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CLINICAL REPORT

Treatment of Disseminated Granuloma Annulare with Low-dose Fumaric Acid

H. Oliver WEBER[1], Claudia BORELLI[2], Martin RÖCKEN[1] and Martin SCHALLER[1]
Department of Dermatology, [1]Eberhard-Karls-University, Tübingen, and [2]Ludwig-Maximilians-University, Munich, Germany

While localized variants of granuloma annulare are typically self-limited, disseminated granuloma annulare tends to be chronic and often therapy-resistant. Treatment with fumaric acid esters is effective for severe forms of psoriasis. Disseminated granuloma annulare has also been reported to respond to fumaric acid esters. We treated 8 patients (mean age 64.2 years; 4 men, 4 women) with low-dose fumaric acid esters for 1–18 months. One patient showed complete clearance, 4 marked improvement, one slight to moderate improvement and one no response. One patient discontinued treatment due to nausea after one month and another stopped it after 18 months. Five out of 8 patients tolerated the treatment well. Six patients developed transient, mild leucopaenia and one eosinophilia. None of these blood abnormalities necessitated discontinuation of therapy. Low-dose fumaric acid esters significantly improve disseminated granuloma annulare in approximately 63% of patients. Larger, controlled, prospective studies are needed to evaluate its efficacy and safety in this setting. ***Key words: granuloma annulare; fumaric acid esters; low dose.***

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Martin Schaller, Department of Dermatology, Eberhard-Karls-Universitaet Tübingen, Liebermeisterstr. 25, DE-72076 Tübingen, Germany. E-mail: martin.schaller@med.uni-tuebingen.de

Granuloma annulare (GA) is a benign, granulomatous disease of unknown origin affecting patients of all ages. GA can be separated into localized and disseminated variants. Localized GA is characterized by erythematous, asymptomatic, grouped papules with an enlarging annular pattern favouring the distal extremities (1). As localized GA progresses, there is central involution, leading to the typical ring form of the lesions. This form is typically self-limited and resolves within one to two years. Disseminated GA is characterized by widespread erythematous papules, and is often chronic and difficult to treat (1). In a recent long-term survey study involving 32 patients, all patients cleared within 20 years and none developed any other inflammatory disorder (2). However, it is unclear whether these patients had localized or disseminated GA and what treatment was used.

The cause of GA remains unclear. In contrast to other granulomatous diseases, such as necrobiosis lipoidica, there is no association of GA with type 2 diabetes mellitus (3). Because of histological similarities to tuberculosis, GA has been suggested to represent a delayed-type hypersensitivity (Th1) reaction, resulting in matrix degradation induced by inflammatory cells. Indeed, *in situ* hybridization combined with immunofluorescence showed large numbers of infiltrating CD3+ lymphocytes expressing interferon-gamma and CD3+ lymphocytes and CD68+ macrophages expressing tumour necrosis factor-alpha and matrix metalloproteinases (4). This strengthens the concept that Th1-cytokine-dominated immune responses are important for the development of GA.

There are no well-designed randomized controlled trials on the treatment of localized GA owing to the self-limited nature of the disease. In the case of persistent, localized GA, topical treatments such as glucocorticosteroids or cryotherapy may be helpful.

In disseminated GA, systemic treatment may be necessary. There have been reports of successful treatment of disseminated GA with dapsone, isotretinoin, etretinate, hydroxychloroquine, cyclosporine, niacinamide, psoralen plus ultraviolet A (PUVA) (5), vitamin E, tacrolimus, pimecrolimus, potassium iodide or infliximab (6). None is effective in more than 50% of patients and some of these treatments may have severe side-effects. Therefore, there is a need for a therapy with little or no side-effects. Recently, there have been reports on the successful treatment of disseminated GA with fumaric acid esters (FAE) (7–9). Side-effects were usually mild, and included gastrointestinal symptoms and flushing. In this clinical report, we have retrospectively analysed the therapeutic efficacy of low-dose FAE in 8 patients with disseminated GA. Patients were treated in an off-label and compassionate drug use case series and not in a formal trial. The aim of our investigation was to evaluate whether a low-dose regime is as efficient as the conventional dosage and if unwanted side-effects can be minimized.

PATIENTS AND METHODS

The study population consisted of 8 patients (4 men, 4 women; mean age 64.2 years) with disseminated GA treated with FAE in our hospital from 2005 to 2007. Diagnosis of disseminated GA was confirmed by the typical clinical presentation and histology

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(patient 7, Fig. 1c). The mean age of the patients was 64.2 years. FAE were administered in tablets using two formulations differing in strength: Fumaderm initial® (Fumedica-Arzneimittel GmbH, Herne, Germany) as low strength tablets (dimethylfumarate 30 mg, monoethylfumarate Ca salt 67 mg, monoethylfumarate Mg salt 5 mg, monoethylfumarate Zn salt 3 mg) and Fumaderm® as high-strength tablets (dimethylfumarate 120 mg, monoethylfumarate Ca salt 87 mg, monoethylfumarate Mg salt 5 mg, monoethylfumarate Zn salt 3 mg). Treatment was initiated with one tablet Fumaderm initial® per day. The dosage was increased by one tablet per day weekly up to a maximum of 4 tablets (3 patients) or 5 tablets (one patient) per day. In 3 patients, treatment was continued with Fumaderm® one to two tablets per day. In case of adverse effects, the dosage was reduced to the highest tolerable level, or treatment was discontinued. Clinical outcome was assessed as "0 = no improvement", "+ = slight to moderate improvement", "++ = marked improvement" or "+++ = cleared".

