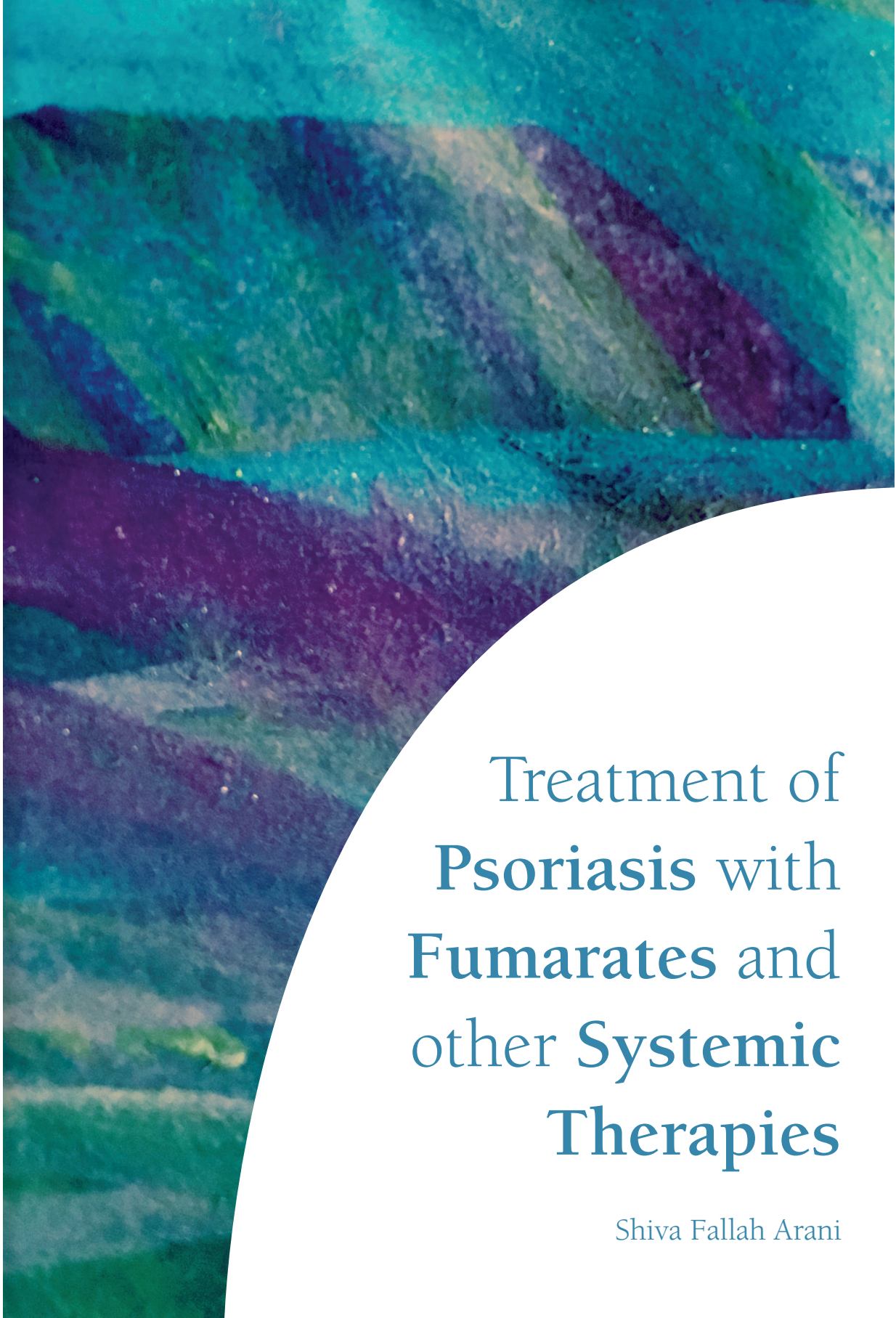

Treatment of **Psoriasis** with **Fumarates** and other **Systemic Therapies**

Shiva Fallah Arani

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Treatment of Psoriasis with Fumarates and other Systemic Therapies

Behandeling van Psoriasis met Fumaraten en andere Systemische Therapieën

Thesis

to obtain the degree of Doctor from the
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by command of the
rector magnificus
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and in accordance with the decision of the Doctorate Board.
The public defence shall be held on
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by

Shiva Fallah Arani
born in Teheran, Iran

Erasmus University Rotterdam

Erasmus University Rotterdam

Doctoral Committee:

Promotor:	Prof. dr. H.A.M. Neumann
Other members:	Prof. dr. dr. P.C.M. van de Kerkhof
	Prof. dr. E. Prens
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"Regard man as a mine rich in gems of inestimable value. Education can, alone, cause it to reveal its treasures, and enable mankind to benefit therefrom."

- Bahá'u'lláh

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Chapter 1

General Introduction and Aims of this thesis

GENERAL INTRODUCTION

Psoriasis vulgaris

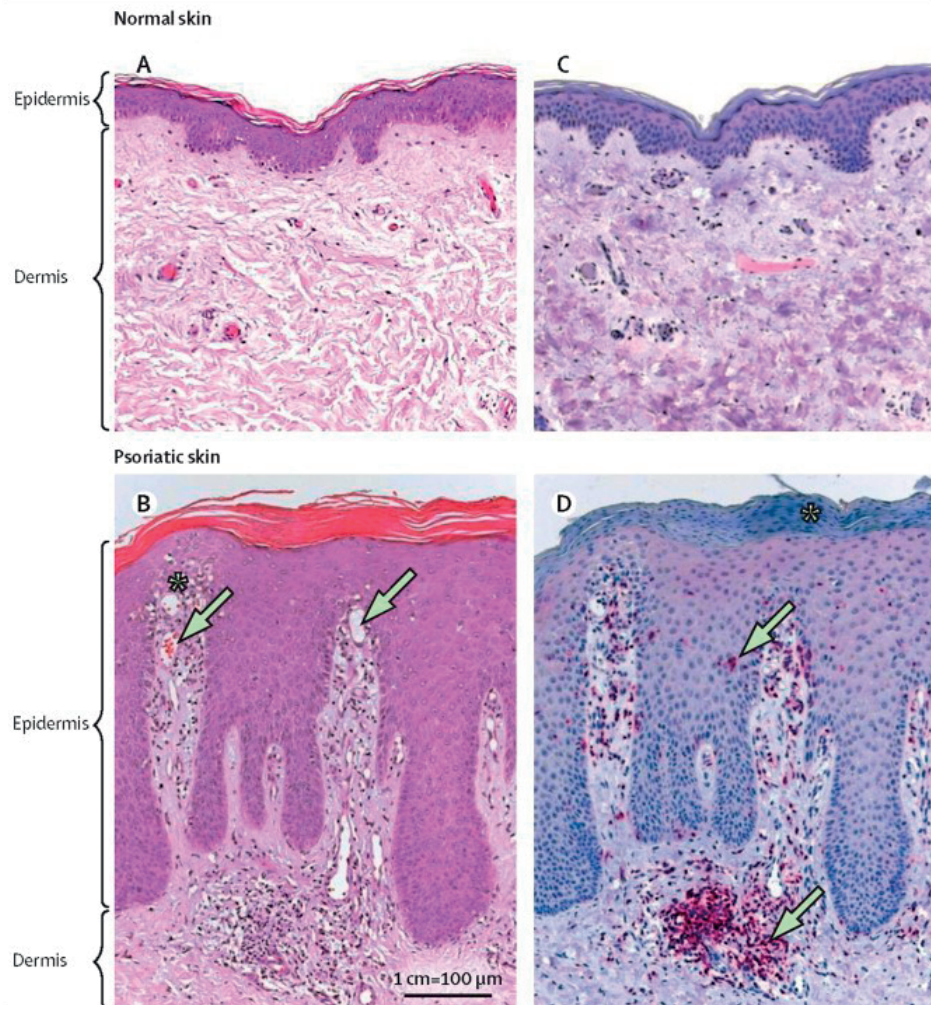
Today, psoriasis vulgaris is recognized as the most prevalent autoimmune disease caused by inappropriate activation of the cellular immune system.[1] It is a chronic, proliferative, and inflammatory skin disease characterized by sharply demarcated red plaques with white scales. Of the many clinical forms of the disease, chronic plaque psoriasis (psoriasis vulgaris) is by far the most common type. The typical histological appearance of psoriasis includes the hyperproliferation and aberrant differentiation of epidermal keratinocytes, dermal infiltration of immunocytes (particularly T-lymphocytes, monocytes, and neutrophils), and hyperplastic blood vessels, which lead to the excessive thickening and scaling of the erythematous skin[2] (Figure 1). Both the rapid epidermal proliferation and dermal inflammatory infiltration are accompanied by the formation of numerous new blood vessels, which starts during the early changes of psoriasis and vanishes after skin lesion clearance.[3]

Psoriasis is a serious skin disease that affects a person's daily life on many levels, including the individual's professional and social life. The physical and psychological impacts of psoriasis are comparable to those of cancer, heart disease, diabetes, or depression.[4]

Pathophysiology

Psoriasis is a T-cell mediated inflammatory condition of the skin. We believe that it is a combination of genetic and environmental factors such as stress, specific drugs, trauma, smoking, or infection with streptococci that triggers a cascade of immunological reactions resulting in inflammation of the skin. Plasmacytoid dendritic cells and keratinocytes produce pro-inflammatory cytokines such as interferon-α, interleukin-1, interleukin-6, tumor necrosis factor-alpha (TNFα), and chemokines. These activate the myeloid dendritic cell, which in turn presents antigens and secretes interleukins, leading to the differentiations of Th-1 and Th-17 helper cells. The T cells then secrete mediators that activate keratinocytes and induce the production of antimicrobial peptides, proinflammatory cytokines, and chemokines. These processes maintain the inflammation in psoriasis.[3]

Continuous research on mediators of inflammation in psoriasis, such as IL-12, IL-23, IL-17, Janus kinases (JAK), and phosphodiesterase 4 (PDE4), has become important for the development of new targets for antipsoriatic therapy.[6] Recently, an imbalance of skin and gut microbiomes has been shown to play a role in skin diseases such as psoriasis.[7-9] Staphylococci and Propionibacteria have shown to be significantly lower in psoriatic skin compared to healthy skin.[10, 11]



Figures 1. Histopathological features of psoriasis
Reprinted from *The Lancet*, WH Boehncke, MP Schoen, Psoriasis, 2015, with permission from Elsevier.
The typical plaque shows marked epidermal acanthosis, hyperkeratosis, and an elongation of rete ridges (A, normal skin and B, lesional psoriatic skin; stained with haematoxylin and eosin). The dermis shows dilated and contorted dermal blood vessels that reach into the tips of the dermal papillae (B, arrows). There, a mixed inflammatory infiltrate with neutrophils accumulating within the epidermis is noted (B, asterisk). Compared to normal skin (C), the immunohistochemical detection of CD3 reveals many T cells in the dermis and epidermis of lesional psoriatic skin (D, arrows). Another characteristic of lesional psoriatic skin is that the cell nuclei are present in the cornified layer of the epidermis (D, asterisk).[5]

CLINICAL PHENOTYPES OF PSORIASIS

Psoriasis is an erythemato-papulo-squamous skin disease with variable morphology, distribution, severity, and course. Despite the classic presentation, the morphology can

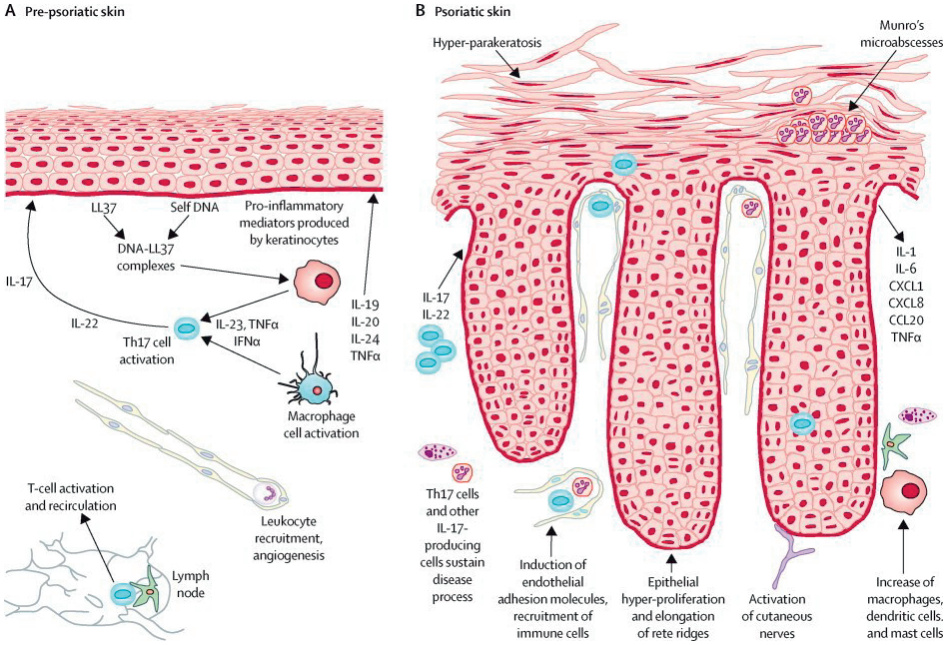


Figure 2. Immune pathogenesis of psoriasis
Reprinted from *The Lancet*, WH Boehncke, MP Schoen, Psoriasis, 2015, with permission from Elsevier.[5]
The pathological changes in pre-psoriatic skin involve a complex interplay of cutaneous cell types, which is dependent on macrophages, dendritic cells, T cells, and other cells of the immune system, including many cytokines and chemokines. The differentiation of Th1 and Th17 cells is stimulated by dendritic cells through IL-23 (A). T cells and cells of the innate immune system (macrophages, mast cells, granulocytes) produce several mediators that induce and maintain psoriatic hallmark features in both the dermis (e.g., endothelial cells) and epidermis (keratinocytes). In turn, the latter cell types facilitate the inflammatory response through their mediators (B). IL=interleukin. TNF=tumor necrosis factor. IFN=interferon.

range from small tear-shaped papules (guttate psoriasis) to pustules (pustular psoriasis) and generalized erythema and scale (erythrodermic psoriasis). In addition, these different forms of psoriasis may be localized or widespread and disabling. Furthermore, psoriasis may follow a variable course, presenting as chronic, stable plaques or acutely, with a rapid progression and widespread involvement. Psoriasis can be symptomatic, with patients complaining of intense pruritus or burning. The various types and presentations of psoriasis are outlined below.

Plaque psoriasis

As the most common form of psoriasis, representing almost 90% of psoriatic patients, plaque psoriasis is also known as psoriasis vulgaris.[12] Patients may have sharply circumscribed, round-oval, or nummular plaques. The lesions may initially begin as erythematous macules (flat and <1 cm) or papules, extend peripherally, and coalesce to

form plaques of one to several centimeters in diameter. A white blanching surrounding ring, known as Woronoff's ring, may be observed.[13]

Scale, which is typically present in psoriasis, is characteristically silvery white and can vary in thickness. Removal of the scale may reveal tiny bleeding points (Auspitz sign). Another well-known feature of psoriasis is the Koebner phenomenon, whereby new lesions may appear in a patient with psoriasis following direct cutaneous trauma.

Guttate psoriasis

Guttate psoriasis, from the Greek word *gutta* meaning a droplet, describes the acute onset of a myriad of small lesions of psoriasis that are 2–10 mm in diameter. These lesions are usually distributed in a centripetal fashion, although guttate lesions can also involve the head and limbs. Classically, guttate psoriasis occurs shortly after an acute group B hemolytic streptococcal infection of the pharynx or tonsils and can be the presenting episode of psoriasis in children or, occasionally, adults. The number of lesions may range from five or 10 to more than 100. Guttate psoriasis accounts for 2% of all cases of psoriasis and is often the first episode of psoriasis for the patient.

Flexural (inverse) psoriasis

Psoriasis affecting the flexures, particularly inframammary, genital, perineal, and axillary, is morphologically distinct from traditional plaques elsewhere on the trunk and limbs. Flexural lesions appear as red, shiny, well-demarcated plaques without the characteristic desquamation and are occasionally confused with candidal, intertrigo, and dermatophyte infections by non-dermatologists.[13] Flexural psoriasis is the first form of psoriasis appearing in children.

Erythrodermic psoriasis

Erythrodermic psoriasis generally develops if there is poor control of a patient's existing psoriasis. Abrupt withdrawal of systemic medication (e.g., corticosteroids) as a response to a drug reaction (e.g., lithium) or due to an underlying systemic infection may impair the thermoregulatory capacity of the skin, leading to hypothermia, high-output cardiac failure, and metabolic changes including hypoalbuminemia and anemia due to the loss of iron, vitamin B_{12}, and folate.[94,95] Secondary infection is common and can lead to sepsis. Erythodermic psoriasis is a serious condition and acquires acute professional care.

Pustular psoriasis

Generalized pustular psoriasis is a rare but serious disease and presents as different clinical subtype with a different genetic background. It is caused by an interleukin 36 deficiency. Initially it shows scattered, subsequently confluent pustules together with fever and generalized lymphadenopathy. This is also known as von Zumbusch psoriasis.[14]

Sneddon-Wilkinson disease, also known as subcorneal pustular dermatosis, is a chronic, relapsing disease presenting pustules and vesicles that move peripherally, forming an annular pattern.[15] The flexural and intertriginous areas are most commonly affected. The pathogenesis of this disease is related to increased production of tumor necrosis factor-α, which leads to a neutrophil infiltration of the skin. Whether Sneddon-Wilkinson disease is a less severe variant of pustular psoriasis is an ongoing controversy; however, patients with pustular psoriasis usually seem more ill and might be febrile.

Palmoplantar pustulosis

Although Palmoplantar pustulosis is often regarded as a subtype, it is a genetically distinct disease that may represent an independent disease entity. It is characterized by fresh yellow and older brownish pustules that appear exclusively on the palms and/or soles.[16]

Acrodermatitis continua suppurativa (Hallopeau)

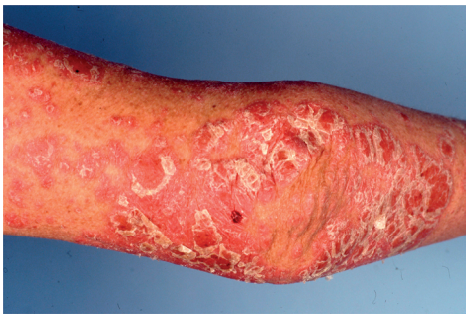
Pustules with severe inflammation on the tips of the fingers and/or toes, often rapidly leading to damage to the nail matrix and nail loss, are the clinical characteristics of this rare variant of pustular psoriasis. The distal phalanges may be destroyed during the course of the disease.[17]

Arthritis psoriatica

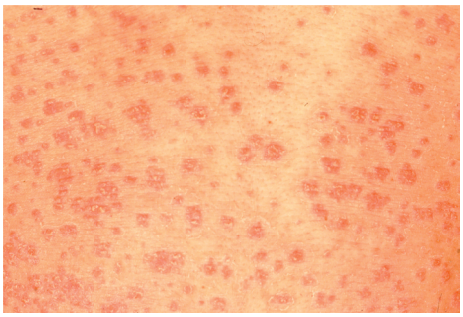
Psoriatic arthritis (PsA), a chronic inflammatory arthritis, affects about 10% of patients with psoriasis overall, with a higher prevalence in patients with more extensive skin disease and a prevalence as high as 30% in dermatology clinics (where patients tend to have more extensive/severe psoriasis).[18-22] Methotrexate has been used to treat PsA for more than 40 years due to its efficacy and low costs. TNF blockade with biologics, or the combination of these therapies, is considered the first-line treatment for patients with moderate to severely active PsA.

GENETICS

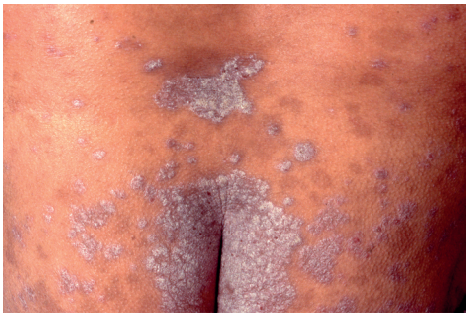
Proof of familial aggregation is the first step in pursuing a possible genetic susceptibility in a disease. Family and twin studies have clearly demonstrated that psoriasis has a strong genetic basis.[23] Genomic imprinting is an epigenetic effect that causes the differential expression of a gene depending on the sex of the transmitting parent.[24] A family study from the Faroe Islands reported a higher penetrance of psoriasis if the father was affected or a presumed gene carrier.[25] Psoriasis shows a clear association with certain alleles of the HLAC gene and specifically with the HLA-Cw6 allele (known as HLA-Cw*0602 when identified through high-resolution genotyping), present in 30% of psoriasis patients (compared with between 10% and 15% in the general population).[26]



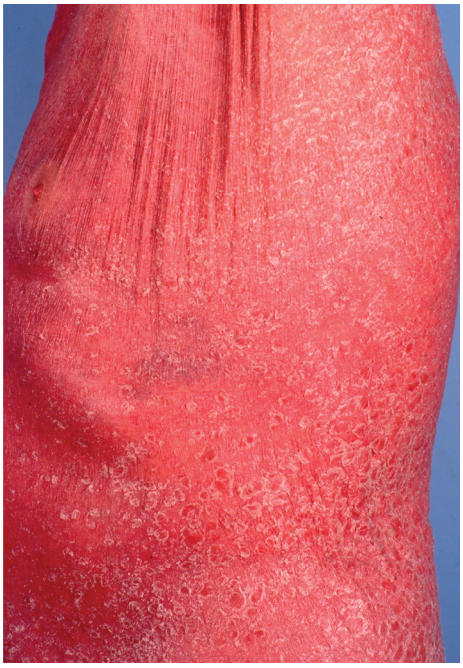
Plaque psoriasis



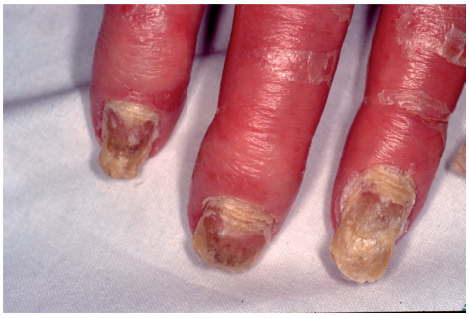
Guttate psoriasis



Flexural (inverse) psoriasis



Erythrodermic psoriasis



Acrodermatitis continua suppurativa (hallopeau)

EPIDEMIOLOGY

Psoriasis is universal in occurrence, although the worldwide prevalence varies between 0.6% and 4.8%.[4] The prevalence of psoriasis in people of Caucasian descent is approximately 2%.[27] In the Netherlands, an estimated 300,000 people have been diagnosed as having psoriasis. Its prevalence is equal in men and women and may begin throughout life, but two peaks have been identified in terms of age of onset: one occurring at 15–25 years old and another later one at around 50–60 years.[17, 28-31] Patients with early onset psoriasis have a tendency ($P < 0.5$) to experience obesity, diabetes, dyslipidaemia, hypertension, and major cardiovascular events (MACE) at higher frequencies.

SEVERITY ASSESSMENTS

Various tools are available for measuring the severity of plaque psoriasis. The most widely used measure is the Psoriasis Area and Severity Index (PASI). According to recent guidelines, moderate to severe disease is defined as having a PASI score >10.[32] PASI 75 and PASI 90 responses are dynamic parameters that indicate the percentage of patients who have achieved an at least 75% or 90% improvement in their baseline PASI score during treatment, respectively. Other measures frequently used to quantify disease severity in psoriasis are the Physician's Global Assessment (PGA) of disease severity, which is based on the measures also encompassed in the PASI, and body surface area (BSA), which represents the percentage of the body surface affected by psoriasis.[16] The BSA is a quick and easy assessment tool for dermatologists to use in their daily practice.

QUALITY OF LIFE

Different questionnaires have been developed to measure the impact of psoriatic disease on patients. To be able to address this matter, it is important to evaluate patient-reported outcome measures (PROMs) such as health-related quality of life (HRQoL)[33]; these differ from one another based on their generic (SF-36, Euro QoI 5D),[34],[35] disease-specific (DLQI, Skindex-29),[36] or psoriasis-related (PsoQoI, PDI) approaches.[16]

PSORIASIS AND COMORBIDITIES

Relatively well-studied possible comorbidities in psoriasis are malignancies,[37-41] infections,[42, 43] non-alcoholic fatty liver disease,[44, 45] osteoporosis,[46] inflammatory bowel disease,[47],[48] , COPD [49] and major adverse cardiovascular events [50, 51] . The concept of comorbidity in psoriasis is based on the hypothesis that psoriasis not only leads to skin inflammation, but also causes systemic inflammation mediated by inflammatory markers such as interleukins and TNFα circulating in the serum.[52] These may alter the function of hepatocytes, endothelial cells, atheroma, and thrombus risk, leading to an increase in cardiovascular risk factors. This "psoriatic march" can eventually lead to atherosclerosis and finally to cardiovascular events.[50, 51] Another hypothesis is that components of the metabolic syndrome are risk factors for psoriatic disease.[51] Smoking, obesity, and high waist circumference can increase the risk of incident of psoriasis.[53, 54]

THERAPIES

Since the epidemiological circumstances surrounding disease debut and the pathogenetic mechanisms inducing the psoriasis skin phenotype are not clearly understood, to date its treatment is non-curative and its goal is to mitigate disease severity and symptoms. Four treatment modalities exist. In increasing order of potency, they are divided into topical therapy, phototherapy, systemic therapy, and biologics. Choices of treatments have to be customized to the patient and are influenced by factors such as disease severity (PASI > or < 10) with or without psoriatic arthritis, clinical phenotypes (psoriasis vulgaris, psoriasis guttata, psoriasis pustulosa, psoriasis inversa, erythrodermic psoriasis), and recalcitrance as well as patient preferences and patient compliance and adherence. Adherence is crucial for the efficacy of chronic treatments. Patients must be actively involved in the choice of the product, formulation, and mode of application. [55] Although there is a wide variety of treatment options available, there is still a need for a simple, safe, and effective long-term therapy. In addition, modern therapy with biologics is expensive; therefore, there is a great need for an effective, safe, long-term, and low-cost treatment.

