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Fumaric Acid and Its Derivatives in the Treatment of Psoriasis Vulgaris: Our Experience in Forty-One Patients

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SUMMARY The use of fumaric acid esters in the treatment of psoriasis was first proposed in 1959. In the 1980s, more standardized oral preparations of fumaric acid esters were developed, containing dimethylfumarate and monoethylfumarate as the main compounds. In 1994, the drug was approved for the treatment of psoriasis in Germany, and since then it has become the most commonly used systemic therapy in this country. In the last few years, an oral integrator containing dimethylfumarate and monoethylfumarate (Psocaps, Dermatika s.r.l., Padua) has also been available in Italy for the treatment of psoriasis. In this paper we report on the history of treatment using fumaric acid esters and we describe our own experience during and following the treatment with such drugs in 41 patients affected by mild vulgar psoriasis. In our trial, an improvement in cutaneous psoriasis was observed in 46% of treated patients, while side effects were noticed in 52% of patients; only three patients dropped out due to gastrointestinal problems. Our results are comparable to literature data in terms of efficacy, safety and side effects.

KEY WORDS: psoriasis, fumaric acid, dimethylfumarate, monoethylfumarate

INTRODUCTION

The use of esters of fumaric acid in the treatment of psoriasis vulgaris was first proposed in 1959 and became the most common systemic treatment for psoriasis in Germany. In other parts of Europe except for Holland, and in the US, this treatment was not used. In the past few years, an oral integrator containing the most active derivatives of fumaric acid, i.e. monoethylesters (MEFAE) and dimethylesters (DMFAE), has been introduced in Italy.

The aim of this paper is to summarize the history of this treatment and to present our experience using fumaric acid derivatives in 41 patients affected by mild skin psoriasis.

History

The esters of fumaric acid have a long tradition in the oral treatment of psoriasis. The first usage was proposed in 1959 by Schweckendiek, a biochemical doctor affected by psoriasis, who used

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fumaric acid derivatives to cure himself (1,2). According to Schweckendiek, psoriasis is a metabolic disease which requires exogenous integration due to insufficient amount of fumaric acid in the psoriatic individual (1,2). This theory, however, has never been confirmed as it was essentially based on empirical principles.

Twelve years later, in 1972, Dubiel and Happle published an experimental study of 6 psoriatic patients that underwent topical and systemic treatment with fumaric acid monoethylester. Throughout the study, the ability of this drug to counteract psoriasis was emphasized; however, nephrotoxicity was too pronounced to allow its clinical use. Moreover, its topical use often caused irritant contact dermatitis (3).

In 1982, Schafer published the first study performed in a large number of patients (N=800) treated with fumaric acid ester (FAE) derivatives (DMFAE and MEFAE) in combination with topical fumaric acid therapy (1% to 3% MEFAE in an ointment or fumaric acid in bathing oils). Schafer reported that 70% of patients showed considerable improvement when using the drug, 15% achieved only modest improvement, whereas the remaining 15% of patients showed no improvement (4). In his quite uncritical article, however, there was no mention of any possible therapy associated side effects. In 1984, Raab published a scientific assessment of this treatment in which he claimed fumaric acid as such to be ineffective in the treatment of psoriasis; monoethylester would prove to be effective, but the therapeutic dose in humans would be burdened by high toxicity. (5).

In the late 1980s, more standardized oral preparations of FAEs were developed containing DMFAE and MEFAE as the main compounds. It was in 1987 that Bayard *et al*. performed an open study in which oral treatment was administered using a preparation containing a mixture of fumaric acid derivatives, both as initial monotherapy (3 months) and as long-term basic therapy (12-14 months), in 13 and 11 patients, respectively. Half of the patients that had responded only poorly to conventional antipsoriatic therapy showed significant improvement in a month period. In four patients the medication had to be withdrawn because of abdominal pain; two patients presented flushing, and four patients complained of gastrointestinal problems. No severe side effects or liver and kidney dysfunction were observed (6).

In 1989, Nieboer *et al*. published an open pilot study including 36 patients treated with a single fumaric acid derivative (instead of a mixture) for 9 months. The results revealed monoethylfumarate to be ineffective at dosages lower than 240 mg; a dosage to up to 720 mg was able to reduce itching and scaling, but did not affect psoriasis extension. On the contrary, DMFAE proved effective at a dosage of 240 mg, induced significant amelioration and prevented extension of the disease. The main side effects of fumaric acid derivatives were nausea, diarrhea, general malaise and severe stomachache (7).

One year later (1990), Nieboer *et al*. carried out a 4-month double-blind study to evaluate the effects of DMFAE (22 patients) and DMFAE plus MEFAE salts (23 patients). In both groups, 50% of patients showed considerable improvement of psoriasis. Therapeutic effects showed no significant differences with respect to either total psoriasis score or different parameters (the effects were slower in the group using DMFAE alone). In both groups, the most common side effects were flushing, stomachache and diarrhea. In laboratory testing, differences were most frequently recorded in lymphopenia and leukopenia. It was concluded that co-administration of MEFAE and DMFAE did not produce significantly better than DMFAE monotherapy (8).