Monitoring once a month included leukocyte differential counts (normal range of white blood cell count: 4000–10000/µl, lymphocytes: 20–45%, eosinophils: 0–4%), liver function tests, serum creatinine, and urinary status.

RESULTS

Seven out of 8 patients were able to undergo treatment for at least 2 months (Table I). One patient discontinued because of diarrhoea after one month, and another patient stopped treatment after 18 months due to nausea and diarrhoea. At the beginning of treatment, disseminated GA improved markedly in this patient, but then remained stable (rated +). Of the remaining 6, one patient showed no improvement, 4 patients showed marked improvement and one patient cleared completely (patient 7, Fig. 1a and b). One patient necessitated decrease of dosage according to the protocol described above. Six patients developed transient mild leucopaenia, and one eosinophilia (Table I), but none of these blood changes necessitated discontinuation of therapy.

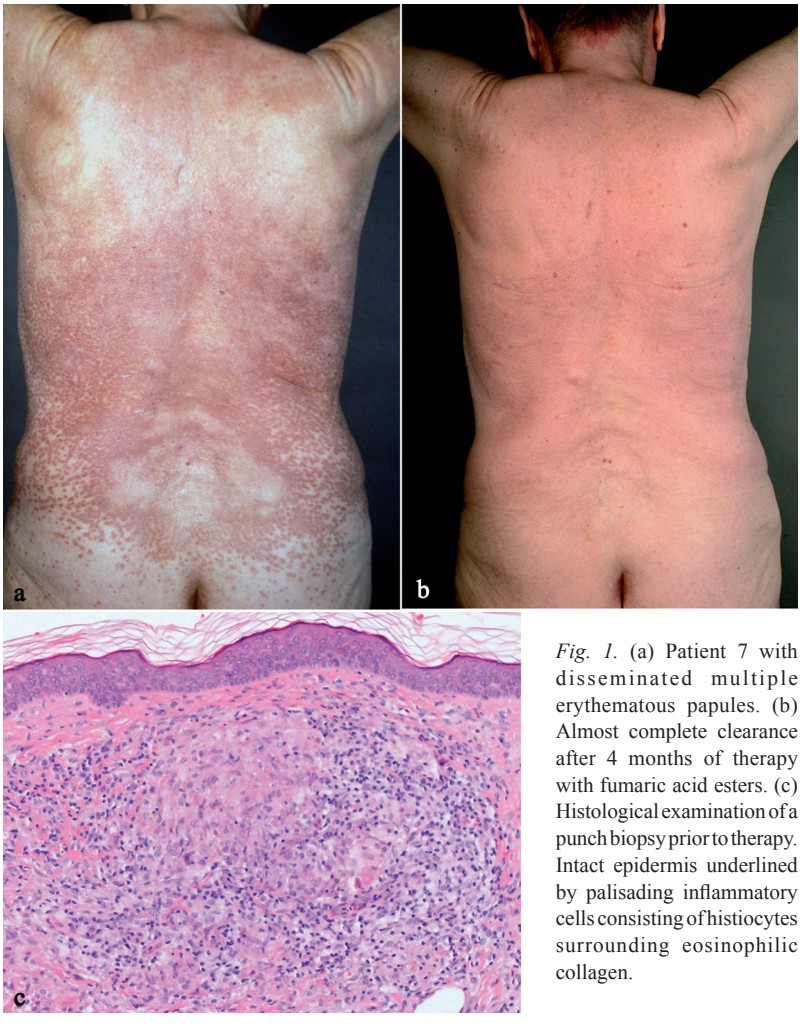

Fig. 1. (a) Patient 7 with disseminated multiple erythematous papules. (b) Almost complete clearance after 4 months of therapy with fumaric acid esters. (c) Histological examination of a punch biopsy prior to therapy. Intact epidermis underlined by palisading inflammatory cells consisting of histiocytes surrounding eosinophilic collagen.

DISCUSSION

Disseminated GA is a rare disease and no reproducible effective treatment has been established, with the exception of topical glucocorticoids for localized applications. The described systemic therapies are all immunosuppressive with potential side-effects. Thus, effective therapies with minimal side-effects are needed. Fumaderm®, a combination of fumaric acid esters, is a widely used and highly effective therapy for severe psoriasis. In the standard therapy regimen, FAE therapy is started at a low dose (one tablet Fumaderm initial®). Subsequently, doses are slowly increased (up to 3 tablets Fumaderm initial®). Then, FAE therapy is continued with high-dose tablets (Fumaderm®) up to 6 tablets per day. In most patients, about 1/6 to 1/3 of the maximal therapeutic dose is sufficient, at least as treatment of psoriasis. This is important, as side-effects are strictly dose-dependent. If side-effects occur, dose adjustment to a well-tolerated level is needed.

