

Case report

Treatment of disseminated granuloma annulare with fumaric acid esters

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Abstract

Background: Granuloma annulare is a granulomatous disease of unknown etiology. Various therapies have been tried in disseminated granuloma annulare (DGA), including corticosteroids, several variants of psoralen plus ultraviolet-A radiation, ultraviolet- A1 radiation, systemic retinoids, and dapsone, with variable success. We report a patient with recalcitrant DGA who was treated with fumaric acid esters (FAE).

Case presentation: A 40-year old Caucasian woman presented with a 25-year history of recalcitrant DGA. On both legs and the abdomen there were erythematous annular plaques. She was 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). After three-month therapy, an almost complete clearance of skin lesions was achieved. With the exception of temporary lymphopenia, no adverse effects were observed. The patient remained in remission during a six-month follow up period.

Conclusions: Our observation has demonstrated that FAE is a potentially beneficial therapeutic option for patients with recalcitrant DGA. However controlled trials are necessary to fully explore the efficacy, optimal dosage, and safety of FAE in the management of DGA.

Background

Granuloma annulare is a granulomatous disease of unknown etiology. Disseminated granuloma annulare (DGA) is characterized by a chronic course of disease and frequent association with systemic disorders such as diabetes mellitus. Although spontaneous resolution can occur in some cases various therapies have been tried in DGA, including corticosteroids, several variants of psor-

alen plus ultraviolet-A radiation, ultraviolet- A1 radiation, systemic retinoids, and dapsone, with variable success [1–5]. We report a patient with recalcitrant DGA who was treated with fumaric acid esters (FAE).

Case presentation

A 40-year old Caucasian woman presented with a 25-year history of DGA on both legs. Since one year, she also had



Figure 1
Long-standing disseminated granuloma annulare on the left leg.



Figure 2
Almost complete clearance of disseminated granuloma annulare after 3 months of therapy with fumaric acid esters.

lesions on the abdomen. Previous treatments with various therapeutic modalities (e.g., corticosteroids, dapsone, and bath psoralen plus ultraviolet-A radiation) were ineffective. On examination, she had erythematous annular plaques on the abdomen and on both legs (Fig. 1). Histopathologic examination of a punch biopsy specimen from the left leg revealed a normal epidermis. Below the epidermis there was mild collagen degeneration surrounded by palisading inflammatory cells. The infiltrates consisted of a mixture of monocytes, histiocytes, and occasional giant cells. These findings were consistent with the diagnosis of DGA. Complete work-up did not reveal evidence of malignancies, infections, and internal diseases such as diabetes mellitus.

Since the disease had been recalcitrant to various conventional therapies, we decided to start oral treatment with fumaric acid esters. The patient was 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® (Fumedica GmbH, Herne, Germany) [6]. Dosage of FAE was performed according to the standard therapy regimen for psoriasis patients displayed in Table 1. After two months, a complete clearance of skin lesions on the abdomen was achieved. Long-standing lesions on the legs improved after three-month therapy (Fig. 2). No subjective side effects were observed during treatment. Regular laboratory investigations, including differentiate blood count and kidney function, did not revealed abnormal findings during therapy, with the exception of slight lymphocytopenia. After discontinuation of

treatment with FAE the patient remained in remission during a six-month follow up period.

Table 1: Dosage schedule of fumaric acid esters used for the presented patient with disseminated granuloma annulare

Week	Morning*	Noon*	Evening*	FAE formulation
1	1	-	-	Fumaderm® initial
2	1	-	1	Fumaderm® initial
3	1	1	1	Fumaderm® initial
4	1	-	-	Fumaderm®
5	1	-	1	Fumaderm®
6-12	1	1	1	Fumaderm®

* = number of tablets

Discussion

FAE has been shown to be an effective therapy option in patients with severe psoriasis vulgaris [6,7]. During therapy with fumaric acid a persistent decrease in the lymphocyte count and stimulation of TH2 cytokine responses have been observed. Since psoriasis is regarded as a TH1-type inflammatory disorder, the immunomodulation away from the TH1 cytokine IFN- γ to the TH2 cytokine IL-10 may lead to improvement of the disease. Furthermore the anipsoriatic activity of fumaric acid may also be mediated by diminishing proinflammatory cytokine overexpression and the antigen-presenting capacity of monocytes and macrophages [8,9].

It has been reported that FAE induce apoptosis in human dendritic cells as well as keratinocytes [10]. Histopathologically, localized granuloma as well as DGA are characterized by lymphohistiocytic and monocytic infiltrates that form palisading granulomas with central necrobiotic changes. In a recent study, numerous apoptotic macrophages have been observed within the necrobiotic areas [11]. A popular view concerning pathogenesis holds that granuloma annulare is based on a delayed-type hypersensitivity reaction to as yet undefined cutaneous antigens. Phototherapy (e.g., psoralen plus ultraviolet-A radiation, ultraviolet-A1 radiation) is effective in DGA and is known to suppress delayed hypersensitivity responses in the skin [3-5]. Previous findings suggest that a T cell-mediated immune response producing cytokines may be the dominant pathogenic factor in granuloma annulare [12]. Thus the efficacy of FAE in DGA may be mediated by similar immunomodulatory mechanisms that are observed in the treatment of psoriasis. Notably it has been observed that treatment with FAE was also effective in cutaneous sarcoidosis and necrobiosis lipoidica which are closely related to granuloma annulare U. Nowack, MD, and T.

Gambichler, MD; unpublished data). Schulze-Dirks and Petzoldt [13] reported a female with a one-year history of DGA which resolved after six-week treatment of FAE. Since our patient had long-standing DGA, which was recalcitrant to potentially helpful therapeutic modalities, we do not consider that the therapeutic effect was due to spontaneous resolution. It has been demonstrated that FAE are well tolerated drugs suitable for long-term management (> 6 months) in psoriasis. Subjective adverse effects such as flushing and gastrointestinal symptoms are frequently observed. Relative lymphocytopenia is the most frequent laboratory finding in long-term users. Therefore therapy with FAE should only be performed under controlled conditions [14]. FAE are a potentially beneficial therapeutic option for patients with recalcitrant DGA. Controlled trials are however necessary to fully explore the efficacy, optimal dosage, and safety of FAE in the treatment of DGA.

List of abbreviations

DGA: disseminated granuloma annulare

FAE: fumaric acid esters

Competing interests

None declared

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