proach, the lesson here includes the utility of a multifaceted approach to AD management that addresses infection.

**IL-21R Is Essential for Epicutaneous Sensitization and Allergic Skin Inflammation in Humans and Mice**


**PURPOSE OF THE STUDY.** To examine the role of interleukin 21 (IL-21) in the pathogenesis of atopic dermatitis (AD).

**STUDY POPULATION.** Nine subjects with acute AD lesions and 5 healthy control subjects.

**METHODS.** Samples were obtained for skin biopsy and immunohistochemical analysis of IL-21 and IL-21 receptor (IL-21R) levels. A murine model for epicutaneous sensitization and dermatitis induced by repetitive application of antigen (ovalbumin) or hapten (oxazolone) after mechanical injury (tape stripping) was then used to examine the role of the IL-21 pathway in dendritic cell activation and migration and T cell stimulation.

**RESULTS.** The expression of IL-21 and IL-21R was elevated in acute AD lesions, compared with the normal skin of healthy control subjects. IL-21 was most strongly expressed in keratinocytes. Two wild-type mouse strains develop allergic epicutaneous sensitization after antigen or hapten application to skin that has been damaged by tape stripping. *Il-21r*-deficient knockout mice, which lack expression of the receptor, are deficient in both the development of local inflammation and the associated T-helper 2-skewed systemic immune response. *Il-21r*-deficient dendritic cell populations are normal in their capacity to induce naive T cell activation; however, they are abnormal in their ability to upregulate chemokine receptor 7 and to migrate appropriately to draining lymph nodes after minor skin trauma.

**CONCLUSIONS.** IL-21 and IL-21R expression is elevated in acute AD lesions, and IL-21R is required in a model of epicutaneous allergic sensitization that resembles human AD.

**REVIEWER COMMENTS.** The etiology of AD is unknown, although recent studies underscored a role for skin barrier defects that might enhance allergic sensitization. The discovery in this report of the importance of IL-21 for epicutaneous sensitization, along with the observed elevation of IL-21/IL-21R in human AD lesions, suggests that this pathway may be a key player in the vicious cycle of barrier defect, sensitization, inflammation, and worsening barrier defect. IL-21 is also known in other models to induce T-helper 17 cells and to suppress immunoglobulin E, neither of which was reported in this study and which may not accord so well with our current understanding of AD. Nevertheless, this early report may be a first step toward identifying a new target for intervention and treatment.

**Interruption Therapy for Flare Prevention and Long-term Disease Control in Stabilized Atopic Dermatitis: A Randomized Comparison of 3-Times-Weekly Applications of Tacrolimus Ointment Versus Vehicle**


**PURPOSE OF THE STUDY.** To determine the efficacy and safety of 3 times per week maintenance use of tacrolimus in the prevention of atopic dermatitis (AD) exacerbations.

**STUDY POPULATION.** Multicenter, randomized, double-blind, placebo-controlled study of 383 patients over the age of 2 years with moderate-to-severe AD.

**METHODS.** The study consisted of stabilization and maintenance phases. During stabilization, subjects received tacrolimus ointment (0.03% [2–16 years] or 0.1% [>16 years]) or corticosteroid (alclometasone dipropionate, 0.05% ointment [2–16 years], or triamcinolone acetonide, 0.1% ointment [>16 years]) twice daily for 4 days at AD flare sites, followed by a 2-week, open-label phase. Subjects demonstrating a response to tacrolimus were then asked to participate in the maintenance portion of the study. The maintenance phase was a randomized, double-blind, vehicle-controlled, 40-week study in which topical application was performed once daily, 3 times per week, at previous eczema flare sites.

**RESULTS.** Subjects receiving tacrolimus experienced more symptom-free days (177 vs 134 days; *P* = .003). Time to relapse was longer in patients treated with tacrolimus versus vehicle (169 vs 43 days; *P* = .037). Patients receiving tacrolimus seemed less likely to experience relapse (62% vs 66% with ≥1 relapse during treatment; *P* = .55) and had fewer relapses during the treatment period (maximum of 3 relapses in 5.6% of the tacrolimus group versus 3–6 relapses in 16.9% of the vehicle group). The severity of relapses was milder in the treatment group, with only 29% in the tacrolimus group having moderate relapse, compared with 51% in the vehicle group. During the open-label trial, 83% of pa-
tients in both the tacrolimus and vehicle groups responded to tacrolimus treatment of relapse. With regard to safety, patients treated during the stabilization phase with tacrolimus versus topical steroid were more likely to have cutaneous site reactions (18% vs 9%; \(P = .015\)) during the first 4 days of treatment; this was not seen during the rest of the treatment course.

