British Journal of Dermatology 2004; **150:** 630–632. DOI: 10.1111/j.0007-0963.2004.05903.x

TOPICAL REVIEW

Fumaric acid esters, their place in the treatment of psoriasis

A.D.ORMEROD AND U.MROWIETZ*

Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB15 8SG, U.K.
**Department of Dermatology, University of Schleswig-Holstein, Campus Kiel, Schittenhemstrasse 7, 24105 Kiel, Germany*

Accepted for publication 18 November 2003

Fumaric acid esters (FAE) have evolved as a therapy for psoriasis through an unusual route, beginning with self-experimentation by the German chemist Schweckendiek whose premise was that psoriasis might be due to an aberration of the citric acid cycle. While this is not the case, our understanding of the active moiety, its mode of action and place in psoriasis therapy are still developing. However, there is cumulating evidence that dimethylfumarate (DMF), the main ingredient of the marketed mixture, is the active compound.

Hoefnagel *et al.* recently reported on the long-term effects and safety of FAE[1] and Mrowietz *et al.* published a consensus statement regarding the appropriate use of this therapy in psoriasis in 1998.[2] An article in this issue of the journal[3] is among the first to explore the possibilities of combination therapy, adding FAE to other second line drugs to treat patients with more difficult and severe psoriasis that is unresponsive to conventional modalities.

The clinical development has been partly in the Netherlands but mainly in Germany where the German psoriasis patient organization promoted licensing of the product Fumaderm® (Fumapharm AG, Lucerne, Switzerland) which constitutes a mixture of dimethylfumarate and calcium, magnesium, and zinc salts of monoethyl hydrogen fumarate.

A large number of patient-years' experience of therapy have been established in the German experience after inauguration of treatment in 1959 and registration of Fumaderm® in 1994. Nugteren-Huying *et al.*[4] showed that lesional area was reduced by 68% with the combination of DMF and monoethylfumarate. The long-term safety and efficacy of the commercial product were demonstrated in an open study of 196 patients treated with Fumaderm® or DMF alone for up to 2 years.[5] In a first double-blind, placebo-controlled study the efficacy of Fumaderm® in the treatment of severe psoriasis vulgaris was established.[6] Another prospective study of 101 patients showed a 75% reduction in psoriasis area and severity index (PASI) in 4 months observed in the per protocol population of 70 patients.[7] However, all studies have a high dropout rate because of gastrointestinal complaints which occur in up to 60% of patients, and flushing in 30% of patients which is worse at the onset of therapy. There is some evidence that pentoxifylline helps prevent flushing[8] and that flushing declines with ongoing therapy.

Recently, Hoefnagel *et al.*[1] reported a useful series of long-term follow-up studies of 41 patients treated for a year and 12 treated for 10–14 years with FAE. Of these patients, 73% had adverse events, usually mild, consisting of flushing, diarrhoea, nausea, tiredness and stomach pains while, in the blood, transient eosinophilia was observed in 14–25% and lymphocytopenia (less than 20% of white cells) was observed in 76% leading to withdrawal of treatment in four patients. The median lymphopenia was a 5·5% reduction and reached a plateau without progressive lymphopenia between 1 year and 12 years of therapy. Raised liver enzymes, usually γ-glutamyl transpeptidase, are a common finding found in 25% of patients; this is usually reversed on stopping therapy. Raised creatinine was found in one patient who was subsequently retreated without this problem. Overall there are no reports of severe long-term toxicity or development of neoplasias or a higher susceptibility for bacterial infections, thus making FAE a safe regimen compared with other agents. Published guidelines for therapy[2] recommend a schedule of gradual incremental introduction and reduction if lymphocytes fall below $0{\cdot}5 \times 10^9\ L^{-1}$ or leucocyte counts below $3{\cdot}0 \times 10^9\ L^{-1}$.

However, the guidelines do not allow for combination therapy with drugs other than topical treatments

Correspondence: A.D.Ormerod.
E-mail: a.d.ormerod@btinternet.com

as explored by Balasubramaniam *et al.* in this issue.[3] Balasubramaniam *et al.*[3] have pioneered the combination of FAE in combination with second line drugs—ciclosporin, methotrexate, hydroxyurea and acitretin for additional benefit or to facilitate dose reduction in second line therapeutic agents. Inevitably the numbers of patients so treated are small and it is too early to conclude the safety of these combinations; nevertheless a new potential avenue for combination therapy is presented and once more FAE appear less toxic than other drugs, potentially making the combinations ideal. By way of caution patients were closely monitored and the dose escalation proceeded more slowly and cautiously than for FAE monotherapy.