In the same year, Nugteren-Huying *et al*. published the results of their randomized, double-blind placebo-controlled study. There was evidence that FAEs were effective in psoriasis and there were statistically significant differences between fumaric acid derivatives and placebo ($P<0.01$) (9).

In 1993, at the 4th European Symposium on Psoriasis in Trieste, Altmeyer described significant results from a 4-month randomized double-blind study in 100 patients. The study, published in 1994, compared a well-characterized formulation of fumaric acid derivatives at different concentrations with placebo in order to evaluate its therapeutic value. FAEs were administered in increasing dosage up to the maximum of 6 tablets a day (720mg/die). The results indicated statistically significant superiority of the fumaric acid derivatives over placebo. After 15-30 days of therapy, 53% of patients showed a 70% reduction of psoriasis; 19 patients dropped out due to gastrointestinal problems. However, only 25% of patients did not present any side effects. No response was observed in 18% of study patients (10).

In 1996, Altmeyer included 83 patients in a long-term open clinical trial to evaluate the efficacy and safety profile of FAE preparations as oral long-term therapy (12 months). The antipsoriatic effect was clear, with an average reduction of

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76% in PASI. Side effects were observed in 62% of study patients (11).

Up to the present day, therapeutic effects of fumaric acid derivatives are still being the subject of many multicenter trials that have confirmed the beneficial effects of a defined mixture of different FAEs in psoriasis; such trials have also confirmed the nature of side effects, usually flushing, diarrhea, nausea, tiredness and stomach complaints. Flushing, specifically, presents with erythematous eruption affecting the face and upper trunk. It is known to appear in the first hour following drug administration and usually disappears spontaneously in about an hour. Flushing does not represent a reason to justify interruption of treatment. Relative lymphocytopenia, transient eosinophilia and moderate liver enzyme elevation were observed in numerous patients. All these alterations are reversible upon therapy discontinuation. About 50%-70% of patients that achieved PASI 75 reported improvement within four months of treatment without any long-term toxicity, immunosuppressive effects or increased risk of infection or malignancy (12-17).

As far as data relating to the potential dose-sparing effect and safety issues are concerned, the studies showed that, when FAEs are combined with other systemic agents, they are generally able to bring about useful overall reductions in the doses of other drugs. There was no evidence of drug interactions; side effect profile of FAEs was similar to that previously reported (18).

We identified relevant articles and reviews, by systematic electronic searches, regarding the tolerability of therapy with FAEs in order to determine the safety aspects of their long-term use. The reported data relating to adverse events support previous results and suggest that FAEs offer a safe, efficacious and well-tolerated long-term oral treatment of psoriasis even in those patients that have previously been intolerant to conventional systemic therapy (19-23).

Their relatively low toxicity and hepatotoxicity make FAEs a reasonable first-line systemic treatment in selected patients with medium to severe psoriasis.

The systematic review and meta-analysis of randomized controlled trials on the efficacy and tolerability of biologic and nonbiologic systemic treatments for psoriasis, performed by Schmitt *et al*. in 2008, deserve consideration in that efalizumab was found to be significantly less efficacious than FAEs (24).

Pharmacokinetics

Several clinical studies have shown systemic therapy with FAEs to be efficacious and to have a good long-term safety profile in patients with moderate to severe psoriasis. For therapeutic use, tablets with a defined mixture of FAEs (dimethylfumarate [DMF] and three different salts of monoethylfumarate) have been registered in Germany. There is evidence that DMF is the most essential component in this formulation with an antipsoriatic effect (12,13). 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 human plasma after oral administration of FAEs (25). However, the molecular mechanisms of DMF activity are not completely understood.

Psoriasis is a chronic inflammatory skin disorder in which T cell-mediated immune responses are thought to play a prominent role. FAEs have proved to be an effective systemic treatment for psoriasis. DMF is known to induce potent depression of inflammatory cytokine secretion in human keratinocytes and peripheral blood mononuclear cells; it is also known to induce a Th2-like cytokine secretion pattern in T cells and to reduce keratinocyte proliferation *in vitro*, by mediating its immunomodulatory activity *via* the induction of the anti-inflammatory stress-protein heme oxygenase 1 (ho-1) (26-31). The more so, as dendritic cells (DC) regulate differentiation of T helper (Th) cells, and T cells play a crucial role in the pathogenesis of psoriasis, FAEs in psoriasis involve modulation of DC to allow these cells to down-regulate IFN-gamma production by Th cells (30). Additionally, it has been demonstrated that nuclear translocation of the activated transcription nuclear factor kappaB (NF-kappaB) is inhibited in human endothelial cells and fibroblasts activated by tumor necrosis factor-alpha (TNF-α). The NF-kappaB pathway plays a major role in regulating inflammatory cytokine production as well as in cell differentiation and apoptosis. T cell survival is also dependent on the activation of NF-kappaB and it has been demonstrated *in vitro* that DMF is an inducer of apoptosis in activated T cells (26,32). The evidence for a specific effect of DMF on NF-kappaB supports previous results suggesting that DMF specifically inhibits MSK1 and 2 activation and subsequently inhibits NF-kappaB-induced gene transcriptions, which are believed to be important in the pathogenesis of psoriasis (33). Furthermore, Rubant

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et al. provide early evidence that DMF affects adhesion molecule expression on human leukocytes and their rolling behavior *in vivo*, indicating that DMF directly affects the initial step of leukocyte extravasation (36).

