Antipsoriatic effect of fumaric acid derivatives

Results of a multicenter double-blind study in 100 patients

Peter J. Altmeyer, MD,[a] Ulrich Matthes, MD,[a] Frank Pawlak, MD,[a] Klaus Hoffmann, MD,[a] Peter J. Frosch, MD,[b] Peter Ruppert, MD,[b] Sawko W. Wassilew, MD,[c] Thomas Horn, MD,[c] Hans W. Kreysel, MD,[d] Gerhard Lutz, MD,[d] Joachim Barth, MD,[e] Ilona Rietzschel, MD,[e] and Rajendra K. Joshi, PhD[f] *Bochum, Dortmund, Krefeld, Bonn, and Dresden, Germany; and Zurich, Switzerland*

Background: Psoriasis vulgaris may benefit from treatment with fumaric acid and/or its derivatives; however, because different preparations have been used, results have been contradictory and difficult to interpret.
Objective: The purpose of this clinical trial was to evaluate the therapeutic value of fumaric acid derivatives.
Methods: A randomized double-blind study was carried out in patients with psoriasis, comparing a well-characterized formulation of fumaric acid derivatives with placebo.
Results: The results indicated statistically significant superiority of the fumaric acid derivatives over placebo. Adverse events (flush, gastrointestinal disturbances) were initially relatively frequent, but decreased thereafter.
Conclusion: Fumaric acid derivatives were found to be effective and safe in the treatment of psoriasis.
(J Am Acad Dermatol 1994;30:977-81.)

The use of "fumaric acid" as antipsoriatic therapy has been controversial for more than 30 years.[1] Insufficient knowledge of the pharmacologic and toxicologic properties of this highly potent material resulted in widespread abuse. Uncontrolled ingestion and overdose from combined topical and systemic therapy led to considerable nephrotoxic side effects in some patients and negative publicity.[2-4]

A distinction must be made between fumaric acid, which has no effect on psoriasis, and its esters, which may possess antipsoriatic activity. In the past primarily the monoethyl and dimethyl esters of fumaric acid, or a mixture of the two, were used. In contrast to pure fumaric acid these esters can be absorbed by the body and are thus systemically active.

From the Dermatological Clinic, University of Bochum[a]; Municipal Hospital, Dortmund[b]; Municipal Hospital, Krefeld[c]; Dermatological Clinic, University of Bonn[d]; Dermatological Clinic Medical Academy "Carl Gustav Carus," Dresden[e]; and the Department of Pharmacy, Federal Institute of Technology, Zürich.[f]

Reprint requests: Peter J. Altmeyer, MD, Professor, Director of the Dermatological Clinic, University of Bochum, Gudrunstr. 56, D-44791 Bochum, Germany.

0190-9622/94 $3.00 + 0 **16/1/52297**

The pharmacologic effects of the fumaric acid esters are still largely unknown. A few older publications reported effects in lymphocyte cultures.[5,6] In phytohemagglutinin-stimulated human lymphocytes fumaric acid monoethyl ester inhibited the incorporation of thymidine and uridine into nucleic acids and of alanine and leucine into proteins.[5] In 1985 van Dijk[7] reported the use of fumaric acid derivates in 32 patients. Efficacy was good in most patients; adverse events involved mainly the gastrointestinal tract. In 1987 Bayard et al.[8] evaluated 11 patients who received a combination of fumaric acid derivatives for 3 months. Good results were noted in more than half of these patients. In 1989 Nieboer et al.[9] described 136 patients who had been treated in variously designed studies and confirmed the efficacy of the fumaric acid derivatives. In the first placebo-controlled, double-blind study of fumaric acid derivatives Nugteren-Huying et al.[10] confirmed the positive results of earlier studies.

To reexamine the clinical efficacy and side effects of fumaric acid derivatives, a large, randomized, double-blind, placebo-controlled study was conducted.

