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Fumaric acid therapy in psoriasis: Results and side effects of 2 years of treatment

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Fumaric acid (FA) therapy for psoriasis consists of the daily oral intake of either dimethyl fumaric acid ester (DMFAE, monotherapy) or DMFAE taken with salts of monoethyl FA (MEFAE) (FAC, combination therapy). Information on background and details of this therapy have been given in a previous report.[1] The efficacy of this treatment has been confirmed in several double-blind 4-month studies.[1, 2] No significant differences could be found between DMFAE monotherapy and FAC therapy when equivalent dosages of DMFAE were taken.[3] In these reports several side effects were observed. In addition, serious kidney disturbances (acute tubular necrosis) have been reported.[4, 5] Only two controlled studies of long-term FA therapy have been published with limited numbers of patients.[1, 6] This article reports the long-term effects of DMFAE monotherapy and FAC therapy.

MATERIAL AND METHODS

Patients. Patients ($N = 196$) older than 18 years of age with nummular and plaque-type psoriasis with at least 10% involvement of the body surface were included. Twenty-three had arthralgia, 15 in the DMFAE group and 8 in the FAC group. Patients with generalized pustular psoriasis were excluded. Other contraindications were pregnancy, history of stomach or intestinal disease, liver or kidney disorders, and cardiovascular complaints. Women of child-bearing age were treated only if adequate contraceptive measures were taken. The choice of therapy was determined by a patient's insurance; only some could recover the costs of FAC therapy.

Medication. The DMFAE group ($n = 129$) was treated with capsules filled with 60 mg of semienteric coated granulate of DMFAE. In the first week the dosage was 60 mg/day. This was increased weekly by 60 mg to a maximum of 240 mg/day. The FAC group ($n = 67$) was treated with two types of enteric-coated (Fumaderm) tablets: (1) "Mite," containing 30 mg of DMFAE, 5 mg Mg-, 3 mg Zn-, and 56 mg Ca-MEFAE; or (2) "Forte," containing 120 mg of DMFAE, 5 mg Mg-, 3 mg Zn-, and 87 mg Ca-MEFAE. Medication started with one "Mite" tablet per day to be increased weekly to three tablets per day. In the fourth week medication was switched to one "Forte" tablet per day and this was increased weekly to a maximum of four tablets per day, in two divided doses after meals. Topical treatment consisted of the application of a bland cream or ointment or a mild topical corticosteroid.

Evaluation. Therapeutic evaluation was done in the periods 3 to 6 months, 6 to 12 months, 12 to 18 months, and 18 to 24 months. The results were scored according to a simplified severity score as described previously.[1] Improvement of more than 75% was considered *sufficient*; less extensive improvement, deterioration, and exacerbation were called *insufficient*. Statistical analysis was done with the chi-square test. Side effects were noted. Laboratory tests included urinalysis, white blood cell count with differential, as well as determination of hemoglobin, serum creatinine, blood urea nitrogen (BUN), and transaminase and alkaline phosphatase levels.

RESULTS

The percentage of patients that continued the therapy was significantly higher in the FAC group than in the DMFAE group after 6 months (Table I). After 24 months 55% continued the FAC medication versus 16% of the DMFAE users. In Table II the therapeutic results after 3 months are shown. Sufficient results were obtained in approximately 50% of the FAC-treated patients during the entire study. In the DMFAE group the percentage of sufficient responders declined from 32 to 18 during the 24 months. These differences were statistically significant. The first signs of improvement were usually noted after 3 weeks. Disappearance of the lesions started in the following weeks. Improvement of nail dystrophy occurred in about half the patients after several months of therapy. A decrease in arthralgias was noted in 27% of the DMFAE-treated and in 50% of the FAC-treated patients.

The most important reason to discontinue the therapy was an insufficient result in the DMFAE group (36%). Side effects were the most frequent

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Table I. Data of patients treated with DMFAE ($n = 129$) and FAC therapy ($n = 67$)

Period (mo)	DMFAE treatment*			FAC treatment†		
	Treated (per period)	Discontinued (per period)	Discontinued (cumulative)	Treated (per period)	Discontinued (per period)	Discontinued (cumulative)
3	129 (100%)	25 (19%)	25 (19%)	67 (100%)	7 (11%)	7 (11%)
6	104 (81%)	36 (28%)	61 (47%)	60 (90%)	9 (13%)	16 (24%)
12	68 (53%)	23 (18%)	84 (65%)	51 (76%)	3 (4%)	19 (28%)
18	45 (35%)	15 (12%)	99 (77%)	48 (72%)	9 (13%)	28 (42%)
24	30 (23%)	9 (7%)	108 (84%)	39 (58%)	2 (3%)	30 (44%)

*Dimethylfumaric acid ester, 120 to 240 mg/day.
†Fumaric acid combination (see text). Dosage of DMFAE: 240 to 480 mg/day.