TOPICAL THERAPIES

Topical therapy is considered first-line therapy for the majority of patients with mild plaque psoriasis. Most patients on systemic treatments also benefit from concurrent topical treatment for the greatest clearance of disease. First-line management of mild psoriasis involves topical treatment, primarily with corticosteroids and vitamin D analogues. However, with topical products, non-adherence is further exacerbated by the need for application, which can be cumbersome and time-consuming, combined with patients' poor acceptability of certain treatment vehicles, such as ointments, which are perceived as messy.[56-63] Topical corticosteroid use can be limited by local and systemic adverse effects, such as the atrophy of the skin and tachyphylaxy, especially if higher potency corticosteroids are used over the long term. Vitamin D analogues are more likely than corticosteroids to cause local skin irritation, and their use can be limited in terms of the application amount and body region.[64] Head-to-head studies with topical corticosteroids have shown that Vitamin D3 analogues such as calcipotriol are as effective, except for when calcipotriol is compared to a combination of potent corticosteroids and calciptriol. Coal tar and dithranol are some of the oldest topical treatments used in psoriasis patients; however, they are less commonly used due to side effects such as local skin irritation and the staining of skin and clothing.[65, 66] Topical retinoids such as tazarotene (not available in the Netherlands) modulate keratinocyte proliferation and

differentiation and are anti-inflammatory, but also cause irritation and erythema at the site of application; therefore, they are not commonly used.[67-69] Tacrolimus can be used to treat facial psoriasis.

Phototherapy and photochemotherapy

Historically, Balneo-phototherapy at the Dead Sea has been shown to be a beneficial treatment for most patients with psoriasis. Its clinical effect is based on the very high concentration and special salt contents of the Dead Sea water in combination with sunlight. Results of in vitro and in vivo studies have shown that narrow-band ultraviolet B (UVB) light and Dead Sea salt together have a multiple, synergistic effect on psoriatic skin. Both are effective in reducing the number and activity of Langerhans cells.[70]

Narrowband UVB (NBUVB) and psoralen ultraviolet A (PUVA) therapy cause the depletion of cells involved in the pathogenesis of psoriasis, including lymphocytes, macrophages, and dendritic cells.[71, 72] NBUVB has proven to be more effective than broadband UVB (BBUVB).[73] The maximum dose depends on the minimal erythema dose (MED), and patients are treated two or three times a week. PUVA monotherapy refers to the use of 8-methoxypsoralen, which sensitizes the cells to the effects of longer-wave-length UV light and can be administered topically or orally.[16] Cyclosporine greatly increases the risk of squamous cell carcinoma in patients with psoriasis who have been exposed to PUVA.[74] Although the role of PUVA therapy in skin carcinogenesis in patients with psoriasis has been well documented, there is still uncertainty regarding the risk of skin cancer with BBUVB and NBUVB. It has been estimated that the increased annual risk of non-melanoma skin cancer (NMSC) associated with UVB radiation was likely to be < 2%.[70]

Photodynamic therapy (PDT)

Photodynamic therapy (PDT) is a technique that involves the delivery of a photosensitive agent to targeted areas of the skin, leading to selective cell death upon irradiation with visible light. Since the early 1900s, clinical applications have included the treatment of skin malignancies, lupus vulgaris, syphilis, molluscum contagiosum, pityriasis versicolor, and psoriasis.[75] In 1994, Boehncke et al. reported complete clearance of psoriatic plaques treated with topical ALA and PDT in three patients.[76] The specific mechanism behind PDT for psoriasis is not completely known, but evidence suggests that key components involve the apoptosis of lesional T-lymphocytes and inhibition of inflammatory cytokines (TNF-a, IL-1, and IL-6).[77] Early reports on the complete clearance of plaques after topical ALA–PDT application were promising for the birth of a new phototherapeutic modality for psoriasis. However, as more research has been performed, including randomized, blinded, and placebo-controlled studies, the clinical efficacy of topical ALA–PDT use was underwhelming and inconsistent. Compounding the relatively

unimpressive clinical results, the painful side effect of topical ALA–PDT application is another major drawback to its use.[78]

Pulsed dye laser therapy

The flash lamp pumped pulsed dye laser (PDL) was the first laser specifically developed for the treatment of vascular lesions. The mode of action of the PDL is based on the principle of selective photothermolysis, a targeted damaging of specific structures in the skin, without damaging the surrounding area, through direct cutaneous immunologic activation.[79-81] Clinical studies describing the treatment of localized psoriasis have mostly concerned chronic, stable plaque psoriasis, sometimes explicitly described as recalcitrant, that does not respond to conventional therapy such as potent topical steroids, UVB, psoralen plus UVA, and tar.[82-89] No large RCT (randomized controlled trials) on the efficacy of PDL for psoriasis were performed. Practically, PDL treatment is limited to a few psoriasis plaque lesions resistant to conventional therapy. [12]

SYSTEMIC THERAPY

Methotrexate

Methotrexate (MTX) has been used in the treatment of psoriasis since 1958 and is widely employed in Europe.[90] In dermatology, methotrexate is used most frequently for the treatment of moderate to severe plaque-type psoriasis, especially in cases with joint involvement or in pustular or erythrodermic forms.[91] MTX, an analogue of folic acid, competitively inhibits the enzyme dihydrofolate reductase and several other folate dependent enzymes. The main effect of methotrexate is the inhibition of thymidylate and purine synthesis, resulting in decreased synthesis of DNA and RNA. The inhibition of nucleic acid synthesis in activated T cells and in keratinocytes is believed to account for the antiproliferative and immunomodulatory effects of methotrexate, which are considered the main mechanisms of the therapeutic effect of methotrexate in psoriasis vulgaris.[16] Nevertheless, methotrexate has severe adverse events. The two most important adverse reactions are myelosuppression and irreversible hepatotoxicity. These side effects are dose-dependent.

Multiple stresses on the hepatocyte, such as diabetes, obesity, and overconsumption of alcohol, which are features of the metabolic syndrome psoriasis patients frequently have, appear to contribute to the development of fibrosis. Recently, van der Voort et al. demonstrated that psoriasis is independently associated with nonalcoholic fatty liver disease in patients 55 years old or older.[45] Some have speculated that patients with psoriasis drink more alcohol, which may explain why liver damage occurs more often in patients with psoriatic than rheumatoid conditions. Another reason why methotrex-

ate is widely used as the "golden standard" for psoriasis is that it is more cost-effective, especially compared to biologics.

Ciclosporine

Ciclosporine is a calcineurin inhibitor and immune modulator that inhibits the production of pro-inflammatory cytokines and the activity of T-lymphocytes. The European guidelines recommend ciclosporine primarily for induction therapy due to its rapid efficacy and long-term side effects. The clinical improvement of psoriasis occurs after approximately 4 weeks, and maximum response is seen after about 8 to 16 weeks. The efficacy is dose-dependent, and the PASI 75 response is 50% at 8 weeks with a daily dose of 3mg/kg.[16]

Studies comparing high-dose ciclosporine (5 mg/kg) with low-dose cyclosporine (2.5–3 mg/kg) have indicated a higher efficacy with high-dose ciclosporine. In head-to-head trials, ciclosporine was superior to etretinate, superior to 7.5 mg of MTX weekly, and similar in efficacy to 15 mg of MTX weekly. Nevertheless, the use of cyclosporine is limited by its side effects, such as nephrotoxicity. The benefit/risk ratio appears to be better for patients without risk factors for nephrotoxicity—namely, non-obese patients without hypertension who are younger than 60 years of age.[92]

Acitretin

Oral retinoids such as acitretin have antiproliferative and anti-inflammatory properties. They have teratogenic properties and therefore cannot be administered in women of childbearing age. The most common side effects are mucocutaneous dryness and hyperlipidemia. Acitretin is not recommended as a first choice in monotherapy for plaque psoriasis; however, its use in combination with topical calcipotriol or phototherapy (Re-UVB or Re-PUVA) has proven effective.[93]

Phosphodiesterase 4 inhibitor

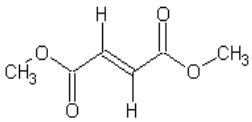
In March 2014, the Food and Drug Administration (FDA) approved apremilast (Otezla, Celgene Corporation), the first selective inhibitor of phosphodiesterase 4 (PDE4) indicated for adults with active PsA. Advantages to the use of apremilast include its oral administration, minimal drug interaction potential, and what appears to be a fairly safe AE profile, particularly compared to the profiles of methotrexate and biologics. The cost of apremilast is also lower than that of biologics. Nevertheless, the twice-daily dosing might not be advisable if nonadherence is a concern, and the gastrointestinal side effects may be troublesome.

Biologics

As recently as a decade ago, psoriasis pathophysiology was thought to begin with a yet-to-be identified antigen, which was transported by an antigen-presenting cell to a skin-draining lymph node, wherein T-cell activation began. The T cells were believed to be transported back to the skin through the vasculature and, upon re-entry, to trigger the release of inflammatory mediators, including tumor necrosis factor (TNF)-α. This conceptual framework of psoriasis led to the development of first-generation biologic agents, alefacept and efalizumab, which targeted T-cell activation.[3] Efalizumab was approved in 2003, but was withdrawn from the market in 2009 due to the increased risk of progressive multifocal leukoencophalopathy. Many other biologicals followed: the TNFα antagonist adalimumab, etanercept and infliximab, and the interleukin-12/23 antagonist ustekinumab. These therapies attain a PASI 75 response varying from 30% to 80% at 12 weeks. A recently published study showed no significant difference in drug survival, mean PASI change, or Skindex-29 response among etanercept, adalimumab, and ustekinumab at 12 or 52 weeks.[94] As these drugs are being administered to patients, new biologic treatments emerge aiming at inhibiting novel and already known pathways involved in psoriasis. Recent examples are the anti-interleukin-17A receptor antibodies secukinumab, brodalumab, and ixekizumab.

Although biologic agents have clinically proven efficacy, their use is associated with a much higher cost compared with traditional treatment options, and long-term safety aspects are still not well known. This is why fumarates hold a special place in the treatment of psoriasis, which we thought to mention as the last systemic therapy.

Fumarates



Fumarates (FAE), which are ester derivatives of fumaric acid, are small molecules with immunomodulating properties.[95] FAE were first described as an oral anti-psoriatic treatment by the German chemist Schweckendick in 1959.[40] Treatment with FAE was further developed in Switzerland in the 1970s and 1980s.[41] The first randomized clinical trials with oral FAE were published in the early 1990s, and in 1994 treatment with FAE became approved in Germany for the treatment of adult patients with severe psoriasis. Fourteen years later, in 2008, the approved indication of FAE was extended to include patients with moderate psoriasis.[96] The licensed fumarate formulation in Germany is Fumaderm (Biogen Idec GmbH, Ismaning, Germany), which consists of a mixture of the fumarates dimethylfumarate (DMF) and monoethylfumarate (MEF) in two strengths: Fumaderm initial 105 mg tablets containing 30 mg of DMF and 75 mg of MEF, and Fumaderm 215 mg

tablets containing 120 mg of DMF and 95 mg of MEF. Fumaderm is dosed according to a standardized incremental dosage regimen up to 215 mg of Fumaderm six times a day.[3]

To date, Fumaderm is one of the most prescribed systemic treatments for psoriasis in Germany.[43] In other European countries, like the Netherlands and the United Kingdom, the use of FAE for the treatment of moderate to severe psoriasis has been increasingly reported, although their use in these countries remains unlicensed. In the Netherlands, FAE are not approved, but regarded and reimbursed as a rational pharmacotherapy for psoriasis. Several standardized but unlicensed Dutch FAE formulations are in use in the Netherlands, containing either DMF and calcium-MEF, DMF, or DMF through slow release.

The mechanism of action by which FAE improve psoriasis is only partially understood. The major mechanism of action is thought to be the interaction between DMF and intracellular glutathione, leading to the inhibition of nuclear factor kappa B (NF-kB)-mediated transcription of pro-inflammatory mediators and adhesion molecules. Other mechanisms of DMF are linked to impairing dendritic cell maturation, shifting cytokine production by T helper cells, and inducing apoptosis.[3] DMF is considered the most active FAE and thought to improve psoriasis via various immunomodulating, antiproliferative, and anti-angiogenic effects.[97-100] It is important to understand that DMF is a pro-drug. The metabolites monomethylfumarate (MMF) and S-(1,2-dimethoxycarbonylethyl) glutathione (GS-DMS) are the in vivo moieties; MMF is the bioactive metabolite.[101, 102] Furthermore, pharmacokinetic studies in psoriasis patients showed that, after the oral administration of FAE only MMF is detectable in serum.[103] In addition, a small randomized controlled trial among 45 psoriasis patients reported that the clinical efficacy of DMF alone is not significantly different from that of DMF with MEF.[104]

The long-term safety profile of FAE is favorable as an increased risk of infections and malignancies has not yet been described in patients treated continuously with FAE for more than 10 years.[105] Inconvenient adverse events such as gastrointestinal complaints and skin flushing occurring in the beginning of FAE treatment led to treatment discontinuation in about 30 to 40% of patients. Several approaches have been undertaken or suggested to bypass this limiting factor for continuing FAE. First, a decrease of gastrointestinal complaints is achieved by using enteric-coated tablets. Second, fumarate formulations containing solely DMF, without MEF, may be associated with less adverse events.[106] Finally, slow-release formulations of FAE may further decrease the incidence of adverse events.[49] It is important to mention that that, since 2013, several cases of progressive multifocal leukoencephalopathy (PML) have been reported during treatment with FAE.[107-116] However, the occurrence of PML as a result of therapy with FAE for the treatment of psoriasis is very rare, and extra vigilance is needed.

Summary of the effect of FAE in different cell types

Cell Type	Cytokine/Signaling Effect	MMF/DMF	Effect
T-cells	IL-10↑, IL-5↑,	MMF/DMF	"TH1""TH2" shift, HO-1↑ reduced CD4+, CD8+numbers
PBMC	CXCL8, 9, 10↓ TNF-α ↑, IL-10↑ IL-1RA↑ IL-4↑, IL-5↑	DMF	Superoxide anions↑
B-cells	NF- κB↓	n.d	Bcl-2↓, induce apoptosis
Keratinocytes	IFNγ↓,IL-10↓, IL-6↓, TGF-α↓, CXCL8, 9, 10, 11↓	DMF	HLA-DR↓,ICAM-1↓
Dendritic cells	Il-12↓,	MMF/DMF	induce apoptosis, prevent cell differentiation
Endothelial cells	prevent NF-κB translocation	DMF	TNF α↓, ICAM-1↑, E-selectin↑ VCAM-1↑
Glia cells	TNF-α↓, IL-1β↓, IL-6↓	DMF	NQO-1↑,cellular Glutathion↑, NO↓

This table has been reproduced from *Curr Neuropharmacol* with permission from Bentham Science Publishers.[117]
n.d = no data

FUMARIC ACID AND FUMARIC ACID ESTERS

Fumaric acid is an organic dicarboxylic acid (C4H4O4); it occurs naturally in the metabolism and plays a role in the tricarboxylic cycle (TCA cycle) and the carry-over of the amino-N from aspartate. Succinate (acetyl-CoA and oxaloacetate are synthesized to citrate, which is—through multiple steps—converted to succinate) is oxidized to fumarate. Succinate also enters the TCA-cycle as succinyl-CoA, a conversion product of the glucogenic amino acids methionine, isoleucine, and valine. The glucogenic amino acids phenylalanine and tyrosine enter the TCA cycle at the fumarate stage. Fumaric acid itself is poorly absorbed and has no therapeutic effect. Therefore, its esters are used for treatment.

OFF-LABEL USE OF FAE

Although FAE formulations were initially developed for the systemic treatment of psoriasis, there are now an increasing number of reports of beneficial effects of FAE for several inflammatory and granulomatous skin diseases, such as cutaneous sarcoidosis, necrobiosis lipodica, granuloma annulare, and lichen planus.[118] However, FAE is not limited to the treatment of dermatological diseases. A DMF-formulation (BG-12) was effective in the treatment of multiple sclerosis in two phase 3 clinical trials.[119, 120] Since

October 2014, BG-12 (Tecfidera®) has been registered for relapsing-remitting multiple sclerosis. Currently, FAE is being tested in pre-clinical studies for a variety of diseases.[121]

AIMS OF THIS THESIS

In an era of worldwide escalation of healthcare costs and the high expense of continuous approval of new biologics, the scrutiny of biologics in fair comparison to more affordable medications such as FAE is necessary. We need to recognize the life-long nature of psoriasis and the need for long-term maintenance therapy using systemic medication that is effective, safe, and affordable.

First, we investigated if FAE is an effective and safe treatment for psoriasis vulgaris. In our systematic review, we summarized and critically evaluated the current evidence of the efficacy, effectiveness, and safety of FAE in the treatment of psoriasis and concluded that FAE is considered suitable as a systemic treatment for moderate to severe plaque psoriasis (Chapter 2).

Thus, we first compared FAE to methotrexate, the past and present golden standard in the treatment of psoriasis (Chapter 3). With this study, we wanted to prove that FAE is as effective as the conventional systemic therapies for psoriasis. After concluding that FAE is as effective as methotrexate, we were interested in determining whether they are used as a popular psoriasis therapy in the Netherlands and how many Dutch dermatologists are using FAE for the treatment of their patients with psoriasis. (Chapter 4). The results indicated that FAE is a well-prescribed treatment for psoriasis in the Netherlands.

Some reasons for patients' discontinuation of this therapy included the common adverse events, such as diarrhea and flushing. In our view, these adverse events could be histamine induced. Therefore, we decided to investigate the use of antihistamines in the treatment with FAE to reduce adverse events (Chapter 5). Another reason why many patients discontinue their treatment with FAE in an early stage is the slow efficacy in the beginning of therapy due to the incremental dosage regimen. Thus, we thought that an alternative induction therapy with a combination of FAE and cyclosporine for approximately the first 12 weeks could offer a good solution for this obstacle (Chapter 6).

In cases when cyclosporine does not show rapid efficacy or when a patient experiences contraindications to the use of cyclosporine, we looked for a legitimate alternative—a therapy similar to cyclosporine, only without the serious side effects such as nephrotoxicity. Thus, we decided to investigate mycophenolate sodium (Myfortic®). Mycophenolate mofetil (Cellcept®) has been shown to be effective in dealing with psoriasis, but Myfortic® has not previously been used for the treatment of psoriasis. Therefore, we investigated the efficacy and safety of this therapy for patients with moderate to severe psoriasis (Chapter 7).

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Appendices

Instructions for use of FAE for the daily dermatological practice

BEFORE AND DURING TREATMENT:

- Objective assessment of the disease (BSA)
- Laboratory controls
- Set the expectations
- Education on the nature of AEs before starting treatment (e.g., types, severity (PML), frequency, transient nature)
- Positive encouragement; emphasizing product efficacy and the importance of staying on therapy

RECOMMENDED LABORATORY CONTROLS

Parameter	Period in weeks			
	Pretreatment	Month 1	Every 4 weeks until month 4	Thereafter
Liver enzymes	**X**	**X**	**X**	**Every 8 weeks**
Serum creatinine	**X**	**X**	**X**	**Every 8 weeks**
Urine status	**X**	**X**	**X**	**Every 8 weeks**
Pregnancy test	**X**			
Blood count*	**X**	**X**	**X**	**Every 4 weeks**

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk and exposure.

*If leukocytes are <3000/µl, fumarate therapy needs to be stopped. If lymphocytes are <700/µl, patients should be kept on half of the last dose for 2–4 weeks and stopped if lymphocytes remain below 700/µl; if lymphocytes are <500/µl, treatment must be terminated.

This table was adapted from "European S3-Guidelines on the systemic treatment of psoriasis vulgaris – Update 2015 – Short version – EDF in cooperation with EADV and IPC" by A. Nast et al., 2015, J Eur Acad Dermatol Venereol, Volume 29, p. 2277-2294. Copyright 2015 by John Wiley& Sons, Inc.. Adapted with permission.

DOSING REGIMEN FOR MODERATE PLAQUE PSORIASIS

Week	No. of tablets a day 30mg DMF	No. of tablets a day 120mg DMF
Week 1	**1**	
Week 2	**2**	
Week 3	**3**	
Week 4		**1**
Week 5		**2**
Week 6		**3**
Week 7		**4**
Week 8		**5**
Week 9		**6**

DOSING REGIMEN FOR SEVERE PLAQUE PSORIASIS (IN COMBINATION WITH CSA)

Week	No. of tablets a day 120mg DMF	mg/kg per day CsA
Week 1	**1**	**5**
Week 2	**2**	**5**
Week 3	**3**	**5**
Week 4	**4**	**5**
Week 5	**5**	**5**
Week 6	**6**	**5***
From Week 12	**decrease/increase to/with 1 or 2 tablets gradually depending on PASI reduction**	**STOP**

* Continue till 80% DMF dosage or week 12 depending on PASI reduction

IN CASE OF ADVERSE EVENTS SUCH AS GASTROINTESTINAL COMPLAINTS AND FLUSHING

- Administration with food or milk
- Cetirizine 10 mg or Levocetirizine 5mg once or twice daily.
- Temporary dose reduction

IN CASE OF INTOLERABLE FLUSHING SYMPTOMS WITHOUT GASTROINTESTINAL COMPLAINTS

- Non enteric-coated aspirine (up to 325mg) 30 minutes prior to each DMF dose

Pros of FAE therapy for plaque psoriasis	Cons of FAE therapy for plaque psoriasis
❑ Effective	❑ Unlicensed treatment
❑ Favorable risk/benefit profile	❑ Slow acting drug/long induction period
❑ Suitable as a first-line therapy	❑ Sometimes intolerable gastrointestinal adverse events
❑ Eligible for maintenance therapy	❑ Very rare risk of progressive multifocal leucoencephalopathy (PML)
❑ No drug interactions	
❑ Suitable for combination therapy with other systemic therapies	
❑ Easy oral administration	
❑ Not time-consuming which results in better patient compliance	
❑ Cost-effective compared to expensive biologics	

Chapter 2

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

D.M.W. Balak
S. Fallah Arani
E. Hajdarbegovic
C.A.F. Hagemans
W.M. Bramer
H.B. Thio
H.A.M. Neumann

ABSTRACT

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

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

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

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

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

INTRODUCTION

Fumaric acid esters (FAEs) are small molecules that have immunomodulating properties.[1] Oral FAEs have been used to treat psoriasis for 5 decades. There is a long- standing tradition in Germany and the Netherlands to treat psoriasis patients with FAEs as a first-line systemic treatment.[2,3] In other countries such as the U.K., FAEs are increasingly reported as treatment for psoriasis.[4,5] Globally, FAEs are limited in availability and unlicensed for the treatment of psoriasis, primarily due to a lack of a high-quality evidence-based development with well-performed randomized controlled trials. The development of FAEs was mostly done empirical.

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

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

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

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

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

METHODS

Literature search strategy

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

Selection criteria

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

Data extraction

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

Quality assessment

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

Outcomes and data analysis

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

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

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

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

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

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

RESULTS

Literature search

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

RCTs on FAEs treatment for psoriasis

Characteristics of RCTs

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

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

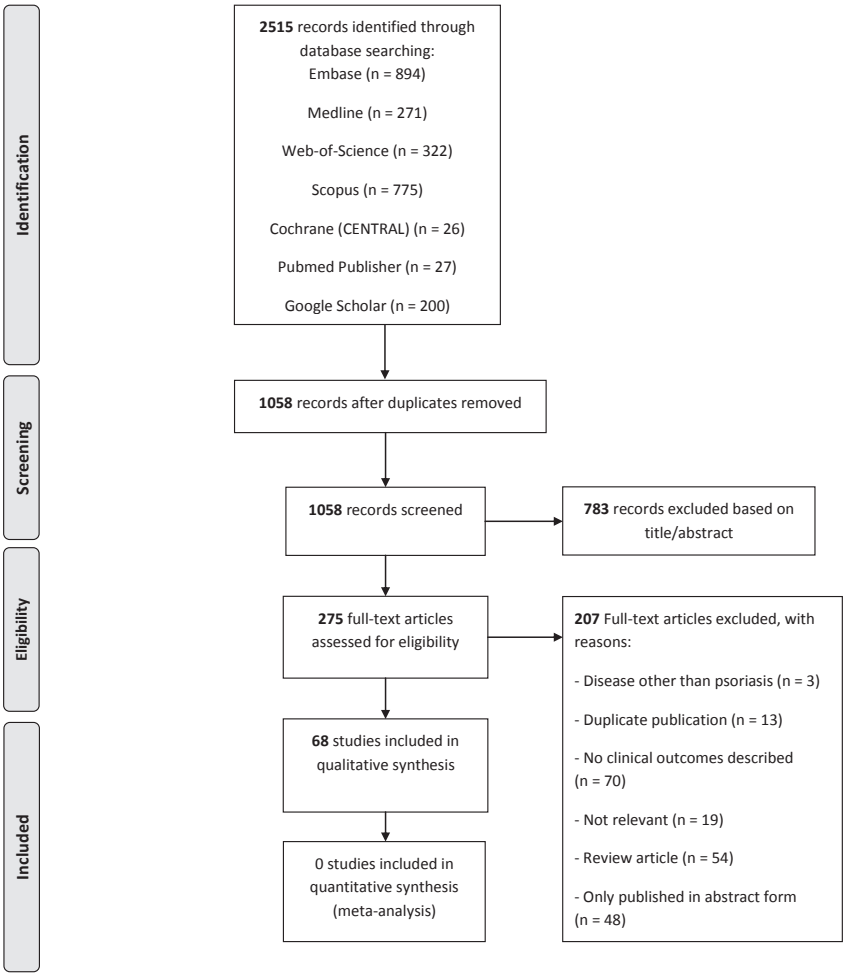

Figure 1: Overview of literature search and selection

treatment duration was relatively short, ranging from 2.8 to 4 months. There were differences in the evaluated FAEs-formulations. Most RCT's applied the standardized incremental dosage regimen up to FAEs 215 mg six times a day (equals 720 mg DMF). The study of Nieboer[18] used a different dosage regimen up to FAEs 215 mg four times a day (equals 480 mg DMF).

Methodological quality assessment of RCTs

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

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

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

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

Efficacy outcomes reported in RCTs

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

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

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

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

Safety outcomes in RCTs

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

Observational studies on FAEs treatment for psoriasis

Characteristics of observational studies

There were 37 observational studies included from the period 1987-2015 with a total of 3457 patients. There was considerable clinical heterogeneity in FAEs formulations and treatment duration. The characteristics of the included observational studies are summarized in Table 2 The majority (73%) of these studies were open-label, single-

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

Quality assessment of observational studies

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

Effectiveness in observational studies

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

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

Safety outcomes in observational studies

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

Forty-five to 87% of patients had experienced an adverse event. The proportion of patients discontinuing FAEs treatment due to adverse events ranged from 6% to 47%.

