Fumaric Acid Esters in Severe Ulcerative Necrobiosis Lipoidica: A Case Report and Evaluation of Current Therapies

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Sir,

Necrobiosis lipoidica (NL) was first described by Oppenheim in 1929. NL is a granulomatous skin disease with association with diabetes mellitus (DM) in 10–40% of cases, but less than 1% of patients with DM develop NL. Additional risk factors for NL include other granulomatous diseases, such as granuloma anulare (GA), sarcoidosis, colitis ulcerosa and Crohn's disease. Middle-aged women are mainly affected. The lesions typically present as irregular or ovoid plaques with a central yellow atrophic area and a violaceous border; telangiectasia is often present. Ulcerations occur in approximately one-third of patients and complicate the clinical course. The most common sites of NL manifestation are the lower legs. Topical glucocorticosteroids represent the standard treatment of NL. In more complicated cases, glucocorticosteroids are given systemically. Several other therapies, including phototherapy, as well as systemic treatment with antimalarial drugs, cyclosporine and tumour necrosis factor (TNF) antagonists have been reported (Table I). However, a constantly effective and safe treatment has not yet been established. Especially in patients with steroid-refractory severe ulcerative NL, safe and effective therapies are needed. We report here the first case of a young woman with long-standing ulcerative NL who did not respond to topical and systemic glucocorticosteroids or phototherapy, but was treated successfully with fumaric acid esters (FAE).

Table I. *Therapeutic options in necrobiosis lipoidica*

Therapeutic modality (ref.)	Efficacy[a]	Evidence level[b]
Topical therapy		
Glucocorticosteroids (x)	+ to ++	III
Calcineurin inhibitors (x)	–/+	III
Creme PUVA (3)	+ to ++	II
PUVA bath (x)	+ to ++	III
UVA-1 (4)	+	II
Photodynamic therapy (5)	+	II
Systemic therapy		
Acetylsalicylic acid (6)	–/+	I–II
Pentoxyfylline (7)	+	III
Glucocorticosteroids (8)	+	II
Fumaric acid esters (1, 2)	+ to ++	II
Nicotinamide (9)	+	II
Antimalarial agents (10)	+	III
Cyclosporine (11)	+	III
TNF antagonists (x)	–/+	III
Mycophenolate mofetil (x)	–/+	III
Thalidomide (x)	–/+	III

[a]++: Healing; +: improvement; –/+: unclear efficacy; 0: no efficacy.
[b]I: prospective controlled trial; II: retrospective study or large case series; III: small case series or individual case reports.
x: for extra references please contact the authors.
TNF: tumour necrosis factor; PUVA: psoralen plus ultraviolet A; UVA: ultraviolet A.

CASE REPORT

A 42-year-old Caucasian woman presented with a 7-year history of NL and a 2-year history of severe ulcerations of the lesional skin of both lower legs accompanied by dysesthesia and pain (Fig. 1A). A skin biopsy from the lower left leg showed typical features of NL: a superficial and deep perivascular infiltrate of lymphocytes and plasma cells as well as epithelioid histiocytes, arranged in clusters and in a palisade shape surrounding areas of thickened bundles of collagen and degenerated collagen. Diabetes screening, X-ray of the chest and ultrasound of the abdomen revealed no signs of NL-associated diseases. Therapy with topical glucocorticosteroids, topical tacrolimus (0.1%) and compression did not lead to any improvement. Phototherapy with topical psoralen plus ultraviolet A (PUVA) over a period of 12 weeks (total cumulative dose: 77.4 J/cm^2) and subsequent UVA-1 phototherapy for an additional 12 weeks (total cumulative dose: 1535 J/cm^2) showed only minimal and transient improvement, but no healing. Systemic therapy with prednisolone up to 50 mg daily over 4 months was not helpful.

Since FAE have been reported to be efficient in patients with NL and other granulomatous diseases, we decided to treat the patient with FAE (1, 2). Two formulations of FAE in capsule form exist: Fumaderm® Initial and Fumaderm® (Almirall Hermal GmbH, Reinbek, Germany). The capsules differ in the composition of their active compound dimethylfumarate (DMF). The low-dose capsule Fumaderm® Initial contains 30 mg DMF, whereas the high-dose Fumaderm® formulation consists of 120 mg DMF. Dosage of FAE was administrated following the standard therapy regimen for patients with psoriasis. During therapy with FAE, the patient was regularly monitored for clinical outcome, adverse effects and laboratory tests. Laboratory tests showed no abnormalities in the differential blood count, transaminases or creatinine. Only a slight increase in the blood cholesterol level was noticed, which was unlikely to be related to the medication with FAE. At a dosage of 240 mg DMF per day, the patient reported mild gastrointestinal adverse effects, which disappeared after reducing the dosage to 120 mg DMF per day. Six weeks after the therapy was started, a major clinical improvement was noticed. After 6 months of therapy with 120 mg DMF per day, the ulcerations had completely healed (Fig. 1B). At the same time, dysesthesia and pain disappeared. This therapy was continued for a further 6 months. During follow-up no signs of newly developing NL lesions or ulcerations were observed and no adverse effects or laboratory abnormalities were noticed.