PATIENTS, MATERIALS AND METHODS

Our study included 41 patients, 23 male and 18 female, mean age 53 (range 27-81) years, affected by mild vulgar psoriasis (PASI ranging from 4 to 10, mean 5.9). All patients were treated with an oral integrator (Psocaps, Dermatika s.r.l., Padua) containing the two most important fumaric acid derivatives, monoethylfumarate and dimethylfumarate. Only emollient creams were allowed to be used in association with systemic treatment. Each tablet contained both monoethylfumarate and dimethylfumarate at a dose of 42 and 72 mg, respectively (Table 1).

In the first week, 1 tablet a day (DMF 72 mg) was administered followed by 1 tablet twice a day in the second week and 1 tablet three times a day (216 mg a day of DMF) from the third week onwards.

Prior to taking part in the trial, patients were tested for complete blood count, creatinine, urea and liver enzymes. Complete blood count was then checked every month as a routine.

RESULTS

After 4 months of treatment, improvement was observed in 19 patients, whereas ten patients reported no changes, and six patients showed worsening of their skin condition. Three patients dropped out of the experiment, one due to follicu-

Table 1. Formulation of Psocaps (Dermatica s.r.l. Padua)

Micronized cellulose	154 mg
Ca carbonate	155 mg
Mg carbonate	100 mg
K carbonate	50 mg
Mg stearate	9 mg
Zinc oxide	6.25 mg
Glicine	6 mg
Vitamin B6 33%	3 mg
DMF	2 mg
MEF	42 mg

DMF = dimethylesters; MEF = monoethylesters

litis and two due to serious gastrointestinal pain. Flushing was the most common minor side effect, reported by nine patients. Other side effects were nausea and abdominal pain.

PASI was 5.9 at T0; 4.5 at one month of therapy; and 3.0 at four months of therapy. Study results are summarized in Table 2.

DISCUSSION

Fumaric acid esters (FAEs) are chemical compounds derived from unsaturated dicarbonic fumaric acid and their usage in the treatment of psoriasis was introduced late in 1982. In 1994, Fumaderm, an enteric-coated tablet containing DMF and calcium, magnesium and zinc salts of MEF, was approved for the treatment of psoriasis in Germany.

Several clinical studies have shown that systemic therapy with FAE in patients with moderate to severe psoriasis is efficacious and has a good long-term safety profile, even though the mechanisms of action have not yet been completely elucidated. Moreover, the relatively low toxicity and the absence of hepatotoxicity make FAE derivatives a reasonable first-line systemic treatment. Recently, Schmitt *et al*. performed a systematic review and meta-analysis of randomized controlled trials. They have consequently reported efficacy and tolerability of biologic and non-biologic systemic treatments approved for moderate to severe psoriasis by means of PASI: there is evidence that FAEs represent another therapeutic option for mild to medium (PASI 5-10) and medium to severe (PASI >10) psoriasis (24).

Unfortunately, there have been only few controlled studies so far and an effective therapeutic dosage has not yet been established.

We consider it noteworthy that FAE treatment is applicable, relatively well tolerated and requires few hematochemical controls.

Our data, although applying to a limited group (41 patients), were similar to those reported in the literature (Table 2). In our study, 46% of patients were successfully treated and 52% of patients reported side effects. Both these percentage figures are slightly lower than those found in the literature, possibly because a lower dosage of DMF (216 mg/die) was administered to our patients. The more so, we treated patients with mild psoriasis instead of medium to severe psoriasis. As for side effects, flushing and gastrointestinal problems were most commonly observed. It should be noted that we used an oral integrator containing both MEFAE

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Table 2. Literature data on therapeutic success and side effects (percentage)

	No. of patients	Therapeutic success	Side effects
Altmeyer *et al*. Hautarzt 1996	83	50%	62%
Mrowietz *et al*. Br J Derm 1998	101	63%	69%
Hoefnagel *et al*. Br J Derm 2004	66	73%	
Carboni *et al*. J Dermatol Treat 2004	40	82%	10%
Harries *et al*. Br J Dermatol 2005	58	55%	66%
Kokelj *et al*. 2009	41	46%	52%

and DMFAE; this preparation is chemically different from the drug used in Germany, therefore our data were not strictly comparable with those obtained by use of Fumaderm. Also, in the past different FAE preparations were used in previous studies and consequently the results were contradictory and difficult to interpret.

In conclusion, we can confirm that the efficacy of treatment with fumaric acid derivatives is readily visible as early as after 30-40 days, and that the benefit of combining a specific diet with the treatment, as first proposed by Schafer, still needs to be evaluated. However, following Schafer's intuition over 25 years ago, it is nowadays widely recognized that psoriasis is a metabolic syndrome and, consequently, an appropriate dietary regime is undoubtedly welcome in these patients.

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