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

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

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

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

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

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

The most common cause for early treatment discontinuation was intolerable gastrointestinal symptoms and, to a lesser extent, severe flushing symptoms. There were few reported treatment discontinuations due to laboratory abnormalities.

There were few studies that specifically evaluated long-term treatment with FAEs. The available data indicated no increased risk for infections, malignancies, or other serious adverse events associated with long-term FAE treatment. In a small, retrospective single

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

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

center study among patients treated with FAE continuously for up to 10 to 14 years, no serious adverse events or malignancies were observed.[53] Similar safety results were reported in a large, German study among nearly 1000 patients treated with FAE for a mean duration of 3.5 years.[42]

Case reports on adverse events of FAEs

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

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

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

DISCUSSION

FAEs have a long history as a systemic psoriasis treatment, but their development was not based on high-quality evidence. Here, we assessed studies on efficacy and safety of FAEs in psoriasis treatment. The available evidence was limited with 7 RCTs with relatively small sample sizes and an unclear risk of bias. Overall, mean PASI decreased with 42-65% following 12-16 weeks of treatment. The number of observational studies (n=37) was much larger, but the majority were uncontrolled and with a high risk of bias. The safety profile of FAEs was well-characterized. Intolerable gastrointestinal complaints and flushing led to early treatment withdrawal in 6-40%. Lymphocytopenia, eosinophilia, increased liver enzymes, and proteinuria were commonly observed, but rarely resulted in FAEs discontinuation. Studies with long-term data were lacking.

To appreciate our results, several aspects of this systematic review need to be considered. Strengths of our study include the extensive literature search involving multiple bibliographic databases and the fact that we did not exclude specific study types or

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

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

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

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

Since the mid-1990s, FAEs are increasingly being used and regarded as a systemic treatment with a favorable risk-benefit ratio. FAEs have several advantages. FAEs seem suitable for psoriasis patients with comorbidity. Also, there are no known drug-interactions. Also, FAEs appear to have no increased risk of significant immunosuppressive adverse events, in contrast to other systemic classical treatments.[84] Although lymphocytopenia is relatively frequently observed during FAEs treatment in about 50% of patients, in most cases the lymphocyte reductions are mild.[30] A small proportion of patients of circa 3% has a severe lymphocytopenia during FAEs treatment.30 FAEs-induced lymphocytopenia does not seem to cause significant immunosuppression as long as lymphocyte-counts are closely monitored according to the guidelines.[85] FAE dosage

reduction is recommended in case of lymphocyte-counts below 700 per cubic mm and direct FAE discontinuation is recommended in case of lymphocyte-counts below 500 per cubic mm.[29,30] The occurrence of opportunistic infections during FAEs treatment was linked to exposure to prolonged severe lymphocytopenia or to other known risk factors.

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

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

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Chapter 3

Fumarates versus methotrexate in moderate to severe chronic plaque psoriasis: a multi-centre prospective randomized controlled clinical trial

S. Fallah Arani
H.A.M. Neumann
W.C.J. Hop
H.B. Thio

ABSTRACT

Background: Methotrexate and fumarates are effective systemic therapies for moderate to severe psoriasis according to the European S3-guidelines. We conducted a randomised, controlled trial comparing the effectiveness and the adverse events of methotrexate and fumarates.

Methods: A total of 60 patients with moderate to severe psoriasis vulgaris were randomly assigned to treatment for 16 weeks with either methotrexate (30 patients; 15 mg per week) or fumarates (30 patients; 30 mg, followed by 120 mg orally according to a standard progressive dosage regimen) and were followed-up for 4 weeks. The primary endpoint with respect to the efficacy was the difference in mean change from baseline in PASI after 12 weeks of treatment.. The study was powered to detect a difference of 5 points. Analyses were by intention to treat. This study was registered with trialregister.nl, number ISRCTN76608307.

Results: Six patients were excluded because five were not eligible and one withdrew the informed consent. Two patients in the methotrexate group and one in the fumarate group dropped-out during the 12 weeks of treatment because of non-appearance at the outpatient clinic. A total of 25 patients in the methotrexate group and 26 in the fumarate group were evaluated in the primary analysis. After 12 weeks of treatment, the mean (±SD) PASI decreased from 14.5±3.0 at baseline to 6.7±4.5 in the 25 patients treated with methotrexate, whereas it decreased from 18.1±7 to 10.5±6.7 in the 26 patients treated with fumarates. After adjustment for baseline values, the absolute difference (fumarates minus methotrexate) in the mean values at 12 weeks was 1.4 (95 percent confidence interval, –2.0 to 4.7; P=0.417).

Conclusion: In this randomised trial methotrexate and fumarates were found to be equally effective in the treatment of patients with moderate to severe psoriasis. No serious or irreversible adverse events were observed in any of the patients.

INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin disease with the prevalence of 2-3% in the worldwide Caucasian population. [1,2] Systemic therapy with methotrexate is known to be effective in the treatment of severe psoriasis.[3] Like other currently used systemic treatments for the long-term therapy of psoriasis, methotrexate is hampered by its cumulative adverse events, especially hepatotoxicity. Recently, the Dutch public health authority issued a warning to medical professionals, particularly oncologists, rheumatologists and dermatologists on the use of methotrexate and its fatal adverse events generally through prescription errors, overdoses and lack of monitoring.[4]

Fumarate therapy, an oral mixture of dimethylfumarate and salts of monomethylfumarate was designed in 1959 by the German chemist Walter Schweckendiek. Fumarate therapy is only registered in Germany and has proven to be a safe and effective systemic treatment for psoriasis vulgaris over the years.[5,6] The mode of action of fumarates is thought to be via an anti-proliferative effect on keratinocytes and modulation of T-cell activity partly via the induction of preferential apoptosis of activated T cells .[7]

To date no head-to-head randomised clinical trials with fumarate therapy and other systemic therapies for psoriasis have been reported. Comparing fumarates with methotrexate may provide us with important information on the differences between these therapies, which may be of great help for the safety and the overall quality of life of patients with psoriasis. Moreover, in this era of biologicals costs play an important role in the decision making with regard to therapy in psoriasis. At present, methotrexate and fumarates are by far the cheapest systemic therapies for psoriasis.

We compared the clinical outcome and the adverse events profile in patients with moderate to severe psoriasis vulgaris (en plaque) who were either treated with methotrexate or fumerates in a multi-centre, prospective, randomised controlled clinical trial. We investigated the difference in the means between the PASI after 12 weeks of treatment to determine the efficacy. Adverse events in all the patients were also recorded.

METHODS

Patients

Patients with moderate to severe psoriasis were recruited between October 2006 and February 2009 from the Departments of Dermatology at the Erasmus MC, Rotterdam and from the Catharina Hospital, Eindhoven. Eligible patients were at least 18 years old suffering from chronic plaque-type psoriasis with a psoriasis area-and-severity index (PASI) of at least 10. The PASI combines assessments of psoriasis-induced erythema, scaling and skin thickness each weighted according to the size of the affected area. All

the patients provided signed informed consent. The study was approved by the medical ethics committees at both the institutions.

The exclusion criteria were: (1) patients with other clinical forms of psoriasis like psoriasis guttata or pustulosa; (2) patients in need of co-medications that may interfere with the psoriasis; (3) patients with toxicity for either fumarates or methotrexate; (4) acute infections requiring antimicrobial therapy; (5) patients with hepatitis B, C, HIV, pregnancy and breast-feeding; (6) patients who desired to have children within 3 months after the cessation of the therapy and non-compliant contraception; (7) patients with relevant cardiovascular, pulmonary, cerebral, neurological, renal and haematological diseases; (8) patients with diabetes mellitus (insulin-dependent); (9) patients with high risk of liver function disturbances and drug or alcohol abuse.

Laboratory investigations

Laboratory tests were performed in all eligible patients. The following haematological values were determined: haemoglobin, haematocrit, red blood cell count, total white cell count, leukocyte differential counts and platelet count. Blood chemistry analyses consisted of determining the levels of the following: sodium, potassium, calcium, inorganic phosphate, total protein, albumin, glucose, total cholesterol, triglycerides, blood urea (BUN), creatinine, uric acid, total bilirubin, alkaline phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (gamma-GT), creatinine kinase and lactate dehydrogenase (LDH).

Patients who were treated with fumarates underwent laboratory tests and urine analyses at the screenings visit followed by every 4 weeks (4, 8, 12, 16, 20) and patients who were treated with methotrexate underwent the same laboratory tests and urine analyses on day 3, in weeks 1, 2, 4, 12, 16 and 20.

Study design

All eligible patients were randomly assigned on a 1:1 basis to receive 16 weeks of treatment with either fumarates or methotrexate after all entry criteria had been met and informed consent had been obtained. Randomisation could not be blinded because treatment intake differed in both groups. Randomisation was performed centrally according to a computer-generated randomisation list. Only the research-nurse, who had no contact with the patients before randomisation had insight into the allocation schedule.

Study endpoint

The primary endpoint with respect to the efficacy was the difference in the mean change from the baseline iPASI after 12 weeks of treatment. The screening period, during which no active treatment for psoriasis was allowed, lasted two weeks in patients who had

received topical therapies and four weeks for those who had received UVB-light therapy, PUVA photo-chemotherapy, or systemic drugs ('wash out period'). Patients on fumarate therapy returned for clinical evaluation (including physical examination, vital signs, concomitant medications, monitoring for adverse events and evaluation of psoriasis activity (PASI) and photographs) every 4 weeks (weeks 4, 8, 12, 16) and patients on methotrexate therapy in weeks 1, 2, 4, 12, 16. The treatment was stopped after 16 weeks and all the patients were followed-up for another 4 weeks.

Treatment regimens

Patients received 30 mg and 120 mg fumerates orally according to a standard progressive dosage regimen. After week 9, the therapy was continued at the maximum dose of 720 mg of fumarate.[8] We used fumarates consisting of dimethylfumarate and salts of monoethylfumarate (Magistrale Bereider Oud-Beijerland, Oud-Beijerland, the Netherlands). The methotrexate group 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/week in three equal doses of 5 mg each 12 hours apart. The dose was tapered to 12.5 mg/week at week 13, 10 mg/week at week 14, 5 mg/week at week 15 and 2.5 mg/week at week 16. After 16 weeks the medication was stopped. During the systemic treatment and the follow-up period, no concomitant anti-psoriatic therapy was permitted, with the exception of emollients. Drugs known to interfere with psoriasis or with the systemic treatments (or with both) were not allowed.

OUTCOMES

Clinical efficacy

The PASI was the primary outcome measure and was determined at the baseline and at week 4, 12, 16 and 20 in the fumarate group and the methotrexate group by the same trained assessors (one trained physician and a research-nurse in consensus at each site).

Adverse events

We evaluated adverse events known to be associated with methotrexate or fumarates and those that the patient deemed to be relevant to the treatment. Patients had to keep a diary on all adverse events and necessary co-medications. Adverse events that did not require additional medications or discontinuation of the study medication were classified as mild.

Statistical analysis

Comparison of baseline PASI was done using the Mann-Whitney test and the chi-square test for continuous and categorical variables, respectively. Mean changes in the PASI after the start of the treatment were evaluated using repeated measurements Anova (SAS PROC MIXED using an unstructured covariance matrix SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Time (week of treatment) was included in this analysis as a fixed factor and the baseline PASI was used as a covariate.

When designing this trial, we calculated that 25 patients in each group were needed in this trial to have a 90% power to detect a difference of 5 points in the mean PASI after 12 weeks of treatment, assuming a SD of 5.3. Sixty patients were randomised (30 patients in each group) to allow for any eventual drop-outs. Analysis was by intention-to-treat and two-sided P-values of 0.05 were considered to indicate statistical significance.

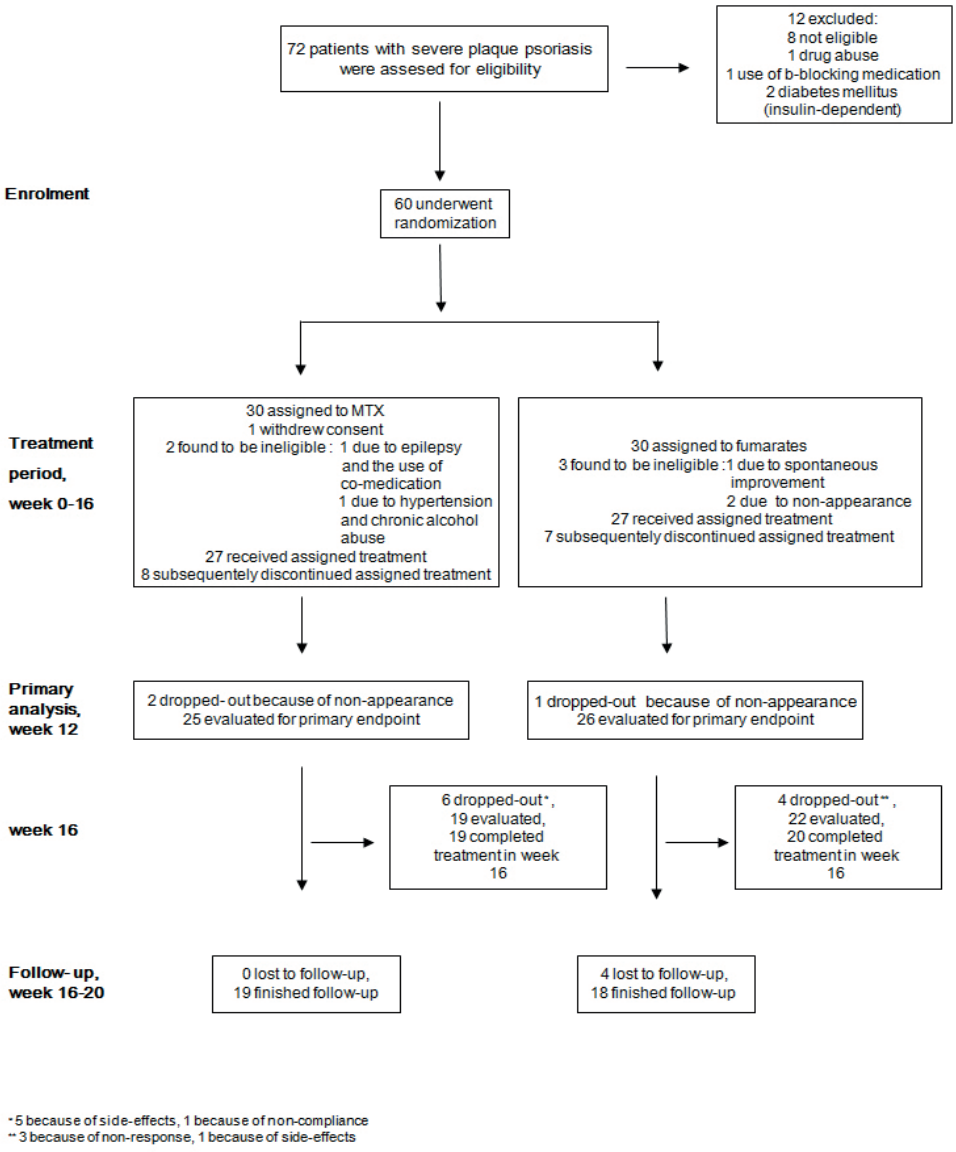
RESULTS

Patients

Baseline demographics and clinical characteristics are summarised in Table 1. Between October 2006 and February 2009, 72 patients with moderate to severe psoriasis were screened, 60 of whom were randomized (Fig. 1). Six patients (3 in the methotrexate and 3 in the fumarate group) were subsequently excluded because 5 were not eligible and one withdrew informed consent. Two patients in the methotrexate group and 1 patient in the fumarate group dropped-out during the first 12 weeks of treatment because of non-appearance at the outpatient clinic (1 patient stopped visiting the outpatient clinic in week 4 and 2 patients in week 6). A total of 25 patients in the methotrexate group and 26 patients in the fumarate group were evaluated for the primary endpoint PASI at week 12.

After 12 weeks of treatment, the mean (+/- SD) PASI decreased from 14.5 ± 3.0 at the baseline to 6.7 ± 4.5 in the 25 patients in the methotrexate group, whereas it decreased from 18.1±7.0 to 10.5 ± 6.7 in the 26 patients in the fumarate group. After adjustment for the baseline PASI, the absolute difference (fumarates minus methotrexate) in mean values at 12 weeks was 1.4 (95 percent confidence interval, –2.0 to 4.7; P=0.417) (Fig. 2). At week 4 the baseline adjusted difference was 4.1 (95% CI: 1.9 to 6.3; P=0.001).

Eleven (42%) of the 26 evaluated patients in the fumarate group and 15 (60%) of 25 evaluated patients in the methotrexate group had a 50% reduction in the PASI (P=0.325) after 12 weeks of treatment (Figure 2). Partial remission (defined as a reduction of more than 75% in the baseline PASI) was achieved in 5 (19%) of the 26 evaluated patients in the fumarate group and 6 (24%) of the 25 evaluated patients in the methotrexate group after 12 weeks of treatment (P=0.941). An almost complete remission (defined



*5 because of side-effects, 1 because of non-compliance
** 3 because of non-response, 1 because of side-effects

Figure 1. Enrollment, Randomization, and Treatment through week 20.

as a reduction of more than 90% in the baseline PASI) during the 12 weeks of treatment was noted in 1 (4%) of the 26 evaluated patients in the fumarate group and 2 (8%) of the 25 evaluated patients in the methotrexate group (P=0.610).

We found no significant differences in the percentages of patients with partial remission (PASI ≥ 75% decrease, both P ≥ 0.65) and almost complete remission (PASI ≥ 90%, P ≥ 0.96) after oral treatment was stopped in week 16.

Table 1 Demographic and clinical characteristics of included patients

Characteristic	Methotrexate (n=27)	Fumarates (n=27)
Age (years), mean ± SD	41±14	43±16
Sex, n (%)		
Male	16 (59)	20 (74)
Female	11 (41)	7 (26)
Weight (kg), mean ± SD	83± 17	87±21
Duration psoriasis in years	17±14	16±9
Previous treatment, n (%)	26 (96)	24 (89)
Topical agent a	26 (96)	24 (89)
Phototherapy b	13 (48)	16 (59)
Conventional systemic agents c	16 (59)	17 (63)
Biological agents d	2 (7)	2 (7)
Baseline PASI-score, mean ± SD	14.7±3.0	18.0±6.9

a Patients had to have discontinued topical therapies (except moisturizers and shampoos) 2 weeks, conventional systemic therapies and biological agents 4 weeks before randomization. b Includes ultraviolet B light and psoralen plus ultraviolet A. c Includes psoralen plus ultraviolet A, fumarates, methotrexate, acitretin, and cyclosporin. d Includes etanercept, efalizumab, infliximab, and adalimumab. PASI, Psoriasis Area and Severity Index (scale 0 - 72)

In week 20, 13 (72%) of the 18 evaluated patients in the fumarate group and 10 (53%) of the 19 evaluated patients in the methotrexate group had a 50% reduction in the PASI (P=0.374), 7 (39%) of the18 evaluated patients in the fumarate group and 6 (32%) of the19 evaluated patients in the methotrexate group had a 75% reduction in the PASI (P=0.642). One (6%) of the 18 evaluated patients in the fumarate group and 2 (11%) of the 19 evaluated patients in the methotrexate group achieved a 90% reduction in the PASI (P=1.00). Three patients in the methotrexate group showed a worsening in the PASI as compared with the baseline PASI (with the highest worsening of the PASI from 11.7 to 14.8) in week 20 as compared with no patients in the fumarate group.

Adverse events

The total number of reported adverse events was 60 in the fumarate group and 78 in the methotrexate group. Adverse events were reported by 24 patients in the fumarate group and 27 patients in the methotrexate group (P=0.236). Significantly more patients reported flushing (13 in the fumarate group and 2 in the methotrexate group, P=0.002) and flu-like symptoms (1 in the fumarate group and 7 in the methotrexate group, P=0.050). Additional medication to relieve adverse events was not necessary in either group.

Overall, the tolerability of both drugs was good. Two (8%) of the 26 patients in the fumarate group had to discontinue treatment because of diarrhoea, worsening of the psoriasis and itch. Four (16%) of the 25 patients in the methotrexate group had to stop

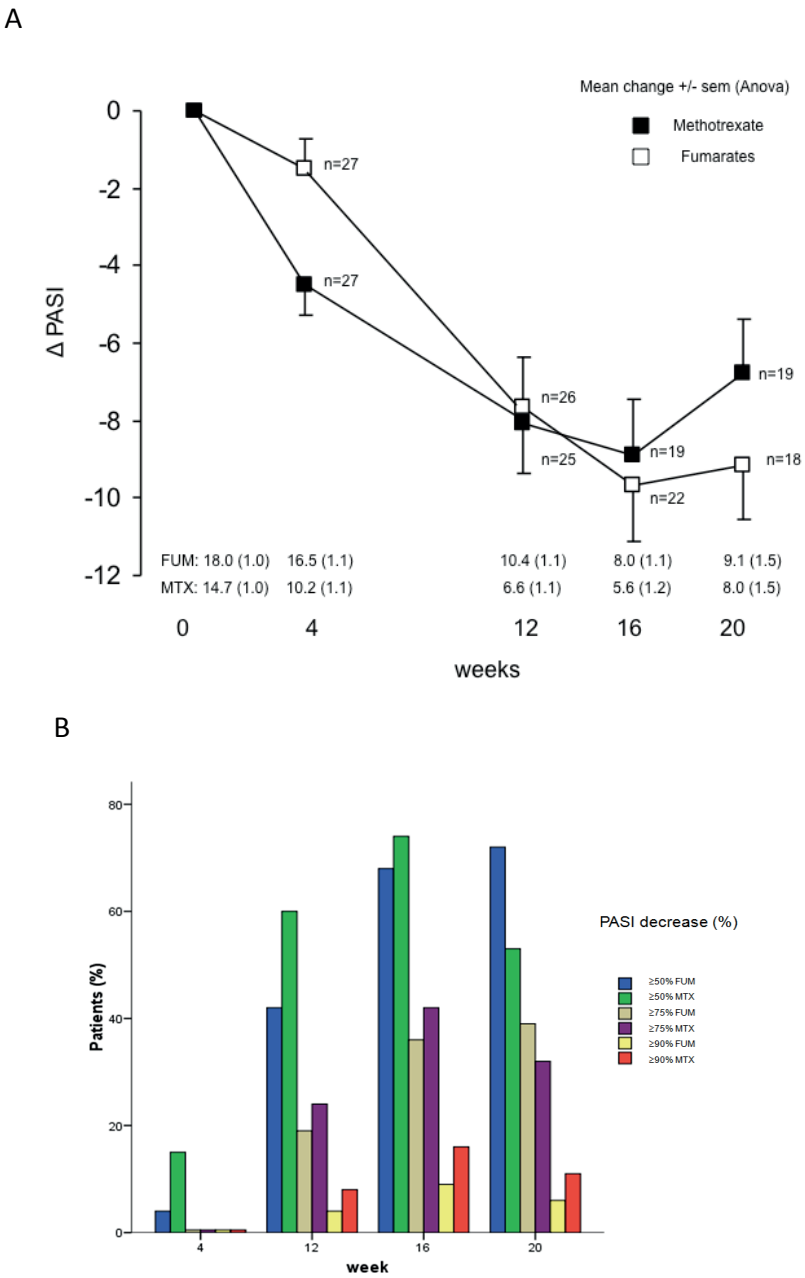


Fig 2. a) Clinical response to treatment expressed as the **c**hange from baseline of the Psoriasis Area-and-Severity Index (PASI)-score over time. FUM=fumarates group, MTX=methotrexate group. Meanchanges (±SE) of the PASI-scores during the treatment and the follow-up. The mean values of PASI, with SE between parentheses, at the various time points are shown at the bottom. b) The proportions of patients randomly assigned to receive either fumarates or methotrexate till week 20 at each time point, according to variable degrees of improvement (50%, 75%, 90%) in the PASI-score.

treatment, two because of elevations in their liver enzymes and one because of recurrent angina. The elevations in the liver enzymes were mild and all values returned to normal within four to eight weeks after stopping the treatment. Elevations in liver enzymes during methotrexate treatment have been well documented. Whether the hepatotoxicity of methotrexate is reduced by folic acid supplement is not clearly understood. However, since folic acid has no known serious adverse events and is cheap, it was prescribed to our patients. No serious or irreversible adverse events were observed in any of the participating patients.

Laboratory investigations

Treatment had to be discontinued in four (15%) of the 27 patients in the methotrexate group because of elevated liver enzyme levels of 200-300% of the values at the screening visit (the highest measured values were AST 66 U L^{-1}, ALT 140 U L^{-1}, LDH 290 U L^{-1}). These laboratory abnormalities were transient and the levels returned to normal within 4–8 weeks after treatment was stopped. No patient in the fumarate group had to stop treatment because of abnormal laboratory values. Transient elevation of liver enzymes of 100–200% of the value at screening visit were seen in eight (30%) of the 27 patients in the methotrexate group and three (11%) of the 27 patients in the fumarate group with the highest measured values being AST 71 U L^{-1}, ALT 82 U L^{-1}, GGT 80 U L^{-1}. Moreover, five (19%) of the 27 patients in the fumarate group showed a transient eosinophilia (maximum measured level 1·55 X 109 L^{-1}), but this was not observed in any patient in the methotrexate group. One (4%) of the 27 patients in the fumarate group showed a transient leucocytopenia (2·1 X 109 L^{-1}), but this was not observed in any patient in the methotrexate group. One (4%) of the 27 patients in the methotrexate group had a transient thrombocytosis (with a maximum level of 422 X 109 L^{-1}) that was not observed in any patient in the fumarate group. Transient lymphocytopenia (8% with a minimum level of 15%) was encountered in one (4%) of the 27 patients in the fumarate group, but was not observed in any patient in the methotrexate group. Eight (30%) of the 27 patients in the fumarate group and eight (30%) of the 27 patients in the methotrexate group showed a transient proteinuria.

