PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the Children's Medical Center at the University of Virginia

Volume 8 Number 5 May 2002

Topical Macrolactam Immunomodulators for Atopic Dermatitis

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Atopic dermatitis is the most common dermatologic condition of childhood, affecting approximately 10% of children. It is a chronic recurring inflammatory skin disease, with erythema, exudation, and severe pruritus that may result in excoriation and infection of the skin, as well as disturbance of normal activities and sleep. The management of atopic dermatitis has traditionally consisted of avoidance of triggering factors, emollients, antihistamines, and periodic application of anti-inflammatory agents when the disease flares. Topical corticosteroid preparations are usually effective in managing flares, but may result in skin atrophy (thinning), hirsutism, telangiectasia, dyspigmentation, and striae formation. There is also a risk for systemic corticosteroid absorption, leading to suppression of the hypothalamic-pituitary-adrenal axis. For steroid-intolerant or refractory cases, many clinicians have turned to other systemic immunomodulatory agents. Cyclosporin, methotrexate, azathioprine, mycophenolate, and tacrolimus have all been studied as alternatives. The oral administration of these agents, while effective, may result in more serious adverse effects and systemic immunosuppression.[1-3]

The utility of immunomodulatory agents in atopic dermatitis changed with the introduction of topical preparations. The potency and smaller molecular weight of the macrolactam agents made them ideal for this route of administration. Two drugs from this class are currently available in topical formulations. Tacrolimus ointment (Protopic®; Fujisawa) was approved by the Food and Drug Administration (FDA) on December 8, 2000. Pimecrolimus cream (Elidel®; Novartis) was approved on December 13, 2001. Both are indicated for the short-term and intermittent long-term therapy of atopic dermatitis in adults and children $\geq$ 2 years of age.[1-6]

Mechanism of Action

Topical macrolactam immunomodulators appear to reduce the symptoms of atopic dermatitis by inhibiting T-lymphocyte activation. Both tacrolimus and pimecrolimus, as well as the oral agent sirolimus, bind to an intracellular protein, macrophilin-12 (or FKBP-12), which forms a complex with calcium, calmodulin, and calcineurin. The resulting complex inhibits the phosphatase activity of calcineurin. This step prevents the dephosphorylation and translocation of NF-AT (nuclear factor of activated T-cells), inhibiting the transcriptional activation of lymphokines, such as interleukin-2, which are involved in producing the inflammatory symptoms of atopic dermatitis. The macrolactam immunomodulators also inhibit the release of cytokines and inflammatory mediators from anti-IgE-activated skin mast cells and basophils.[1,4,7,8]

Clinical Trials

A large number of case series and clinical trials are available which substantiate the efficacy and safety of the topical macrolactam immunomodulators in patients with atopic dermatitis. In 1998, Boguniewicz and colleagues, working as the Pediatric Tacrolimus Study Group, conducted a double-blind, placebo-controlled, multicenter trial of tacrolimus ointment for the treatment of moderate to severe atopic dermatitis in children.[9] The patients were randomized to receive twice daily applications of tacrolimus (0.03%, 0.1%, or 0.3%) or vehicle alone (no active drug) for 22 days with a 14 day follow-up. One hundred and eighty children (7-16 years of age) were enrolled. The Investigator's (Physician's) Global Evaluation (IGE) showed improvement in 69% of the 0.03% tacrolimus group, 67% in the 0.1% group, and 70% in the 0.1% group, versus only 38% in the group receiving the vehicle alone. The modified Eczema Area and Severity Index (EASI) at the end of treatment was also significantly better for tacrolimus compared to vehicle (72% improvement for the 0.03% group, 77% for the 0.1% group, and 81% for the 0.3% group, versus 26% for vehicle alone). Head and neck region scores and patient self-assessments were also

significantly better in the treatment groups. Seven of the 131 treated patients (5%) showed no improvement, compared to 16 of the 42 patients (38%) receiving vehicle alone. The only adverse effect noted significantly more frequently in the treatment groups was pruritus (74-89% in the treatment groups versus 51% with the vehicle). Systemic absorption was minimal; mean tacrolimus serum concentrations at days 4 and 22 were below 0.20 ng/ml in all groups. As anticipated, serum concentrations decreased over time, reflecting a decrease in absorption as the skin healed.