Table I. Remission indexes based on the PASI score

	Remission index
Complete remission	>95%
Good improvement	70%-95%
Moderate improvement	30%-69%
Slight improvement	<30%
No change	0%
Deterioration	<0%

PATIENTS AND METHODS

One hundred patients of both sexes were admitted to the study (women of child-bearing age only after exclusion of pregnancy). The patients 18 to 70 years of age (drug group: mean 41.1 years [range 21 to 69 years]; placebo group: mean 39.0 years [range 19 to 67 years]) had psoriasis (chronic plaque type, exanthematic guttate type, pustular type, psoriatic erythroderma) for at least 2 years and were no longer or only insufficiently responsive to external therapy. Only patients in whom more than 10% of the body surface was affected were included. Topical antipsoriatic drugs had to be withdrawn at least 2 weeks before entering the study. Other concomitant treatment not affecting psoriasis was to be kept constant whenever possible and was monitored particularly with respect to possible interactions. Topical preparations such as ointments and bath oils were allowed.

The exclusion criteria were impaired kidney or liver function, cardiac disease, pregnancy (contraception was required during therapy), gastrointestinal disorders, or hematologic disorders.

All patients were treated with either placebo or drug in tablet form according to a uniform randomization schedule. The drug consisted of a mixture of dimethylfumarate and monoethylhydrogenfumarates. It was available in two different enteric-coated formulations: low-strength tablets containing 105 mg of ester mixture (30 mg dimethylfumarate/75 mg monoethylhydrogenfumarate as calcium, magnesium, zinc salts) and as "forte" tablets containing 215 mg of ester mixture (120 mg dimethylfumarate/95 mg monoethylhydrogenfumarate as calcium, magnesium, zinc salts).

The patients were treated with ascending doses as follows: In the first week 105 mg of the ester mixture or placebo daily, in the second week 210 mg per day. After the second week the "forte" form was given and the dose increased by 215 mg per day (week 3) up to a maximum dose of 1290 mg (week 16) ester mixture per day. Patients receiving placebo were given the corresponding numbers of tablets.

The following laboratory studies were performed on day 0 (T0) and after 2 (T1), 4 (T2), 6 (T3), 8 (T4), 12 (T5), and 16 (T6) weeks: hemoglobin; erythrocyte, leukocyte, and differential counts; platelet count; levels of bilirubin, creatinine, urea, uric acid, glucose, alkaline phosphatase, transaminases, gamma-GT, cholesterol, triglycerides, calcium, sodium, and potassium; as well as urinalysis. Creatinine clearance was determined at T0 and after 16 weeks.

The status of the disease was measured by determining the Psoriasis Area and Severity Index (PASI). The PASI values (P) were then used for calculation of a remission index (RI) giving the percentage improvement in the psoriasis at the time TI (TI = T1-T6) compared with the starting time. The following formula was used:

$$RI\,(\%) = \frac{PASI\,T0 - PASI\,TI}{PASI\,T0} \times 100$$

The calculated remission values were used as a basis for the classification listed in Table I. The clinical findings were evaluated at times T0 (initial examination) and T1-T6 (after 2, 4, 6, 8, 12, and 16 weeks). In addition, the pruritus, arthralgia, and nail deformities were assessed on the basis of a clinical score from 0 to 4 (0 = none to 4 = very severe). At each visit both the physician and the patient were asked to assess the outcome of therapy and any side effects. At the end of the study a global evaluation of the outcome of treatment was made as well as a comparison with the results of previous treatments.

The following statistical tests were used: Wilcoxon-Mann-Whitney U test, Mantel-Haenszel test, and chi-square test for two or more factors. The laboratory results were examined for transitions with the t test and frequency tables. In addition to the initial statistical methods the t test for unequal variances (Welch approximation) was used when the conditions for the t test were not fulfilled (significant F test, $\alpha = 0.005$). In general the significance level was $\alpha = 0.05$.

RESULTS

A predominance of male patients was found in both the drug group and the placebo group. The patients in the drug group had psoriasis for an average of 14.6 years (2 to 45 years) and those in the placebo group for an average of 15.6 years (2 to 51 years). The distribution of the different forms of psoriasis was homogeneous in the two groups. Evaluation of homogeneity showed no significant differences between the individual centers.