DISCUSSION

In this study in patients with moderate to severe psoriasis vulgaris, we noted that methotrexate and fumarates were equally effective at week 12 (Fig. 2). After 12 weeks of treatment, the mean adjusted absolute difference between the groups was only 1.4 points. The PASI started to decrease in both the groups once treatment was started. Eleven (42%) of the 26 evaluated patients in the fumarate group and 15 (60%) of the 25

evaluated patients in the methotrexate group had a ‡ 50% reduction in PASI (P = 0.325). There were no significant differences in the efficacy except in week 4 (P = 0.001) when the PASI in the methotrexate group had decreased more rap- idly than in the fumarate group, which was already expected because of the known long induction time of fumarates. The recruitment phase was slow (October 2006 until February 2009). Most of the patients preferred to be treated with fumarates and did not want to take the risk of being randomized into the methotrexate group because they were afraid of the adverse events, mainly hepatotoxicity.

In our study we used a starting dose of 5 mg followed by 15 mg of methotrexate per week and tapered it off in the last 4 weeks (from week 12). We chose this dose following the reported randomized study by Heydendael et al.[9] who compared the efficacy of methotrexate and ciclosporin in the absence of evidence from dose-finding and treatment-duration studies.

Biological agents have recently attracted much attention. To date, three biologicals (adalimumab, etanercept, infliximab) have been approved by the U.S. Food and Drug Administration for the treatment of psoriasis. However, a main concern with biologicals is their higher costs as compared with those of the traditional systemic therapies. The estimated annual cost of treatment with biologicals may range from €9200 to €21 200 per patient. Sizto et al.[10] reported in their meta-analy- sis that methotrexate and ciclosporin were the most cost-effective treatments for moderate to severe psoriasis. However, while most cost-effective, neither methotrexate nor ciclosporin is recommended for prolonged use in the majority of patients, because of their high potentials for long-term toxicity. Therefore, we believe that treatment with fumarates should be considered as a first-choice treatment for moderate to severe psoriasis because of its low costs as compared with those of biologicals, and proven long-term efficacy and safety.

The clinical efficacy and safety of fumarates was reported in two double-blind, placebo-controlled, randomized trials.[5,11] In the European S3 guidelines, systemic therapy with fumaric acid esters is recommended especially for the long-term therapy of patients with moderate to severe psoriasis on the basis of the favourable benefit-risk profile.[6] The product is highly practical.[12]

A major strength of this study is that it is the first prospective randomized multicentre clinical trial in an outpatient setting on the effectiveness and the adverse events profile of fumarates in moderate to severe psoriasis as compared with those of methotrexate. Moreover, costs play an important role in the decision making with regard to therapy in psoriasis. At present, methotrexate and fumarates are by far the cheapest systemic therapies in moderate to severe psoriasis: methotrexate costs €44.80 for 22.5 mg tablets once weekly for 1 month compared with fumarates which cost €98 for six tablets of 120 mg daily for 1 month.

A limitation of this study is that we did not measure the quality of life of the patients because it was designed primarily to compare the clinical effectiveness and the safety of both drugs. Future study designs should include the quality of life score as an additional assessment tool.

It is well known that UV radiation therapy followed by treatment with immunosuppressive drugs, especially ciclosporin, increases the risk of skin malignancies by 6.9 fold.[13] Therefore, there is a great need to offer an effective, patient- friendly and safe alternative to patients with moderate to severe psoriasis, especially young patients, who do not respond well to topical treatments. Fumarates are particularly suited as a first-line systemic therapy in such patients.

This randomized controlled trial adheres well to the requirements outlined in published guidelines.

In conclusion, the results of this study showed that the effectiveness and the tolerability of fumarates were similar to those of methotrexate. Methotrexate is not recommended for prolonged use because of its high potential for long-term toxicity, especially hepatotoxity and fatal adverse events. Fumarates have a good and sustained clinical efficacy that is statistically similar to that of methotrexate, combined with a favourable safety profile with no serious adverse events in long-term therapy. Further comparative studies are warranted to confirm the results of this study.[14]

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Chapter 4

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

S. Fallah Arani
D.M.W. Balak
C.M. Venema
H.A.M. Neumann
H.B. Thio

ABSTRACT

Background: Fumaric acid esters (FAEs) are considered an effective and safe long- term treatment for psoriasis. However, 30–40% of patients need to discontinue FAE treatment due to intolerable adverse events.

Objectives: To assess whether the addition of cetirizine, an oral histamine-1 receptor antagonist, to FAEs would reduce the incidence of adverse events.

Methods: In a randomized, double-blind, placebo-controlled trial, patients with psoriasis with a Psoriasis Area and Severity Index ≥ 10 starting an FAE up to a dose of dimethylfumarate 720 mg per day were randomized 1 : 1 to receive either additional cetirizine 10 mg once daily (n = 25) or placebo (n = 25) for 12 weeks. Randomization and treatment allocation were done at our hospital trial pharmacy. Primary outcomes were the incidence of adverse events and the proportion of patients discontinuing treatment.

Results: Fifty patients (33 male, 17 female; median age 44 years) were enrolled. Addition of cetirizine did not reduce the incidence of adverse events compared with placebo (84% vs. 84%, P = 1.00). The types of adverse events were not different between the cetirizine and placebo groups, the most common being gastrointestinal complaints (68% vs. 64%) and flushes (60% vs. 48%). The proportion of patients discontinuing treatment was not statistically different between the cetirizine and placebo groups (24% vs. 32%, P = 0.53). Conclusions Addition of oral cetirizine 10 mg once daily to FAE treatment did not reduce adverse events in patients with psoriasis during the first 12 weeks of treatment. The mechanisms underlying FAE-induced gastrointestinal and flushing symptoms likely involve mediators other than histamine.

INTRODUCTION

Fumaric acid esters (FAEs), or fumarates, are small molecules with immunomodulatory properties.[1] For over three decades, FAEs have been used as an oral treatment in patients with chronic plaque psoriasis, with a favourable long-term efficacy and safety profile.[2,3] The efficacy of FAEs is comparable with that of methotrexate.[4,5] To date, there are no indications that long-term FAE treatment is associated with an increased risk of malignancies or infections, making FAEs particularly suit- able for maintenance therapy of psoriasis.[3,6]

An important limitation of FAE treatment is intolerable adverse events, which result in treatment discontinuation in 30–40% of patients.7,8 The most commonly occurring adverse events of FAEs are gastrointestinal complaints and flushing. These relatively mild but inconvenient side-effects occur pre- dominantly during the first 3 months of FAE treatment. In order to improve the tolerability of FAEs, the current guide- lines recommend slowly increasing the dosage of the FAE using a standardized progressive dosing regimen.[2] In this dosing regimen, the maximum daily dosage of 720 mg dimethylfumarate is reached within 9 weeks. If patients have adverse events, it is advised that they increase the dosage more slowly, decrease the dosage, or temporarily stop the FAE.

Another strategy pursued in daily clinical practice when patients on FAEs experience adverse events is to prescribe an oral histamine antagonist in order to decrease these symptoms.[9,10] The adverse events frequently reported during FAE treatment are similar to several histamine-mediated symptoms, such as diarrhoea, abdominal complaints and flushing.[11] Blocking histamine might therefore be helpful in decreasing these adverse events during FAE treatment. Furthermore, treatment with a histamine antagonist could have an additional clinical benefit in patients with psoriasis, as histamine antagonists may have antipsoriatic effects.[12,13] However, to date there is no clear evidence that the addition of a histamine antagonist to FAE treatment improves the tolerability or the efficacy of FAE in the treatment of psoriasis.

In this randomized placebo-controlled trial, we aimed to determine whether the addition of cetirizine, an oral histamine-1 receptor antagonist, to FAE treatment would reduce the incidence of adverse events in patients with moderate-to- severe plaque psoriasis. In addition, we aimed to assess whether the addition of cetirizine to FAE treatment would increase the efficacy of the FAE.

PATIENTS AND METHODS

Study design

This was an investigator-initiated, single-centre, randomized, double-blind, placebo-controlled trial conducted at the derma- tology outpatient clinic of Erasmus Medical Center, Rotterdam, The Netherlands in the period 2009–2012. This study was approved by the medical ethics committee of the Erasmus Medical Center (MEC 2005-500). The study was conducted according to the principles of the Declaration of Helsinki. All patients gave written informed consent. The trial protocol was

registered at the Dutch Trial Registry (http://www.trialregis- ter.nl/) under registration number NTR744. There were no funding sources.

Study population

Eligible for inclusion were patients aged 18 years or older with moderate-to-severe chronic plaque psoriasis, who had a Psoriasis Area and Severity Index (PASI) ≥ 10 and who were candidates to start FAE treatment. The exclusion criteria were renal disease, liver disease, a medical history of malignancies, pregnancy and lactation. Patients had to discontinue all psoriasis treatments before enrolment, with a washout period of 4 weeks for systemic treatment and phototherapy, or 2 weeks for topical psoriasis treatment. During the study psoriasis treatments were not allowed expect for bland emollients.

STUDY PROCEDURES

Enrolled subjects were randomized at baseline in a 1:1 ratio to receive either FAE plus cetirizine 10 mg once daily or FAE plus a matching placebo for 12 weeks, followed by a follow- up period of 8 weeks. Randomization and treatment allocation were done at the hospital trial pharmacy. Patients and physician assessors were both blinded for the allocated treatment group.

All patients were treated with a Dutch FAE formulation with enteric-coated tablets containing 105 mg FAE (30 mg dimethylfumarate and 75 mg calcium monoethylfumarate) for the first 3 weeks, followed by tablets of 215 mg FAE (120 mg dimethylfumarate and 95 mg calcium monoethylfumarate) (Pharmacy 'De Magistrale Bereider', Oud-Beijerland, The Netherlands). In previous studies we analysed this FAE formulation for pharmacokinetic properties and for efficacy compared with methotrexate.[4,14] FAEs were given according to a standardized progressive dosing regimen, starting at 30 mg dimethylfumarate per day with an incremental increase up to a maximum daily dosage of 720 mg dimethylfumarate within 9 weeks.[2]

Patients were seen at weeks 0, 4, 8, 12 and 20. At each study visit adverse events were reviewed and routine laboratory testing was performed: full blood count with differential, liver function tests, serum creatinine levels, cholesterol levels and urine analysis. Furthermore, PASI was recorded at each study visit, and health-related quality of life was measured using the Skindex-29 questionnaire at week 0 and week 12. Skindex-29 is a validated questionnaire that measures dermatology-specific health-related quality of life on a scale ranging from 0 to 100, with higher scores indicating lower quality of life.15 There are currently several instruments available to measure dermatology-specific health-related quality of life, but there is no clear consensus on which instrument to use.[16] The Dermatology Life Quality Index is a widely used instrument, but there are some limitations to its use.[17] At our department the Skindex-29 questionnaire is routinely used in daily clinical practice to measure dermatology-specific health-related quality of life. Therefore, we chose to use Skindex-29 in this study.

Outcomes

The primary outcomes were the incidence of adverse events and the proportion of patients discontinuing FAE treatment. Secondary outcomes were changes in PASI and changes in health-related quality of life.

Statistical analysis

Data are presented as mean ±SD, or as median with inter- quartile range (IQR) when not normally distributed. Analysis was by intention to treat. Differences in categorical variables and continuous variables between the two groups were tested with the Kruskal–Wallis or v2-test, respectively. A P-value ≤ 0.05 was considered statistically significant.

We calculated a sample size of 50 patients to give 90% power with a two-sided 5% significance level to detect a reduction of 55% in the incidence of adverse events.

RESULTS

Patient characteristics

In total, 50 patients were enrolled and included in the trial (Fig. 1). The demographic and clinical characteristics of the study population are summarized in Table 1. The median age was 44 years (IQR 30–56) and the median duration of psoriasis was 11 years (IQR 5–21). Most patients had been treated previously with phototherapy (36%). Few patients had been previously treated with a classical systemic psoriasis treatment (28%) or with a biological (4%).

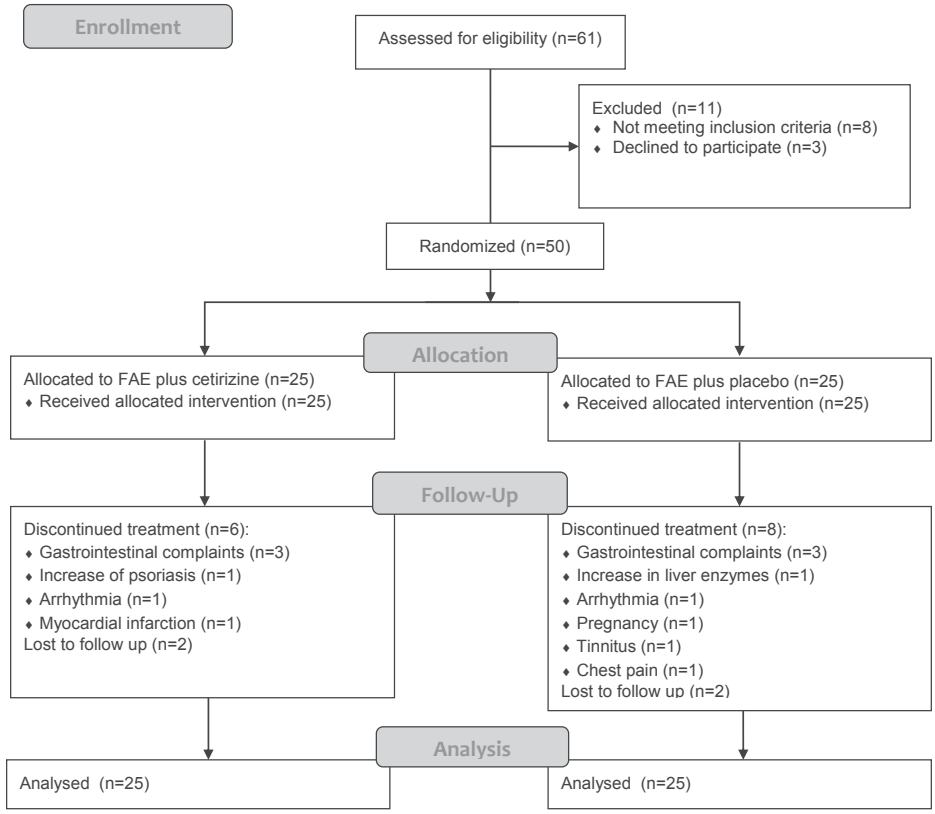

Figure 1: Flow diagram

Incidences of adverse events during FAE treatment

Overall, 21 (84%) of 25 patients in the cetirizine group and 21 (84%) of 25 patients in the placebo group experienced an adverse event during the first 12weeks of treatment (Table 2). The addition of cetirizine to the FAE did not reduce the incidence of adverse events in the cetirizine group com- pared with the placebo group (84% vs. 84%, P = 1.00).

The most common adverse events in the cetirizine group were gastrointestinal complaints (68%), flushes (60%) and pruritus (28%). Similar frequencies were observed in the placebo group, with the most commonly reported adverse events being gastro-intestinal complaints (64%), flushes (48%) and headache (28%). The incidences of the different types of adverse events were not significantly different between the cetirizine and placebo groups. There were no differences between the two groups in the 8-week follow-up period following week 12.

Table 1: Baseline demographic and clinical characteristics of the study population

Characteristic	FAE with cetirizine (n=25)	FAE with placebo (n=25)
Age	46 (31-62)	38 (30-54)
Sex		
Male	15 (60%)	18 (72%)
Female	10 (40%)	7 (28%)
Duration of psoriasis in years	11 (5-19)	12 (5-24)
History of psoriatic arthritis	8 (32%)	5 (20%)
Previous psoriasis treatments		
Phototherapy	10 (40%)	8 (32%)
Classical treatment (methotrexate, ciclosporin)	8 (32%)	6 (24%)
Biologic treatment	2 (8%)	0 (0%)
PASI at baseline	12.7 (10.8-16.0)	14.5 (12.0-16.7)

Data are numbers (percentages) or medians (interquartile ranges)

Table 2: Subjective adverse events

Characteristic	FAE with cetirizine (N = 25)	FAE with placebo (N = 25)
Gastrointestinal complaints	17 (68%)	16 (64%)
Flushing	15 (60%)	12 (48%)
Pruritus	7 (28%)	6 (24%)
Headache	2 (8%)	7 (28%)
Fatigue	5 (20%)	4 (16%)
Lower extremity edema	2 (8%)	2 (8%)
Dermatitis	0 (0%)	1 (4%)
Chest pain	0 (0%)	1 (4%)
Tinnitus	0 (0%)	1 (4%)
Flu-like symptoms	1 (4%)	0 (0%)
Dizziness	1 (4%)	0 (0%)

Data are numbers (percentages)

Tolerability

Six (24%) of 25 patients in the cetirizine group had discontinued FAE treatment. The reasons for discontinuing treatment were intolerable gastrointestinal complaints (n=3), an increase of psoriasis (n=1), arrhythmia (n=1), and myocardial infarction (n=1). In the placebo group the number of patients discontinuing FAE treatment was slightly higher, with 8 (32%) of 25 patients who discontinued treatment. The reasons for discontinuing treatment were gastrointestinal complaints (n=3), an increase in liver enzymes (n=1), arrhythmia (n=1), pregnancy (n=1), tinnitus (n=1), and chest pain (n=1). The proportion

of patients discontinuing FAE treatment was not statistically different between the cetirizine and the placebo group (P=0.53). There were two (8%) patients in the placebo-group and two (8%) patients in the cetirizine-group who were lost to follow up.

Safety

Abnormal laboratory tests were observed in 24 (96%) patients of the cetirizine group versus 21 (84%) patients in the placebo group (Table 3). The most common abnormal laboratory tests seen in both groups were an increase in liver enzymes, an eosinophilia, and a proteinuria. A decrease in lymphocyte counts was seen in 5 (20%) patients treated with additional cetirizine versus 4 (16%) patients in the group who received placebo. In all cases the laboratory abnormalities were mild with changes of less than twofold the limits of normal value, and all laboratory abnormalities normalized without any intervention and while continuing FAE treatment. There was only 1 (4%) patient in the FAE plus cetirizine group who had a more than twofold increase in alanine transaminase and in aspartate transaminase following 4 weeks of treatment with FAE and who therefore had to discontinue FAE treatment. The increase in transaminases normalised within 2 weeks.

Table 3: Laboratory adverse events

Characteristic	FAE with cetirizine (N = 25)	FAE with placebo (N = 25)
Increase in liver enzymes	13 (52%)	15 (60%)
Eosinophilia	10 (40%)	8 (32%)
Proteinuria	8 (32%)	5 (20%)
Lymphocytopenia	5 (20%)	4 (16%)
Decrease in creatinine	4 (16%)	0 (0%)
Increase in urea	2 (8%)	1 (4%)
Increase in cholesterol	2 (8%)	1 (4%)
Decrease in thrombocytes	0 (0%)	1 (4%)
Increase in haemoglobin	1 (4%)	0 (0%

Data are numbers (percentages)

Efficacy

The median improvement in PASI at week 12 compared to baseline was 65% (IQR 52-79) among patients treated with FAE plus cetirizine (Fig. 2). In the group of patients receiving FAE plus placebo a similar improvement in PASI at week 12 was seen, with a median improvement of 66% (IQR 49-78). The proportion of patients achieving at least 75% improvement in PASI at week 12 was 20% in both the cetirizine group and the placebo group.

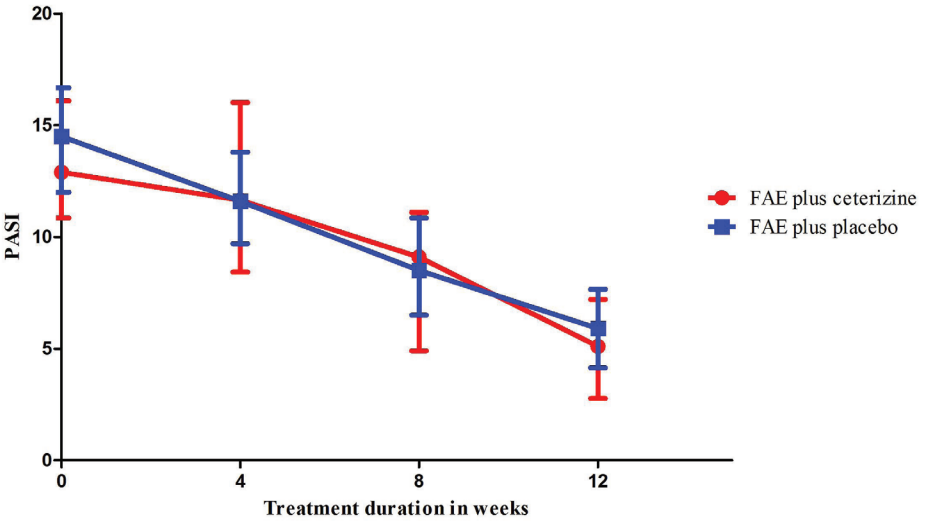

Figure 2: changes in PASI during 12 weeks of FAE treatment in patients treated with FAE plus cetirizine (n=25) and in patients treated with FAE plus placebo (n=25). Error bars show median and interquartile range.

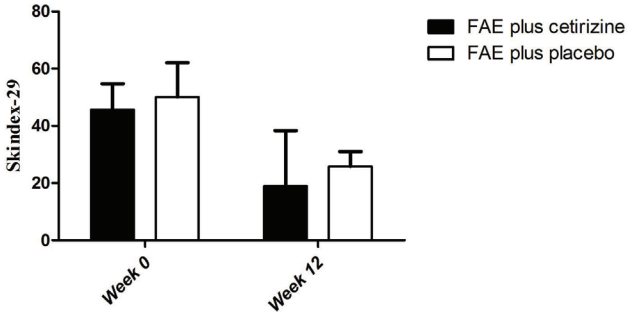

Figure 3: changes in Skindex-29 scores during 12 weeks of FAE treatment in patients treated with FAE plus cetirizine (n=25) and in patients treated with FAE plus placebo (n=25). Error bars show median and interquartile range.

Health-related quality of life

The health-related quality of life as measured by the Skindex-29 improved during the 12-week FAE treatment (Fig. 3). In the group of patients treated with FAE plus cetirizine the median improvement at week 12 was 39% (IQR 20-62). Among patients who received FAE plus placebo the median improvement at week 12 was 55% (IQR 21-77). The improvements in Skindex-29 scores were not statistically different between the cetirizine and the placebo group (P=0.87).

DISCUSSION

In this randomized double-blind placebo-controlled trial among 50 patients with moderate-to- severe psoriasis treated with FAE for 12 weeks, the addition of the oral histamine-1 receptor antagonist cetirizine 10 mg once daily to FAE did not reduce or improve the tolerability of FAE treatment. Furthermore, the addition of cetirizine did not increase the efficacy of FAE compared to treatment with FAE alone.

To translate these findings into implications for clinical practice, several aspects of our study need to be considered. Firstly, we used a randomized, double-blind study design and a matching placebo for cetirizine so that both the patients and the physician assessors were blinded for the allocated treatment group. Secondly, we used a suitable histamine-1 receptor antagonist that has shown to be well-tolerated with favourable pharmacological properties in other patient populations.[18] In addition, the effects of cetirizine were studied previously in patients with psoriasis.[12,19] A limitation of our study is the relatively small sample size, owing to our pre-study power calculation. However, if a greater sample size were required to detect a statistically significant difference, the clinical value of adding a histamine antagonist to FAE would likely be small. Furthermore, we did not quantify the severity of flushing and gastrointestinal symptoms. However, we did look specifically for the incidence of adverse events requiring FAE treatment discontinuation, for which we found no statistically significant differences between the cetirizine and placebo groups. Lastly, we chose a Short-term study duration of 12 weeks, considering that adverse events occur predominantly at the beginning of FAE treatment.

In this study, treatment with an oral histamine-antagonist had no effect on the occurrence of the adverse events during FAE treatment. Therefore, the mechanisms underlying FAE-induced gastrointestinal and flushing symptoms likely involve mediators other than histamine. Alternatively, histamine may play only a minor role in the generation of adverse events associated with FAE. In recent experimental studies it has been shown that FAE-induced flushing is mediated through activation of the G-protein-coupled receptor GPR109A located on Langerhans cells and on keratinocytes, which via cyclooxygenase-1 and -2 enzymes leads to prostaglandin release.[20] Further evidence for this mechanism comes from a clinical trial involving 56 healthy volunteers, in which aspirin, a cyclooxygenase inhibitor, decreased the incidence and severity of flushing symptoms of dimethylfumarate.[21]

The mechanisms leading to gastrointestinal complaints in FAE treatment are not yet understood. One hypothesis involves the FAE-triggered release of tumour necrosis factor alpha (TNF-α) as a mechanism leading to gastrointestinal complaints.[22] In a previous clinical study, co-treatment of FAE with pentoxifylline, a methylxanthine derivative with some anti-TNF-α properties, reduced the frequency of gastrointestinal complaints.[23] This study, however, was open-label and uncontrolled so that bias of these results cannot be excluded. Another potential mechanism may involve dimethylfumarate-induced allergic

contact mucositis of the gastrointestinal tract.[24] Hessam *et al.*[24] described three patients who had to discontinue FAE due to gastrointestinal complaints and who had a positive patch test reaction to dimethylfumarate. Considering that dimethylfumarate is a potent contact sensitizer, systemic treatment with dimethylfumarate could induce an allergic contact mucositis, and thus causing gastrointestinal symptoms. Future studies could focus on these mechanisms to find new strategies to improve the tolerability of FAEs.

In this study, cetirizine at a daily dosage of 10 mg did not reduce FAE-induced adverse events. One can speculate whether higher dosages of cetirizine may be more effective. In the cur- rent guidelines on the treatment of chronic urticaria, the daily dose of cetirizine may be increased up to fourfold when a single dose of cetirizine 10 mg is ineffective.[25] Similarly, cetirizine in higher doses might be effective to decrease FAE-induced adverse events. We did not test this hypothesis in this current study.

