



Fumaric acid esters

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Abstract Several clinical studies have shown that systemic therapy with fumaric acid esters (FAEs) in patients with moderate to severe psoriasis is effective and has a good long-term safety profile. For therapeutic use, tablets with a defined mixture of FAEs (dimethylfumarate [DMF] and three different salts of monoethylfumarate) are registered in Germany. There is evidence that DMF is the most essential component in this formulation with an antipsoriatic effect. Currently, there are few data on the pharmacokinetics of fumarates in human beings. DMF seems to act as a prodrug for its main metabolite: monomethylfumarate. This hypothesis was supported by the observation that only monomethylfumarate was detected in the plasma of human beings after the oral administration of FAEs. FAEs have been tested in different biological assays, and effects such as inhibition of the nuclear factor kappa B pathway or induction of apoptosis by DMF have been described. For these data, the role of DMF as a modulator of intracellular glutathione plays an important role.

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Introduction

The antipsoriatic effect of fumaric acid esters (FAEs) was first discovered by the German chemist Schweckendiek,¹ who had psoriasis in 1959. His hypothesis was that a deficiency of fumaric acid, which is a physiologic part of the citric acid cycle, may be crucial in the pathogenesis of psoriasis. Because orally administered fumaric acid caused severe irritancy reactions and was not successful in treating psoriasis, Schweckendiek esterified fumaric acid. Irritant reactions were then less pronounced, and although they could not fully be circumvented he was able to treat himself successfully.

Fumaric acid is a dicarbonic acid. From the chemical point of view, such a polar compound has a low bioavailability. A common prodrug principle to increase bioavailability is the formation of carbonic acid esters. The “masking” of carbonic acids also leads to decreased side effects.

To minimize the rate of adverse gastrointestinal side effects, tablets containing fumarates were enteric coated. A defined mixture of FAEs, Fumaderm, has been registered for the oral treatment of psoriasis vulgaris since 1994 only in Germany (Fig. 1, Table 1). The produced tablets are available in low-strength (Fumaderm initial) and high-strength (Fumaderm) forms to allow a therapy with increasing doses (Table 2).

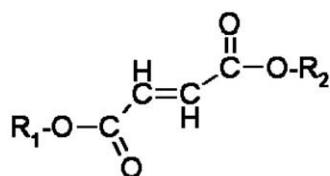
Although the mode of action of FAEs remains unclear, there is evidence that interaction with the citric acid cycle is not involved. The essential component of Fumaderm is dimethylfumarate (DMF).

Clinical use

The administration of Fumaderm follows the empiric dosing schedule given in Table 2. In clinical practice, the dose of Fumaderm is increased until a clinical response is achieved. Slowly increasing doses improves the tolerance of

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	R ₁	R ₂
Fumaric acid	-H	-H
Monomethylfumarate	-H	-CH ₃
Dimethylfumarate*	-CH ₃	-CH ₃
Monoethylfumarate*	H	-C ₂ H ₅

Fig. 1 Structures of fumaric acid, MMF, DMF, and MEF.
*Ingredients of Fumaderm.

the drug. A clinical effect is expected after approximately 6 weeks of treatment (Fig. 2). Thereafter it is recommended to reduce the dose to an individual maintenance (Fig. 3).

Clinical experience shows that the maintenance dose has considerable individual variation. In some patients therapeutic effects can be maintained at a low dose of one or two tablets of Fumaderm per day, whereas other patients require the maximum dose of six tablets per day (720 mg DMF). There is no parameter to predict the individual dose necessary to induce and maintain remission of psoriasis lesions during Fumaderm therapy.

Contraindications are severe gastrointestinal disorders and severe liver or kidney disease. Fumaderm should not be used in pregnancy and while breastfeeding. Case studies have highlighted the clinical response in patients with pustular psoriasis and in children.²

The consensus guidelines³ recommend treating patients with psoriasis with Fumaderm until there is an improvement of lesions or the patient is satisfied with the treatment outcome. A significant improvement of the symptoms should be obtained during 3 months of therapy. A maintenance treatment to stabilize clinical improvement can be performed for up to 2 years^{4,5} or more.⁶ The general recommendation is to reduce the FAE dose to an individual level, maintaining an improved disease state.