Using this treatment regimen, FAE are generally well-tolerated drugs suitable for long-term treatment in psoriasis (10). Adverse effects include usually mild flushing and gastrointestinal symptoms, which resolve normally at lower doses or by slower dose increase. Relative lymphopaenia is the most frequent laboratory finding in long-term users and only needs interruption at very low leukocyte counts, as it is probably a consequence of altered redistribution. The exact mode of action remains open, although several activities of FAE have been uncovered. FAE treatment suppresses Th1 cell-associated cytokines, such as interleukin 12 and interferon-

Table I. *Therapeutic effects of fumaric acid esters: n=8, 0= no improvement; +=slight to moderate improvement, ++=marked improvement, +++=cleared, FI=Fumaderm initial® (low strength tablets), F=Fumaderm® (high strength tablets). For details see Material and Methods*

Patient	Age (years)	Gender	Duration of disease*/treatment (months)	Maximum dose (tablets)	Response to FAE/months	Side-effects/reason for discontinuation	Blood count abnormalities	Previous therapies	Other diseases
1	65	M	24/2	4 FI	0		No	Unknown	None
2	69	M	9/2	5 FI	++/1		No	Phototherapy	None
3	67	F	24/1	2 FI	0	Nausea/yes	No	Unknown	None
4	57	F	18/6	1 F	++/4		No	Unknown	None
5	52	F	3/18	4 FI	+/5	Nausea, diarrhea/yes	Lymphocytes 12.3%	Phototherapy	None
6	46	F	30/12	4 FI	++/6		Transient: Leukocytes 3400/µl Stable: Lymphocytes 11.5%	Unknown	None
7	80	M	24/4	2 F	+++/4		Transient: Leukocytes 3960/µl Transient: Lymphocytes 18.1%	PUVA phototherapy, retinoids, topical steroids	Prostata hyperplasia
8	78	M	6/2	2F	++/2	Abdominal pain/no	Leukocytes 7630/µl Lymphocytes 14.9% Eosinophils 12.2%	Unknown	None

*Duration before start of therapy.
FAE: fumaric acid esters; PUVA: psoralen plus UVA.

gamma (11, 12), and promotes Th2-cytokines such as interleukin 4, 5 or 10 (13, 14). It also inhibits NFκB translocation and induces apoptotic phenomena (15). As development of psoriasis is associated with, and probably dependent on, a Th1-cytokine milieu (16), the switch from a Th1- to a Th2-cytokine profile may be important for the effect of FAE in psoriasis. It has been shown that functional depletion of intracellular glutathione leads to the induction of the anti-inflammatory active stress protein HO-1, which, at least in part, is responsible for the diminished secretion of inflammatory cytokines (11). Likewise, granuloma formation depends on Th1-cytokines and on tumour necrosis factor (TNF) (4). Yet, it remains questionable, whether therapies with TNF-antagonizing agents, that are associated with such a strong immunosuppressive effect, are justified in this disease. In addition, it could be demonstrated that inhibition of leukocyte rolling through modulation of adhesion molecule expression contributes to the list of FAE-mediated anti-inflammatory activities (17). Based on this rationale and reports showing that FAE may be effective in patients with a variety of non-infectious granulomatous skin diseases, including 13 patients with disseminated GA (7), we reviewed 8 consecutive patients who have received FAE for GA. In another study, 8 patients with disseminated GA also showed significant improvement in 7 out of 8 patients with side-effects in 6 out of 8 patients (8). Moreover, in 18 patients with necrobiosis lipoidica, FAE therapy improved the disease significantly in 15 out of 18 patients (9).

While the latter studies used the standard treatment regimen described for psoriasis, we used a low-dose approach not exceeding a maximum dose of 2 tablets Fumaderm® per day. Gastrointestinal side-effects of FAE occurred only in 2 patients; 6 out of 8 patients tolerated treatment very well when FAE were adapted to the individually tolerated dose. Blood count abnormalities included transient mild leucopaenia in 2 patients, lymphopaenia in 4 patients and eosinophilia in one patient (Table I), but did not require discontinuation of the therapy. Thus, 6/8 patients improved, a success rate obtained with the most promising alternative treatments, such as bath PUVA therapy (5). The frequency of side-effects under low-dose therapy was strongly reduced compared with the data published in the literature for higher dose regimes. Discontinuation of the therapy was seen in 8 out of 13 (7) and 4 out of 8 patients (8) compared with 2 out of 8 patients in the presented study. In this report we are able to present data demonstrating a similar efficacy for low-dose therapy of disseminated GA compared with conventional dosage. It is tempting to speculate that the *benefit-risk ratio* of this low-dose regime appears to be *increased due to the better tolerability of lower FAE dosages*. In our opinion continuation of a lower FAE dosage over a long period of time seems to be more relevant for therapeutic success than a higher

but shorter treatment approach. Larger controlled prospective studies are needed to investigate the ideal treatment regimen and the effectiveness of FAE in patients with disseminated GA.

The authors declare no conflict of interest.

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