In Fig. 1 the PASI scores in the drug group are compared with those in the placebo group. The data indicate that there was a definite and continuous drop in the index in the drug group. Compared with a starting value of 21.57 (T0) the PASI determined in the sixteenth week (T6) was 10.77. In contrast, the PASI in the placebo group remained practically

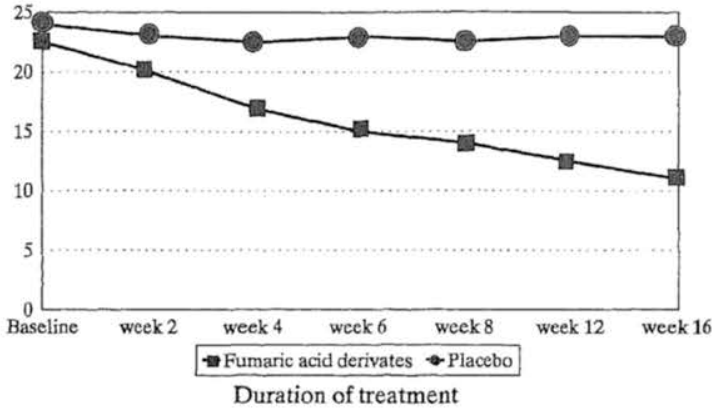

Fig. 1. Influence on mean PASI of fumaric acid derivatives and placebo during 16 weeks of treatment.

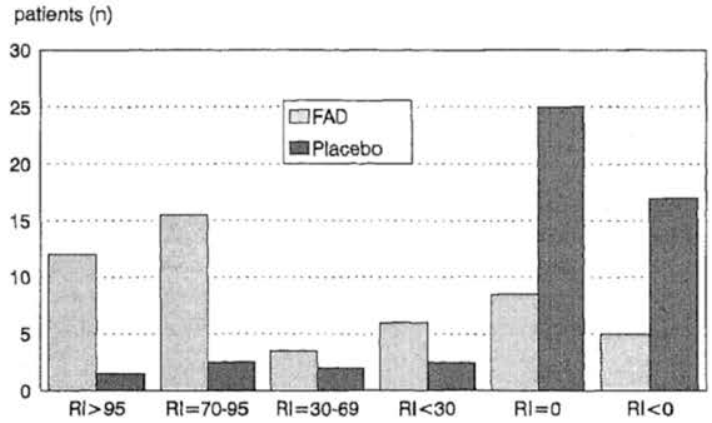

Fig. 2. Physicians' judgment of the therapeutic effect of fumaric acid derivatives *(FAD)* and placebo. *RI*, Remission index.

constant during the entire test period. The difference between the groups at T6 (week 16) is significant ($p < 0.0001$).

At the end of the study physicians were requested to assess the effects of treatment as follows: complete remission, good improvement, moderate improvement, slight improvement, no change, deterioration. A significant difference ($p < 0.0001$) in favor of the drug group was found (Fig. 2). In 71.3% of the drug-treated patients the degree of remission was described as complete, good, moderate, or slight. In addition, 18% showed no response and 10.2% showed deterioration. In the placebo group 18% had an complete remission to slight improvement, whereas 82% remained unchanged or deteriorated. Analysis of the individual data of the patients with a positive response shows that the most marked treatment effects were found between the second and twelfth treatment weeks. In 13 of 36 patients with a positive response the greatest tendency towards improvement was between the second and fourth weeks; in five this occurred between the twelfth and sixteenth weeks.

At the end of the study the clinical symptom arthralgia had been alleviated in the drug group compared with the placebo group ($p < 0.002$). No statistically significant differences were found with respect to "nail changes," although in individual patients ($n = 15$) marked improvement in onychodystrophy was seen. There was a marked difference ($p < 0.0001$) between the two groups at the end of the study with respect to adverse reactions. In the

drug group adverse reactions occurred in 75.5% of the patients and in the placebo group in 16.0%. During the entire study period abdominal disturbances such as diarrhea were reported 27 times (placebo twice), stomachache or stomach cramps 35 times (placebo twice). Flush was reported 21 times (placebo none), skin burning twice (placebo once), itching once (placebo none), and heat sensations three times (placebo none). These figures refer to the total number of side effects during the entire study, that is, a single symptom occurring several times in one patient was counted several times.