It has been suggested that the histamine-antagonist cetirizine may be beneficial in psoriasis treatment.[12,26] In this study, we could not detect an additional improvement by cetirizine. The improvement in PASI in the FAE plus cetirizine group was equal compared to treatment with FAE alone. Other histamine antagonists like ranitidine, a histamine-2 receptor antagonist, did show improvements of psoriasis in several observational studies but failed to demonstrate efficacy in randomized controlled trials.[27,28]

FAE have a favourable long-term efficacy and safety profile, but the induction phase of FAE treatment can be challenging for patients because of problems with tolerability. Therefore, a gradual increase in dose of FAE is considered standard. A large disadvantage of this approach is that it takes longer to reach the dosage with a satisfactory clinical response. In daily clinical practice, the first clinical response is usually observed following 6 to 8 weeks of treatment.[2] If FAE-induced adverse events can be decreased or even prevented, the optimal dosage of FAE could be reached faster and would thereby increase patient treatment satisfaction. There is evidence that aspirin and non-steroidal anti-inflammatory drugs decrease flushing symptoms, but these drugs to do not affect gastrointestinal complaint. It is our experience that patients on FAE find the gastrointestinal symptoms to be more bothersome that the flushing symptoms. In this study, there were 6 of 50 patients who discontinued FAE due to gastrointestinal complaints and none who had to discontinue FAE due to flushing. In daily clinical practice, gastrointestinal complaints can be managed by symptomatic treatment with proton pump inhibitors, anti-emetics, or anti-diarrhoeal drugs.[10] Given the results of this study, adding a histamine antagonist to FAE is not helpful in reducing the adverse events.

In conclusion, the addition of the histamine antagonist cetirizine 10 mg once daily to FAE treatment did not reduce adverse events nor improved tolerability of FAE in psoriasis patients. Our results do not support a beneficial effect of adding a systemic histamine antagonist to FAE treatment in patients with psoriasis.

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Chapter 5

Treatment of psoriasis with non-registered fumaric acid esters in the Netherlands: a nationwide survey among Dutch dermatologists

S. Fallah Arani
D.M.W. Balak
H.A.M. Neumann
M.V. Kuipers
H.B. Thio

ABSTRACT

Background: Psoriasis vulgaris is a T cell-mediated disease that affects 2-3% of the worldwide white-skinned population. Fumaric acid esters are mentioned as an effective therapy for moderate to severe psoriasis vulgaris in adult patients in the new guidelines for psoriasis treatment.

Objectives: To obtain an insight into the use of fumaric acid esters by Dutch dermatologists in the Netherlands.

Methods: This was a cross-sectional postal survey. An anonymous survey was posted to all Dutch dermatologists. In this survey, data was collected on the extent of fumaric acid esters use, the reasons for use, the reasons for non- or limited use of fumaric acid esters, the perception of fumaric acid esters as a mono-therapy with regards to the effectiveness, the safety, the adverse events and the overall satisfaction of fumaric acid esters as a mono-therapy.

Results: Sixty-three per cent of the 300 responders indicated to prescribe fumaric acid esters for the treatment of psoriasis. About 37% of the dermatologists indicated (almost) never to prescribe it. Biologicals were considered as the most effective therapy. Fumaric acid esters were regarded as the safest therapy. They were generally well tolerated by the patients similar to that for methotrexate according to the respondents.

Conclusion: A large proportion of the dermatologists in our survey indicated to prescribe fumaric acid esters. It is considered to be effective, safe and without adverse events profile that is favourable in the practice, also as compared with other systemic therapies such as methotrexate and biologicals.

INTRODUCTION

Psoriasis vulgaris is a T cell-mediated disease that affects 2-3% of the worldwide white-skinned population.[1,2,3] Systemic therapy is often limited because prolonged use of effective doses may lead to severe adverse events.[4]

Fumaric acid esters (FAE) were specifically developed to treat psoriasis vulgaris and were first used in Germany in 1959, where they have been registered for the treatment of psoriasis since 1995.[5,6] However in many other countries this is not the case.

Dimethylfumarate and monoethylfumarate are the used esthers.[7]The most active metabolite is monomethylfumarate that is formed after absorption and hydrolysis of dimethylfumarate. The mode of action of FAE consists of inhibition of both the T cell activity and the keratinocyte proliferation.

Recently, Fallah Arani et al. published in the only prospective randomized study that FAE were as effective as methotrexate in the treatment of psoriasis.[8]

Treatment with FAE is mentioned in several guidelines as an effective induction therapy for moderate to severe psoriasis vulgaris in adult patients.[9, 10]

The aim of this nationwide survey was to obtain an insight into the use of FAE by Dutch dermatologists in the Netherlands, although FAE are not registered in the Netherlands. For this purpose, it was assumed that FAE were mainly prescribed by dermatologists in the Netherlands.

METHODS

Study design

This is a cross-sectional postal survey. An anonymous survey was posted to all members of the Dutch Society of Dermatology and Venereology (NVDV), which includes all practising dutch dermatologists and residents in the Netherlands. All the members of the NVDV received a letter announcing our survey and two full questionnaires between April and August 2010. Non-responders were sent a reminder letter and the questionnaire once more. The completed questionnaires were processed anonymously (only on the basis of zipcode). Subsequently, postcodes with non-responders were mailed the questionnaire again.

The total response after the first round was 33%, which increased to 50% after the second round.

Data collection

Data on the extent of FAE use, the reasons for use, the reasons for non- or limited use of FAE; the perception of FAE as a mono-therapy with regards to the effectiveness, the

safety, the adverse events and the overall satisfaction of FAE as a mono-therapy was collected in this survey. In addition, we also included questions involving other systemic treatments for psoriasis vulgaris so as to enable an indirect comparison between FAE and various other systemic treatments.

The group of patients with mild disease who did not require systemic treatment was excluded.

RESULTS

General information on respondents

More than 75% of the respondents were dermatologists, the remaining were residents in dermatology. From here onwards residents in dermatology are included when "dermatologists" are mentioned.

A total of 300 dermatologists responded. The largest proportion of the respondents (66%) had a peripheral hospital as their primary work address, that is to say the work address at which most of the patients were treated. About 24% of the respondents worked at a teaching hospital, and the remaining 10% at a Healthcare centre or at another type of location. More than 61% were practicing dermatologists for 10 years or longer. A considerably smaller proportion of the responders were practicing dermatologists for either 5 to 10 years (18%), or 2 to 5 years (13%), or less than 2 years (8%).

About 11% of the respondents indicated to treat 20 to 50 patients with moderate to severe psoriasis per week. A larger proportion (37%) treated 10 to 20 patients per week. More than half of the dermatologists treated 10 patients or less per week.

More than half of the respondents reported that up to 30% of their patients with moderate to severe psoriasis would qualify for a systemic treatment or for phototherapy. Only a small proportion of the respondents indicated that 50% or more of their patients had moderate to severe psoriasis.

Use of fumaric acid esters in psoriasis vulgaris

189 (63%) of the responders indicated to prescribe FAE for the treatment of psoriasis. About 103 (35%) of the dermatologists indicated (almost) never to prescribe FAE. The most important reasons for not prescribing FAE were lack of experience during residency, no experience, and that FAE were not registered in the Netherlands.

From these about 20(19.4%) from the 103 respondents indicated that there were no thinkable circumstances under which they would be willing to prescribe FAE. The remaining 83 (81%) respondents were willing to prescribe FAE for patients who did not respond to other systemic therapies or when more clinical studies were under taken.

The 189 (63%) dermatologists who did prescribe FAE did so mainly because of good experiences with the therapy and because of few serious adverse events due to its long-term effectiveness and safety.

In the daily practice, FAE were generally prescribed as a mono-therapy or started as a mono-therapy and then combined. More than 120 (40%) of the respondents indicated to directly combine it mainly with topical vitamin D_3-preparations or topical corticosteroids.

Phototherapy

It appeared from the various types of phototherapy that were used at the dermatological out-patient department that UV-B therapy was the most popular followed by UV-B home therapy. PUVA, used either as bath or non-bath PUVA was almost never used by most of the dermatologists.

Systemic therapies

It appeared that oral methotrexate was used the most followed by cyclosporine and acitretin.

Etanercept (Enbrel®) was prescribed the most from the biologicals, followed by adalimumab (Humira®), infliximab (Remicade®) and the more recently available ustekinumab (Stelara®) to treat psoriasis.

Perception of systemic therapies

Finally, the picture of various systemic therapies with respect to their effectiveness, their safety, (not serious) adverse events and the general satisfaction was requested. It was mentioned for all criteria that it concerned the picture as a mono-therapy and that it involved "own experience" and did not involve the results of clinical investigations known to the respondents. On each of the 4 criteria, a report figure of 1 ("very poor") to and including 10 ("very good"), or that one had no experience with a certain therapy could be given per systemic therapy. The latter was not included in de next evaluation.

Effectiveness as mono-therapy

Biologicals are considered as the most effective therapy, whereby etanercept (Enbrel®) is considered to be slightly less effective than the other three Methotrexate (oral or via injection) is considered to be almost as effective as etanercept (Enbrel®). Cyclosporine in turn is considered to be somewhat less effective than methotrexate, but as somewhat more effective than FAE (Figure 1).

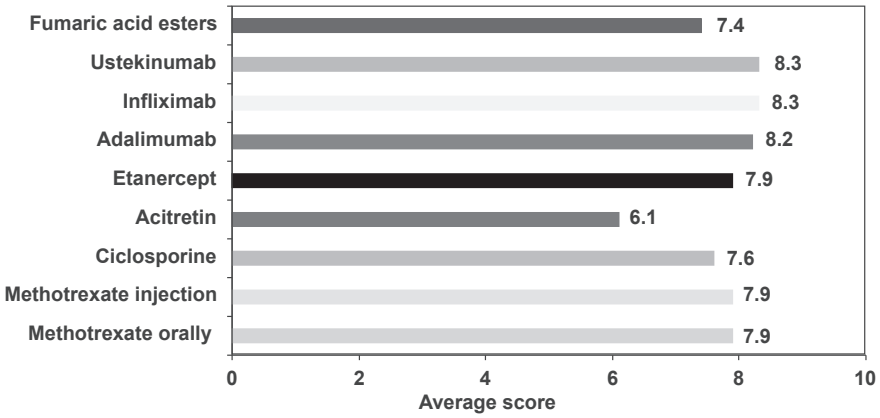

Figure 1. Perception of efficacy per treatment (as mono-therapy).

Safety as mono-therapy

Safety is defined here as "the absence of serious adverse events". FAE are regarded as the safest therapy for psoriasis vulgaris followed by the rest at some distance. The biologicals also lie close together in this respect, whereby infliximab (Remicade®) also scores somewhat lower than the rest of the biologicals in this respect. Cyclosporine has the worst score in the safety criterion (Figure 2).

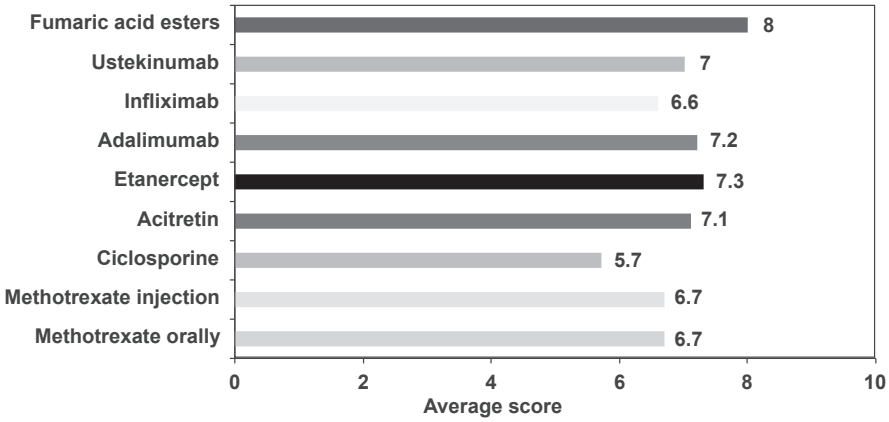

Figure 2. Perception of safety per treatment (as mono-therapy).

Adverse events as mono-therapy

The criterion "adverse events" was defined in the questionnaire as "the occurrence of non-serious adverse events". Respondents generally consider the biologicals to be slightly better than the other therapies. Similar to methotrexate, FAE are generally well-

tolerated by the patients according to the respondents. This is less valid for cyclosporine and acitretin (Figure 3).

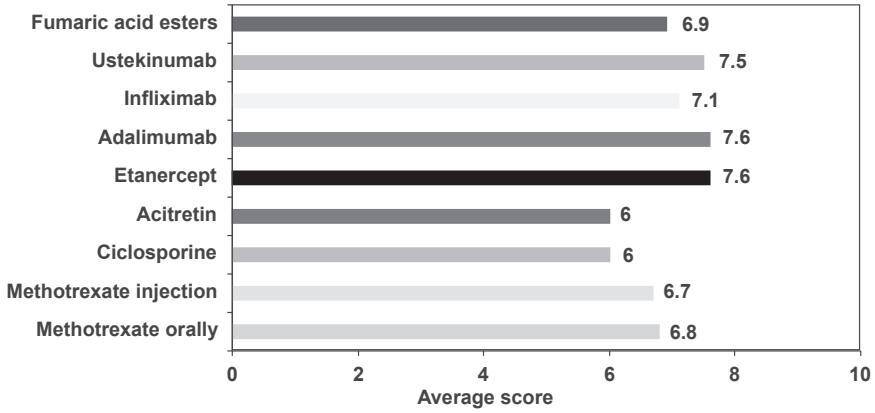

Figure 3. Perception of the adverse events per treatment (as mono-therapy).

Satisfaction as mono-therapy

The complete picture of the effectiveness, the safety and the adverse events is understood under "Satisfaction". It appears from Figure 4 that the various drugs differed very little form each other as far as the dermatologists were concerned. Only cyclosporine and acitretin scored lower than the rest, but still narrowly achieved an adequate.

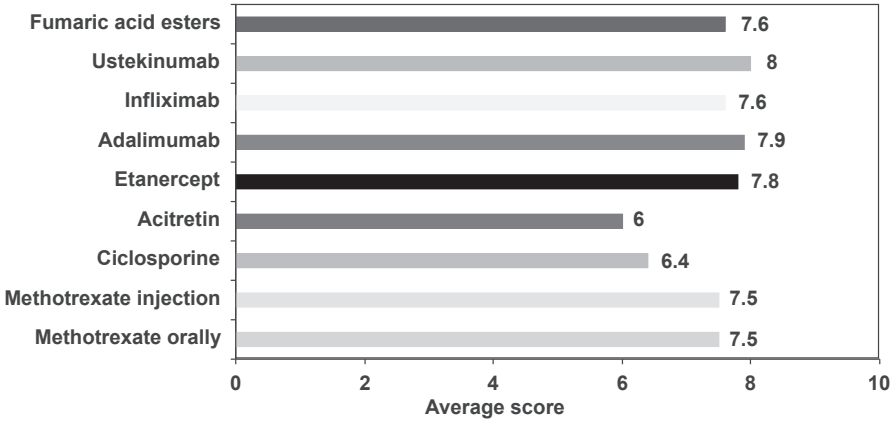

Figure 4. Overall satisfaction per treatment (as mono-therapy).

DISCUSSION

This survey was set-up to obtain an insight on the use of FAE in the Netherlands and to assess the attitudes of Dutch dermatologists towards the use of FAE. The position of FAE appeared to be more favourable than would be expected. A large proportion of the dermatologists in our survey indicated to prescribe FAE although they are not registered yet in the Netherlands and are magisterially prepared in the absence of industrial production according to good manufacturing practice (GMP) standards. The dermatologists who did prescribe FAE were generally satisfied to very satisfied.

This survey provides a clearer picture on the systemic therapies for psoriasis vulgaris on the basis of the high response rate. To our knowledge, a similar survey as that reported here has not been undertaken previously in the Netherlands. Nonetheless, this survey may have certain limitations. Our results may be biased because dermatologists who are in favour of using FAE were probably more inclined to participate in this survey than those who did not use FAE or reverse. We do not have data on non-responders. Therefore, we cannot fully exclude response bias.

FAE-therapy is considered to be effective, safe and without adverse events profile that is favourable in the daily practice also as compared with other systemic therapies such as methotrexate and biologicals. They are a relatively inexpensive, certainly as compared with biologicals. Based on this one can recommend registration of FAE and for its industrial production according to the GMP standards.

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Chapter 6

Induction therapy with a combination of fumarates and cyclosporine: a benefit for the patient?

S. Fallah Arani
H.A.M. Neumann
H.B. Thio

ABSTRACT

Fumarates or fumaric acid esters derivates (FAED) have appeared to be as effective and less toxic than other systemic treatments for psoriasis. Due to it's safe adverse event profile FAED can be used as a long-term maintenance therapy. One of the greatest reasons why FAED are not preferred as a first line treatment is that according to the recommended dosing schedule, clinically meaningful improvement is seen just after 6 to 8 weeks of therapy. In this manuscript we suppose an alternative induction scheme with a combination therapy of fumarates and cyclosporine for a more rapid improvement and better compliance.

A broad spectrum of anti-psoriatic treatments such as fumarates are available in the management of psoriasis. Evidence-based guidelines can be used for this however mostly only a tailor made treatment will fulfill patient's needs.[1] One of these needs is to achieve a more rapid reduction in the treatment with fumarates in moderate-to-severe psoriasis patients with a minimum of adverse events?

Fumarates or fumaric acid esters derivates (FAED) have appeared to be as effective and less toxic than other systemic treatments for psoriasis.[2,3] Due to it's safe adverse event profile FAED can be used as a long-term maintenance therapy.[4] One of the greatest reasons why FAED are not preferred as a first line treatment for moderate-to-severe psoriasis is that according to the recommended dosing schedule, clinically meaningful improvement is seen just after 6 to 8 weeks of therapy. This has an impact on the compliance, which already is affected by several adverse events such as flushing and nausea occurring in the induction phase of the FAED therapy. A quick induction of the clinical efficacy will increase the compliance and patients will be more willing to continue FAED therapy. Therefore we would like to propose an alternative induction dosage regimen, which includes a combination between FAED with another anti-psoriatic drug. Little is known about combinations of FAED with other systemic drugs. In some case reports successful combination with other systemic agents such as methotrexate and cyclosporine are reported, where FAED generally enabled the doses of the more hazardous drugs to be reduced.[3]

The European S3-guidelines on the systemic treatment for psoriasis vulgaris recommend cyclosporine primarily for induction therapy, because of its rapid efficacy.[1] Cyclosporine is a calcineurin inhibitor and immune modulator and inhibits the production pro-inflammatory cytokines and activity of T lymphocytes. Clinical improvement of psoriasis occurs after approximately 4 weeks, and maximum response is seen after about 8 to 16 weeks. [1] Cyclosporine would be the best candidate to combine with FAED for a rapid induction.

Therefore we would like to introduce an alternative starting dosage scheme for therapy with FAED and cyclosporine, which will give a quick satisfactory improvement of psoriasis with a relatively low adverse event profile:

FAED can be given according to the established dosage scheme (fig. 1) starting of with FAED 120mg once daily Next to FAED cyclosporine can be started with 5 mg/kg daily.

Since Wilsmann-Theis et al. have recently described 2 patients with severe psoriasis vulgaris being treated with a combination of FAED and cyclosporine whereby therapy with cyclosporine was stopped in one patient already after 6 weeks after achieving a PASI reduction from 12.0 to 3.0,[6] we expect a PASI 50% reduction after 2 weeks of treatment. Cyclosporine can be stopped after reaching 80% from the maximum dosage of FAED depending on the PASI reduction or with a PASI reduction of 50% but not later than week 12. FAED can be continued according to the established dosage scheme to

	120 mg dimethyl fumarate	Cyclosporine
	No. of tablets per day	mg/kg per day
Week 1	0-0-1	5
Week 2	1-0-1	5
Week 3	1-1-1	5
Week 4	1-1-2	5
Week 5	2-1-2	5
Week 6	2-2-2	5 (continue till 80% FAED dosage or week 12)
From week 12	decrease/increase with/to 1 or 2 tablets gradually depending on individual PASI reduction	STOP

Figure 1. Dosage induction scheme for FAED and cyclosporine

a maximum dosage of 740mg per day as a single treatment. We expect improvement of the PASI score (PASI 50%) after 2 weeks with 120mg FAED in combination with cyclosporine, which will enhance the overall adherence. The dosage of FAED is dependent on each individual patient and his/her response to therapy and can be managed during the long-term maintenance treatment by lowering or increasing de dosage with not more than 1 tablet of 120 mg daily per week.[4]

Laboratory, urine analyses, and blood pressure measurements are mandatory as usual.[3] Since FAED and cyclosporine are immunosuppressive agents screening for hepatitis B, C, HIV and active infections including history of recurring or persistent infections or underlying conditions that may predispose to infections (e.g. chest infections or previous septic joint in situ) and tuberculosis (Mantoux-test) are necessary before starting the therapy.

Recently cases of progressive multifocal leukoencephalopathy (PML) caused by JC virus have been reported in patients treated with FAED, therefore monitoring of the blood count is important, since FAED are known to induce lymphocytopenia and leucocytopenia.[5] If leucocytes drop below 3000/µL and lymphocytes below 500/µL, the dose must be reduced or the treatment stopped.[1]

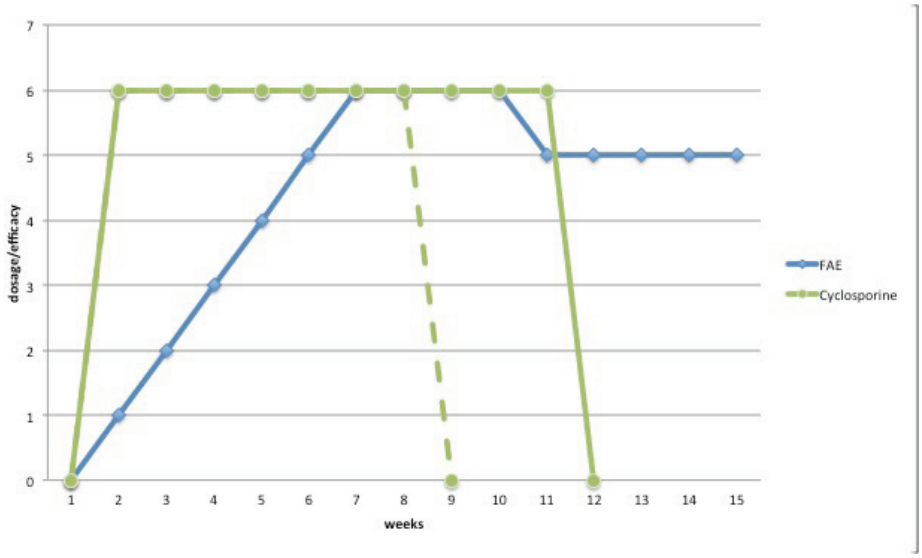

Figure 2. Dosage/efficacy of FAED and cyclosporine till week 12 and after:
Cyclosporine can be stopped whether after reaching 80% from the maximum dosage of FAED depending on the PASI reduction at week 12.
FAED can be continued according to the established dosage scheme to a maximum of 6 tablets of 120mg (740mg) daily and continued as a single treatment. Depending on the individual PASI reduction FAED can be gradually decreased to 1 or 2 tablets of 120mg (120 – 240 mg) daily as a maintenance therapy.

Although there is limited experience in combination therapy with FAED and cyclosporine [3,6], we believe that this alternative treatment induction scheme can be beneficial and a fast, cost-effective and safe alternative, especially compared to the more expensive biologic therapies. In the literature no evidence of any clinically significant drug interactions has emerged when FAED treatment was combined with cyclosporine, acitretin, hydroxyurea and methotrexate.[3] Nevertheless frequent laboratory monitoring is mandatory. This combination therapy is more cost-effective comparing to the expensive biologic therapies and can enhance efficacy and especially compliance, which often leads to discontinuation of therapy in patients with psoriasis.

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Chapter 7

Enteric-coated mycophenolate sodium (Myfortic ®) in psoriasis vulgaris: an open pilot study

S. Fallah Arani
R. Waalboer
T. Nijsten
H.A.M. Neumann
H.B. Thio

ABSTRACT

Background: Psoriasis is a chronic inflammatory T-cell mediated skin disease. Mycophenolate mofetil is a well known immunosuppressive agent in transplantation medicine. The efficacy of enteric-coated mycophenolate sodium (EC-MPS) was confirmed in other inflammatory skin diseases, including atopic dermatitis and subacute cutaneous lupus erythematosus.

Objective: To investigate the efficacy and the tolerability / short term safety of enteric-coated mycophenolate sodium (EC-MPS) in patients with moderate to severe chronic plaque psoriasis.

Patients and methods: An open label pilot study in which 20 patients with a Psoriasis Area and Severity Index (PASI) $\geq$10 received EC-MPS 720 mg twice daily for 6 weeks followed by 360 mg twice daily for another 6 weeks. Patients who completed the 12-weeks of treatment were followed up for an additional 12 weeks. Treatment outcomes were assessed with PASI50% and PASI75%.

Results: 18 males and 2 females (mean age 46 years) entered the study. 65% (13/20) finished the treatment period. In week 6, no patient achieved PASI75% and 8/20 patients achieved a PASI50%. Compared to week 6, 4/13 showed a deterioration of their psoriasis at week 12. 25% (2/8), achieved a PASI 75% in week 24. The most reported adverse events were itching (30%), diarrhea (10%) and a reversible elevation of the triglycerides level.

Conclusion: EC-MPS does not seem effective as monotherapy for moderate to severe psoriasis, but might be used at a dosage of 1440mg daily in well-selected patients with treatment resistant psoriasis. The treatment was reasonably tolerated with no serious adverse events.

INTRODUCTION

Psoriasis is a chronic inflammatory, T-cell mediated, skin disease that worldwide affects 2% of the population (ref Stern et al, 2004). Currently there are several topical and systemic treatment options for psoriasis. Whereas topical treatments are usually prescribed when skin lesions are confined to small areas, phototherapy and systemic treatments are used when extensive involvement of the skin is present. Potentially serious adverse effects often hamper the continuous use of some systemic antipsoriatic agents.

