

Letters to the Editor

Topical tacrolimus for recalcitrant leg ulcer in rheumatoid arthritis

SIR, Chronic leg ulcers have been reported to occur in up to 10% of patients with rheumatoid arthritis (RA) at some stage of their disease [1]. Most patients reveal seropositive erosive disease with significant functional impairment and high levels of rheumatoid factor [2]. With regard to aetiological factors, venous insufficiency, trauma or pressure, and peripheral arterial disease appear to be common causes [2, 3]. However, other disorders such as cutaneous vasculitis, pyoderma gangrenosum or Felty's syndrome need to be considered [2–4]. Notably, vasculitis has been estimated to play a key role in 18–37% of leg ulcers in RA [3]. These 'vasculitic' ulcers tend to persist and are refractory to local treatment, including skin grafting [2, 3]. Systemic administration of glucocorticosteroids and/or non-steroidal immunosuppressive agents may be limited by serious adverse effects. Here, we describe a patient with severe RA, glucocorticosteroid-related osteoporosis and recalcitrant 'vasculitic' leg ulcer which healed under topical treatment with tacrolimus (FK506).

A 65-yr-old woman with an 8-yr history of severe RA developed a painful atrophie blanche transforming into a rapidly growing ulcer on the lateral side of her left ankle. Previous treatments for her RA included gold injections, methotrexate, azathioprine, sulphasalazine and chloroquine, which were either ineffective or had to be stopped due to serious adverse effects. Long-term administration of glucocorticosteroids had caused osteoporosis and fracture of the neck of the right femur. Upon admission, the patient was taking prednisone 5 mg/day and indomethacin 50 mg twice a day.

Examination revealed an ulcer of 5.8×4.7 cm with punched-out, erythematous margins on the lateral side of the left ankle (Fig. 1A). Sensation and peripheral pulses were normal, and chronic venous insufficiency could be excluded. Seropositive RA had involved 14 joints with partial mutilation (Steinbrocker class 4), including large Baker's cysts in both knees.

Blood tests showed mild anaemia, leucocytosis ($12\,100/\mu\text{l}$) with mainly neutrophils (82.3%), thrombocytosis ($572\,000/\mu\text{l}$), elevated C-reactive protein (87.6 mg/l; normal: <5) and a positive rheumatoid factor (95 IU/ml). Tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies and cryoglobulins remained negative. A skin biopsy taken from the margin of the ulcer revealed leucocytoclastic vasculitis with fibrinoid necrosis of the vessel walls and thrombosis in some vessels.

Topical administration of potent glucocorticosteroids under hydrocolloidal wound dressings initially stopped further enlargement of the ulcer. A concomitant superinfection with *Staphylococcus aureus* was treated with oral clindamycin. However, neither reduction in size nor

healing of the ulcer were observed during 8 months of intensive local treatment including cyclosporin A (10% solution; Sandimmun®). With regard to glucocorticosteroid-induced osteoporosis and previous adverse reactions to non-steroidal immunosuppressants, an appropriate systemic therapy could not be initiated. Alternatively, daily topical applications of FK506 (0.5% solution; Prograf®) under hydrocolloidal wound dressings were started. Within 5 months, this treatment led to an almost complete resolution of the skin lesion (Fig. 1B). Apart from a burning pain during application, neither side-effects to FK506 nor systemic uptake of the drug were detectable.

The most common type of rheumatoid vasculitis affecting the skin is small-vessel vasculitis due to immune complex formation [4]. Apparently, high titres of rheumatoid factor, as observed in our patient, have been associated with extra-articular disease in RA, including cutaneous vasculitis. Biopsies from leg ulcers in RA, however, were not extensively studied and frequently failed to show evidence of vasculitis [2, 3]. In the present case, histology confirmed leucocytoclastic vasculitis as the aetiological factor of recalcitrant skin ulceration. For this condition, systemic glucocorticosteroids and/or non-steroidal immunosuppressive agents represent the mainstay of therapeutic strategies [3, 4]. With regard to other inflammatory skin diseases, promising results were obtained with macrolide lactones, i.e. cyclosporin A and FK506 [5]. Long-term systemic administration of these compounds, however, may be limited by severe adverse effects. Notably, FK506 also exerts significant local immunosuppression upon topical application [5–7], whereas cyclosporin A does not penetrate human skin in relevant amounts [8]. A recent study demonstrated that FK506 ointment is highly effective in the treatment of atopic dermatitis [7]. Moreover, pyoderma gangrenosum, a progressive necrotizing skin disease, was successfully treated with topical FK506 [9].

