

# Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use

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## Summary

Fumaric acid ester (FAE) therapy has proved to be safe and effective in patients with severe psoriasis vulgaris. This treatment was introduced nearly 30 years ago, but is only now gaining renewed interest among dermatologists. FAE therapy is licensed in Germany and registration is pending in many European countries. Multicentre trials have confirmed the beneficial effect of FAE in psoriasis and have defined the spectrum of its adverse effects. Although the mode of action of FAEs in the treatment of psoriasis is not fully understood, recent experimental data point towards a skewing of the Th1-dominated T-cell response in psoriasis to a Th2-like pattern, and inhibition of proliferation of keratinocytes. This article reviews the experimental and clinical information on FAEs in psoriasis and provides guidelines for the clinical use of FAEs derived from a consensus meeting of leading experts.

*Key words:* fumaric acid esters, psoriasis, treatment guidelines

In 1959, the German chemist Schweckendiek first reported a beneficial effect of fumaric acid in the systemic treatment of psoriasis.<sup>1</sup> He suffered from this disease himself and hypothesized that disturbances in the citrate cycle might result in the clinical appearance of psoriatic lesions. Schweckendiek tried several forms of fumarates himself and developed a mixture of different fumaric acid esters (FAEs) with a higher efficacy and bioavailability than fumaric acid itself. Since then, FAEs have been used experimentally by a number of physicians, mainly in Germany and the Netherlands. In recent years, the effectiveness of FAEs has been proven in controlled clinical trials;<sup>2,3</sup> and a defined mixture of FAEs has been registered for the treatment of psoriasis.

## Pharmacological properties of fumaric acid esters

Fumaric acid and its esters are a group of simple-structured compounds (Fig. 1). Because fumaric acid itself is poorly absorbed after oral intake, esters are used for treatment. In Germany, a defined mixture of FAEs is registered. The composition of this mixture is shown in Table 1. FAEs are almost completely absorbed in the

small intestine. Dimethylfumarate is rapidly hydrolysed by esterases to monomethylfumarate, which is regarded as the active metabolite. Monomethylfumarate is further metabolized in the citrate cycle into water and carbon dioxide (R.K.Joshi, Fumapharm AG, Switzerland, personal communication). There is no evidence for a cytochrome P450-dependent metabolism of FAE. Excretion of metabolites is mainly through breathing, with only small amounts being excreted via urine or faeces.

Dimethylfumarate has a half-life of about 12 min, and monomethylfumarate of 36 h. Peak concentrations of monomethylfumarate are seen between 5 and 6 h. Dimethylfumarate and free fumaric acid do not bind to serum proteins. Monomethylfumarate shows a protein binding of about 50%. Studies in animals showed no teratogenic potential of FAEs in therapeutic concentrations. There is no evidence for mutagenicity of the single compounds of the FAE mixture in humans (R.K.Joshi, personal communication).

## Mode of action

In recent years, many investigations have been performed in order to define the mode of action of FAEs in the treatment of psoriasis. De Jong *et al.*<sup>4</sup> showed modulation of cytokine secretion in activated T cells

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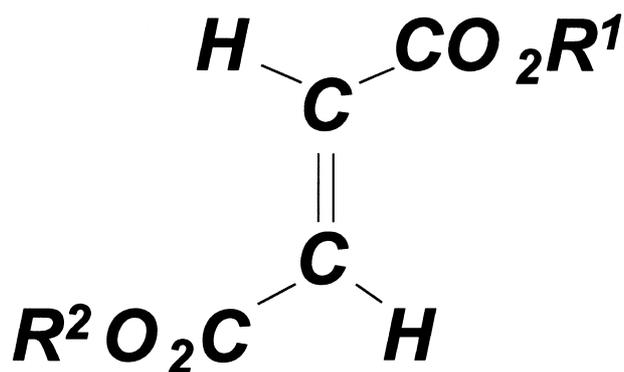


Figure 1. Chemical structure of fumaric acid esters.

by monomethylfumarate. They found a 10-fold increase in the production of interleukin (IL)-4 and IL-5 in CD2/CD8 monoclonal antibody-stimulated CD4 + CD54RO – (primed) T cells by monomethylfumarate without an effect on the production of IL-2 and interferon (IFN)- $\gamma$  or on cell proliferation. Monomethylfumarate induced IL-4 and IL-5, but no IFN- $\gamma$  secretion, in Th1/Th0 clones challenged with bacterial antigen. In experiments using psoriatic and normal keratinocytes cocultured with HUT78 T cells, dimethylfumarate inhibited IFN- $\gamma$  secretion and enhanced the production of the Th2 cytokine IL-10.<sup>5</sup> In human peripheral blood mononuclear cells, monomethylfumarate was found to increase production of tumour necrosis factor (TNF)- $\alpha$ , IL-10 and IL-1 receptor antagonist, without an effect on IL-12 secretion.<sup>6</sup>

Previous studies have repeatedly shown a persistent decrease in the lymphocyte count during FAE therapy. Flow cytometric analysis in 10 patients with psoriasis showed a significant decrease in peripheral T cell numbers during FAE therapy for 1 year (CD8 + cells, 90% reduction; CD4 + cells, 53% reduction).<sup>7</sup> These data indicate a shift towards Th2-like cytokine secretion induced by dimethylfumarate and its metabolite monomethylfumarate.

