Topical Tacrolimus Ointment Is an Effective Therapy for Hailey-Hailey Disease

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

**REPORT OF A CASE**

A 67-year-old man with a 10-year history of flexural blistering eruptions also affecting 3 of his brothers was first evaluated in 1987. The patient presented with vesicles, erosions, and erythema in the intertriginous areas but also as multiple truncal plaques (Figure 1). Biopsy specimens showed intraepidermal clefts of varying sizes both suprabasally and higher in the epidermis, as well as the characteristic incomplete acantholysis in large parts of the epidermis, giving it the appearance of a “dilapidated brick wall” (Figure 2). The findings of a direct immunofluorescence evaluation were negative, which is consistent with a diagnosis of Hailey-Hailey disease (or chronic benign familial pemphigus).

A daily application of an ointment of betamethasone—a potent corticosteroid ointment—and clindamycin for 3 months gave no improvement in the condition. Similarly, neither topically applied clobetasol nor systemic antibiotics directed against *Staphylococcus aureus* had any disease-modifying effect. Then, 100 mg of dapsone daily and later 100 to 150 mg of azathioprine daily were administered successively for 3 months without significant beneficial effect. Oral daily treatment with 5 mg/kg of cyclosporine for 6 months reduced the activity of the disease, but this treatment was stopped owing to severe headache. Finally, 1% cyclosporine cream applied twice daily for 3 months did not result in healing. Because of the disseminated distribution of the lesions, carbon dioxide laser treatment was not considered an appropriate therapeutic option.

**THERAPEUTIC CHALLENGE**

As multiple therapies were either ineffective or associated with unacceptable side effects, topical therapy with 0.1% tacrolimus ointment (Protopic; Fujisawa Ireland LTD, Killorglin, Ireland) was initiated in April 2000.

**SOLUTION**

The patient was offered treatment with 0.1% tacrolimus ointment applied once daily to the affected areas. Clearance of the cutaneous lesions was observed within 1 month (Figure 3). A total amount of 30 g of tacrolimus ointment was needed to induce remission. Since then, the disease has been controlled by intermittent applications of tacrolimus ointment once daily for 2 to 3 weeks, without symptoms or signs of local or systemic toxicity. Routine blood test results and blood pressure measurements were within normal ranges. Blood levels of tacrolimus were not estimated during therapy. Interrupting tacrolimus ointment therapy resulted in gradual recurrence of vesicobullous lesions, but resuming tacrolim-
Mus treatment was associated with the disappearance of lesions within a few weeks. Hailey-Hailey disease is often difficult to treat. Therapeutic options include antibiotics to control secondary bacterial and viral infections. Immunomodulating therapy with corticosteroids, systemic and topical cyclosporine, oral retinoid, and the topical vitamin D analogue tacalcitol have been associated with reduced disease activity. This indicates that an inflammatory response is involved in the pathogenesis of the disease, which prompted us to evaluate the efficacy of 1% topical tacrolimus ointment (Protopic). What provokes the breakdown of the desmosome-keratin tonofilament complexes resulting in acantholytic keratinocytes is unknown. Tacrolimus, like cyclosporine, targets a calcium-activated phosphatase called calcineurin, thereby blocking the expression of several cytokines (interleukin [IL] 2, IL-3, IL-4, IL-5, granulocyte-monocyte colony-stimulating factor, and tumor necrosis factor alpha). It is suggested that the mechanism of action of topically applied tacrolimus ointment in Hailey-Hailey disease must be related in some way to the immunomodulating effect of the compound. Further studies are needed to define its mode of action at the molecular level. During therapy with tacrolimus we could not detect symptoms or signs of systemic toxicity. However, we suggest that patients treated with tacrolimus ointment for Hailey-Hailey disease have a blood test to ensure that the concentration of tacrolimus is below the levels associated with immunosuppression. Accepted for publication April 17, 2003.

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