There were no changes in hemoglobin or erythrocyte count during the 16 weeks. No differences were detectable either between groups or within groups. Leukocytes showed a mild decrease in week 8 in both the drug group and the placebo group but showed no further changes after this time. The between-group comparison showed no significant difference for week 16, whereas the within-group comparison showed a significant decrease in the drug group ($p = 0.0163$). Eosinophils showed a significant increase in the drug group from 2.0% (T0) to 3.4% (T2) ($p < 0.05$). A further increase was observed at T4 (4.7%) but was not significant. Eosinophilia of 28% was found in one patient. Eosinophil counts remained unchanged in the placebo group. In the drug group a nonsignificant reduction in lymphocyte counts was measured between T0 and T6. In the placebo group the values remained unchanged. The values for platelets, bilirubin, urea, creatinine, glucose, alkaline phosphatase, transaminases, gamma-GT, cholesterol, triglycerides, and urinalysis did not change significantly in either group. There were no significant differences in creatinine clearance in either group.

Treatment was terminated prematurely in 19 patients (38.8%) in the drug group and 29 (58.0%) in the placebo group. These withdrawals had no negative influence on the value of the study because the "carry forward last value" method was applied. The 19 patients in the drug group terminated treatment for the following reasons: four because of side effects, five because of deterioration; 10 gave several reasons (e.g., "no change, increase in the extent of the disease, and side-effects"). Gastrointestinal side effects were the main reasons for termination. By comparison most of the drop-outs in the placebo group were due to worsening ($n = 22$), one because of gastrointestinal disturbances and six because of general dissatisfaction with the outcome of treatment.

DISCUSSION

The results of our multicenter, randomized, double-blind clinical trial clearly confirm the antipsoriatic efficacy of the fumarate mixture. It is indicated for treatment of extensive severe psoriasis that no longer responds to external therapy but not for stable chronic plaque psoriasis.[12] The clinical results were good in labile or pustular psoriasis.

The main side effects of the fumarates are diarrhea, nausea, or other gastrointestinal complaints[7-9] that limit the use of the preparation. Expected gastrointestinal problems were the reason we chose a slow increase in dosage in the first weeks of treatment. Experience has shown that this leads to better tolerability. Flushing occurs ½ to 2 hours after taking the fumaric acid esters and persist for up to ½ hour. They were described as tolerable by all patients and did not lead to discontinuation of treatment in any of them. The reason for the flush is not known.

The relatively late response of some patients to treatment should be noted. In 36.1% of responders, the maximal effect was between the second and fourth week. Five patients were distinct late responders with a maximal effect between the twelfth and sixteenth weeks. We suspect that fumarates show clinical effects only after a saturation phase of several weeks. A definite disadvantage of the study design was the composition of the drug itself. The administered preparation was composed of several fumaric acid esters and their salts so that conclusions from this study can be made only with respect to the overall mixture and not to an individual component. In addition, for gastrointestinal reasons the study protocol prescribed use of a low-strength form in the first 2 weeks of treatment that contained a different mixture ratio from that of the "forte" form.

Some noteworthy individual findings were not revealed by a purely statistical evaluation (e.g., the improvement in patients with severely mutilating onychodystrophy). Striking improvements were observed from treatment with the fumaric acid esters. In some patients with psoriatic arthropathy ($n = 7$), the joint complaints did not respond despite noticeable effects on the skin, whereas others showed impressive clinical improvement in the joint pain.