### Effects of fumaric acid esters on keratinocytes

Several investigations have focused on the effect of FAEs

on keratinocyte proliferation and activation. Sebök *et al.*<sup>8</sup> reported inhibition by dimethylfumarate (0.4–960  $\mu\text{mol/L}$ ) of HaCaT cell proliferation as measured by [<sup>3</sup>H]thymidine incorporation. Other FAEs tested were less potent compared with dimethylfumarate. However, in this study, cellular cytotoxicity of dimethylfumarate increased continuously above a concentration of  $\geq 12 \mu\text{mol/L}$ , as determined by the release of lactate dehydrogenase.

Thio *et al.*<sup>9</sup> showed a rapid and transient release of intracellular calcium induced by dimethylfumarate and monomethylfumarate in normal human and SV40-transformed keratinocytes. Furthermore, the authors observed an almost complete (90%) inhibition of keratinocyte proliferation at 100  $\mu\text{mol/L}$  dimethylfumarate and 1000  $\mu\text{mol/L}$  monomethylfumarate. Cytotoxicity was not detected at concentrations of FAEs tested in the range 200–800  $\mu\text{mol/L}$ .

A subsequent investigation demonstrated that dimethylfumarate dose-dependently inhibited the expression of intercellular adhesion molecule-1 (ICAM-1) in IL-1 $\alpha$ -stimulated HaCaT cells.<sup>10</sup> In a recent study, it was shown that dimethylfumarate suppressed IFN- $\gamma$ -induced expression of ICAM-1 and HLA-DR in HaCaT cells, but not, however, in IFN- $\gamma$ -exposed normal human keratinocytes in primary culture.<sup>11</sup>

### Other *in vitro* effects of fumaric acid esters

Nibbering *et al.*<sup>12</sup> demonstrated that in human neutrophil granulocytes, dimethylfumarate and monomethylfumarate inhibited the formylated peptide-induced respiratory burst, but enhanced cellular polarization, chemotaxis and calcium mobilization. Vandermeeren and coworkers<sup>13</sup> showed inhibition of TNF- $\alpha$ -induced expression of ICAM-1, E-selectin and vascular cell adhesion molecule-1 by dimethylfumarate in human umbilical vein endothelial cells.

As compared with other compounds used for the systemic therapy of psoriasis (e.g. cyclosporin), relatively high doses of FAEs are required to exert pharmacological effects *in vitro* and *in vivo*. The inhibitory

Table 1. The composition of the mixture of fumaric acid esters licensed in Germany

	Fumaderm® initial (low strength tablets)	Fumaderm® (high strength tablets)
Dimethylfumarate	30 mg	120 mg
Ethylhydrogenfumarate Ca salt	67 mg	87 mg
Ethylhydrogenfumarate Mg salt	5 mg	5 mg
Ethylhydrogenfumarate Zn salt	3 mg	3 mg

**Table 2.** Concentrations of fumaric acid esters (FAEs) required to obtain significant *in vitro* effects on different target cells and cellular activities

Target cells	Cellular activity	Inhibition/ stimulation	FAE	Concentration	First author and reference
Lymphocytes	Proliferation	Inhibition	Monoethylfumarate	1000 µmol/L	Petres <sup>2,3</sup>
Lymphocytes	IL-4/IL-5 production	Stimulation	Monomethylfumarate	200 µmol/L	De Jong <sup>4</sup>
HaCaT cells	Proliferation	Inhibition	Dimethylfumarate	0.4-960 µmol/L <sup>a</sup>	Sebökö <sup>8</sup>
Endothelial cells (HUVEC)	Expression of ICAM-1, VCAM-1 and E-selectin	Inhibition	Dimethylfumarate	100 µmol/L	Vandermeeren <sup>13</sup>
Neutrophil granulocytes	Respiratory burst	Inhibition	Monomethylfumarate	200 µmol/L	Nibbering <sup>12</sup>

<sup>a</sup> At dimethylfumarate concentrations  $\geq 12$  µmol/L, a significant release of lactate dehydrogenase from HaCaT cells was observed after 48 h, indicating a toxic effect of the compound. IL, interleukin; HUVEC, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

activity of FAEs on the proliferation of lymphocytes and human keratinocyte cell lines, as well as on the production of Th2 cytokines, with regard to the concentrations necessary to obtain a significant effect, are shown in Table 2. In summary, the experimental data published so far reveal a rather complex mode of action of FAEs in psoriasis, targeting mainly T cells and keratinocytes.

