Topical tacrolimus therapy of resistant cutaneous lesions in lupus erythematosus: a possible alternative

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Objective. To determine the efficacy of tacrolimus ointment 0.1% on resistant cutaneous lesions in patients with lupus erythematosus.

Methods. Twelve patients with skin manifestations were studied. Six had discoid lupus (DL), four subacute cutaneous lupus erythematosus (SCLE) and two systemic lupus erythematosus (SLE). All patients had extensive skin lesions refractory to previous treatment. Patients received topical tacrolimus 0.1% for a minimum of 6 weeks and response was evaluated by physicians’ and patients’ assessment and documented with photographs at baseline and at the end of the treatment.

Results. Eleven of 12 patients completed the therapy. One patient with DL discontinued because of side-effects—peeling and a burning sensation. Six patients were clearly improved, one patient had a minor remission of his face lesion while in four the rashes remained the same. Two patients with SCLE had significant regression of their lesions while the other two had no improvement. In DL, two had certain improvement, one minor improvement and two were without response. The patients with SLE had significant amelioration of their extensive photosensitive rash.

Conclusion. Tacrolimus ointment 0.1% may be an effective alternative in patients with severe resistant cutaneous manifestations in lupus erythematosus.

Key words: Tacrolimus, Cutaneous lupus erythematosus.

Cutaneous lesions are a common and often disfiguring manifestation of autoimmune connective tissue diseases. Cutaneous lupus erythematosus is a broad term which includes a variety of lesions such as malar, butterfly or widespread photosensitive rash, subacute cutaneous, chronic cutaneous (classical discoid lupus, lupus profundus, lupus pernio/chilblains), urticarial or purpuric vasculitis and vascular lesions (periungual erythema, livedo reticularis, Raynaud’s, telangiectasia).

Administration of systemic agents such as corticosteroids, hydroxychloroquine (HCQ), mepacrine, methotrexate (MTX), mycophenolate mofetil (MMF), cyclophosphamide (CPM) and/or azathioprine (AZA) for the underlying systemic disease leads in many cases to remission of the cutaneous lesions. The results are better when topical treatment (steroids, sun protection) is used. Nevertheless, many patients suffer from resistant cutaneous lesions despite therapy. On the other hand, cutaneous lesions may be the only manifestation of the disease such as subacute cutaneous lupus erythematosus (SCLE) and discoid lupus (DL), making it difficult to justify systemic agents because of their side-effects. A variety of systemic [dapsone, thalidomide, retinoids, intravenous immunoglobulins (i.v. IG)] and topical agents (thalidomide, intralesional steroids, retinoids) as well as laser therapy, phototherapy, photopheresis and cryotherapy have been used for resistant cutaneous lesions [1].

Tacrolimus, isolated in 1984 from the fungus Streptomyces tsukubaensis, is a macrolide immunomodulator FK506, which acts on T lymphocytes and inhibits interleukin-2 transcription as well as other cytokines [2]. Since 1989 it has been widely used in preventing graft rejection after transplantation (liver, kidneys, lungs) [3]. Because of its anti-inflammatory action, in November 2000 the US FDA Dermatologic Committee [4] approved tacrolimus ointment for the treatment of moderate to severe atopic dermatitis in children and adults. Efficacy is similar or even better than that of corticosteroids (especially in children or in facial lesions where only weak steroids can be used), without the adverse effects of skin atrophy (no impairment of collagen synthesis) and serious systemic absorption [5]. Common side-effects are burning sensations, itching or erythema, which usually decline with continuance of treatment due to improvement of the skin’s condition [6]. Tacrolimus also appears to be effective in resistant cutaneous lesions of other diseases such as psoriasis [7], localized scleroderma [8], chronic actinic dermatitis [9], pyoderma gangrenosum [10], Behçet’s disease [11], lichen planus [12], rheumatoid ulcers [13] and steroid rosacea [14].

The aim of this preliminary study was to assess the efficacy of tacrolimus ointment on resistant cutaneous lesions in lupus erythematosus.

Materials and methods

Twelve patients participated in this study. The patient group consisted of nine women and three men with mean age of 38.2 yr, ranging from 22 to 74. All had extensive cutaneous lesions resistant to previous treatment (Table 1).
All patients applied tacrolimus ointment 0.1% over the cutaneous lesions twice a day for at least 6 weeks. Laboratory investigation at baseline and after treatment included antinuclear antibodies (ANA), double-stranded deoxyribonucleic acid (ds-DNA), extractable nuclear antigens (ENA), C3, C4, anticycliclipoprotein IgG and IgM antibodies, lupus anticoagulant, full blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The results of the treatment were evaluated after 6 weeks by clinical assessment and documented with photographs before and after treatment.

This study was approved by the St Thomas’ Hospital Ethics Committee and all patients gave full informed consent.

### Results

Eleven of 12 patients completed the therapy. One patient with DL discontinued because of side-effects—peeling and a burning sensation. The first six patients were certainly improved (Fig. 1), the seventh patient had a minor remission of his arm lesion while in four the rashes remained the same. Two patients with SCLE had significant improvement while the other two had no improvement. In DL, two had certain improvement, one minor and two were without response. The patients with systemic lupus erythematosus (SLE) had significant amelioration of their extensive photosensitive rash.

Laboratory investigations showed no difference before and after treatment. This was not surprising as the ointment is rarely absorbed enough to affect the systemic disease.

### Discussion

Cutaneous lesions in connective tissue diseases may prove very resistant to classical systemic and topical agents. These lesions usually appear in visible areas resulting in significant psychological effects. Therapy of resistant disease is often unsatisfactory due to recalcitrant disease or serious side-effects, as with thalidomide [15].

Over the last two decades, tacrolimus has emerged as an effective immunosuppressive and anti-inflammatory agent. Its systemic use is confined to preventing allograft rejection because of potential serious side-effects. Topical tacrolimus is much safer and is very effective in severe and resistant atopic dermatitis, especially in children or on facial lesions where only weak topical steroids can be used. The ointment is expensive, but a recent cost-effectiveness analysis showed that in the long term the cost is similar for tacrolimus and high-potency topical corticosteroids [16]. Topical tacrolimus is not systemically absorbed, even when large areas of skin are affected. The most common adverse effect is a burning sensation which may settle with continued use. Recently, topical tacrolimus has been used in other chronic inflammatory conditions such as psoriasis, dermatomyositis and cutaneous lupus erythematosus. There are a few case reports suggesting a good therapeutic efficacy in SCLE, DL and SLE but the number of patients is insufficient for an objective conclusion [17, 18]. For DL patients in particular the results so far seem to be controversial [19, 20]. Other topical agents including pimecrolimus may also emerge as useful therapies but have not yet been studied in detail.

The results of our study are encouraging, particularly for SCLE and DL, which are the most resistant cutaneous lesions of lupus.
erythematosus. More than 50% of patients had an improvement after 6 weeks of therapy. Interestingly, two of these patients were improved after the third week of therapy, probably reflecting the chronicity of the lesions. These results, combined with the absence of serious side-effects, suggest that tacrolimus should be considered as an alternative treatment for resistant cutaneous lesions in lupus erythematosus.

The authors declare no conflicts of interest.

References