REFERENCES

1. Schweckendiek W. Heilung von Psoriasis. Med Monatschr 1959;13:103-4.
2. Roodnat JI, Christiaans MHL, Nugteren-Huying WM, et

al. Akute Niereninsuffizienz bei der Behandlung der Psoriasis mit Fumarsäureester. Schweiz Med Wochenschr 1989;119:826-30.
3. Dubiel W, Happle R. Behandlungsversuch mit Fumarsäuremonoethylester bei Psoriasis vulgaris. Z Haut-Geschl Kr 1972;13:545-50.
4. Raab W. Treatment of psoriasis with fumaric acid and fumarates. Z Hautkr 1959;10:671-9.
5. Petres J, Kalkoff KW, Baron D, et al. Der Einfluss von Fumarsäuremonoethylester auf die Nucleinsäure und Proteinsynthese PHA-stimulierter menschlicher Lymphozyten. Arch Derm Forsch 1975;251:295-300.
6. Hagedorn M, Kalkoff KW, Kiefer G, et al. Fumarsäuremonoethylester: Wirkung auf DNA-Synthese und erste tierexperimentelle Befunde. Arch Derm Forsch 1975; 254:67-73.
7. van Dijk E. Fumaarzuur voor de behandeling van patienten met psoriasis. Ned Tijdschr Geneesk 1985;129:485-6.
8. Bayard W, Hunziker Th, Krebs A, et al. Perorale Langzeitbehandlung der Psoriasis mit Fumarsäurederivaten. Hautarzt 1987;38:279-85.
9. Nieboer C, de Hoop D, Van Loenen AC, et al. Systemic therapy with fumaric acid derivatives: new possibilities in the treatment of psoriasis. J AM ACAD DERMATOL 1989; 20:601-8.
10. Nugteren-Huying WM, van der Schroeff JG, Hermans J, et al. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. J AM ACAD DERMATOL 1990;22:311-2.
11. Fredriksson T, Petterson U. Severe psoriasis: oral therapy with a new retinoid. Dermatologica 1978;157:238-44.
12. Matthes U, Pawlak F, Altmeyer P. Oral therapy of severe psoriasis by derivatives of fumaric acid: an open long-term study over one year [Abstract]. Presented at the 18th World Congress of Dermatology, New York, June 12-18, 1992. 1992:146A.

Cutaneous candidiasis as a cause of delayed surgical wound healing

Martin B. Giandoni, MD, and William J. Grabski, MD *San Antonio, Texas*

Background: Reports in the literature of surgical wounds infected with *Candida* species are scant.
Objective: We describe a subset of patients with cutaneous candidiasis whose only clinical finding was delayed wound healing.
Methods: Surgical wounds managed with moist occlusive postoperative dressings were observed for delayed healing.
Results: Three patients are described who demonstrated delayed wound healing with failure to epithelialize. Fungal cultures from each patient revealed heavy growth of *Candida*. The problem resolved quickly with a modified wound care regimen and application of an antiyeast cream.
Conclusion: Cutaneous candidiasis can be a cause of delayed wound healing, especially in surgical wounds treated with antibacterial ointments and occlusive dressings.
(J AM ACAD DERMATOL 1994;30:981-4.)

Cutaneous candidiasis associated with a surgical wound is probably more common than is generally recognized.[1,2] Cutaneous candidiasis usually appears as a brightly erythematous eruption with superficial erosions, crusting, and small pustules in both a central and satellite distribution. Occasionally this appearance is associated with a surgical wound, but few reports in the literature describe this complication. We describe three illustrative patients, although we have seen many more, with surgical wounds that failed to heal completely after an extended period. We postulate that cutaneous candidiasis associated with a surgical wound that fails to reepithelialize is common. This phenomenon has been briefly noted previously,[2] and we believe that it should be emphasized further. We discuss the spectrum of clinical presentation of this condition, the factors that favor cutaneous candidiasis in a surgical wound, and a simple regimen to treat the condition.

From the Dermatology Service, Brooke Army Medical Center.

Presented at the national meeting of The American Society for Dermatologic Surgery, Charleston, S.C., March 18, 1993.

Reprints not available.

16/1/52479

CASE REPORTS

Case 1. An 81-year-old woman had a large basal cell carcinoma excised from her left cheek. The defect re-