### Clinical experience

Following Schweckendiek's original observation, for some time only case reports and open studies with a small number of patients were published, and provided conflicting data about the effectiveness of FAEs in psoriasis. Nieboer *et al.*<sup>14</sup> were the first to investigate the clinical effect of different FAEs in a comparative study in psoriatic patients. They found that a combination of monoethylfumarate and dimethylfumarate was superior to dimethylfumarate alone, whereas monoethylfumarate alone was ineffective.

The first randomized, double-blind trial of FAE therapy for psoriasis was published by Nugteren-Huying *et al.*<sup>15</sup> in 1990. Three groups consisting of a total of 39 patients with psoriasis were treated for 4 months with FAEs. The first group of patients received a mixture of dimethylfumarate and monoethylfumarate (calcium, magnesium and zinc salts), while the second group was treated with a mixture of octylhydrogenfumarate and monoethylfumarate as zinc and magnesium salts. Placebo tablets were given to the third group. The results showed a reduction in the lesional skin area of 68% in the group treated with a combination of dimethylfumarate and monoethylfumarate, while the groups treated with octylhydrogenfumarate and

monoethylfumarate or with placebo showed only a marginal clinical response.

In a further clinical study conducted as an open trial, Kolbach and Nieboer<sup>16</sup> treated 196 psoriasis patients with a commercial formulation of FAEs (Fumaderm<sup>®</sup>) or with dimethylfumarate alone for up to 2 years. In this study, the mixture of FAEs was clearly superior to dimethylfumarate treatment alone with regard to clinical efficacy. Thio *et al.*<sup>17</sup> confirmed the results obtained in previous studies in 83 psoriasis patients treated with the commercial mixture of FAEs for up to 3 years.

A randomized, double-blind, placebo-controlled study with FAEs for severe psoriasis was initiated by Altmeyer and coworkers.<sup>2</sup> This study showed improvement of lesions in 70% of patients after 4 months of treatment with the commercial mixture. In addition, a recent prospective multicentre study of 101 patients revealed a mean reduction in the psoriasis area and severity index of 80% after 4 months of treatment with Fumaderm<sup>®</sup>. This was seen in the 70 patients who completed the study.<sup>3</sup> Discontinuation of therapy was mainly due to gastrointestinal complaints as well as non-compliance. In 10% of patients, the relative number of lymphocytes, as determined by the differential count, decreased below 50% of baseline values after 4 months of FAE treatment. Eosinophilia above 20% was seen in 9% of patients between weeks 4 and 8 of FAE therapy, and decreased to normal values at the end of the study.

The clinical trials conducted so far clearly demonstrate that FAE therapy is an effective and safe regimen for patients with severe psoriasis. In recent studies,<sup>2,3,17</sup> a licensed defined mixture of different FAEs was used, and the results obtained have substantiated the clinical

experience in the older reports. There is a characteristic spectrum of adverse events in FAE treatment, and patients can be easily monitored during the course of therapy.

### Adverse events in fumaric acid ester therapy for psoriasis

The most frequently noted adverse events associated with FAE treatment are gastrointestinal complaints, which occur in more than two-thirds of patients.<sup>3,18</sup> The symptoms vary from mild stomach upsets, increased frequency of stools and tenesmus, to stomach cramps, tympanites and diarrhoea; these become most frequent between weeks 4 and 12.<sup>18</sup> Flushing is seen in about one-third of patients treated with FAE. Symptoms include a sudden redness of the skin and a sensation of heat lasting between a few minutes and a few hours. Headaches may be associated. Frequency of flushing is greatest at the onset of therapy and decreases with prolonged treatment time. Both adverse events lead to drug withdrawal in about 7% of patients.<sup>3</sup>

A significant decline in lymphocyte numbers is observed in nearly all (94%) psoriasis patients under FAE treatment.<sup>19</sup> In about 10% of patients, a decrease of > 50% compared with baseline values is seen.<sup>2,3,18</sup> Both T cells and B cells are decreased during FAE treatment.<sup>19</sup> A steady rise in lymphocyte numbers up to baseline values after drug withdrawal is observed. Transient eosinophilia is a laboratory abnormality associated with FAE therapy, occurring in about 50% of patients, with a maximum frequency between weeks 4 and 8.<sup>3,18</sup> In some patients, the relative number of eosinophils in the differential count exceeds 40%.

Older case reports documented acute renal failure linked to FAE therapy for psoriasis.<sup>20–22</sup> However, in subsequent studies and multicentre trials, there has been no evidence for an impairment of renal function. In the light of these data, it can be concluded that FAEs do not possess nephrotoxic potential when used as recommended.