The most frequently adverse events reported are diarrhea, flushing, and a relative lymphocytopenia.^{7,8} Monitoring should include leukocyte differential counts, liver function tests, serum creatinine, and urinary status.

Table 1 Composition of fumaderm initial and fumaderm

	Fumaderm initial	Fumaderm
Dimethylfumarate (mg)	30	120
Mono-ethylfumarate Ca-salt (mg)	67	87
Mono-ethylfumarate Mg-salt (mg)	5	5
Mono-ethylfumarate Zn-salt (mg)	3	3

Drug names: a defined mixtures of FAEs.

Table 2 Dosing schedule for fumaderm treatment

Week	Fumaderm initial	Fumaderm
1	1-0-0	
2	1-0-1	
3	1-1-1	
4		1-0-0
5		1-0-1
6		1-1-1
7		2-1-1
8		2-1-2
9		2-2-2

According to the consensus guidelines,³ a reduction in FAE dose is necessary when the total leukocyte count is less than $3 \times 10^9/L$, the lymphocyte count is less than $0.5 \times 10^9/L$, there is a persistent eosinophilia greater than 25% in the differential count, there is an increase in serum creatinine of 30% more than baseline values, or proteinuria develops. If the abnormalities improve, treatment can be continued with the reduced dose. In case of a persistent abnormality or a further deterioration, FAE treatment must be stopped.

Fumaderm treatment can be combined with all topical therapies or bland emollients. A combination with ultraviolet light, psoralen ultraviolet A-range, or other systemic treatment is not generally recommended, although it was shown that a combination of Fumaderm with other systemic agents may be successful in patients with highly recalcitrant psoriasis.^{3,9}

Clinical studies

FAEs have been used to treat psoriasis for more than 30 years. The most work, however, has been done since 1990, during which a rather dramatic increase in clinical trials of FAEs has been observed. The first clinical studies, before the registration of Fumaderm in 1994, showed that DMF is essential for the successful treatment of

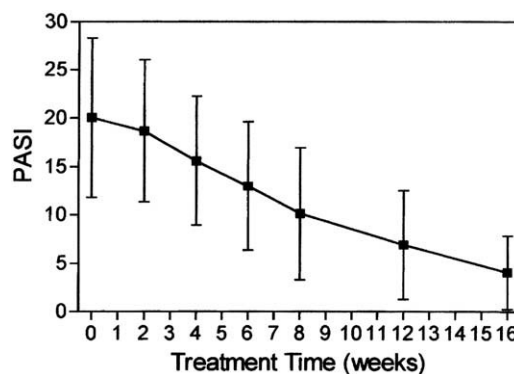


Fig. 2 With permission from Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol* 1998;138:456-60. Psoriasis Area and Severity Index.

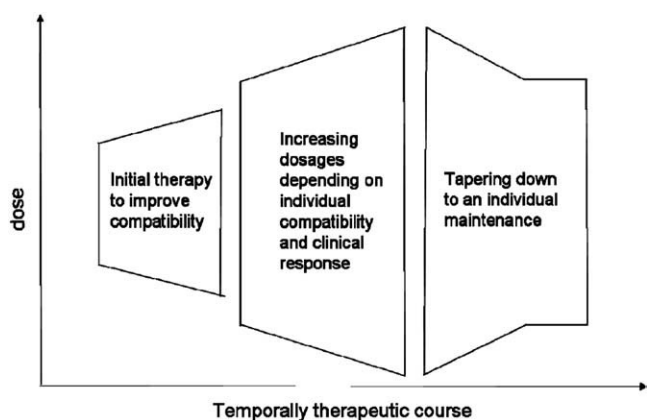


Fig. 3 Fumarate dosage during the therapeutic course.