DISCUSSION

In contrast to other inflammatory skin diseases, evidence-based therapeutic guidelines for NL are missing. This is mainly due to the relatively low prevalence of

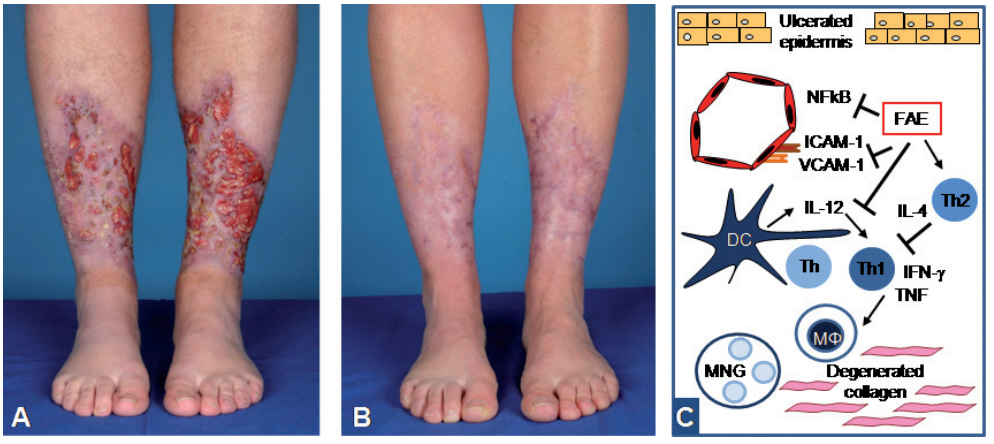

Fig. 1. Ulcerative necrobiosis lipoidica (NL) treated with fumaric acid esters (FAE): Lower legs presenting with irregularly shaped painful ulcers with violaceous borders (A) before treatment and (B) 6 months after treatment with FAE showing complete healing. (C) Potential interactions of FAE with cellular and molecular pathways in NL pathogenesis. Macrophage (Φ), multinucleated giant cell (MNG). DC: dendritic cell; Th: T-helper cell; TNF: tumour necrosis factor.

NL and also to our incomplete understanding of NL pathogenesis. It remains to be clarified whether vascular changes, collagen abnormalities or immune reactions are the primary cause of NL. Collagen degeneration may precede a granulomatous response, followed by thickening of blood vessel walls, thickening of the basement membrane and fat deposition. Vascular changes, such as antibody-mediated vasculitis, may also be responsible for disease development. The observation that NL is often associated with DM supports the contention that microangiopathy initiates NL pathogenesis. Alternatively, inflammation triggered by altered metabolism or trauma may be the primary cause of NL, since impaired neutrophil migration has been suggested to result in an increased number of macrophages, which are typical cellular components of granuloma. The specific antigenic stimuli and molecular pathways that initiate granuloma formation in granulomatous diseases are unknown. Stimulation of innate immune cells results in the release of TNF and interferon (IFN-)γ. TNF induces the expression of adhesion molecules, such as ICAM-1 and VCAM-1, facilitating tissue recruitment of leukocytes. IFN-γ seems to be responsible for the activation of resident dendritic cells (DC) and macrophages. Activated DC and macrophages traffic to draining lymph nodes and to the dermis, secrete inflammatory cytokines such as interleukin (IL-)12 and induce the differentiation of IFN-γ-producing T helper (Th) 1 cells (Fig. 1C).

The critical role of immune cells and inflammatory cytokines establishes the rationale for immunosuppressive therapy of NL. The most common treatments of NL are potent topical glucocorticosteroids or calcineurin inhibitors. Phototherapy is efficient, induces local immunosuppression and reduces sclerosis by inducing tissue collagenases (3–5). Systemic rheological therapy might be helpful in some patients (6, 7). In patients with NL resistant to topical treatment and phototherapy, systemic administration of glucocorticosteroids is recommended as first-line therapy (8). For non-responders, several second-line therapies with different efficacies and evidence levels have been reported (9-11) (Table I). Nonetheless, in a subset of patients none of the traditional treatments leads to satisfying clinical outcome, especially in cases with severe ulcerations.