Table II. Results of treatment with DMFAE or FAC per observation period after 3 months

Period (mo)	DMFAE treatment			FAC treatment		
	No.	Results		No.	Results	
		Sufficient*	Insufficient†		Sufficient	Insufficient
3-6	104	41 (32%)‡	63 (49%)	60	32 (48%)	28 (42%)
6-12	68	41 (32%)	27 (21%)	51	31 (46%)	20 (30%)
12-18	45	34 (26%)	11 (9%)	48	34 (51%)	14 (21%)
18-24	30	23 (18%)	7 (5%)	39	31 (46%)	8 (13%)

*Sufficient: Improvement more than 75%.
†Insufficient: Exacerbation, no improvement, or improvement less than 75%.
‡Percentages of the entire patient population.

reason to stop in the FAC group (i.e., in 18%). For the DMFAE group this percentage was 26%, but this difference was not significant. In the first 6 months gastrointestinal complaints were the most frequent in both groups. Later general malaise and abnormal laboratory values became important. Mild deviations of liver and kidney functions were seen in three patients and one patient, respectively. They disappeared promptly after discontinuation. Leukocytopenia occurred in 4%. The most frequently occurring laboratory deviation was lymphopenia that started to appear after 3 months. After 24 months 86% of the DMFAE-treated and 81% of the FAC-treated patients were so affected. Discontinuation of the therapy led to normalization in most cases, but this required several months up to more than 6 months.

Recurrence of psoriasis after discontinuation of therapy varied. In cases of complete or almost complete healing, recurrence, if any, occurred after more than 6 months. When the medication was stopped for other reasons, worsening was observed within 4 weeks. A rebound phenomenon was not seen.

DISCUSSION

FAC treatment was significantly superior to DMFAE. The amounts of DMFAE in the FAC therapy were twice that of the DMFAE monotherapy. Apparently a dosage of 480 mg of DMFAE per day is necessary to achieve a satisfactory improvement in approximately 50% of the patients. This is a slightly lower rate than has been described with long-term retinoid therapy.[7]

The mechanism of FA therapy is still unknown. There are strong indications that FA esters have antiproliferating properties.[8-11] Immunologic modulation might be another possibility. Additional pharmacologic and pharmacokinetic studies are necessary.[12] Another aspect of FA therapy is side effects. Flushing occurs in 50% of patients but this is usually tolerable. Gastrointestinal complaints are the most important symptoms in the first months. With enteric coating these are less severe. Acute tubular necrosis was not seen in our series. This is probably due to the low initial dosage and the slow increase in dosage.[13] The most frequent side effect was lymphopenia in 85% of patients still in treatment after

2 years in both series. This lymphopenia is caused by loss of suppressor T cells and B lymphocytes[1] and seriously restricts FA therapy. Unless this complication can be eliminated, FA therapy should only be prescribed under well-controlled conditions, with timely interruptions to normalize the lymphocyte count.

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Traumatic folliculitis of the legs: A persistent case associated with use of a home epilating device

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A 31-year-old woman had a prolonged case of folliculitis after using a home epilating device for hair removal from the legs. I have seen other cases of traumatic folliculitis, and there are several reports in the literature that have involved home epilating devices.[1-5]

CASE REPORT

A 31-year-old white woman had an eruption on her legs of 6 months' duration. The problem developed after she had been using an epilating device for approximately 1 year. The device produced a circular motion over hair-bearing areas. She treated half of one leg about every 3 weeks. Because of the eruption, she had discontinued the use of the epilating device 5 months earlier. Subsequent hair removal involved shaving with a safety or an electric razor. She denied plucking the hairs or use of a depilatory. For several months before the onset of the eruption and up until the time it began, she had been running a treadmill in tights three times per week.

Physical examination revealed numerous erythematous, follicular, crusted papules on the legs. A potassium hydroxide preparation and bacterial culture were negative. Initial treatment with 2.5% hydrocortisone cream and 2% mupirocin ointment provided only slight improvement. Additional treatment with systemic and topical erythromycin, topical benzoyl peroxide, and 0.025% triamcinolone cream was ineffective. A skin biopsy specimen showed a prominent ingrown hair in the reticular dermis with granulomatous inflammation (Fig. 1). Subsequent treatment included UVB phototherapy with slow gradual improvement. She has now had the problem for more than 16 months after discontinuing use of the epilating device.

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