psoriasis.^{10,11} Studies have shown the clinical efficacy and safety of Fumaderm during a 4-month treatment of severe psoriasis vulgaris.^{4,5} Because psoriasis is a chronic disease, the long-term clinical efficacy and adverse events of FAEs are important factors. FAEs were also effective after a treatment of 2 and 3 years.^{12,13}

In 2003, Hoefnagel and colleagues⁶ confirmed that FAEs are safe for long-term treatment in patients with severe psoriasis. A total of 41 of 66 patients received FAEs for at least 1 year, and 12 of these 41 patients received FAEs for 10 to 14 years continuously. Adverse events were reported in 73% of the patients, and the spectrum resembled that of short-term treatment. There was no evidence of a higher susceptibility to develop malignancies or infections.

In vivo pharmacokinetics of fumaric acid esters

Currently, little is known about the pharmacokinetics of FAEs, but it is generally recognized that DMF is the most important ingredient of Fumaderm. We describe the metabolic fate of DMF, according to the state of scientific knowledge, after oral intake in the form of enteric-coated tablets.

Once DMF has been released in the small intestine, it is partially saponified (basic hydrolysis) to its main metabolite monomethylfumarate (MMF) in the alkaline environment of the small intestine.¹⁴ At the same time, DMF is exposed to various esterases, a class of enzymes associated with the intestinal lumen and mucosa. These enzymes could hydrolyze DMF, also forming MMF (Fig. 1). Studies with excised porcine intestinal mucosa proved that no DMF penetrates through this layer.¹⁵ These findings clearly demonstrate that the mucosa and intestinal alkaline milieu represent a strong presystemic metabolic barrier for DMF on its way into the systemic circulation.

In case of penetration of DMF, which was eventually not metabolized at this "barrier," it would be transported via the blood of the portal vein to pass the liver first. The liver is an

organ with a high metabolism rate and esterases are located in high concentrations. Metabolism studies with liver S9 fractions showed a complete degradation of DMF within 1 minute.¹⁵

To summarize, DMF underlies a strong first-pass metabolism. This may explain why DMF's main metabolite MMF, but no DMF, has been detected in the plasma of human beings after the oral intake of DMF along with calcium MEF in the form of enteric-coated tablets.¹⁶

A further degradation of systemic MMF to fumaric acid, resulting in higher plasma levels of fumaric acid, was not observed,¹⁶ which is why Schweckendiek's¹ original idea that psoriasis results from a fumaric acid deficiency is no longer accepted today.

Cytochrome P450 is an essential detoxifying enzyme system (phase I metabolism) of the body. Interactions with enzymes of this system could lead to insufficient detoxification of xenobiotics. This is of particular importance because psoriasis is frequently associated with other diseases requiring concomitant medications. There is no metabolism of FAEs through cytochrome P450-dependent pathways, and drug interactions have not been reported.^{15,17}

In regard to the extent of adverse effects such as flush or diarrhea, considerable individual differences were observed. These adverse effects seem to correlate with the individual resorption capability. There is no evidence for mutagenic or teratogenic effects of FAEs.

Fumaric acid ester therapy: Important pathogenetic components of psoriasis

The characteristics of psoriasis are hyperproliferation of keratinocytes and infiltration of inflammatory cells, including dendritic cells (DCs), lymphocytes, and granulocytes, into the skin.

Psoriasis is regarded as an immune disorder in which a putative antigen presented to T cells by antigen-presenting DCs leads to the generation of specifically activated T cells. In skin lesions, T cells producing type 1 cytokines are dominant^{18,19} and the majority of DCs promote T-helper (Th) 1-mediated immune responses. Of interest is whether FAE can influence this inflammatory process by modulation of T-cell activation or cytokine production. The effects on DCs, which regulate the development of various Th subsets, were investigated.

