Successful Treatment of Epidermolysis Bullosa Pruriginosa With Topical Tacrolimus

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 53-year-old white woman with epidermolysis bullosa (EB) pruriginosa presented to the dermatology clinic seeking therapy for localized severe and intractable pruritus. At the age of 4 years the patient developed an extremely pruritic bullous eruption characterized by fragile blisters, erosions, and excoriations affecting sites subject to friction and pressure, particularly the ankles and knees. By the age of 21 years, the patient had large lichenified plaques, areas of linear violaceous scarring, multiple milia, and erosions over much of the extensor surfaces of the legs, forearms, buttocks, and dorsum of the feet (Figure 1A and B). All of her 20 nails were grossly dystrophic (Figure 1C). Mucous membranes were normal. There was a family history of EB pruriginosa, as the patient’s younger brother and daughter were similarly affected.

Electron microscopical features supported the diagnosis of EB pruriginosa: separation at the sublamina densa level of the dermoeipidermal junction and abnormal anchoring fibrils that were scanty, disorganized, and not fully developed (Figure 2). Blood cell count and serum biochemistry findings were normal. Serum levels of thyroid hormones, ferritin, and IgE were all within normal ranges.

Throughout the course of the disease, intractable pruritus was the most prominent and severe feature, far outweighing the significant cosmetic disability. Continuous rubbing and scratching generated large areas of disease over the shins and forearms. The patient often presented with areas of frank bleeding resulting from deep excoriations. Treatments included inpatient and outpatient care with a combination of intensive emolliation, potent topical corticosteroids, sedating antihistamines, and behavioral therapy. These resulted in short-term control of the cutaneous manifestations, but not sustained improvement or control of the pruritus. Thinning of the skin secondary to the ongoing use of potent topical steroids was also evident.

Therapeutic Challenge

Epidermolysis bullosa pruriginosa is a rare condition of poorly understood pathogenesis. Therapeutic results are currently disappointing as targeted treatments are yet to be defined. In our patient, intractable pruritus was by far the most troublesome feature. A vicious cycle was established as the extreme itch precipitated paroxysms of scratching, resulting in new and persistent areas of disease. Our patient had been relatively unresponsive to topical steroids and long-term use had compounded the skin fragility by inducing significant cutaneous atrophy. The patient was reluctant to take any systemic medication.
Our challenge was to find a safe and effective therapy that would target the pruritus without the side effects of topical corticosteroids.

Since systemic cyclosporine has been used in EB pruriginosa with some success, topical tacrolimus was considered as an alternative therapeutic approach. Therapy was initiated with 0.03% tacrolimus ointment to the legs and forearms twice daily. Within 1 week of applying the ointment, a significant decrease in the pruritus was reported, resulting in a marked reduction in scratching. Progression of the lichenified plaques, linear violaceous scars, milia, and erosions was arrested and in some areas the lichenified plaques were reduced (Figure 3). The patient has used 0.03% tacrolimus ointment for 6 months without complication and remains under excellent symptomatic control.

Epidermolysis bullosa pruriginosa is a form of dystrophic EB characterized by prurigolike or lichenified lesions associated with scarring. It is usually confined to the shins and forearms. The ultrastructural hallmark is a sublamina densa split associated with an alteration in the number and structure of the anchoring fibrils at the dermal-epidermal junction. The onset of clinical features may be evident in early childhood, as in our patient, but in some cases appears later, in the second and third decades of life.

The mode of inheritance is variable. McGrath et al described 8 unrelated cases of EB pruriginosa, of which 5 were sporadic, 2 were autosomal dominant, and 1 was recessive. Mellerio et al described both dominant and recessive type VII collagen gene (COL7A1) mutations underlying the EB pruriginosa phenotype. Yu-Yun Lee et al and Jiang et al examined separate Chinese families with dominant EB pruriginosa who had different COL7A1 mutations. Our patient has a brother and a daughter similarly affected, and the mode of inheritance appears to be autosomal dominant.

The development of EB pruriginosa phenotype has yet to be defined. Molecular heterogeneity and compound heterozygosity in COL7A1 mutations have been demonstrated in patients with EB pruriginosa. Other genetic and environmental factors are also likely to contribute to this specific phenotype, as mutations in COL7A1 have been demonstrated in patients with both EB pruriginosa and dystrophic EB of nonpruriginous phenotype.

Treatment is aimed at controlling pruritus and halting the progression of cutaneous lesions. Potent topical steroids and intralesional triamcinolone have been reported to reduce the pruritus in some cases, but do not produce sustained improvement. Systemic therapy with histamine1 antihistamines, corticosteroids, or etidronate had no sustained effect. Oral administration of cyclosporine has been reported in 1 case as controlling the cutaneous lesions and decreasing the pruritus.

The aim of treatment in our patient was to eliminate the pruritus, as her scratching was traumatizing the skin and contributing to disease progression. The pathogenesis of the pruritus is poorly understood. Raised serum levels of IgE have been noted in some patients with EB pruriginosa, although elevated IgE levels do not specifically account for a pruriginosa phenotype.

Tacrolimus is a macrolide immunosuppressant produced by the soil fungus Streptomyces tsukubaensis. Topical application of tacrolimus in treating atopic eczema is well described. Cases of steroid-induced rosacea, pyoderma gangrenosum, lichen planus, and ichthyosis linearis circumflexa have been successfully treated with topical tacrolimus.

Figure 2. Electron microscopic appearances of lesional skin on the shin showing (1) keratinocytes, (2) lamina densa above the level of separation, (3) separation at the sublamina densa level of the dermoepidermal junction, and (4) upper dermis (original magnification × 76000).

Figure 3. Six months after treatment the forearms demonstrate reduction in lichenification, with persistent background milia and scarring.
Topical tacrolimus was considered in our patient because the literature suggests that it has an antipruritic action.\textsuperscript{15-17} The exact mode of this action is unclear. De Paulis et al\textsuperscript{20} showed that tacrolimus acted on skin mast cells challenged with anti-IgE antibodies to inhibit histamine release in a concentration-dependent manner and impair de novo synthesis of prostaglandin D\textsubscript{2}. Eberlein-König et al\textsuperscript{17} demonstrated that tacrolimus diminished the enhancing effect of interleukin-3 on anti-IgE-antibody–induced histamine release from basophils. The relevance of this phenomenon to EB pruriginosa is unclear because it is considered a mechanobullous disease.

Treatment with topical tacrolimus in our patient had minimal effect upon preexisting visible disease. The lack of a dramatic effect on established skin lesions was not unexpected, as EB pruriginosa is associated with an underlying COL7A1 mutation and tacrolimus does not affect collagen synthesis.\textsuperscript{18}

We believe that topical tacrolimus has potential benefits over topical corticosteroids when treating EB pruriginosa. There are currently no reports of systemic adverse effects after topical tacrolimus application.\textsuperscript{19} Although topical corticosteroids are generally well tolerated, they may cause systemic problems such as acne, hyperglycemia, growth retardation, and adrenal insufficiency when applied to large areas.\textsuperscript{20} Most importantly, tacrolimus, unlike topical steroids, does not cause cutaneous atrophy.\textsuperscript{18,21} These were important considerations in our patient whose pathological cutaneous fragility was compounded by steroid-induced atrophy.

To the best of our knowledge, this is the first reported case of EB pruriginosa successfully treated with topical tacrolimus. By alleviating our patient’s itch, disease progression was slowed and her quality of life was markedly improved. With its steroid-sparing effects and lack of documented systemic adverse reactions, we consider topical tacrolimus to be of significant benefit in treating EB pruriginosa.

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