Similar to cyclosporin A, FK506 acts via inhibition of interleukin (IL)-2 gene expression in T cells [5]. Data obtained from murine models provide evidence that topical FK506 interferes with epidermal cytokine networks, maturation of antigen-presenting cells, T-cell activation and migration, and concomitant B-cell activation [6]. In addition, FK506 is capable of decreasing the expression of IL-8 and its receptor, resulting in impaired chemotaxis for neutrophils by human keratinocytes [5]. In contrast to glucocorticosteroids, FK506 did not show significant antiproliferative effects and therefore should not impair wound healing [5, 10].

The present observation indicates that recalcitrant 'vasculitic' leg ulcers associated with RA may be successfully treated with topical FK506. The drug could inhibit both skin-infiltrating autoimmune T cells and amplification of destructive skin inflammation following local immune complex precipitation. From a pharmacological

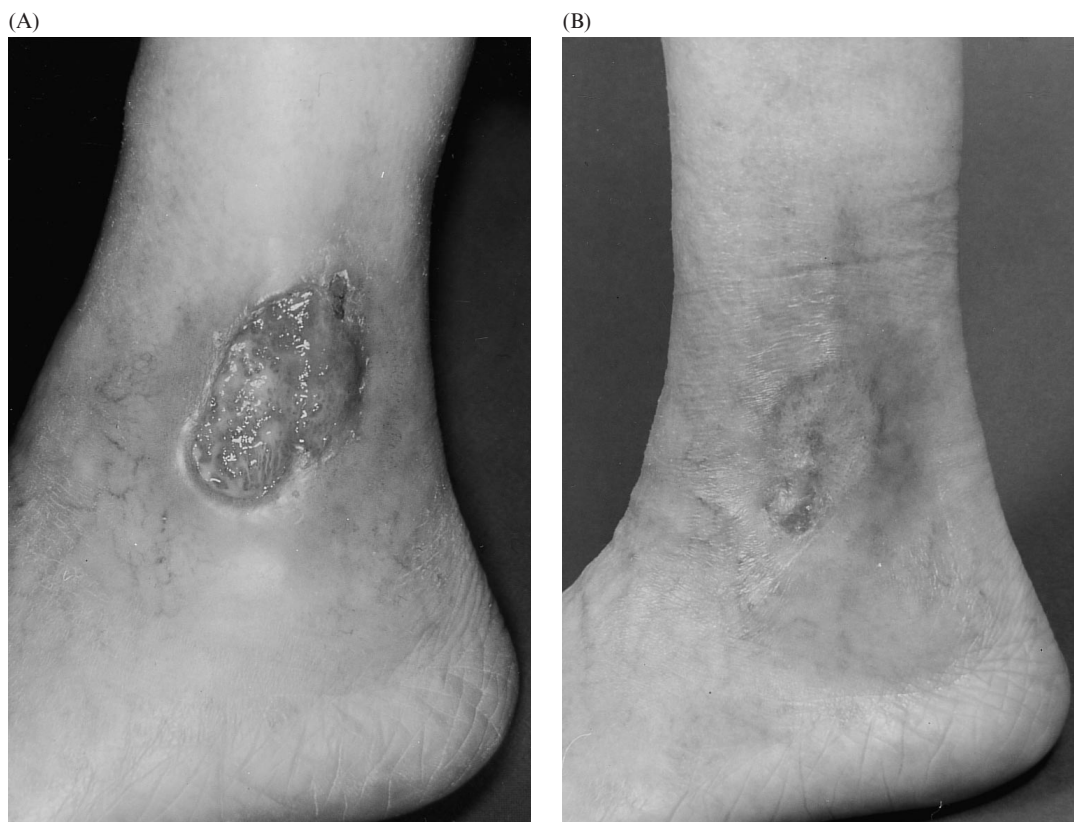


FIG. 1. (A) Chronic leg ulcer in a 65-yr-old patient with RA. (B) Healing of the ulcer within 5 months of topical treatment with FK506.

point of view, this new approach allows the reduction of severe adverse effects associated with systemic administration of immunosuppressants, including the complications of prolonged glucocorticosteroid treatment. However, randomized controlled trials are needed for further assessment of the therapeutic efficacy of topical FK506 in leg ulcers associated with RA.

The authors wish to thank Dr Bernadette Schubert, Dermatologisches Zentrum am Krankenhaus Buxtehude, for kindly providing microscopic slides of the skin biopsy.

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Accepted 13 July 1999

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