# Topical Tacrolimus in Severe Chronic Graft-Versus-Host Disease

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*Accepted November 22, 2004.*

*Sir,*

Graft-versus-host disease (GVHD) is a T-cell-mediated immunological complication in bone marrow transplantation (1). The skin is the most often involved organ in chronic GVHD (2). Treatment is mainly systemic with immunosuppressive agents. Topical treatment is adjunctive and commonly steroid creams have been used. Recently, adjunctive topical application of calcineurin inhibitors in patients with systemic immunosuppression has been described in the treatment of cutaneous GVHD lesions (3–5). We present here a case with severe GVHD with progredient erosive and ulcerating lesions in spite of topical steroids and extracorporal photopheresis. Application of tacrolimus ointment led to very satisfying improvement of the skin lesions.

## CASE REPORT

A 52-year-old female developed a centroblastic/centrocytic lymphoma grade IV with first diagnosis in September 1998. Remission after chemotherapy with etoposide and bendamustin was transient and treatment was continued with mitoxantron and rituximab. In September 2001, acute myeloic leukaemia (M4 according to the French-American-British classification) was diagnosed and chemotherapy with cytarabine and idarubicin or mitoxantron was performed. After conditioning with busulfan and fludarabine, allogenic stem cell transplantation (brother) was conducted in October 2001. In January 2002, under treatment with cyclosporine, severe chronic GVHD developed.

At the first consultation in our hospital in March 2003, the patient received 4 mg/day Prograf® (tacrolimus) and 5 mg/day prednisolone. The skin examination showed poikiloderma with large erythematous and widespread erosive areas, hyper- and hypo-pigmentation, vitiligo patches, sclerosis and scarring (Fig. 1a). Further findings were mild erosive mucositis, almost complete baldness, ectropion, kerato-conjunctivitis sicca and cataracta incipiens. The laboratory findings showed impaired liver function. Histological examination of the skin biopsy showed basal vacuolization in the epidermis, keratinocyte necrosis, melanophages and a predominantly lymphocytic infiltration in the upper dermis (Fig. 2) comparative with GVHD. Treatment with extracorporeal photopheresis was initiated in April 2003 and conducted in monthly cycles. Topically, betamethasone-valerate ointment was prescribed. In August 2003, hypertrophic skin lesions on the cheeks were observed. Multiple biopsies confirmed reactive lesions and excluded malignant infiltrates. Topical treatment was conducted with soft silicone-faced polyurethane foam dressings and betamethasone-valerate ointment without benefit. Starting in

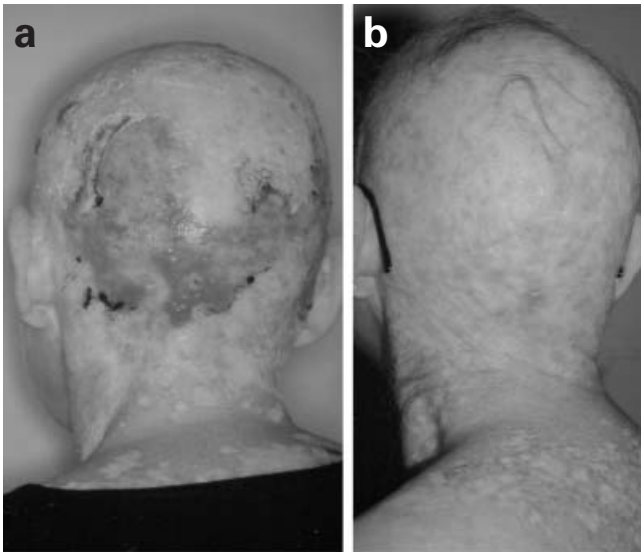


*Fig. 1.* (a) A patient with large erythematous and erosive areas, hyperpigmentation and hypopigmentation, vitiligo patches, sclerosis and scarring in the occipital region. (Dec 2003). (b) After 3 months of treatment with topical tacrolimus 0.1%. Former erythematous and erosive areas showed complete healing in the occipital region (April 2004).


DOI: 10.1080/00015550510027775

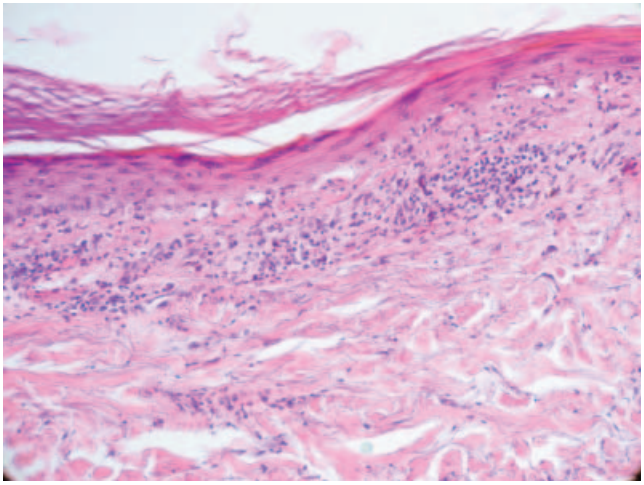

*Fig. 2.* Basal vacuolisation of the epidermis, keratinocyte necrosis, melanophages and a predominantly lymphocytic infiltration in the upper dermis. Skin biopsy from July 2003 (upper arm). H&E stain, 1:100.

December 2003, tacrolimus 0.1% ointment (Protopic®, Fujisawa) was applied on the erosive areas on the shoulder. In January 2004, mild improvement was seen and she was then instructed to use tacrolimus 0.1% on every erosive or erythematous lesion. All treated areas were monitored before application and after 1 and 3 months of therapy. A slow and nearly complete healing of the formerly progressive and therapy-resistant lesions was noticed (Fig. 1b).

## DISCUSSION

Chronic GVHD occurs in 60–80% of long-term survivors of allogeneic bone marrow transplantation (6). GVHD may involve multiple organs, primarily the skin as well as the gastrointestinal tract, liver, oral mucosa, eyes and the respiratory tract (7). Our patient presented with chronic GVHD of sclerodermatous type and in addition liver function impairment and eye involvement. Tacrolimus (FK506) is a calcineurin inhibitor isolated from the soil microbe *Streptomyces tsukuba,* which is meanwhile a widely used topical drug in the management of atopic dermatitis (8). First evidence of the benefits of adjunctive topical treatment of cutaneous GVHD was provided by Choi & Nghiem (3). They reported good responses in 13 of 18 patients with GVHD treated with systemic immunosuppression and adjunctive topical therapy. Similar data were reported in another small series of patients (5). The mechanism by which topical tacrolimus may be effective in GVHD is the suppression of local cytokine secretion such as interleukin-2, interferon-$\gamma$ and tumour necrosis factor-$\alpha$ in the skin (5). Intriguingly, the erosive lesions developed in spite of systemic tacrolimus while application of topical tacrolimus led to nearly complete healing. This observation is in complete accordance with the literature; however, a conclusive explanation is still lacking (9). One possible explanation of this phenomenon could be different local cutaneous concentrations of tacrolimus during systemic and topical applications.

To the best of our knowledge this is the first report documenting the successful combination of extracorporeal photopheresis and adjunctive topical tacrolimus therapy in a patient presenting with severe ulcerating GVHD lesions. Despite failure of conventional combination therapies, a dramatic response to the application of topical tacrolimus was observed. Combination therapy with extracorporeal photopheresis and adjunctive topical tacrolimus offers an alternative, less toxic treatment of severe or unresponsive GVHD than other therapeutic interventions.

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