Mycophenolate mofetil (MMF) is an immunosuppressive drug containing mycophenolic acid (MPA) as the active substance. It is widely used in the prevention of organ allograft rejection [1]. More recently its use has been expanded to successfully treat several autoimmune and inflammatory skin disorders, including atopic dermatitis, subacute cutaneous lupus erythematosus (SCLE) and psoriasis [2, 3]. MPA is a potent and selective inhibitor of IMPDH (inosine monophosphate dehydrogenase), the control enzyme of the de novo synthesis of guanosine nucleotides in purine metabolism, and hence also a potent inhibitor of DNA and RNA synthesis in activated T cells [4]. Inhibition of lymphocyte proliferation reduces this predominant inflammatory cell type in psoriatic lesions and indirectly reduces the hyperproliferation of epidermal keratinocytes. A number of adverse effects are associated with the use of MMF such as hematological disorders, lymphoproliferative disease, increased risk of opportunistic infections (particularly cytomegalovirus) and gastrointestinal (GI) disorders (e.g. nausea, vomiting, diarrhea and gastritis), which limits its widespread use in clinical settings. To reduce the GI adverse events of MMF, enteric-coated mycophenolate sodium (EC-MPS), a prodrug of MMF, was designed that delays the release of MPA until reaching the small intestine. At a dose of 720 mg, EC-MPS exhibits equivalent MPA exposure and maximal MPA concentration to MMF 1000 mg [5]. Studies have confirmed that patients with a maintenance MMF dosage regimen can be safely converted from MMF to EC-MPS without change in efficacy or safety profile. Therefore, EC-MPS appears to be a valid alternative MPA therapy with a comparable efficacy and safety profile to MMF with improved GI tolerability [5]. If effective, EC-MPS may be useful for psoriasis patients contraindicated or resistant to other conventional and systemic drugs. The choice for the systemic treatment of psoriasis beside biologicals is mainly limited to Methotrexate (MTX) and cyclosporine. There is certainly a need for more drugs, especially those with a favorable risk/benefit ratio. For this reason we studied the possible role of MPA in psoriasis treatment.

PATIENTS AND METHODS

Study population

Patients were eligible to enter this open label study if they were at least 18 years of age and had a clinical diagnosis of moderate to severe stable psoriasis vulgaris (PASI > 10) at baseline. Consecutive patients at the Department of Dermatology of Erasmus MC were screened and invited to participate. Subjects were excluded if they had any other chronic internal diseases, chronic co-medication, were female and pregnant or breastfeeding or considering becoming pregnant during the study, had a history of clinically significant drug or alcohol abuse in the last year, had a positive test result for hepatitis B, C or HIV, had a history of opportunistic infections and are known to have a hereditary deficiency of the hypoxanthineguanine-phosphoribosyl-transferase (HGPRT).

All subjects provided written informed consent before inclusion into the study. The medical ethical commission of the Erasmus Medical Center Rotterdam approved the study protocol.

Study design and methods

All eligible subjects received open-label oral EC-MPS 720 mg twice daily for 6 weeks followed by 360 mg twice daily for 6 weeks, according to a previous treatment protocol. This study followed the treatment protocol as previously reported by Geilen et al. in their clinical trial with MMF [9]. Subjects were not permitted to use any active topical or other systemic antipsoriatic therapy, except indifferent emollients during the period of the study from baseline till week 24. Subjects discontinued any systemic antipsoriatic treatment for 4 weeks and any topical antipsoriatic treatment for 2 weeks prior to study entry ('wash out period'). Women who are not using oral contraception were required to be taking contraceptive drugs during the study and to agree to continue this until at least 6 weeks after completion of the study.

PASI 75% and PASI 50% at week 6 and 12 were used as primary endpoints and were both followed up till week 24. The relapse rate was also assessed at week 24. Clinical and laboratory assessments were performed at baseline and weeks 2,4,6,8 and 12 and follow-up in week 24. Clinical assessments included standard physical examination and PASI-score at baseline, every two weeks during the treatment period (0-12 week) and at the end of the follow up period (week 24) or at time of withdrawal by the same investigator and one research nurse. [6] Laboratory tests included liver enzymes (g-glutamyltransferase, aspartate aminotransferase), renal parameters (urea, creatinine), blood cell count, lipids, CRP and BSE. At each scoring visit patients were questioned regarding adverse events using a standardized format. Tolerability was assessed throughout the study, including analysis of adverse events, potential infections, and premature withdrawal from the study.

Table 1. Patients characteristics and pasi-scores.

			PASI - SCORE											
PATIENT	SEX	AGE	WEEK 0	WEEK 6		WEEK 12		WEEK 24	FOLLOW-UP WEEK 12-24 PASI 50-75%	DISCONTINUATION OF THERAPY OR FOLLOW-UP	REASONS OF DISCONTINUATION	ADVERSE EVENTS	PRIOR MEDICATION	
					PASI 50%		PASI 50%						TOPICAL	SYSTEMIC
1	F	51	13.2	6.3	+	6.4	+	6.5	+			itch	calcipotriol/calcitriol, corticosteroids	none
2	M	46	22.2	10.6	+	8.1	+	6.2	+				calcipotriol/calcitriol, corticosteroids	UVB, PDL, fumarates, LFA 3/IgG
3	M	40	24.2	26.9	-	-	-	-	-	week 8	worsening	itch, diarrhea, pain	calcipotriol/calcitriol, corticosteroids	UVB, PUVA, methotrexate cyclosporine, fumarates
4	M	62	12.6	11.2	-	5.5	+	3.1	+				calcipotriol/calcitriol, corticosteroids, tazarotene	UVB, PUVA, methotrexate cyclosporine, fumarates, etanercept
5	M	72	41.1	28.2	-	32.2	-	-	-	week 16	non-responding		calcipotriol/calcitriol, corticosteroids	UVB, PUVA, methotrexate cyclosporine, fumarates, acitretine
6	F	45	28.4	14.4	+	32.8	-	-	-	week 16	relapse		calcipotriol/calcitriol, corticosteroids	UVB, bath-PUVA, methotrexate, fumarates
7	M	37	16	18.7	-	-	-	-	-	week 8	non-compliance	tiredness, itch	calcipotriol/calcitriol, corticosteroids	UVB, methotrexate, fumar etanercept
8	M	35	19	16.3	-	10.1	-	13.6	-				calcipotriol/calcitriol, corticosteroids	UVB
9	M	37	22.9	23.9	-	-	-	-	-	week 8	non-compliance		calcipotriol/calcitriol, corticosteroids	UVB, PUVA
10	M	27	18.2	6.5	+	17.2	-	-	-	week 16	relapse + use of calcipotriol	abdominal pain, headache	calcipotriol/calcitriol, corticosteroids	UVB, PDL
11	M	53	45.8	14.5	+	3	+	21	-				calcipotriol/calcitriol, corticosteroids	UVB, PUVA, methotrexate cyclosporine, fumarates, acitretine, etanercept
12	M	26	17.8	8.2	+	11.4	-	-	-	week 16	relapse	conjunctivitis, dry mouth	calcipotriol/calcitriol, corticosteroids	UVB
13	M	46	14	7.5	+	8.9	-	3.7	+				calcipotriol/calcitriol, corticosteroids	UVB, cyclosporine, fumara efalizumab
14	M	43	15	13.7	-	-	-	-	-	week 7	liverfunction-elevation		calcipotriol/calcitriol, corticosteroids	UVB, PUVA, methotrexate cyclosporine, fumarates, acitretine, etanercept
15	M	38	28.8	-	-	-	-	-	-	week 1	side-effects	headache, itch, diarrhea, pain	calcipotriol/calcitriol, corticosteroids	UVB, fumarates, etanerce
16	M	46	18.8	9.7	+	8.2	+	-	-	week 17	non-compliance		calcipotriol/calcitriol	UVB
17	M	67	13.8	9.9	-	8.4	-	10	-			itch, throat pain	calcipotriol/calcitriol, corticosteroids	UVB, PDL, cyclosporine
18	M	47	18.6	25.4	-	-	-	-	-	week 8	worsening		calcipotriol/calcitriol, corticosteroids	UVB, methotrexate, etane
19	M	46	11.5	9.8	-	10	-	13.4	-			tiredness	calcipotriol/calcitriol, corticosteroids	UVB
20	M	49	35.1	22.1	-	-	-	-	-	week 6	non-responding	itch	calcipotriol/calcitriol, corticosteroids	PUVA, methotrexate, cyclosporine, fumarates, etanercept

RESULTS

Study population

In total, 20 patients (18 males, 2 females) with severe plaque psoriasis with a mean PASI 21.9 ± 9.6 (age 45.8 ± 11.5) were enrolled in this study. Of the 20 enrolled patients, all had used several topical antipsoriatic therapies (i.e., glucocorticoids, calcipotriol, calcitriol, tazarotene), 3 had received treatment with pulsed dye laser, 19 ultraviolet-B (UVB), 14 patients had been treated earlier with conventional systemic agents and 8 patients had used biologicals. (Table 1)

Clinical efficacy

At baseline, the mean PASI was 21.9 ± 9.6 (age 45.8 ± 11.5). After the first 6 weeks of high dose EC-MPS, the mean PASI was 14.9 ± 7.21(age 28.2 ± 6.3) and 8/20 patients achieved a PASI50%, but no patients scored a PASI75%. A worsening of PASI was observed in 4 patients. Between week 6 and 12 the dose of EC-MPS was reduced by half (from 1440mg to 720mg daily) for the subsequent 6 weeks. At week 12, one patient achieved PASI75%. Of the 13 patients who were assessed at week 12, 4 showed a deterioration of their psoriasis compared to week 6. 8 patients completed the treatment and the 24-week follow-up period. 2/8 patients (25%) achieved a PASI 75% in week 24.

The relapse rate of the 8 patients who completed the 24-week follow-up period is 25% (2/8 patients).

Short term safety

The most commonly self-reported adverse events were itching (30%) and diarrhea (20%). One patient discontinued therapy in week 1 due to side effects such as headache, itch, pain and diarrhea. Of the laboratory test, a reversible elevation of the triglycerides level was noted in 6 patients and cholesterol levels in 2 patients. At week 7, one patient discontinued therapy because of mild liver dysfunction (γ-GT 102 U/l, ASAT (GOT) 43 U/l). No other laboratory abnormalities were observed during the study period in the followed patients.

Follow up

Of the 20 eligible subjects, 13 patients finished the treatment period of 12 weeks and only 8/13 patients completed the 24-week open-label study. Seven patients discontinued therapy before week 12. 5 patients were lost to follow-up. (Table 2) 40% (n=8) completed the study (week 0-24), 65% (n=13) finished the treatment period (week 12), 35% (n=7) discontinued the study before week 12 due to worsening (10%, n=2), non-compliance (10%, n=2), liver dysfunction (5%, n=1%) and side-effects (5%, n=1). 25%

(n=5) were lost to follow-up due to non-responding (5%, n=1), relapse (15%, n=3) and non-compliance (5%, n=1).

DISCUSSION

To our knowledge, this is the first study using EC-MPS to treat patients with moderate to severe chronic plaque psoriasis.

The results of this small open label pilot study showed that this two-dose EC-MSP regimen was not effective in the treatment of moderate to severe psoriasis. The higher dose of EC-MPS (1440 mg daily) appeared to be more effective than the low dose, because several patients' psoriasis worsened after dose reduction. Some case reports and short series of patients have revealed the efficacy of MMF in the treatment of moderate-to-severe psoriasis [7-13]. At usual doses, MMF is generally well tolerated. Compared to other immunosuppressants, such as methotrexate and cyclosporine, the lack of end-organ toxicity with MMF offers an important therapeutic advantage. Pedraz et al compared MMF with cyclosporine in a prospective, cross-over, non-randomized, two-phase, open label study the efficacy and toxicity of MMF with cyclosporine in 8 patients with moderate-to-severe chronic plaque psoriasis for 16 weeks. They concluded that cyclosporine is more effective, fast, and predictable in its effect than MMF to control moderate-to-severe chronic plaque psoriasis, and that both drugs are well tolerated in short courses of treatment [7]. The most common side-effects of MMF include gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation and dyspepsia) and bone-marrow suppression (mainly leukopenia), which are generally seen in patients receiving more than 2 g daily or who simultaneously receive other immunosuppressants. Comparative data for EC-MPS and MMF are mainly available in renal transplant patients, but not in psoriasis. EC-MPS recipients had a lower rate of serious infections and serious pneumonia. GI symptoms in MMF recipients reduced significantly when being switched to EC-MPS. GI tolerability in a randomized, double blind, multinational trial showed no difference between MMF and EC-MPS. [14, 15]

However in dermatological practice there are no comparative studies for adverse events. One prospective study with MMF involving 23 psoriasis patients showed 5 patients (22%) with transient and mild GI symptoms. One patient developed pruritus and another angioedema. Only one patient developed laboratory abnormalities (mild leukopenia). [16] Another study involving 8 patients reports anorexia, constipation, insomnia, meteorism, nausea, palpitations and polyuria. Every adverse event reported occurs only once. [7] A recent review of Orvis et al shows GI complaints (nausea, diarrhea, vomiting, abdominal pain, soft stools, anal tenderness, frequent stools and constipation) up to

20% of patients using MMF. Hematological adverse events (anemia, leucopenia and thrombocytopenia) occur in less than 5%. [17]

Adverse events that occurred in our 20 patients receiving the therapy were acceptable, with no serious adverse effects regarding the severity and history. The most common adverse events were itching, diarrhea and a reversible elevation of the triglycerides level. In a study with EC-MPS in patients with atopic dermatitis (AD), there was no itch reported as adverse event, while in our study 6 patients reported itch. [18] This is most likely caused by the more severe pre-existing itch in AD patients.

Overall, treatment of patients with moderate-to-severe psoriasis vulgaris with EC-MPS 720 mg twice daily may be useful therapeutic in psoriatic patients unresponsive to or intolerant of other conventional treatments and the biologicals. A study with high dose EC-MPS in long-term treatment of patients with moderate-to-severe psoriasis vulgaris is neccesary.

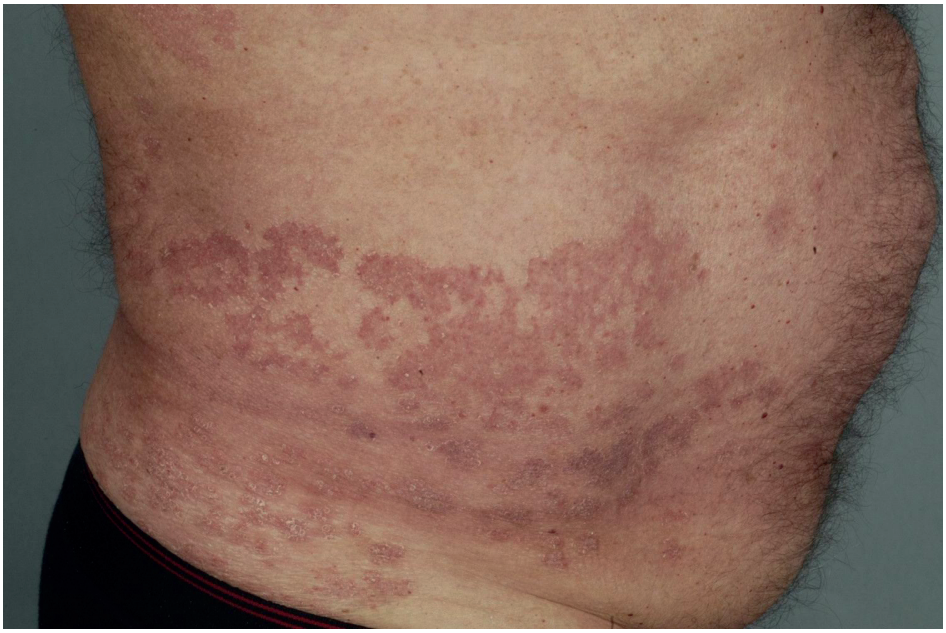

Figure 1 Improvement of psoriasis after 4 weeks of treatment

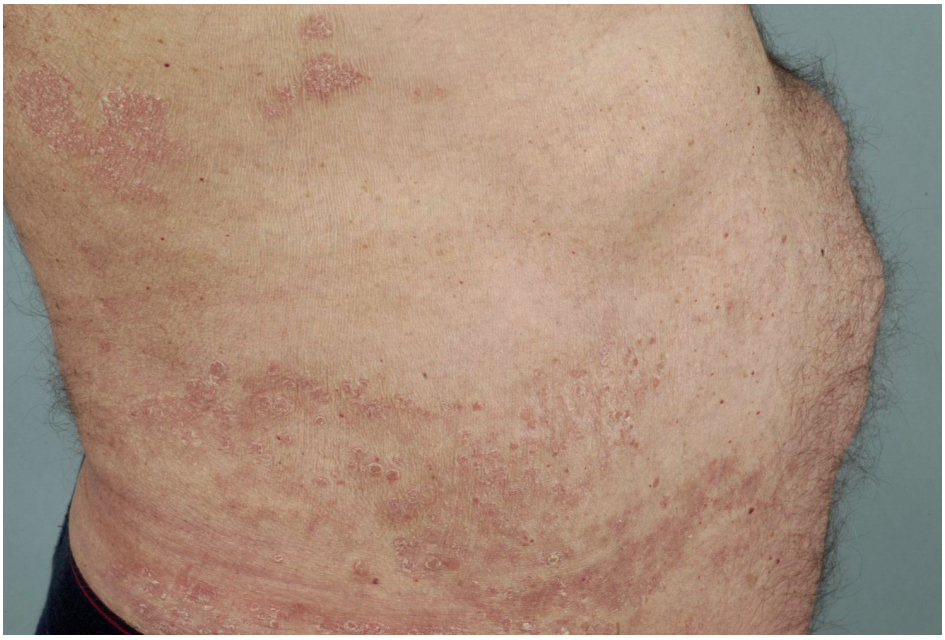

Figure 2 Improvement of psoriasis after 10 weeks of treatment

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Chapter 8

General Discussion and future directions

In this era of expensive biologics, which have gained popularity as safe, effective, and convenient therapies for the treatment of chronic, moderate to severe plaque psoriasis, costs play an important role in the decision making with regard to therapy for psoriasis. Sizto et al. reported in their meta-analysis that methotrexate (MTX) and ciclosporine were the most cost-effective treatments for moderate to severe psoriasis.[1] However, despite being the most cost-effective options, neither MTX nor ciclosporine is recommended for prolonged use in the majority of patients because of their high potentials for long-term toxicity. Therefore, there is a great need for effective and low-cost treatment, such as fumarates (FAE), as compared with biological treatments with long-term efficacy and safety. Thus, we first investigated the overall efficacy and safety of FAE.

In Chapter 2 we summarized and critically evaluated the current evidence of the efficacy, effectiveness, and safety of FAE in the treatment of psoriasis. In total, 35 studies published between 1987 and 2014 and involving 3372 patients were included in this review. The available evidence of randomized controlled trials (RCTs) was limited. Six RCTs were available with relatively small sample sizes. Overall, data from the included RCTs seem to indicate that mean PASI decreases 42% to 66% following 12 weeks of FAE treatment. Gastrointestinal and flushing symptoms were usually reported during the first three months of FAE treatment and then typically decreased over time. However, several case reports were found that described rare adverse events associated with FAE treatment, such as an important and rare complication of progressive multifocal leukoencephalopathy (PML) recently described in patients with FAE treatment for multiple sclerosis and severe lymphocytopenia. We concluded that FAE can be used as a suitable, effective, cheap, and safe treatment for moderate to severe psoriasis. However a simple but adequate monitoring of the patient is mandatory.

When we compare our findings to the current literature, we see that Zweegers et al. [3]showed in their systematic review of real-world evidence on the effectiveness of biologics (adalimumab, etanercept, infliximab, and ustekinumab) and conventional therapies (acitretin, cyclosporine, FAE, and MTX) that, in the included retrospective studies, between 40% and 49% of patients treated with 10–20 mg of MTX weekly achieved PASI 75 at week 12[4, 5]; PASI 75 response was attained at week 12 by 27% of patients treated with a mean dose of 0.38 mg/kg/day of acitretin, 46% of patients treated with ciclosporine,[5] and 47% of patients treated with FAE.[4] This review showed a similar efficacy of FAE compared to other conventional therapies. Our findings also concur with a recent Cochrane review from Atwan et al., which included six RCTs that involved 544 participants.[6] Five RCTs compared FAE with a placebo, and our study was the only RCT that compared FAE with MTX. The researchers concluded that the evidence indicates that oral FAE is superior to the placebo and may be similar in efficacy to MTX.

As previously mentioned, we compared FAE to the "gold standard" MTX to evaluate its efficacy and safety. MTX was the first drug approved by the US Food and Drug Admin-

istration for the treatment of psoriasis, at a time (i.e., 1972) when there were no well-designed studies of this agent. Despite the availability of newer biologic therapies, MTX has remained the gold standard systemic therapy for psoriasis for nearly five decades due to its efficacy and cost-effectiveness.[7] Although MTX is known to be an effective treatment for psoriasis, it is also known for its serious side effects, such as hepatotoxic and teratogenic effects, and its interactions with many other drugs. Recently, the Dutch public health authority issued a warning to medical professionals, particularly oncologists, rheumatologists, and dermatologists, about the use of MTX and its fatal adverse events, generally through prescription errors, overdoses, and lack of monitoring.[8]

In Chapter 3, we demonstrated that FAE and MTX were equally effective. After adjusting for baseline values, the absolute difference (FAE minus MTX) in the mean values at 12 weeks was 1.4 (95% confidence interval; -2.0 to 4.7; P = 0.417).

Inzinger et al. showed consistent findings in their retrospective analysis, whereby they compared the primary efficacy of MTX versus FAE under daily life conditions in patients with moderate to severe psoriasis treated with those drugs over a seven-year period.[4] Among patients who completed at least three months of treatment, the response to primary treatment with MTX versus FAE did not differ significantly at any point in time. In the intention-to-treat worst-case analysis at month 3, complete remission rate, PASI90, PASI75, and PASI50 rates were 6%, 7%, 24%, and 39% in MTX-treated patients versus 1%, 5%, 27%, and 44% in FAE-treated patients.

Not much is known about the effect of FAE in the treatment of arthritis psoriatica. A small RCT of FAE in the treatment of psoriatic arthritis shows minimal improvement of the arthritis.[9]

We can conclude that FAE is as effective and yet safer to use for psoriasis vulgaris with a more favorable benefit/risk ratio compared to MTX.[10] Therefore, we recommend FAE as a suitable first-line therapy for moderate to severe psoriasis,[11] as it is currently being used as in Germany.[12] Still, many dermatologists prefer UVB phototherapy as a first-line treatment for moderate psoriasis in adult patients,[13] despite the large body of evidence confirming the mutagenic and immunosuppressive effects of UVB radiation in vitro[16–20] and extended UVB exposure seems to be one of the major risk factors in the induction of non-melanoma skin cancer in mice and humans.[21–24] This is why we especially recommend the use of FAE in young adults before or instead of using UVB phototherapy. Furthermore, treatment with FAE is straightforward. The tablets are taken up to three times daily. Only simple routine examinations are needed, while UVB phototherapy is time-consuming for the patient and frequent sessions are difficult for employed persons. For fragile or disabled patients, phototherapy while standing is not feasible either.

	Pros	Cons
UVB phototherapy	- effective - can be combined with other systemic therapies - only a few side-effects (e.g.burning)	- high risk factor: induction of non-melanoma skin cancer - For fragile or disabled patients, phototherapy while standing is not feasible - time-consuming, 2-3xweek for approximately 32 treatments, which is difficult for employed persons
FAE therapy	- effective - safe - straightforward (tablets are taken up to 3 x/daily) - only simple routine examinations are needed - no drug interactions - eligible as longterm therapy on a low dosis (1-2 tablets a day)	- Adverse events: gastrointestinal complaints, flushing - Long induction period

Another reason why FAE should be used as a first-line therapy for moderate to severe psoriasis is because FAE does not show any interactions with metabolic drugs, like MTX or other systemic treatments.[14, 15] Patients with psoriasis are known to have comorbidities such as high alcohol consumption, obesity, hepatitis, and diabetes mellitus.[16] Dermatologists need a treatment that is effective, eligible for long-term treatment, and safe but does not interact with patients' co-medications. Different drugs interact with MTX, and many patients with psoriasis have comorbidities whose combination lead to a higher risk of hepatotoxicity, which is in itself also a contraindication of MTX. Consequently, its clinical application is restricted by severe adverse drug reactions, including hepatotoxicity, bone marrow suppression, and gastrointestinal ulcerations. The precise selection of and frequent follow-up with each patient are necessary with MTX, which is not the case for FAE. Therefore, FAE can be given to a broad patient population.

However, an important limitation of therapy with FAE is the intolerable adverse events that lead to the discontinuation of therapy in 30%–40% of patients.[11, 17] The most common cause of early treatment discontinuation is intolerable gastrointestinal symptoms and, to a lesser extent, flushing symptoms. These relatively inconvenient side effects occur predominantly during the first few weeks of FAE treatment and require thorough education of the patient.[14] In order to improve the tolerability of FAE, the current guidelines recommend slowly increasing FAE dosage using a standardized progressive dosing regimen.[10, 14] In this dosing regimen, the maximum daily dosage of 720 mg of FAE is reached within 9 weeks. If patients have adverse events, it is advised that they increase the dosage more slowly, decrease the dosage, or temporarily stop using the FAE.