In psoriasis patients treated with FAEs for up to 3 years, liver enzymes (40% of patients), cholesterol (17%), triglycerides (8%), serum potassium (15%) and serum creatinine (4%) as well as proteinuria (11%) were found to be increased.<sup>17</sup> However, in other studies, significantly elevated liver enzymes have not been reported as a result of FAE therapy.<sup>2,3</sup> An increased risk of infectious diseases, secondary infections or cancer has not so far been reported in patients treated with FAEs.

### Guidelines for the treatment of severe psoriasis with fumaric acid esters

In order to improve safety and efficacy of FAE treatment for psoriasis, the following guidelines have been established. They are the result of a German consensus meeting of experts in the field of psoriasis treatment with particular experience of FAEs. The guidelines represent the state-of-the-art knowledge about the clinical use of FAEs for patients with severe psoriasis. As the licensing of FAEs is pending in several European countries, these guidelines may be a valuable resource for dermatologists using these drugs for the first time.

#### Who should be treated?

Patients should be more than 18 years of age with a severe, relapsing psoriasis vulgaris which is refractory to conventional therapy. There are reports on the beneficial effect of FAE therapy for pustular psoriasis and psoriatic arthritis.

Patients with severe concomitant diseases, chronic diseases of the gastrointestinal tract and/or the kidneys, or with diseases leading to leucocytopenia or leucocyte dysfunction should not be treated with FAEs. Pregnant or lactating women and patients with malignant diseases (including a history of malignancy) should be excluded from FAE treatment. In children, FAEs should be used with great caution due to current lack of experience.

#### Dosage and monitoring

The dosage in FAE treatment should follow the established schedule shown in Table 3. After treatment response is achieved, the dose should be individually adjusted. The maximum dose is 1.2 g/day FAE (six high strength tablets). In special cases the dose can be increased more rapidly, but this procedure requires close clinical and laboratory monitoring.

Patients should be followed regularly under FAE treatment. Besides clinical assessment, the following laboratory parameters should be monitored: serum creatinine, blood urea nitrogen, alanine and aspartate aminotransferases and gammaglutamyl transferase, routine haematology including white cell differential count, and urine dip-stick. Laboratory parameters should be determined before starting FAE therapy (baseline visit), at monthly intervals for the first 6 months, and bimonthly thereafter.

Week	Morning	Noon	Evening	FAE formulation
1	1	–	–	A
2	1	–	1	A
3	1	–	1	A
4	1	–	–	B
5	1	–	1	B
6	1	1	1	B
7	2	1	1	B
8	2	1	2	B
9	2	2	2	B

**Table 3.** Dosage schedule (number of tablets) for treatment of severe psoriasis with fumaric acid esters (FAEs) using the commercial FAE mixture Fumaderm<sup>®</sup>

A, low strength (Fumaderm<sup>®</sup> initial); B, high strength (Fumaderm<sup>®</sup>).

### Duration of treatment

Treatment with FAEs should be continued until an improvement in psoriasis is achieved and the patient is satisfied with the therapeutic result. Prolonged therapy (up to 2 years) to prevent relapse in psoriasis patients with high disease activity is possible. Another therapeutic option for FAE treatment is short-course intermittent therapy. FAEs are given until a major improvement is achieved and are then withdrawn. After occurrence of new lesions, FAEs can be re-introduced. If a patient remains lesion-free during prolonged treatment, the FAE dose should be gradually decreased to reach the individual's threshold.

### Reduction of dose and termination of treatment

A reduction in FAE dose is required in the following situations: decrease in leucocyte count to below  $3.0 \times 10^9/L$ ; decrease in lymphocytes to below  $0.5 \times 10^9/L$ ; persistent eosinophilia  $\geq 25\%$ ; rise in serum creatinine 30% above baseline; development of proteinuria. If the abnormal parameter improves, treatment with FAEs can be continued at a reduced dose. In case of a persistent abnormality or a further deterioration, FAEs must be withdrawn.

Termination of treatment is indicated if there is no treatment response, or in case of severe adverse events, occurrence of pregnancy during treatment (as a precaution pending further clinical experiences) or development of malignancy. Therapy with FAEs can be stopped abruptly. Rebound phenomena have not been observed.

### Combination treatment and drug interactions

FAEs are recommended in combination with topical

antipsoriatic compounds such as salicylic acid, dithranol, vitamin D<sub>3</sub> analogues, retinoids (tazarotene), corticosteroids, coal tar and bland emollients. FAEs should not be combined with ultraviolet (UV) treatment (UVA, UVB or photochemotherapy), as FAEs may be immunosuppressive agents. There are, however, no reports on the development of cutaneous malignancies using a combination of FAEs and UV radiation. Immunosuppressive agents or compounds with nephrotoxic potential should not be used in combination with FAEs. There are no reported interactions of FAEs with other drugs.

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