The patient described here did not respond to any of the common topical or systemic therapies. Cyclosporine was not administered, since the patient was already on phototherapy. Only 6 weeks after the initiation of FAE therapy, our patient showed clinical improvement and subsequent complete healing of ulcerations. This corroborates the findings of Kreuter et al. (1). The exact mode of action of FAE is still unclear. In the case of granulomatous diseases, FAE could theoretically interfere with multiple steps of granuloma formation (Fig. 1C). Although a subset of patients treated with FAE develops lymphopenia, no lymphopenia occurred in our patient. Preceding therapies with immunosuppressants were ineffective. Thus, immunomodulatory effects rather than immunosuppression seem to be mediated by FAE (12). Interestingly, FAE have been reported to act on endothelial cells (EC) and also on DC, both assumed to be relevant cell types in NL pathogenesis. FAE have been shown to inhibit the activation of NFκB as well as the expression of ICAM-1 and VCAM-1 in EC (13, 14). Moreover, FAE inhibit the production of IL-12 by activated DC and induce the production of anti-inflammatory cytokines such as IL-4 (12, 15). The anti-inflammatory effects of FAE in combination with its effects on EC may be responsible for the clearance of ulcerative NL, as seen in our patient.

The authors declare no conflict of interest.

REFERENCES

1. Kreuter A, Knierim C, Stucker M, Pawlak F, Rotterdam S, Altmeyer P, et al. Fumaric acid esters in necrobiosis lipoidica: results of a prospective noncontrolled study. Br J Dermatol 2005; 153: 802–807.
2. Breuer K, Gutzmer R, Volker B, Kapp A, Werfel T. Therapy of noninfectious granulomatous skin diseases with fumaric acid esters. Br J Dermatol 2005; 152: 1290–1295.
3. De Rie MA, Sommer A, Hoekzema R, Neumann HA. Treat-

ment of necrobiosis lipoidica with topical psoralen plus ultraviolet A. Br J Dermatol 2002; 147: 743–747.
4. Beattie PE, Dawe RS, Ibbotson SH, Ferguson J. UVA1 phototherapy for treatment of necrobiosis lipoidica. Clin Exp Dermatol 2006; 31: 235–238.
5. Berking C, Hegyi J, Arenberger P, Ruzicka T, Jemec GB. Photodynamic therapy of necrobiosis lipoidica – a multicenter study of 18 patients. Dermatology 2009; 218: 136–139.
6. Statham B, Finlay AY, Marks R. A randomized double blind comparison of an aspirin dipyridamole combination versus a placebo in the treatment of necrobiosis lipoidica. Acta Derm Venereol 1981; 61: 270–271.
7. Noz KC, Korstanje MJ, Vermeer BJ. Ulcerating necrobiosis lipoidica effectively treated with pentoxifylline. Clin Exp Dermatol 1993; 18: 78–79.
8. Petzelbauer P, Wolff K, Tappeiner G. Necrobiosis lipoidica: treatment with systemic corticosteroids. Br J Dermatol 1992; 126: 542–545.
9. Handfield-Jones S, Jones S, Peachey R. High dose nicotinamide in the treatment of necrobiosis lipoidica. Br J Dermatol 1988; 118: 693–696.
10. Durupt F, Dalle S, Debarbieux S, Balme B, Ronger S, Thomas L. Successful treatment of necrobiosis lipoidica with antimalarial agents. Arch Dermatol 2008; 144: 118–119.
11. Smith K. Ulcerating necrobiosis lipoidica resolving in response to cyclosporine-A. Dermatol Online J 1997; 3: 2.
12. Ghoreschi K, Rocken M. Immune deviation strategies in the therapy of psoriasis. Curr Drug Targets Inflamm Allergy 2004; 3: 193–198.
13. Loewe R, Holnthoner W, Groger M, Pillinger M, Gruber F, Mechtcheriakova D, et al. Dimethylfumarate inhibits TNF-induced nuclear entry of NF-kappa B/p65 in human endothelial cells. J Immunol 2002; 168: 4781–4787.
14. Vandermeeren M, Janssens S, Borgers M, Geysen J. Dimethylfumarate is an inhibitor of cytokine-induced E-selectin, VCAM-1, and ICAM-1 expression in human endothelial cells. Biochem Biophys Res Commun 1997; 234: 19–23.
15. Litjens NH, Rademaker M, Ravensbergen B, Rea D, van der Plas MJ, Thio B, et al. Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses. Eur J Immunol 2004; 34: 565–575.