

## TOPICAL REVIEW

## Fumaric acid esters, their place in the treatment of psoriasis

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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<sup>1</sup> and Mrowietz *et al.* published a consensus statement regarding the appropriate use of this therapy in psoriasis in 1998.<sup>2</sup> An article in this issue of the journal<sup>3</sup> 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<sup>®</sup> (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<sup>®</sup> in 1994. Nugteren-Huying *et al.*<sup>4</sup> 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<sup>®</sup> or DMF alone for up to 2 years.<sup>5</sup> In a first double-blind, placebo-controlled

study the efficacy of Fumaderm<sup>®</sup> in the treatment of severe psoriasis vulgaris was established.<sup>6</sup> 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.<sup>7</sup> 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<sup>8</sup> and that flushing declines with ongoing therapy.

Recently, Hoefnagel *et al.*<sup>1</sup> 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  $\gamma$ -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<sup>2</sup> recommend a schedule of gradual incremental introduction and reduction if lymphocytes fall below  $0.5 \times 10^9 \text{ L}^{-1}$  or leucocyte counts below  $3.0 \times 10^9 \text{ L}^{-1}$ .

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

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as explored by Balasubramaniam *et al.* in this issue.<sup>3</sup> Balasubramaniam *et al.*<sup>3</sup> have pioneered the combination of FAE in combination with second line drugs—cyclosporin, 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<sup>9</sup> 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.<sup>10</sup> Also very rare cases of secondary osteomalacia have been reported.<sup>11</sup>

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,<sup>12</sup> 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)- $\gamma$ . *In vitro* studies showed that in psoriatic keratinocyte and lymphocyte cocultures IFN- $\gamma$  was inhibited and IL-10 was increased.<sup>13</sup> 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.<sup>14</sup> However, *in vivo* studies showed that in longer-term treatment, IL-4 and IL-10 levels diminish with IFN- $\gamma$  in response to phytohaemagglutinin stimulation of peripheral blood mononuclear cells.<sup>15</sup> 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.<sup>16</sup> DMF was also shown to induce apoptosis in higher concentrations.<sup>16</sup> 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.<sup>17,18</sup>

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<sup>®</sup>.

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