: dropout rate due to adverse effects. CI, confidence interval.

dropped out because of adverse effects. Variation in FAE dose increments may also have had an impact on the magnitude of treatment benefit and risk of adverse effects. More recently, the European S3 psoriasis guidelines have standardized the schedule of dose increments,[22,23] which may help to inform future FAE trial designs. We were unable to establish whether the use of DMF alone has a similar efficacy and safety profile to the mixture of DMF plus monoethylfumarate.

Other non-Cochrane systematic reviews have also reported the superiority of FAEs over placebo in the treatment of psoriasis,[24–26] and similar efficacy to methotrexate.[24,26] However, GRADEpro assessment of the level of quality of evidence in our review demonstrated that the latter conclusion is unreliable due to the very low quality of evidence. There is a relative paucity of RCTs comparing other conventional oral treatments for psoriasis with placebo.

Bansback *et al.*[27] reported in meta-analyses an RR of PASI 50 response of 4·74 with methotrexate 15–22·5 mg weekly (95% CI 3·52–5·73), with an NNTB of 2; and 4·06 with ciclosporin 3 mg kg^{-1} per day (95% CI 2·54–5·73), with an NNTB of 2. These are comparable with our findings of FAE efficacy with a PASI 50 RR of 4·55 compared with placebo (95% CI 2·80–7·40) and an NNTB of 2. However, the dropout rates and risk of adverse effects were not reported by Bansback *et al.* Three RCTs from the 1980s[28–30] demonstrated that acitretin 50–75 mg daily was significantly better than placebo and a lower acitretin dose (10–25 mg daily) in treating psoriasis, but no PASI scores were reported and the dropout rate due to adverse effects was unclear. A Cochrane systematic review is currently underway to examine all systemic pharmacological interventions for psoriasis.[31]

Most of the studies included in our review were not fully reported and were performed before the requirement of trial registration. As a result we downgraded the evidence quality to low or very low. The findings in our review reinforce the conclusion of 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'.[22] Our review also highlights the inadequate reporting of adverse effects, which should be based on the Consolidated Standards of Reporting Trials (www.consort-statement.org). Application of these standards and consistency in reported outcomes based on the Core Outcome Measures in Effectiveness Trials initiative are necessary to enhance the quality and robustness of evidence in future FAE trials. There remains a need to establish the long-term safety of FAEs, an evidence gap that is being addressed by the British Association of Dermatologists' Biologic Interventions Register[32] and other psoriasis databases.

Acknowledgments

The authors would like to thank Chris Taylor, who commented on the plain language summary, glossary and the readability of the first draft of the review. Also, the authors would like to thank the Cochrane Skin Group for their editorial support and guidance throughout the review process.

References

1 Lebwohl M. Psoriasis. *Lancet* 2003; **361**:1197–204.
2 Schweckendiek W. Treatment of psoriasis vulgaris. *Med Monatsschr* 1959; **13**:103–4.
3 Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. *Br J Dermatol* 1999; **141**:424–9.
4 Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends Mol Med* 2005; **11**:43–8.
5 Atwan A, Ingram JR, Abbott R *et al.* Oral fumaric acid esters for psoriasis. *Cochrane Database Syst Rev* 2015; **8**:CD010497.
6 Atwan A, Abbott R, Kelly M *et al.* Oral fumaric acid esters for psoriasis. *Cochrane Database Syst Rev* 2013; **4**:CD010497.
7 Schunemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendation

2013. Available at: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html (last accessed 4 July 2016).
8 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Available at: http://handbook.cochrane.org/ (last accessed 4 July 2016).
9 Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
10 O'Rourke K, Detsky AS. Meta-analysis in medical research: strong encouragement for higher quality in individual research efforts. *J Clin Epidemiol* 1989; **42**:1021–4.
11 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* 2015; **172**:754–9.
12 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. *Acta Derm Venereol* 2001; **81**:429–30.
13 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.
14 Nieboer C, de Hoop D, Iangendijk 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.
15 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.
16 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.
17 Langner A, Roszkiewicz J, Baran E, Placek W. Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis (abstract P075). European Congress on Psoriasis 2004. *J Eur Acad Dermatol Venereol* 2004; **18**:798.
18 Mrowietz U, Reich K, Spellman M. Efficacy, safety, and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis: results of a phase 3 study. *J Am Acad Dermatol* 2006; **54** (Suppl.):AB202.
19 Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 1990; **22**:311–12.
20 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.
21 Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. *Br J Dermatol* 2011; **164**:855–61.
22 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.
23 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.
24 Ceglowska U, Wlodarczyk A, Slomka M. Clinical effectiveness of fumaric acid esters (Fumaderm) in psoriasis: a systematic review of literature. Presented at the ISPOR 17th Annual European Congress, Amsterdam, the Netherlands, November 2014; abstr. PSS6.
25 Griffiths CE, Clark CM, Chalmers RJ *et al.* A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; **4**:1–125.
26 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.
27 Bansback N, Sizto S, Sun H *et al.* Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. *Dermatology* 2009; **219**:209–18.
28 Goldfarb MT, Ellis CN, Gupta AK *et al.* Acitretin improves psoriasis in a dose-dependent fashion. *J Am Acad Dermatol* 1988; **18**:655–62.
29 Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 1989; **20**:1088–93.
30 Olsen EA, Weed WW, Meyer CJ, Cobo LM. A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. *J Am Acad Dermatol* 1989; **21**:681–6.
31 Sbidian E, Le Cleach L, Trinquart L *et al.* Systemic pharmacological treatments for chronic plaque psoriasis. *Cochrane Database Syst Rev* 2015; **2**:CD011535.
32 Burden AD, Warren RB, Kleyn CE *et al.* The British Association of Dermatologists' Biologic Interventions Register (BADBIR): design, methodology and objectives. *Br J Dermatol* 2012; **166**:545–54.

Supporting Information

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

Audio S1. Author audio.