Summary Systemic treatment of psoriasis with fumaric acid esters (FAE) has been found effective by empirical means. In recent years clinical studies have confirmed the antipsoriatic activity of a defined mixture of different FAE. The aim of the present prospective multicentre study was to investigate further the efficacy and safety of FAE therapy in a large number of patients with severe psoriasis vulgaris. From 101 patients included in the study 70 completed the treatment period of 4 months. Discontinuation was due to adverse events in seven, lack of efficacy in two, and other reasons, such as non-attendance for scheduled visits, in 22 patients. Evaluation of overall efficacy showed a decrease in psoriasis area and severity index of 80% after 4 months of FAE therapy. Laboratory investigations revealed a slight overall decrease of lymphocytes during the treatment period which was more than 50% below baseline in 10 patients. During weeks 4 and 8 mean eosinophil counts were above the normal range. At the end of FAE therapy elevated eosinophil counts had returned to normal values. None of the patients showed changes in renal function parameters throughout the study. Adverse events were reported in 69% of the patients mainly consisting of gastrointestinal complaints (56%) and flushing (31%). In five patients gastrointestinal complaints and in two patients flushing led to withdrawal from the study. Taken together the results of this multicentre study showed in a large number of patients that systemic FAE treatment is effective in severe psoriasis vulgaris. Transient eosinophilia seems to be a characteristic feature of FAE therapy, while lymphocytopenia is usually mild. Adverse effects are dose-related and consist mainly of gastrointestinal complaints and flushing.

In the past, nearly all treatment modalities for psoriasis have been found by empirical means. Based on the assumption that psoriasis represents a disorder with a defective citric acid metabolism, fumaric acid esters (FAE) were given to patients in order to replace an endogenous need for fumaric acid. The first results were published in 1959[1] and during the following years FAE were prescribed by a small group of physicians in Germany, Switzerland and the Netherlands following these assumptions. An antipsoriatic action of FAE was seen in previous studies which were conducted in order to explore the therapeutic potential of FAE.[2–5] These investigations confirmed the efficacy of FAE in psoriasis and characterized possible adverse events.

This report describes the results of a prospective multicentre study conducted in 12 dermatology centres in Germany. The aim of this study was to investigate further the efficacy of FAE treatment in psoriasis in a large number of patients with special emphasis on an individually based dosage of oral FAE. Furthermore, the study attempted to elucidate the rate and nature of adverse events more closely with particular emphasis on changes in blood values and on kidney function.

† Participating centres are listed in the acknowledgments.
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Patients and methods

Patient selection

A total of 101 male ($n = 68$) and female patients ($n = 33$) from 21 to 69 years of age (mean: 43·4 years) was admitted to the study after obtaining written consent. Patients with severe psoriasis of different clinical types (e.g. psoriasis vulgaris, guttate psoriasis, exanthematic psoriasis) were included in the study. The psoriasis area and severity index (PASI) at entry was at least 12.

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4	1	–	–	high strength
5	1	–	1	high strength
6	1	1	1	high strength
7	2	1	1	high strength
8	2	1	2	high strength
9	2	2	2	high strength

[a] Number of tablets.

Patients with erythrodermic psoriasis were excluded from the study.

Patients receiving systemic antipsoriatic treatment within the last 4 weeks, or specific topical therapies including UV radiation within 1 week before FAE treatment were excluded. Furthermore, patients concomitantly treated with nephrotoxic compounds, as well as patients with known hypertension, impaired liver or kidney function, a history of malignancy, leucocytopenia (< 4000/μL) or lymphocytopenia (< 800/μL) did not enter the study.

During the study salicylic acid-containing (< 2%) or urea-containing (< 10%) ointments were allowed for topical treatment.

Study design

The study was carried out as an open multicentre study in 12 dermatology centres in Germany (see acknowledgments). Patients were treated with FAE in tablet form using two formulations differing in strength (low strength tablets: 30 mg dimethylfumarate, 67 mg monoethylfumarate Ca salt, 5 mg monoethylfumarate Mg salt, 3 mg monoethylfumarate Zn salt; high strength tablets: 120 mg dimethylfumarate, 87 mg monoethylfumarate Ca salt, 5 mg monoethylfumarate Mg salt, 3 mg monoethylfumarate Zn salt), supplied as Fumaderm® initial and Fumaderm® by Fumedica GmbH, Herne, Germany. Dosage of FAE was performed according to a schedule displayed in Table 1. The FAE dose was individually adjusted up to a maximum dose of six high strength tablets corresponding to an overall dose of 1·2 g/day. The duration of FAE treatment was 16 weeks with control visits at 0, 2, 4, 6, 8, 12 and 16 weeks.