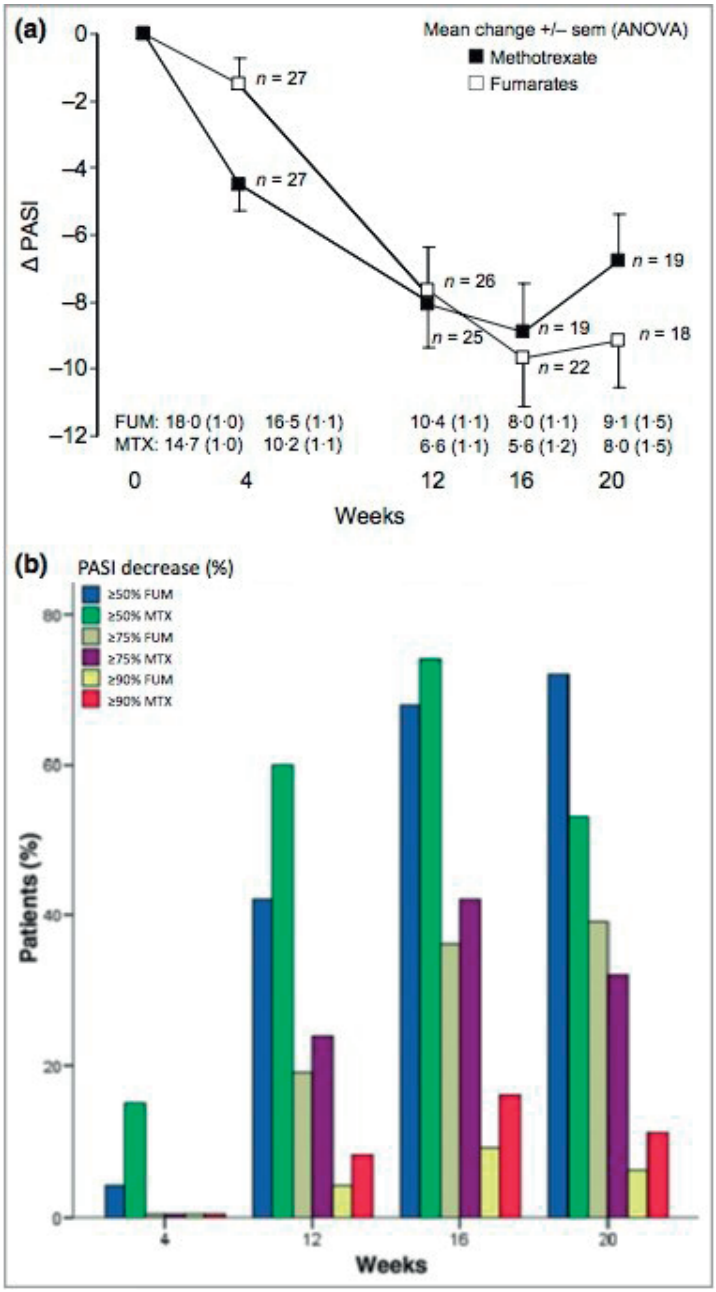

Fig 1. Clinical response to treatment expressed as the change from baseline Psoriasis Area and Severity Index (PASI) over time. FUM, fumarates group; MTX, methotrexate group. Mean ± SE changes in PASI during treatment and follow up are shown. The mean values of PASI, with SE in parentheses, at the various time points are shown at the bottom. (b) The proportions of patients randomly assigned to receive either fumarates or methotrexate until week 20 at each time point, according to various degrees of improvement (50%, 75%, 90%) in PASI. [1]

Getting back to the question posed in the introduction, if the adverse events such as gastrointestinal complaints and flushing were histamine induced, we speculated in Chapter 4 that adding a daily dosage of 10 mg of cetirizine, a histamine 1 (H1) blocker, to FAE would reduce the FAE-induced adverse events. However, we found that the addition of cetirizine did not reduce the incidence of adverse events compared with a placebo (84% vs. 84%, P = 1.00).[18] The types of adverse events were no different between the cetirizine and placebo groups, the most common being gastrointestinal complaints (68% vs. 64%) and flushes (60% vs. 48%). The proportion of patients discontinuing treatment was not statistically different between the cetirizine and placebo groups (24% vs. 32%, P = 0.53). Thus, we could speculate that the mechanisms underlying FAE-induced gastrointestinal and flushing symptoms likely involve mediators other than a histamine, and a histamine may play only a minor role in the generation of adverse events associated with FAE. Another explanation could be that the dosage of cetirizine used in our trial was too low, and patients would benefit more from an intake of 10 mg of cetirizine twice daily, such as is sometimes used with chronic urticaria.[19] The manufacturer of cetirizine recommends a dosage of 10 mg daily, and it is permissible to increase the dose up to 20 mg daily. As cetirizine inhibits histamine-induced reactions dose-dependently,[20] it is plausible that higher doses of the drug will be more effective in controlling the gastrointestinal and flushing symptoms.

Overall, we can conclude that the mechanisms underlying the adverse events induced by FAE are not fully understood, except for the flushing. Recent experimental studies show that FAE-induced flushing is mediated through the activation of the G-protein-coupled receptor GPR109A, located on Langerhans cells and on keratinocytes, which leads to prostaglandin release via cyclooxygenase-1 and -2 enzymes.[21] Further evidence of this mechanism comes from a clinical trial involving 56 healthy volunteers, in which aspirin, a cyclooxygenase inhibitor, decreased the incidence and severity of flushing symptoms from dimethylfumarate.[22]

However, the mechanisms leading to gastrointestinal complaints in FAE treatment are less understood. One hypothesis involves the FAE-triggered release of tumor necrosis factor (TNF)-a as a mechanism leading to gastrointestinal complaints. In a previous clinical study, co-treatment with FAE and pentoxifylline, a methylxanthine derivative with some anti-TNF-a properties, reduced the frequency of gastrointestinal complaints.[23] However, this study was open label and uncontrolled, so the bias of these results cannot be excluded. Another potential mechanism may involve dimethylfumarate-induced allergic contact mucositis of the gastrointestinal tract.[24]

Indeed, it is important to mention that, since 2013, several cases of progressive multifocal leukoencephalopathy (PML) have been reported during treatment with FAE.[25-35] PML is a severe, life-threatening condition caused by the John Cunningham (JC) virus. Antibodies against the JC virus are detectable in more than 80% of adults.[36]

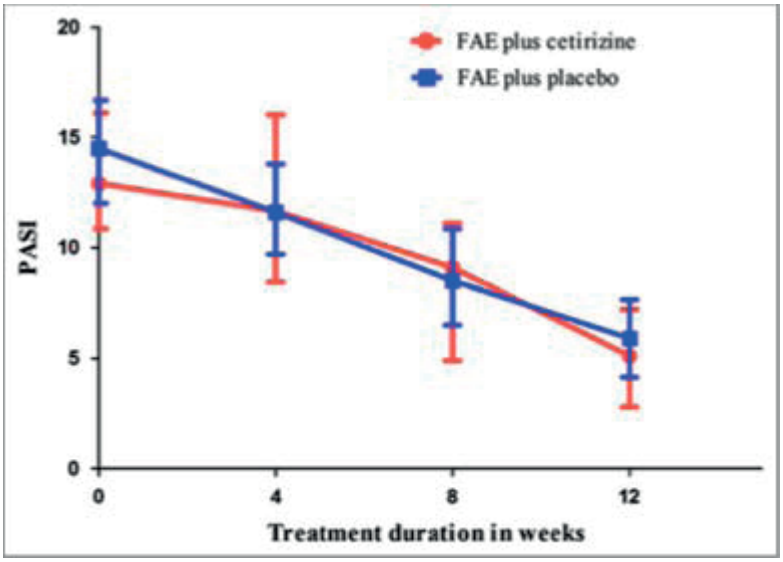

Figure 2. Changes in Psoriasis Area and Severity Index (PASI) during 12 weeks of fumaric acid ester (FAE) treatment in patients treated with FAE plus cetirizine (n = 25) or FAE plus a placebo (n = 25). Error bars show medians and interquartile ranges.[152]

PML is most probably caused through the reactivation of the latent virus.[37] The most common causes of reactivation are hematological malignancies, inflammatory diseases such as sarcoidosis, HIV infection, immunosuppressive therapy, and treatment with immunomodulatory drugs such as monoclonal antibodies (e.g., natalizumab, efalizumab, rituximab).

Still, the occurrence of PML as a result of therapy with FAE for the treatment of psoriasis is very rare. Only five case reports have been published in the literature since 2014,[26, 29, 31-34] and nine reports of PML with the use of FAE are included in the Global Individual Case Safety Reports database (Vigibase) of the World Health Organization as well as two other case reports at the Netherlands Pharmacovigilance Centre Lareb. However, extra vigilance is needed, as it is a serious condition. Prolonged lymphocytopenia could likely play a causative role in the development of PML.

Recently, the European Medicines Agencies (EMA) also reviewed cases of PML occurring with a mixture of dimethylfumartes and monoethylfumarates salts (Fumaderm®, Fumapharm AG, Switzerland) and dimethylfumarates (Psorinovo®, GMP pharmacy Mierlo-Hout, Netherlands). Based on their review, they supported the recommendations of the European S3-Guidelines on the systemic treatment of psoriasis. According to the recommendations, before starting treatment, a complete blood count should be performed; in the presence of values outside the normal range, treatment should not be started. Furthermore, blood cell counts should be monitored every four weeks during

treatment; if the lymphocyte count drops below $0.7x10^9$/L, the dose should be halved. If during a follow-up check after four weeks the lymphocyte count remains below this value, then treatment must be discontinued. If therapy is continued in the presence of a lymphocyte count below $0.7x10^9$/L, the risk of PML cannot be ruled out. We can strongly advise dermatologists to follow these recommendations.

We know that FAE is one of the most commonly used systemic treatments for psoriasis in Germany, where they are only licensed for the treatment of moderate to severe psoriasis as an effective, safe, and cost-effective long-term therapy.[38] Despite the fact that FAE is not registered in the rest of the world, it is increasingly being used as unlicensed treatment in several European countries, including the UK,[39] Ireland,[11] the Netherlands,[2] Austria,[40] and Italy.[41, 42]

To obtain better insights into the use of FAE by Dutch dermatologists in the Netherlands, we conveyed in Chapter 5 a cross-sectional postal survey. The results of this survey demonstrated that FAE is popular in use amongst Dutch dermatologists. A total of 189 (63%) of the responders indicated that they prescribed FAE for the treatment of psoriasis, whereas 103 (35%) of the dermatologists indicated (almost) never prescribing FAE. The most important reasons for not prescribing FAE were lack of experience during residency, no experience, and FAE not being registered in the Netherlands. Twenty (19.4%) of the 103 respondents indicated that there were no thinkable circumstances under which they would be willing to prescribe FAE. The remaining 83 (81%) state they would be willing to prescribe FAE for patients who did not respond to other systemic therapies or when more clinical studies were under taken. The 189 (63%) dermatologists who did prescribe FAE did so mainly because of positive experiences with the therapy and because of few serious adverse events due to its long-term effectiveness and safety.

Overall, a large proportion of the dermatologists in our survey indicated prescribing FAE, although it is not registered yet in the Netherlands and are magisterially prepared in the absence of industrial production according to good manufacturing practice (GMP) standards.

At this point, we know and have proven that FAE is an effective and relatively safe treatment for psoriasis and that FAE is used by dermatologists for the treatment of psoriasis despite the fact that it is not licensed. We also identified two main reasons why some dermatologists are hesitant to prescribe FAE; in addition to the sometimes very inconvenient adverse events, such as gastrointestinal complaints and flushing, there is a long induction period whereby clinically meaningful improvement is seen just after 6 to 8 weeks of therapy. This has an impact on compliance, which is already affected by several adverse events, such as flushing and diarrhea occurring in the induction phase of the FAE therapy.

In Chapter 6, we hypothesized that the introduction of an induction-combination therapy with FAE and ciclosporine, with its rapid efficacy, could offer a good alternative

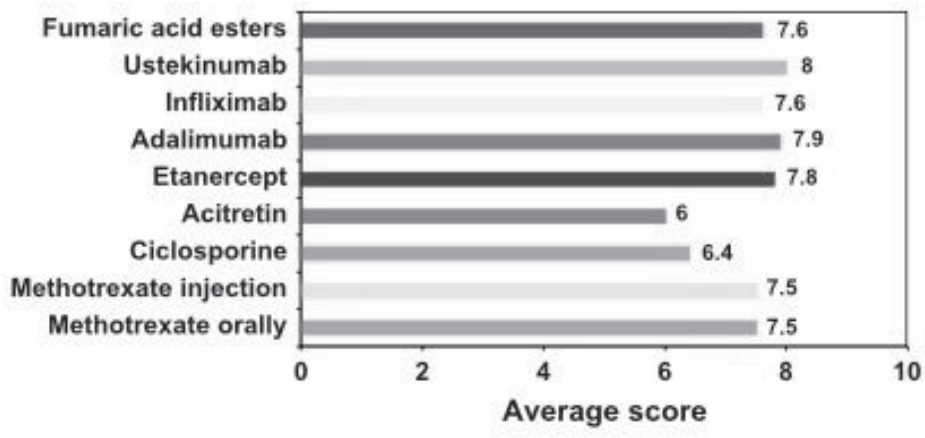

Figure 3. Overall satisfaction per treatment (as monotherapy).[164]

for patients with moderate to severe psoriasis who need to quickly reduce their disease severity. Such an approach could also enhance the patient's compliance, and he/she would be more willing to continue FAE therapy. Little is known about combining FAE with other systemic therapies, such as ciclosporine. Wilsmann-Theis et al. recently described two patients with severe psoriasis vulgaris being treated with a combination of FAE and ciclosporine, whereby therapy with ciclosporine was stopped in one patient as soon as 6 weeks after achieving a PASI reduction from 12.0 to 3.0.[44] In 2004 Balasubramiam et al. retrospectively analyzed the records of patients who had received FAE for severe psoriasis either alone (in two cases) or along with other systemic medications (in 10 cases). Of the 12 patients treated with FAE, one taking a very low dose discontinued the drug very early due to flushing. The other 11 patients all demonstrated an improvement in psoriasis after starting FAE. Nine patients received FAE in combination with other systemic therapies, including ciclosporine, acitretin, hydroxyurea, and methotrexate. Seven achieved useful overall reductions in the dose of the other drugs. In two patients, severe psoriasis was controlled using FAE alone. There was no evidence of drug interactions.[45] Wain et al. performed a single-center, open, nonrandomized, prospective study with 80 patients, of which 59% were taking a concomitant oral anti psoriatic agent, such as MTX, ciclosporine, hydroxyurea, and MMF; 20% achieved PASI 50, 8% PASI 75, and 4% PASI 90 on intention-to-treat analysis at 3 months with an overall, statistically significant, reduction in PASI from 13.9 + or - 9.0 to 11.3 + or - 9.2 ($P < 0.0001$). In addition, by 3 months, 36% of concomitant anti-psoriatic medication had been stopped, and 25% of doses had been reduced without a loss of disease control. The researchers concluded that FAE can allow dose reduction, and subsequent cessation, of other, potentially more toxic agents.[17]

The updated European S-3 guidelines for the treatment of psoriasis currently do not recommend the combination of FAE with other systemic medications, mainly because of medical professionals' lack of experience in combining such medications.[10, 14] Thus, when a patient has to discontinue treatment with FAE, we tried to find alternatives to the common systemic therapies, such as to ciclosporine with a milder and a more favorable risk/benefit ratio. Mycophenolate mofetil (MMF) has shown efficacy in the treatment of autoimmune and inflammatory skin disorders, including atopic dermatitis, subacute cutaneous lupus erythematosus, and psoriasis.[46, 47] To reduce the gastrointestinal adverse events of MMF, enteric-coated mycophenolate sodium (EC-MPS) was designed to delay the release of mycophenolic acid (MPA) in the small intestine. At a dose of 720 mg, EC-MPS exhibits equivalent MPA exposure and maximal MPA concentration to 1000 mg of MMF.[48]

In Chapter 7, we examined the clinical efficacy and safety profile of EC-MPS in patients with psoriasis vulgaris. EC-MPS has shown to inhibit lymphocyte proliferation and indirectly reduce the hyperproliferation of epidermal keratinocytes. Meanwhile, the choice of other systemic treatments besides biologics and the conventional therapies are limited. In an open-label pilot study, we treated 20 patients with a PASI >10. They received 720 mg of EC-MPS twice daily for 6 weeks followed by 360 mg twice daily for another 6 weeks. Patients who completed 12 weeks of treatment were followed up for an additional 12 weeks. Eighteen men and two women (mean age 46 years) entered the study. Sixty-five percent (13/20) finished the treatment period. By week 6, no patient had achieved PASI 75%, and 8 of the 20 patients achieved a PASI 50%. Compared to week 6, 4 of the 13 showed a deterioration of their psoriasis at week 12. Twenty-five percent (2/8) achieved PASI 75% in week 24. We concluded that EC-MPS did not seem effective as monotherapy for moderate to severe psoriasis, but might be used at a dosage of 1440 mg daily in well-selected patients with treatment-resistant psoriasis.

FUTURE DIRECTIONS

Psoriasis is a chronic inflammatory skin disease, and patients are in need of a long-term maintenance treatment that is effective, safe, and not limited by issues of toxicity. Cost-effectiveness on the other hand is another important responsibility of dermatologists in this era of expensive biologics in the evaluation for psoriasis treatments.[1] Biologics are developed to target single cytokines or intracellular key proteins implicated in psoriasis. Ustekinumab, an interleukin interleukin (IL)-12/23 antagonist, was the first anti-cytokine biologic used exclusively by dermatologists and is now being established for PsA. Secukinumab is the second biologic approved by the US Food and Drug Administration

(FDA) in January 2015 that selectively binds to IL-17A and inhibits interaction with the IL-17 receptor.

FAE, on the other hand, seems to deplete glutathione in circulating immune cells,[49] which induces the expression of the anti-inflammatory protein heme oxygenase 1 (HO-1).[50] In turn, this results in the inhibition of the pro-inflammatory cytokine production of TNF-α, interleukin (IL)-12, and IL-23, and FAE has been ascribed to, along with other immunomodulation effects, inducing TH-17 cell differentiation, which results in the inhibition of IL-17 expression.[51] This is a great reason why dermatologists should use FAE as a first-line therapy. Indeed, FAE targets multiple pathways and have multiple immune modulating effects. FAE can compete with MTX and biologics in effectiveness. However, the side effects are minimal, and long-term treatment is simple, cheap, effective, and safe. Therefore, based on all these findings, FAE should obtain a place as a first-line treatment in psoriasis, preferred above UVB phototherapy use, especially in young adults, as we know that UVB phototherapy has mutagenic and immunosuppressive effects and is very time consuming, which again results in patients' non-compliance. Using FAE as a first-line treatment favors the patient as well as the society. The major reason why dermatologists are hesitant to use FAE is the off-label use. The registration of FAE by regulatory agencies, like EMEA, would certainly make dermatologists feel more confident in prescribing FAE.

In 2013, a FAE formulation containing delayed release DMF (BG-12, Biogen Idec, Cambridge, MA, U.S.A.) was approved by the US FDA for the treatment of multiple sclerosis (MS).[51, 52] The nervous system and neuronal factors promote inflammation in psoriasis lesions, which are characterized by a high density of nerves and an increased expression of neurotrophins.[53] The Nrf2 pathway has an important anti-oxidative function and is involved in the epidermal barrier function.[54] FAE seems to induce the activation of the Nrf2 pathway, which is a FAE-specific effect,[51] making FAE the first modern therapy clinically effective for both psoriasis and MS, unlike established biologics.[50, 52, 55] The BG-12 FAE-formulation registered for MS was also in Phase III development for the treatment of psoriasis, but for unknown reasons the development of BG-12 in psoriasis seems to have been interrupted.[56, 57]

Interestingly, the costs of the registered FAE formulation containing delayed-release DMF, BG-12 by Biogen Idec, are 34.06 € per 240 mg versus the same off-label FAE formulation containing delayed-release DMF, Psorinovo®, made by the local GMP pharmacy Mierlo-Hout, Netherlands, which costs 1.37 € per 240 mg—a difference of 67% in price. In other words, the licensing of FAE has increased costs as high as the costs of the present biologics. Biogen Idec has priced this drug at 49,541 € per patient per year. Biogen Idec is not setting the price of Tecfidera based on the costs of producing it as chemical suppliers charge 51.55 € per 1000 grams of DMF. Rather, the high price has been set

based on the value of this product in treating MS based on the benefits for patients and the savings to healthcare systems in treating this disease.

A few different FAE formulations are in use for psoriasis. To date, only one of them, Fumaderm®—a mixture of DMF and the calcium, magnesium, and zinc salt of MEF—has been registered in Germany. Two strengths of tablets are available: Fumaderm® initial 105 mg tablets containing 30 mg of DMF and 75 mg of MEF salts and Fumaderm 215 mg tablets, which contain 120 mg of DMF and 95 mg of MEF salts. DMF is thought to be the active FAE component in Fumaderm treatment, although a double-blind study comparing DMF monotherapy with combination therapy of DMF and MEF salts showed no statistically significant differences in efficacy between the two FAE formulations.[58] In the Netherlands, dermatologists have the ability to prescribe different unlicensed Dutch FAE formulations containing DMF and calcium-MEF, DMF, or DMF in slow release.[59, 60] Several large RCTs are currently being conducted to evaluate novel FAE formulations that only contain DMF. These studies and future studies are necessary to improve the FAE formulation, thereby improving the tolerability of FAE. The dose-dependent and treatment-limiting side effects of FAE therapy are the most common cause for early treatment discontinuation, especially the intolerable gastrointestinal complaints and, to a lesser extent, flushing symptoms. Changes in laboratory tests during FAE are usually mild in severity and transient; thus, in the majority of cases, FAE treatment discontinuation is not necessary.[10, 61] A possible solution to these gastrointestinal complaints could be the oral administration of 10 mg of Cetirizine twice daily.

Furthermore, to date, only one study has suggested that FAE induces an allergic contact mucositis of the gastrointestinal tract. Recently, the position of the gut microbiome in the pathogenesis of inflammatory diseases has attracted our attention.[62-64] Gut dysbiosis may contribute to psoriatic arthritis through the overgrowth of inflammatory strains of bacteria and yeasts, the reduction of tolerogenic strains including F. prausnitzii, or a combination of both.[63] Dysbiosis in the intestine can determine the direction of differentiation of naive CD4+ T cells into either effector T cells or regulatory T cells (Tregs) while an imbalance can lead to chronic inflammation in the joints, skin, or gut.[63] Additional future studies need to be performed to investigate the effects of FAE on the gut microbiome.

Recently, in 2014, apremilast (*Otezla*, Celgene), a selective small molecule inhibitor of phosphodiesterase 4, was approved by the US FDA for treating patients with moderate to severe plaque psoriasis and psoriatic arthritis. Like FAE, it is an orally administered medication that has been shown to have a lower efficacy in plaque psoriasis than FAE, but it is especially effective in nail and scalp psoriasis.[65] For a patient suffering from significant nail, skin, and joint disease, a combination of apremilast with FAE—two small molecules—could be of high interest because FAE targets the plaque psoriasis and

apremilast the psoriatic arthritis and nail involvement. Both drugs are easy in use and considered safe with a favorable risk/benefit profile.

Speaking of combination therapy, nowadays, many dermatologists combine biologics with conventional systemic therapies because monotherapy with a biologic alone is not as promising as claimed when the first biologicals came on the market. A combination can result in greater reduction in disease severity. The combination of etanercept and MTX is more effective than monotherapy with either medication. In addition, combining infliximab with MTX results in greater efficacy than infliximab alone. With concomitant use of acitretin, the dosing of etanercept can be reduced to maintain similar levels of efficacy. Short-term cyclosporine use has been combined with etanercept or adalimumab to control psoriasis flares. Based on the expert opinion of the Medical Board of the National Psoriasis Foundation, the preferred order for combining a second modality with biologics is a combination of biologic and MTX, biologic and acitretin, and then biologic and phototherapy.[66] However, all these second modalities show high toxicities and have no favorable adverse event profiles. Thus, caution and serious safety monitoring are needed when combining them with therapies such as MTX. As we have proven that FAE is equally effective as MTX, but with a more favorable safety profile, dermatologists should consider combining a biologic with FAE as a first choice before considering using other modalities such as MTX, if monotherapy with the biologic alone is not sufficient.[44]

Although combinations of FAE with other systemic treatments are very attractive from a theoretical point of view, we have to make some remarks regarding the lack of good studies.[10, 44] We have to rely on experience out of daily practice. However, FAE does not have significant immunosuppressive effects or show any drug interactions, making it preferable to other systemic treatments in the case of combination treatment. But clinical trials with a combination of FAE and biologics are necessary future steps. An interesting future clinical trial could investigate the efficacy of treatment with a combination of an IL 17 inhibitor such as secukinumab (Consentyx ®, Novartis) and FAE for the first 6 months, with discontinuation of the biologic at 6 months and continuation with FAE as maintenance therapy. Another interesting combination is FAE with pulsed dye laser (PDL) treatment. Single plaque lesions left over after achieving PASI 75 can safely and effectively be treated with PDL.[67, 68]

FAE is definitely a suitable first-line therapy for plaque psoriasis, but it also has certain disadvantages, such as its long induction period of nearly 6 to 8 weeks due to its recommended dosing schedule, which can have an impact on compliance. A combination of cyclosporine with FAE for the first 12 weeks, as we have shown in Chapter 2.4, can give quick satisfactory improvement, which will certainly improve compliance.

Like other immuno-modulating drugs, FAE should have potential benefit in the application for other immune-mediated diseases. FAE has furthermore shown efficacy in other inflammatory diseases such as MS, for which FAE received approval by the FDA

for the treatment of relapsing forms of MS. A few case reports have shown the improvement of cutaneous forms of lupus erythematodus and sarcoidosis with off-label use of FAE through its immunomodulatory mechanism.[69, 70] Future studies are necessary to investigate the efficacy of FAE in other inflammatory diseases.

In conclusion, FAE has proven its efficacy in psoriasis, especially plaque type; with its favorable risk/benefit ratio, it is a definite candidate for first-line treatment in moderate to severe psoriasis. We recommend the use of FAE as a first-line therapy, especially in young adults. Patient education on the nature of the adverse events prior to starting treatment (e.g., types, severity [PML], frequency, transient nature), positive encouragement, and the emphasis of product efficacy and the importance of staying on therapy are key management strategies in treatment utilizing FAE. Approval through the regulatory agencies, the improvement of the tolerability, and the optimization and standardization of the FAE formulation should take place in the near future to ensure an improvement and increase in the use of FAE.

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Chapter 9

Summary/Samenvatting

SUMMARY

Chapter 1 presents a general introduction to this thesis. Psoriasis vulgaris is recognized as the most prevalent autoimmune disease caused by inappropriate activation of the cellular immune system. It is universal in occurrence, although the worldwide prevalence varies between 0.6% and 4.8%. Environmental factors such as stress, medication, trauma, or smoking and genetic factors trigger the production of pro-inflammatory cytokines and chemokines and maintain inflammatory processes in the skin. The most common form is plaque psoriasis, which can be present in combination with psoriatic arthritis, which can also be considered as its own entity.

In the introduction, we explained about the four treatment modalities, which are divided by increasing order of potency into: 1). topical therapy, 2). phototherapy, 3). systemic therapy, and 4). biologics.

Although a wide variety of treatment options are available, there is still a need for a simple, safe, and effective long-term therapy. We explain about fumarates (FAE)—ester derivatives of fumaric acid that are small molecules with immunomodulating properties—and outline their current position in plaque psoriasis as well as highlighted their necessity in an era of worldwide escalation of healthcare costs and the high expense of continuous approval of new biologics as a safe, effective, and low-cost treatment.

Chapter 2 provides a systematic review in which we summarized and critically evaluated the current evidence of the efficacy, effectiveness, and safety of FAE in the treatment of psoriasis. Our goal was to provide a comprehensive summary and appraisal of available studies that reported the clinical effects of FAE in psoriasis patients. We included 68 articles. Seven RCTs (449 patients total) had an unclear risk of bias and were too clinically heterogeneous to allow a meta-analysis. Overall, mean psoriasis area and severity index decreased by 42% to 65% following 12–16 weeks of treatment. In addition, 37 observational studies (3457 patients total) supported the RCT findings, but most were uncontrolled with a high risk of bias. Commonly reported adverse events were gastro-intestinal complaints and flushing, leading to treatment withdrawal in 6% to 40% of cases. Rare adverse events were renal Fanconi syndrome and progressive multifocal leukoencephalopathy. Long-term studies and those comparing other treatments were lacking.

