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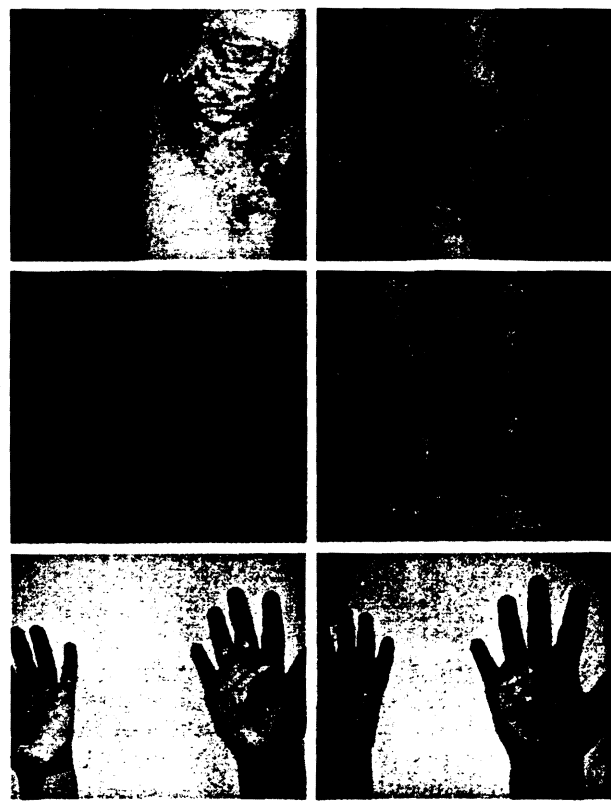
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**Effect of Tacrolimus (FK506) in Dystrophic Epidermolysis Bullosa: Rationale and Preliminary Results**

Progress has been made in understanding skin diseases such as epidermolysis bullosa (EB). Epidermolysis bullosa is characterized by abnormal skin fragility and the formation of blisters and erosions of the skin and mucous membranes in response to minor trauma. The disease manifests in infancy, and, by childhood, patients have cutaneous scarring and mucosal involvement that can be severe. Treatment is palliative. Tacrolimus (FK506) is a new immunosuppressive agent used in organ transplantation. This agent has a number of nonimmune effects, one of which is augmentation of cell regeneration and repair.<sup>1</sup> With the rationale of stimulating wound healing, we administered tacrolimus to a 5-year-old boy with dystrophic EB. There were no toxic effects, and scabs could form and affected areas heal since disease onset and treatment dramatically shortened the time to heal new lesions.

**Report of a Case.** Our patient was normal at birth. Blistering began at 2 months; at 4 months, diagnostic biopsy specimens were obtained that showed an intact epidermis and strands of collagen separating from the dermis sub-lamina densa with sub-lamina densa cleavage. Findings from transmission electron microscopy were compatible and showed reduced anchoring fibrils in areas of blisters. Tests for anti-type VII collagen antibodies showed negative findings and immunofluorescence mapping showed bullous pemphigoid antigen; laminin and type IV collagen were normally expressed along the basement membrane zone. There was no family history of skin disease. The child was enrolled in the National EB Registry, University of Alabama, Birmingham, as dystrophic EB, probably dominant, although a recessive or a spontaneous mutant dominant was possible. As a result of EB, he had multiple wound infections and lost his toenails and fingernails. Diffuse scars and blistering lesions developed. Corneal erosions were noted on two occasions. Findings from barium swallow and endoscopy were negative. The mouth lesions of EB resulted in poor weight gain. The child was treated for 2 years with dilantin without benefit. At baseline evaluation for tacrolimus, he wore mittens constantly and his whole body was being wrapped and treated with topical agents several times daily. Although he was developmentally normal, he was in a special-needs class because of EB and was severely inhibited in his ability to play with other children.



*New skin lesions that occurred on tacrolimus (FK 506) treatment. The photographs illustrate the character of new lesions that continued to occur while receiving tacrolimus. New lesions that developed are shown on the left and the healing that took place is indicated by the follow-up picture of the same area on the right. Some lesions had never healed since onset of disease, and, at baseline, new lesions took more than 30 days to heal and were characterized by blistering. At 2 weeks (top), new lesions were still characterized by blisters (upper left panel). Blisters no longer formed after 2 months (center) of therapy, scabs formed for the first time (bottom), and the time to heal new lesions slowly improved to 10 days at 3 months, 7 days at 6 months, and 3 to 5 days at 9 months, and is currently 3 to 5 days.*

After informed consent, tacrolimus therapy commenced (0.7 mg orally twice a day). The child was photographed serially, and the time to heal new lesions was determined. The activity of his disease was followed by counting the total number of skin lesions and the percentage of skin involved using a modification of the PASI (Psoriasis Activity and Severity Index) score used in psoriasis patients. The total score before treatment was 184.7, at which time he had 29 lesions ranging in size up to a maximum diameter of 83 mm, covering more than 30% of his body. While receiving tacrolimus, the total score as well as the percentage of body involved have decreased to 84.4 and 15%, respectively, although there have been fluctuations due to major skin traumas. The **Figure** shows the healing of lesions while receiving tacrolimus. At 2 weeks, blistering lesions still occurred (upper panels). After receiving tacrolimus for 2 months, the characteristics of the lesions changed to dry abrasions rather than blisters (middle and lower panels). Scabs formed and new and old lesions healed. The time to heal new lesions was greater than 30 days at baseline, decreased to 10 days at 3 months, 7 days at 6 months, 3 to 5

days at 9 months, and is currently 3 to 5 days. New lesions continue to form in areas of trauma. Fingernails and toenails have regrown.

The child has no mouth lesions and has gained 3.6 kg during treatment. Tacrolimus levels have ranged from 0.2 to 0.5 ng/mL with no evidence of toxic effects. The year before tacrolimus therapy began, the child had two infections treated with antibiotics and had an 18.4% absentee rate from school. During 18 months of treatment, he had no infections and had an absentee rate from school of 3.76%. He no longer requires constant wrapping and has been enrolled in a class for normal students.

**Comment.** Epidermolysis bullosa is classified into subtypes that are delineated based on the clinical features, pathologic findings, immune markers, and the mode of inheritance. In patients with dystrophic EB, the number of anchoring fibrils in the upper dermis are reduced and blisters occur below the lamina densa.<sup>2</sup> Increased collagenase activity in fibroblasts isolated from the skin of patients with dystrophic EB has been described and may be a useful probe.<sup>3</sup> Tacrolimus induces TGF-beta gene expression<sup>4</sup> that might increase synthesis of type VII collagen followed by reformation of anchoring fibrils.<sup>5</sup> This might be one mechanism to investigate the possible effects of tacrolimus on wound healing in EB. This disease has periodic fluctuations related to skin trauma, and, with a case report, conclusions cannot be definitive; however,

this child's response to tacrolimus therapy provides an impetus for further studies of its use in EB.

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#### Correspondence

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