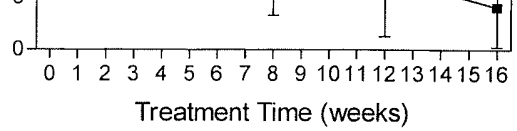

Figure 1. Efficacy of fumaric acid ester treatment in psoriasis as determined by psoriasis area and severity index (PASI) from baseline (week 0) until the end of the study at week 16. Mean and SD, $n = 78$.

Investigations for assessment of efficacy, safety and tolerability

Patients were classified according to the PASI. Pruritus, joint pain and nail involvement were assessed using a five-point score from 0 to 4, in which 0 means complete absence and 4 means most severe involvement. Patients were asked for adverse events at each visit. At the baseline visit and at the end of study, complete skin and physical examinations were performed in order to detect any changes related to FAE therapy. The following laboratory values were determined at each visit: serum creatinine, blood urea and nitrogen (BUN), serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, γ-glutamyl transpeptidase, uric acid, lactate dehydrogenase, alkaline phosphatase, choline esterase, bilirubin, serum cholesterol and triglycerides, electrolytes, urine chemistry, as well as complete haematological values including differential count. Blood pressure and body weight were also determined at each visit.

Results

A total of 70 patients completed the study. Thirty-one patients discontinued the study at various time intervals because of adverse events (gastrointestinal complaints, $n = 5$; flush, $n = 1$; increasing pruritus, $n = 1$), lack of efficacy ($n - 2$), job reasons ($n = 2$) and non-compliance ($n = 20$).

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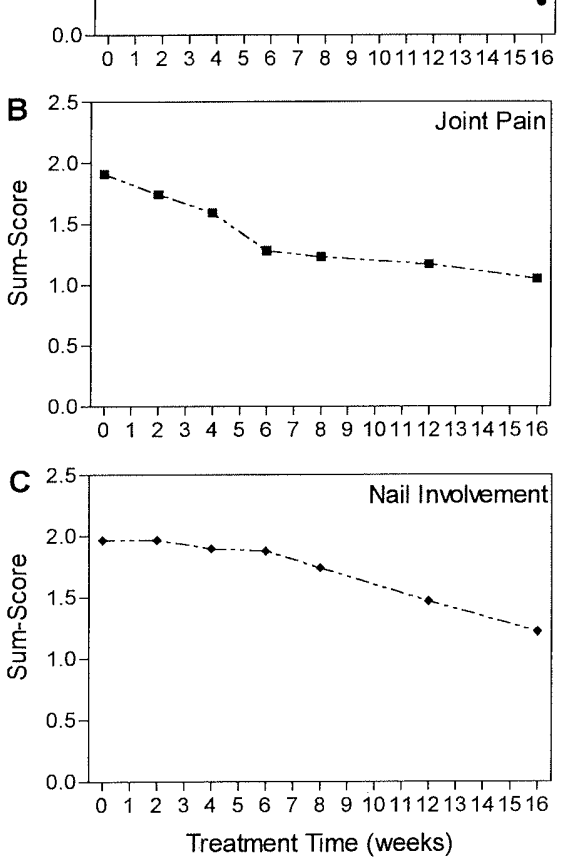

Figure 2. Change in the mean symptom scores for pruritus (A, ●; $n=79$), joint pain (B, ■; $n=33$), and nail involvement (C, ◆; $n=75$) in psoriasis patients where these symptoms were present at the baseline examination during fumaric acid ester therapy for 16 weeks.

Dosage and efficacy

At the end of the study, 33 patients (46%) received the maximum dose of six high strength tablets per day. In eight patients this dose was given until week 10 and subsequently reduced due to treatment response. In 48 patients the individual FAE dose was between one (6%)

a baseline value of 2·04 to 0·27 after 16 weeks of FAE therapy (Fig. 2A). For the symptom of joint pain, a slight reduction was seen during FAE treatment from a mean symptom score of 1·91 at baseline to 1·05 at week 16 (Fig. 2B). Nail involvement showed a slight improvement from a baseline mean score of 1·97 to a mean score of 1·22 at week 16 of FAE therapy (Fig. 2C).