Early studies clearly demonstrated that FAEs have profound effects on the T-cell system. In 94% of Fumaderm-treated patients, leukocytopenia was observed. CD4⁺ and CD8⁺ T cells decreased significantly; however, clinical signs of immunosuppression (eg, infections) were not observed. A decrease in the number of peripheral T cells is associated with a reduction of the lesional T-cell infiltrate.²⁰

A histologic-immunohistologic study of Fumaderm-treated patients, from whom skin biopsies were taken, revealed a significant reduction of T cells beneath the

epidermis.²¹ Although fumarate treatment leads to a profound decrease in the number of T cells in some patients, which may be a reason to stop therapy, adverse events related to a decreased immunosurveillance have not been observed in short- or long-term studies.⁶

In vitro pharmacokinetics

In most biological assays, DMF exerts pharmacodynamic effects that are more potent than those of MMF. In vivo MMF, but neither DMF nor fumaric acid itself, was detected in the plasma of human beings after the oral intake of a single tablet containing DMF along with calcium MEF.¹⁶

MEF seems to be of secondary importance for the treatment of psoriasis. A study in 1989 verified that MEF monotherapy, in contrast with DMF monotherapy, was not superior to placebo.¹⁰ These data suggest that MMF is the active species of FAEs in vivo.

In vitro results describing the pharmacodynamic effects of MMF and DMF have been reported. The focus was the effects of MMF. MMF induced the production of Th2-type cytokines, which are thought to have a protective role in psoriasis by dampening the activity of Th1 cytokines, but showed no effect on Th1 cytokines. By using radioactive labeled MMF and DMF, the authors provided evidence for specific binding sites for MMF on T cells.²²

MMF modulated DC polarization, enabling these cells to down-regulate the production of proinflammatory interferon- γ by Th cells.²³ MMF and DMF inhibited the monocyte-derived DC differentiation, resulting in cells that could not appropriately mature to DCs. These cells were less effective in stimulating type 1 cytokines than type 2 cytokines.^{24,25}

Because granulocytes play an important role in the pathophysiology of psoriasis, the effect of MMF on these cells was investigated. MMF stimulated polarization and elastase release, and enhanced the intracellular killing of bacteria by granulocytes.²⁶ In human macrophages and granulocytes, DMF and MMF stimulated bacteria-induced generation of reactive oxygen intermediates, substantiating that MMF exerts biological effects in certain in vitro systems.^{26,27}

The nuclear factor kappa B (NF κ B) pathway regulates apoptosis and the synthesis of cytokines and adhesion molecules. Loewe and colleagues²⁸ showed that DMF inhibits NF κ B translocation in human endothelial and T cells. Apoptotic phenomena of DMF-treated cells were reported for many cell types (HaCaT keratinocytes, lymphocytes, DC, HL-60 cells) and therefore do not seem to be cell specific.

As an α , β -unsaturated carbonylic compound DMF could react as a Michael-like receptor with the sulfhydryl group of the tripeptide glutathione (gly-cys- γ -glu [GSH]). Intracellular GSH depletion of retinal pigment epithelial cells after the initial treatment with DMF is followed by a time-delayed (>24 hours) increase of GSH of more than 2-fold.²⁹ Intracellular changes of GSH influence the redox potential

of cells. Exner and colleagues³⁰ showed that GSH and the redox potential of the cell are components of the cell-signaling system regulating the nuclear translocation of NF κ B. DMF most likely exerts its effects on NF κ B and the following signal cascades by modulating the GSH content and therefore the redox state of cells. Evidence shows that, in addition to DMF, MMF inhibits NF κ B activation in DCs.²³

Conclusions

DMF is more lipophilic than MMF, so the penetration of DMF into cells occurs at a faster rate and in larger quantities compared with MMF. This indicates a rapid resorption of DMF in the small intestine followed by a pronounced first-pass metabolism, resulting in measurable plasma levels of MMF. DMF seems to act as a prodrug to provide therapeutic levels of MMF or another metabolite of FAEs.

Future research should focus on in vitro experiments with MMF. The time-dependent changes of intracellular GSH and bioavailability of this compound should always be taken into account when interpreting the results in DMF in vitro studies. More in vivo studies are necessary to investigate the pharmacokinetics of FAEs.

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