CONCLUSIONS. Tacrolimus maintenance therapy increased the number of symptom-free days and the time to relapse, compared with vehicle alone.

REVIEWERS COMMENTS. AD is a disease characterized by intermittent flares and symptom-free periods. Maintenance, intermittent, topical corticosteroid dosing regimens have been successful in preventing relapse. The use of maintenance steroid-sparing therapies is desirable. This study indicates that maintenance therapy may prevent relapse occurrence and decrease the severity of disease and provides an interesting treatment option for patients with AD with frequent relapses. Also, in light of recent Food and Drug Administration warnings concerning topical calcineurin inhibitors, it is valuable to know that dosing could be reduced to 3 times weekly for maintenance. Overall, this well-designed study provides convincing support for maintenance therapy of AD with topical nonsteroidal calcineurin inhibitors. Similar results were seen in 3 other studies using 2 or 3 times per week dosing schedules for topical steroids and topical calcineurin inhibitors. These studies indicate that maintenance therapy is superior to as-needed use of topical medications for patients with moderate-to-severe AD.

Three Times Weekly Tacrolimus Ointment Reduces Relapse in Stabilized Atopic Dermatitis: A New Paradigm for Use


PURPOSE OF THE STUDY. To evaluate the safety and efficacy of intermittent topical tacrolimus as maintenance therapy in patients with moderate-to-severe atopic dermatitis.

STUDY POPULATION. Subjects 2 to 15 years of age with moderate-to-severe atopic dermatitis.

METHODS. Subjects underwent stabilization with either 0.05% aclometasone ointment or 0.03% tacrolimus in a double-blind fashion for 4 days, followed by twice-daily, open-label, 0.03% tacrolimus treatment for all subjects. Subjects who became “clear” or “almost clear” entered phase II (maintenance phase) and underwent double-blind, random assignment to either 0.03% tacrolimus or vehicle applied once daily, 3 times per week, for up to 40 weeks. Emollients were permitted, but corticosteroid use was prohibited; open-label tacrolimus use was permitted to treat relapses.

RESULTS. A total of 206 patients were randomly assigned, and 50 subjects completed the study. There were no significant differences between groups at baseline. Aclometasone-treated patients showed more improvement in the acute phase than did tacrolimus-treated patients, and there were no differences in application-site adverse events between groups. During maintenance, tacrolimus-treated patients had a significantly greater number of disease-free treatment days, compared with vehicle-treated patients (mean: 174 vs 107 days; \(P = .0008\)), and a longer time to first relapse (median: 116 vs 31 days; \(P < .04\)).

CONCLUSIONS. Long-term intermittent application of 0.03% tacrolimus to clinically normal-appearing but previously affected skin was significantly more effective than vehicle at maintaining disease stabilization in patients with moderate-to-severe atopic dermatitis. The safety profile of intermittently applied tacrolimus was similar to that of vehicle.

REVIEWERS COMMENTS. Atopic dermatitis is a chronic relapsing disease. Prevention of relapse is aimed at skin hydration and avoidance of triggers. Adverse effects of topical steroids limit their long-term use and, although there are concerns that calcineurin inhibitors may carry an increased risk of malignancy, long-term data on the safety of topical calcineurin inhibitors contradict this notion. This study shows promise that intermittent application of 0.03% tacrolimus offers a novel, steroid-sparing approach to maintaining stabilization of atopic dermatitis that seems both safe and efficacious.

MAS063DP Is Effective Monotherapy for Mild to Moderate Atopic Dermatitis in Infants and Children: A Multicenter, Randomized, Vehicle-Controlled Study


PURPOSE OF THE STUDY. To examine the safety and efficacy of MAS063DP (Atopiclair [Graceway Pharmaceuticals, Bristol, TN]), a topical nonsteroidal antiinflammatory agent, in the management of mild-to-moderate atopic dermatitis in infants and children.
## Intermittent Therapy for Flare Prevention and Long-term Disease Control in Stabilized Atopic Dermatitis: A Randomized Comparison of 3-Times-Weekly Applications of Tacrolimus Ointment Versus Vehicle

Laura Gober and Jonathan M. Spergel

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