Laboratory investigations

No significant decrease in total leucocyte count was seen in the psoriasis patients treated with FAE. When leucocyte subtypes were analysed by differential count a slight decrease in the mean percentage of lymphocytes was noted. However, all values were within the range of laboratory normal values. Only in one patient (patient 66) did the total leucocyte number decrease by more than 50% of baseline values after 16 weeks of FAE therapy (baseline: $9{\cdot}5\times10^3/\mu L$; week 16: $3{\cdot}9\times10^3/\mu L$). In a total of 10 patients the relative number of lymphocytes as determined by differential count decreased below 50% of baseline values. In one patient (patient 81) lymphocytes comprised 29% of white cells in the differential count at baseline and 4% after 16 weeks of FAE treatment.

The mean percentage of eosinophils increased above the laboratory normal values from week 4 to week 8 but was within the normal range at the end of FAE treatment at week 16. In nine patients eosinophil counts exceeded 20%, and in five patients eosinophil counts were between 10 and 20%. The maximum eosinophilia of 45% was seen at week 6 in one patient (patient 81) who had no eosinophils in the differential count at baseline. At the end of FAE therapy the eosinophil count was decreased to 5% in this patient. All other laboratory parameters investigated during this study including serum creatinine and BUN did not show any significant changes. There was no change in blood pressure before and at the end of the study.

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of the skin as well as sudden heat attacks lasting between minutes and a few hours. In seven patients (7%) adverse events led to withdrawal from FAE treatment.

Discussion

The results of this study revealed that FAE treatment for psoriasis is an effective modality as demonstrated by a reduction in PASI of 80% during a 16-week period. These results are in accordance with previous multicentre studies reporting FAE treatment in psoriasis patients.[4,6] Adverse events were seen in 69% of patients and these mainly consisted of gastrointestinal complaints including diarrhoea and stomach ache. Another adverse event specific for FAE therapy consisted of flushing, occurring irregularly and lasting between minutes and hours.

A special emphasis in this study was on the individual dose adjustment in order to achieve an optimal therapeutic response using the lowest dose possible. The results show that 46% of the patients required the maximum dose of six high strength tablets per day. In 17% of these patients the dose could subsequently be reduced while maintaining the therapeutic result. In 6% of the patients a clinical response could be induced with only one high-strength tablet per day. Our data indicate that an individually based dose adjustment should generally be performed according to the treatment response in order to optimize FAE therapy.

Laboratory investigations revealed a slight decrease in leucocytes which was due to a decrease in the relative number of lymphocytes. This observation is known from previous short-term studies[2,4] and was recently reported in psoriasis patients treated with FAE on a long-term basis (up to 3 years).[5] In an additional investigation addressing this issue it was shown that B and T lymphocytes were equally reduced in number with CD8-positive cells being slightly more decreased in number as compared with CD4-positive cells.[7]

In contrast to other systemic antipsoriatic remedies, psoriasis is poorly understood. Earlier work demonstrated antiproliferative activity of FAE for HaCaT keratinocytes *in vitro*.[8] It was also shown that the interleukin(IL)-1α-induced expression of ICAM-1 on HaCaT cells was inhibited by dimethylfumarate.[9]

Other investigations have shown that monoethylfumarate inhibited thymidine incorporation in human lymphocyte cultures, which points towards an antiproliferative effect on these cells.[10] Recently, De Jong and coworkers[11] demonstrated that monomethylfumarate stimulated Th2 responses of human T cells *in vitro*. As psoriasis is regarded as a Th1-type inflammatory disorder, the shift in the direction of a Th2 pattern may lead to improvement of the disease.[12]

The diversity of Th1/Th2 responsiveness could well play a significant part especially under treatment conditions. Thus it has been shown that Th1-regulating compounds, for instance interferon-γ, may worsen psoriasis.

In support of this concept is the (transient) blood eosinophilia as seen in this study and also noted before by others.[2,4,5] As IL-4 is able to stimulate eosinophil-activating cytokines, for example eotaxin,[13] this supports the concept of Th2 activation.

In a recent study it could be demonstrated that dimethylfumarate, but not monoethylfumarate or fumaric acid, inhibits cytokine-stimulated expression of the adhesion molecules ICAM-1, VCAM-1 and E-selectin in human umbilical vein endothelial cells as measured by ELISA and mRNA expression (Northern blotting).[14] As adhesion to endothelial cells is a crucial step before the emigration of leucocytes into the tissue, this observation may be of major importance for the anti-inflammatory effect of FAE. From the results of these first experimental studies, it may be suggested that different FAE could exert differential effects with regard to target cells and cellular functions investigated.

Finally, it is worthwhile noting that nail involvement, pruritus, and as shown by this preliminary evaluation, also joint pain become ameliorated during FAE treatment. These observations indicate FAE effectiveness

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