At the beginning of fumarate treatment rare cases of nephrotoxicity were reported; however, in all controlled trials this adverse event has never occurred. In a prospective study of kidney changes during fumarate treatment a reversible micromolecular tubular proteinuria has been seen, but the glomerular filtration rate was unaffected[9] and it is therefore recommended to monitor also for proteinuria. There is experimental evidence in rats and mice that fumaric acid monoethylester may be responsible for this effect.[10] Also very rare cases of secondary osteomalacia have been reported.[11]

The mode of action of FAE is thought to be mainly an inhibition of T-cell activity partly due to the induction of preferential apoptosis in activated T cells,[12] and there is some evidence for a shift from a T-helper (Th) 1-type response to a Th2-type pattern so that the production of interleukin (IL)-10 inhibits the key Th1 cytokines IL-2, IL-12 and interferon (IFN)-γ. *In vitro* studies showed that in psoriatic keratinocyte and lymphocyte cocultures IFN-γ was inhibited and IL-10 was increased.[13] Activated lymphocytes in the presence of anti-CD3/CD28 showed increased IL-4 and IL-5 production; this is consistent with the eosinophilia observed in the early stages of therapy.[14] However, *in vivo* studies showed that in longer-term treatment, IL-4 and IL-10 levels diminish with IFN-γ in response to phytohaemagglutinin stimulation of peripheral blood mononuclear cells.[15] A very recent investigation showed that the major ingredient DMF is the most potent antiproliferative component. DMF and its main metabolite methyl hydrogen fumarate are potent inhibitors of dendritic cell differentiation.[16] DMF was also shown to induce apoptosis in higher concentrations.[16] Many of the experimental results obtained with FAE may be related to the observation that DMF is also a potent inhibitor of nuclear factor B translocation.[17,18]

Particularly where the wider licensing of fumaric acid esters and its introduction as a combination treatment are concerned it would be desirable to study the cleaner profile of DMF alone, rather than the complex mixture of Fumaderm®.

References

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

2 Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. *Br J Dermatol* 1999; **141**: 424–9.

3 Balasubramaniam P, Stevenson O, Berth-Jones J. Fumaric acid esters in severe psoriasis including experience of use in combination with other systemic modalities. *Br J Dermatol* doi: 10.1111/j.0007-0963.2004.05739.

4 Nugteren-Huying WM, van der Schroeff JG, Hermans J *et al.* [Fumaric acid therapy in psoriasis; a double-blind, placebo-controlled study]. *Ned Tijdschr Geneeskd* 1990; **134**: 2387–91.

5 Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. *J Am Acad Dermatol* 1992; **27**: 769–71.

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

7 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.

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

9 Boesken WH, Oser B, Roth J *et al.* Nephrotoxische Wirkungen durch Fumarsäure-Derivate in der Behandlung der Psoriasis vulgaris. *Nieren Hochdruckkrankheiten* 1998; **27**: 145–50.

10 Hohenegger M, Vermes M, Sadjak A *et al.* Nephrotoxicity of fumaric acid monoethylester (FAME). *Adv Exp Med Biol* 1989; **252**: 265–72.

11 Fliegner L, Spiegel P. Osteomalazie als offenbar seltene Nebenwirkung der oralen Fumarsäuretherapie. *Hautarzt* 1992; **43**: 554–60.

12 Treumer F, Zhu K, Gläser R, Mrowietz U. Dimethylfumarate is a potent inducer of apoptosis in human T cells. *J Invest Dermatol* 2003; **121**: 1383–8.

13 Ockenfels HM, Schultewolter T, Ockenfels G *et al.* The antipsoriatic agent dimethylfumarate immunomodulates T-cell cytokine secretion and inhibits cytokines of the psoriatic cytokine network. *Br J Dermatol* 1998; **139**: 390–5.

14 de Jong R, Bezemer AC, Zomerdijk TP *et al.* Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. *Eur J Immunol* 1996; **26**: 2067–74.

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

16 Zhu K, Mrowietz U. Inhibition of dendritic cell differentiation by fumaric acid esters. *J Invest Dermatol* 2001; **116**: 203–8.
17 Loewe R, Holnthoner W, Groger M *et al.* Dimethylfumarate inhibits TNF-induced nuclear entry of NF-kappa B/p65 in human endothelial cells. *J Immunol* 2002; **168**: 4781–7.
18 Vandermeeren M, Janssens S, Wouters H *et al.* Dimethylfumarate is an inhibitor of cytokine-induced nuclear translocation of NF-kappa B1, but not RelA in normal human dermal fibroblast cells. *J Invest Dermatol* 2001; **116**: 124–30.