We concluded that low-quality evidence exists for recommending the use of oral FAEs in the treatment of plaque psoriasis in adult patients. Studies focusing on long-term safety and comparisons to systemic psoriasis treatments could lead to a better positioning of FAE as a psoriasis treatment.

Chapter 3 compares FAE to the past and present "golden standard" therapy methotrexate (MTX) in a randomized controlled trial comparing the effectiveness and the adverse events of both treatments. Sixty patients with moderate to severe psoriasis vulgaris were

randomly assigned to treatment for 16 weeks with either methotrexate (30 patients; 15 mg per week) or FAE (consisting of DMF and salts of MEF; 30 patients; 30 mg, followed by 120 mg according to a standard progressive dosage regimen) and were followed up for 4 weeks. After 12 weeks of treatment, the mean ± SD PASI decreased from 14·5 ± 3·0 at baseline to 6·7 ± 4·5 in the MTX group, whereas it decreased from 18·1 ± 7·0 to 10·5 ± 6·7 in the FAE group. After adjustment for baseline values, the absolute difference (FAE minus MTX) in the mean values at 12 weeks was 1·4 (95% confidence interval; -2·0 to 4·7; P = 0·417). Thus, we concluded that MTX and FAE were equally effective in the treatment of patients with moderate to severe psoriasis. No serious or irreversible adverse events were observed in any of the patients.

Chapter 4 evaluates whether the addition of cetirizine, an oral histamine-1 receptor antagonist, to FAE would reduce the incidence of adverse events as 30%–40% of patients need to discontinue FAE treatment due to intolerable adverse events. Using a double-blind, placebo-controlled trial, we randomized patients with psoriasis with PASI ≥ 10 starting an FAE up to a dose of 720 mg of DMF per day 1:1 to receive either an additional 10 mg of cetirizine once daily (n = 25) or a placebo (n = 25) for 12 weeks. In total, 50 patients (33 male, 17 female; median age 44 years) were enrolled. The addition of cetirizine did not reduce the incidence of adverse events compared with the placebo (84% vs. 84%, P = 1.00). The types of adverse events did not differ between the cetirizine and placebo groups, and the most common types were gastrointestinal complaints (68% vs. 64%) and flushes (60% vs. 48%). The proportion of patients discontinuing treatment was not statistically different between the cetirizine and placebo groups (24% vs. 32%, P = 0.53). The results showed that the addition of 10 mg of cetirizine orally once daily to the FAE treatment did not reduce adverse events in patients with psoriasis during the first 12 weeks of treatment.

Chapter 5 presents a cross-sectional postal survey to obtain insights into the use of FAE by Dutch dermatologists in the Netherlands. An anonymous survey was posted to all Dutch dermatologists (600). In this survey, data were collected on the extent of FAE use, the reasons for use, the reasons for non- or limited use of FAE, and the perception of FAE as a monotherapy with regard to the effectiveness, safety, adverse events, and overall satisfaction. 300 respondents is considered a proper sample size to determine the level of response. Ultimately, 63% of the 300 respondents indicated prescribing FAE for the treatment of psoriasis. About 37% of the respondents indicated that they (almost) never prescribed it. Biologics were considered to be the most effective therapy. FAE was regarded as the safest therapy followed by the rest at some distance and was generally well tolerated by the patients, similar to that for methotrexate according to the respondents. This study showed that a large proportion of Dutch dermatologists prescribed FAE, which was considered to be effective, safe, and with a favorable risk/benefit profile compared with other systemic therapies, such as MTX and biologics.

Chapter 6 proposes an alternative induction therapy with a combination of FAE and cyclosporine (CsA) for approximately the first 12 weeks because clinically meaningful improvement is seen just after 6 to 8 weeks of therapy, which is a reason for patients with severe psoriasis to discontinue their treatment with FAE in an early stage due to its slow efficacy due to the incremental dosage regimen. We introduced an alternative induction scheme with a relatively low adverse event profile. We suggested that FAE can be given according to the established dosage scheme starting with 120 mg once daily, followed by CsA started at 5 mg/kg daily. CsA can be stopped after reaching 80% from the maximum dosage of FAE depending on the PASI reduction or with a PASI reduction of 50%, but not later than week 12. FAE can be continued according to the established dosage scheme to a maximum dosage of 740 mg per day as a single treatment. We expected improvement of the PASI score (PASI 50%) after 2 weeks with 120 mg of FAE in combination with CsA, which will enhance the overall adherence. The dosage of FAE is dependent on each individual patient and his/her response to therapy and can be managed during the long-term maintenance treatment by lowering or increasing the dosage by not more than one tablet of 120 mg daily per week. Laboratory, urine analyses, and blood pressure measurements should be performed as recommended by the guidelines. Despite limited experience in combination therapy with FAE and CsA, we believe that this alternative treatment induction scheme can be beneficial and a fast, cost- effective, and safe alternative, especially compared to the more expensive biologics.

In **Chapter 7**, we evaluate the efficacy of mycophenolate sodium (Myfortic®) as a legitimate alternative therapy for plaque psoriasis in case patients need to stop FAE due to adverse effects. Enteric-coated mycophenolate sodium (EC-MPS) is similar to CsA, but without the serious side effects, such as nephrotoxicity. In an open-label pilot study, we treated 20 patients with PASI >10 who received 720 mg of EC-MPS twice daily for 6 weeks followed by 360 mg twice daily for another 6 weeks. Patients who completed 12 weeks of treatment were followed up for an additional 12 weeks. Eighteen men and two women (mean age 46 years) entered the study; 65% (13/20) finished the treatment period. By week 6, no patient achieved PASI 75%, although 8 of the 20 patients achieved PASI 50%. Compared to week 6, 4 out of 13 patients showed a deterioration of their psoriasis at week 12. Twenty-five percent (2/8) achieved PASI 75% in week 24. We concluded that EC-MPS did not seem to be effective as monotherapy for moderate to severe psoriasis, but might be used at a dosage of 1440 mg daily in well-selected patients with treatment-resistant psoriasis.

Finally, **Chapter 8** discusses the main findings of the studies presented in this thesis put them into perspective. In addition, we describe the study's limitations and offer recommendations for future research and advice the use of FAE as a first line therapy for moderate to severe psoriasis vulgaris.

SAMENVATTING

Hoofdstuk 1 betreft een algemene inleiding tot het onderzoek dat in dit proefschrift gepresenteerd wordt. Psoriasis vulgaris wordt gezien als een van de meest voorkomende auto-immune ziekten. Psoriasis wordt veroorzaakt door een disregulering van het cellulaire deel van het humane immuunsysteem. De dermatose psoriasis komt wereldwijd voor, echter de prevalentie tussen de verschillende geografische gebieden varieert tussen 0,6% en 4,8%. Omgevingsfactoren zoals stress, medicatie, trauma en roken spelen naast een genetische predispositie een rol resulterend in de productie van pro-inflammatoire cytokines en chemokines met als gevolg het ontstaan van voornamelijk T-cel gemedieerde inflammatoire processen in de huid.

De meest voorkomende klinische vorm is psoriasis en plaque. Dit fenotype kan in combinatie met arthritis psoriatica als een eigen entiteit worden beschouwd.

In de inleiding worden de vier belangrijkste behandelingen beschreven. Zoals veelal gebruikelijk worden de therapieën gerangschikt in volgorde van oplopende effectiviteit: 1). lokale therapie, 2). lichttherapie, 3). conventionele systemische therapie, en 4). biologics.

Hoewel het therapeutisch areaal een brede waaier van verschillende mogelijkheden biedt, bestaat er zeker nog behoefte aan een eenvoudig toepasbaar, veilige en effectieve therapie welke ook langdurig zonder hinderlijke en / of schadelijke bijwerkingen kan worden toegepast.

Wij hebben ons verdiept in de stof fumaarzuur, de zogenaamde fumaraten, als potentieel middel dat in principe aan veel van deze criteria voldoet. Fumaraten (FAE)-ester derivaten of fumaarzuur zelf zijn kleine moleculen met immuno-modulerende eigenschappen welke al decennia lang bij de behandeling van psoriasis, in het bijzonder psoriasis en plaque, als off-label medicijn worden toegepast.

Een overzicht van deze toepassingsmogelijkheden wordt gegeven en wij benadrukken de potentie van FAE mede vanuit de optiek in een tijdperk waarin wereldwijd de kosten van de gezondheidszorg escaleren en waarop de behandeling van psoriasis zeker geen uitzondering vormt. De hoge kosten van de toelating van nieuwe biologicals als een veilige, effectieve behandeling is bij psoriasis, net als bij vele andere immuun gemedieerde zieketen als reumatoïde artritis en de ziekte van Crohn, de oorzaak van de exponentieel gerezen kosten. Dit rechtvaardigt FAE als goedkoop alternatief geneesmiddel bij de behandeling van psoriasis grondig te overwegen.

Hoofdstuk 2 geeft een systematisch review waarin het huidige bewijs van de werkzaamheid, effectiviteit en veiligheid van FAE in de behandeling van psoriasis samengevat en kritisch geëvalueerd wordt. Ons doel is een uitgebreide samenvatting en beoordeling te geven van de beschikbare studies die de klinische effecten van FAE bij psoriasis patiënten beschrijft. Wij konden 68 artikelen includeren, waarvan zeven RCT's met in

totaal 449 patiënten. Al deze studies hebben echter onvolkomenheden en daardoor een risico op een vooroordeel (bias) en zijn ook klinisch te heterogeen om een meta-analyse mogelijk te maken. Wel kan vanuit dit overzicht een aantal belangrijke data gegenereerd worden: over het geheel genomen daalde de gemiddelde Psoriasis Area and Severity Index (PASI) met 42% tot 65% na 12-16 weken behandeling. Daarnaast, bevestigden 37 waarnemingsstudies (3457 patiënten in totaal) de resultaten van de RCT's. Echter de meeste van de waarnemingsstudies betreffen ongecontroleerd onderzoek met een hoog risico op bias.

Vaak vermelde bijwerkingen zijn gastro-intestinale klachten en opvliegers hetgeen leidt tot het voortijdig staken van de behandeling in 6% tot 40% van de gevallen. Zeldzame, doch ernstige bijwerkingen zijn het renale Fanconi-syndroom en progressieve multifocale leuko-encefalopathie.

Het ontbreekt zowel aan lange-termijn studies als aan studies die FAE vergelijken met andere en bij voorkeur standaardbehandelingen voor psoriasis.

Wij concluderen dat door de matige kwaliteit van de beschikbare literatuur onvoldoende bewijs bestaat voor een evidence based gebruik van orale FAE bij de behandeling van psoriasis en plaque bij volwassen. Hierdoor is het op dit moment onmogelijk om op basis van de gewenste bewijskracht verkregen uit degelijke studies FAE te positioneren in de therapeutische waaier voor de behandeling van psoriasis.

Hoofdstuk 3 vergelijkt FAE met de nog immer geldende goud standaard behandeling voor psoriasis en plaque al dan niet in combinatie met een artritis psoriatica: methotrexaat (MTX).

Door het uitvoeren van een prospectief gerandomiseerde gecontroleerd onderzoek, een zogenaamde RCT, waarbij de effectiviteit en bijwerkingen van beide behandelingen, FAE en MTX, objectief worden vergeleken, wordt de werkzaamheid en tolerantie van FAE getoetst aan de goud standaard. Voor dit onderzoek werden zestig patiënten met matige tot ernstige psoriasis vulgaris geselecteerd. Naar willekeur werd de patiënt 16 weken met ofwel MTX (30 patiënten; 15 mg per week) dan wel FAE (bestaand uit DMF en zouten van MEF; 30 patiënten, 30 mg, gevolgd door 120 mg volgens een standaard opbouwschema) behandeld. Hierna werd een follow-up van 4 weken in acht genomen.

Na 12 weken behandeling was de gemiddelde PASI (± sd) van 14·5 ± 3·0 bij aanvang gedaald tot 6·7 ± 4·5 in de MTX groep en in de FAE groep van 18·1 ± 7·0 naar 10·5 ± 6·7. Na correctie van de uitgangswaarden, werd het absolute verschil (FAE minus MTX) van de gemiddelde waarden bij 12 weken behandeling berekend: 1·4 (95% betrouwbaarheidsinterval, -2·0 versus 4·7; P = 0·417).

De conclusie die uit deze RCT getrokken wordt is dat FAE en MTX even effectief zijn bij de behandeling van patiënten met matige tot ernstige psoriasis. Geen ernstige en / of onomkeerbare bijwerkingen werden waargenomen.

Hoofdstuk 4 doet verslag van een onderzoek waarbij de FAE behandeling wordt gecombineerd met additioneel cetirizine, een orale histamine-1 receptor antagonist, met het doel de meest frequente bijwerkingen te verminderen. Aangezien 30% -40% van de patiënten de behandeling met FAE als gevolg van deze bijwerkingen staken, is het voorkomen van bijwerkingen een goede mogelijkheid om de compliance te verhogen. In een prospectief dubbel-blind, placebo-gecontroleerd onderzoek randomiseerden wij twee gelijke en even grote groepen patiënten met psoriasis met een PASI ≥ 10. De behandeling met FAE werd gestart en verhoogd tot een dosis van 720 mg dimethylfumaraat (DMF). Eén groep ontvangt tevens als adjuvans 10 mg cetirizine eenmaal daags (n = 25) en de andere groep een placebo (n = 25) gedurende 12 weken. In totaal werden 50 patiënten (33 mannen, 17 vrouwen met een gemiddelde leeftijd van 44 jaar) geïncludeerd. De toevoeging van cetirizine bleek niet de incidentie van bijwerkingen in vergelijking met placebo (84% vs. 84%, p = 1.00) te verminderen. Ook de aard der bijwerkingen verschilde niet tussen cetirizine en de placebo groep. De meest voorkomende bijwerkingen waren gastro-intestinale klachten (68% vs. 64%) en opvliegers (60% vs. 48%). Het percentage patiënten die de behandeling discontinueerde was niet statistisch verschillend tussen de cetirizine en de placebogroep (24% vs. 32%, p = 0.53).

De resultaten van deze RCT tonen aan dat de toevoeging van 10 mg cetirizine per os eenmaal daags de bijwerkingen van de behandeling met FAE bij patiënten met psoriasis gedurende de eerste 12 weken van de behandeling niet vermindert.

Hoofdstuk 5 behandelt een cross-sectionele enquête welke verricht werd om inzicht te verkrijgen in het gebruik van FAE door Nederlandse dermatologen. Een anonieme enquête werd per reguliere post verstuurd naar alle in Nederland werkzame dermatologen (600). In dit onderzoek werden de gegevens verzameld over de omvang van het gebruik van FAE, motivering over de toepassing, de redenen van het niet toepassen en de perceptie van de dermatoloog bij FAE als monotherapie. Alles met betrekking tot de doeltreffendheid, veiligheid, bijwerkingen en algemene patiënt tevredenheid. Er is met 300 responders sprake van een goede respons.

63% van de 300 responders hebben aangegeven FAE voor te schrijven voor de behandeling van psoriasis. Ongeveer 37% van de responders geven aan (vrijwel) nooit FAE voor te schrijven. Biologicals worden beschouwd als de meest effectieve therapie bij psoriasis. Echter wordt FAE als de veiligste therapie gezien gevolgd door de rest met enige afstand welke volgens de responders bovendien in het algemeen als goed verdraagbaar wordt beschouwd en vergelijkbaar is aan MTX . Deze studie toont aan dat een groot deel van de Nederlandse dermatologen FAE voorschrijft op grond van overwegingen dat FAE een effectief, veilig middel is met een gunstig risico / baten-profiel in vergelijking met andere systemische therapieën, zoals MTX en biologics.

Hoofdstuk 6 betreft een alternatieve inductiebehandeling van FAE door dit middel te combineren met cyclosporine (CsA) gedurende de eerste 12 weken van de behandeling.

Klinisch significante verbetering treedt bij FAE behandeling pas na 6 tot 8 weken op waardoor zichtbare resultaten pas laat optreden. Dit vormt voor een aantal patiënten een reden om in een vroeg stadium de behandeling af te breken. Daarom introduceerden wij een alternatief inductieschema met een relatief laag bijwerkingsprofiel juist met het doel snel klinisch zichtbaar resultaat te boeken. Uitgangspunt is dat vanaf de start met 120 mg DMF eenmaal daags dit gecombineerd wordt met CsA beginnend met 5 mg/kg lichaamsgewicht per dag per os. CsA wordt gestopt wanneer 80% van de maximale dosering FAE en / of een PASI reductie van 50% bereikt is. CsA wordt bovendien niet langer dan tot en met week 12 voorgeschreven. Wel wordt de FAE behandeling als gebruikelijk ook na week 12 voortgezet op basis van het standaard doseringsschema tot de maximale dosering van 740 mg per dag als monotherapie. Wij verwachten een verbetering van de PASI score (PASI 50%) na 2 weken 120 mg FAE in combinatie met CsA, waardoor de therapietrouw zal verbeteren.

De onderhoudsdosering van FAE is afhankelijk van elke individuele patiënt en haar of zijn respons hier op wordt gereguleerd tijdens door het verlagen of verhogen van de dosering echter met niet meer dan één tablet van 120 mg per dag per week. Laboratorium-, urine-analyses, en bloeddrukmetingen moeten worden uitgevoerd zoals aanbevolen in de richtlijnen. Ondanks de beperkte ervaring met combinatietherapie met FAE en CsA, geloven wij dat dit alternatieve behandel-inductieschema voordelig, snel, kosteneffectief en een veilig alternatief. Dit vooral in vergelijking met de veel duurdere biologicals.

In **hoofdstuk 7**, evalueren wij de effectiviteit van natrium-mycofenolaat (Myfortic®) als een legitieme alternatieve therapie voor plaque psoriasis. Maagsapresistent natrium-mycofenolaat (EC-MPS) is verwant aan CsA en eveneens een T-cel manipulator, maar zonder de ernstige bijwerkingen van CsA zoals nefrotoxiciteit. In een open-label pilot studie behandelden wij 20 patiënten met een PASI> 10 met 720 mg EC-MPS tweemaal daags gedurende 6 weken gevolgd door 360 mg tweemaal daags gedurende de volgende 6 weken. Patiënten die 12 weken werden behandeld werden gedurende nog eens 12 weken gevolgd. Achttien mannen en twee vrouwen (gemiddelde leeftijd 46 jaar) werden geïncludeerd. 65% (13/20) doorliepen het gehele behandeltraject. In week 6 bereikte geen enkele patiënt een PASI 75%. 8 van de 20 (40%) patiënten bereikten wel een PASI 50%. Vergelijkend met week 6, constateerden wij bij 4 van de 13 patiënten een verslechtering van hun psoriasis op week 12. 25% van de PASI 50% groep (2/8) bereikte uiteindelijk een PASI 75% in week 24.

Wij concludeerden dat EC-MPS niet effectief is als monotherapie voor matige tot ernstige psoriasis. Echter bij goed geselecteerde patiënten met een therapieresistente psoriasis kan dir middel worden gebruikt in een dosering van 1440 mg per dag als een soort last resort therapie.

Tot slot , worden in **hoofdstuk 8** de belangrijkste bevindingen van de studies in dit proefschrift in het juiste perspectief gezet . Daarnaast beschrijven wij de beperkingen van de studies en bieden aanbevelingen voor toekomstig onderzoek en raden het gebruik van FAE als eerstelijnsbehandeling voor matige tot ernstige psoriasis vulgaris aan.

Appendices

List of abbreviations
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Publications
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Dankwoord (Acknowledgements)

LIST OF ABBREVIATIONS

Bcl2	B-cell lymphoma gene
BSA	Body Surface Area
CsA	Ciclosporine
CXCL	Cysteine X Cysteine Ligand
CXCL8	CXC ligand 8, Interleukin 8
DMF	Dimethylfumarate
EC-MPS	Enteric-coated mycophenolate sodium
EMEA	European Medicine Agencies
E-selectin	Endothelial selectin
FAE	Fumaric acid ester derivates
HLA-DR	Human Leukocyte Antigen - antigen D Related
ICAM-1	Intercellular Adhesion Molecule 1
IL	Interleukin
IL-1RA	Interleukin 1 receptor antagonist
JC virus	John Cunningham virus
MACE	Major Adverse Cardiovascular Events
MEF	Monoethylfumarate
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MTX	Methotrexate
NF-kB	Nuclear Factor kappa B
NO	Nitric Oxide
NQO-1	NAD(P)H Dehydrogenase, Quinone 1
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
PASI	Psoriasis Area Severity Index
PBMC	Peripheral Blood Mononuclear Cells
PGA	Physician's Global Assessment
PML	Progressive Multifocal Leukoencephalopathy
PsA	Psoriatic arthritis
RCT	Randomized controlled trial
TCA cycle	Tricarboxylic cycle
Th cells	T-helper cells
TNF-α	Tumor necrosis factor α
UVB	UV: 320-290 nm
VCAM-1	Vascular Cell Adhesion Molecule 1

LIST OF CO-AUTHORS

D.M.W. Balak
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

W.M. Bramer
Medical Library, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

C.A.F. Hagemans
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

E. Hajdarbegovic
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

W.C.J. Hop
Department of Biostatistics, Erasmus MC, University Medical Center Rotterdam, The Netherlands

M.V. Kuipers
TEVA Nederland B.V., Haarlem, The Netherlands

H.A.M. Neumann
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

T.Nijsten
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

H.B.Thio
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

C.M. Venema
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

R. Waalboer Spuij
Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands

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CURRICULUM VITAE

Shiva Fallah Arani werd op 23 april 1979 geboren te Teheran (Iran). Op een-jarig leeftijd verhuisde zij met haar familie naar Wenen, Oostenrijk. In 1997 behaalde zij haar diploma aan het Gymnasium BG II Zirkusgasse te Wenen. In hetzelfde jaar begon zij met haar studie geneeskunde aan de Universiteit Wenen. Tijdens haar studie werkte zij tevens drie jaar als mentor voor prepareer-cursussen in het "Institut vor Anatomie" te Wenen onder de leiding van Prof. dr. H. Gruber. In 2003 studeerde zij af als "Doctor der gesamten Heilkunde" en ontving een beurs voor uitstekende resultaten. Van 2003 tot medio 2004 werkte zij als basisarts in "Labor Muehl-Speiser", een diagnostisch medisch centrum te Wenen. Eind augustus 2004 verhuisde zij naar Rotterdam, waar zij in september in het Erasmus Medisch Centrum begon met haar wetenschapelijk onderzoek naar psoriasis en behandeling met fumaraten en andere systemische therapieen onder leiding van professor Dr. H.A.M. Neumann en supervisie van dr. H.B. Thio. In 2005 startte haar opleiding tot dermatoloog onder begeleiding van professor H.A.M. Neumann, die zij in april 2010 succesvol heeft voltooid. Vervolgens werkte zij tot begin 2011 als staflid in het Erasmus Medisch Centrum. Daarop aansluitend onderging zij van 2011 tot 2012 als primeur een opleiding "cosmetische dermatologie" bij dr. P. Velthuis in de Velthuiskliniek te Rotterdam. Daarnaast werkte zij vanaf 2011 als dermatoloog in het Albert Schweitzer Ziekenhuis te Zwijndrecht, waar zij in 2014 toegetreden is tot de vakgroep dermatologie van het Albert Schweitzer Ziekenhuis te Dordrecht.

Shiva is getrouwd met Abbas David Tahzib en samen hebben zij twee zonen, Micah (6 jaar) en Noah (0 jaar).

PHD PORTFOLIO

Name PhD student: S. Fallah Arani	PhD period: 2004-2016
Erasmus MC Department: Dermatology	Promotor: Prof. dr. H.A.M. Neumann
	Supervisor: dr. H.B.Thio

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication	2009	20 hours
Research skills		
- DOO course: Evidenced based medicine	2010	20 hours
In-depth courses (e.g. Research school, Medical Training)		
Presentations		
- Primair follicelcentrumcelllymfoom. Nationale wetenschappelijke en huishoudelijke vergadering Nederlandse Vereniging voor Dermatologie en Venereologie, Rotterdam, The Netherlands	2005	6 hours
- Biologicals in psoriasis. Department of internal medicine and dermatology, Erasmus MC, Rotterdam, The Netherlands	2006	3 hours
- Treatment of rosacea papulopustulosa with PDL/IPL**.** European Academy for Dermatology and Venereology (EADV) Vienna, Austria	2007	1 ECST
- Mycophenolate sodium: an open pilot study in patients with severe psoriasis. Internationale meeting Novartis, Rotterdam, the Netherlands	2008	6 hours
- Psoriasis. Huidfondsdag, Erasmus MC, Rotterdam, The Netherlands	2008	6 hours
- Advancement flaps along natural folds. ISDS, Las Vegas, Nevada, USA	2008	1 ECST
- Succesvolle behandeling van systemische lupus erythematosus met fumaraten. SNNDV, Gent, Belgium	2008	1 ESCT
International Conferences		
- European congress on psoriasis, Paris, France	2004	1 ESCT
- 14th EADV congress, London, UK	2005	1 ESCT
- 15th EADV congress, Rhodes, Greece	2006	1 ESCT
- 16th EADV congress, Vienna, Austria	2007	1 ESCT
- World congress on cancers of the skin, Amsterdam, The Netherlands	2007	1 ESCT
- 17th EADV congress, Paris, France	2008	1 ESCT
- ISDS meeting, Las Vegas, USA	2008	1 ESCT
- SNNDV, Gent, Belgium	2008	1 ESCT
- 3rd ESPD Summer School - 20th Course Diagnosis & Therapy in Pediatric Dermatology 'Children's skin and allergy"	2013	1 ESCT
- 23rd EADV congress, Amsterdam, The Netherlands	2014	1 ESCT

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In this era of expensive biologics, which have gained popularity among dermatologists as effective treatments for chronic, moderate to severe plaque psoriasis, there is a great need for an effective, safe, long-term and low-cost therapy such as fumarates.

In this book the authors have investigated its efficacy, safety, adverse-events, popularity among Dutch dermatologists, combination therapy and alternative treatment options.