A longer 12-week trial was conducted by Paller with the Tacrolimus Ointment Study Group.[10] In this multicenter, double-blind trial, 0.03% and 0.1% tacrolimus ointments were compared to the vehicle alone (all applied twice daily) in 351 children. All patients were between 2 and 15 years of age and had moderate to severe atopic dermatitis. As in the earlier study, IGE and EASI scores were used to assess efficacy. Success was defined as clearing of the skin or at least 90% improvement from baseline. Both treatment groups were significantly more effective than the vehicle alone in all measures of efficacy. There were no significant differences in response between patients receiving the 0.03% and 0.1% strengths. The goal of 90% improvement was observed in 35.9% of the 0.03% tacrolimus group and 40.7% of the 0.1% group, versus only 6.9% of the vehicle-treated group. Adverse effects occurring more commonly with the tacrolimus groups were skin burning, pruritus, varicella, and rash and/or blisters. In both trials, the authors concluded that tacrolimus was an effective alternative for the treatment of atopic dermatitis in children.

The effect of tacrolimus on quality of life has recently been studied.[11] Using a set of age-appropriate surveys, Drake and colleagues assessed symptoms, daily activities, and sleep patterns in 145 toddlers (2-4 years), 178 children (5-15 years), and 579 adults receiving either tacrolimus ointment (0.03% or 0.1%) or the vehicle alone. All patients were taking part in one of three randomized, double-blind 12-week clinical trials. In each age group, tacrolimus was associated with significant improvements in quality of life compared with the vehicle. In the adult group, the 0.1% ointment produced slightly greater benefit than the 0.03%. In toddlers and children, the two strengths produced equal improvement. Of the adults, 79.7% of those receiving 0.1% tacrolimus and 68.8% of those receiving 0.03% reported that they would continue or be very likely to continue treatment. More than 80% of the parents of the toddlers and children provided similar positive responses.

A longitudinal study of tacrolimus in children was published in 2001 by Kang for the Tacrolimus Ointment Study Group.[12] A total of 255 children (2-15 years of age) were monitored for up to one year in this open-label, noncomparative trial. Tacrolimus 0.1% ointment was applied twice daily to areas of active disease until 1 week after complete clearing. Patients were evaluated at baseline, week 1, and three month intervals thereafter. In addition, the frequency of treatment episodes was recorded, as well as the percent of body affected and EASI scores. Improvement in all variables was noted within a week of starting therapy, and patients continued to improve throughout the year. There was no indication that efficacy waned with continued use. In the 61 patients determined to have complete clearing, the average length of time to achieve resolution of symptoms was 92 days. The most frequent adverse effects were a feeling of skin burning (25.9%) and pruritus (23%). There was no increase in infections compared to baseline.

The efficacy of tacrolimus has also been compared to topical corticosteroid therapy. Earlier this year, the results of a multicenter, randomized, double-blind, parallel-group study in children were published by Reitamo for the European/Canadian Tacrolimus Ointment Study Group.[13] The investigators randomized 560 children (2-15 years of age) to receive either tacrolimus (0.03% or 0.1%) or 1% hydrocortisone acetate ointment applied twice daily for 3 weeks. A modified EASI score was used to assess efficacy. Both tacrolimus groups showed significantly greater improvement than the hydrocortisone group. The higher strength was also shown to be significantly better than the lower strength. Transient burning occurred in a greater number of tacrolimus patients than in the hydrocortisone group (17.5 and 19.0% for tacrolimus 0.03 and 0.1% strengths versus 7% for hydrocortisone). Other adverse effects, including skin infections, were no different.

Less is known of the efficacy and safety of pimecrolimus in pediatric patients; although, it is anticipated that more information will be published within the year. Harper and colleagues recently reported the results of a trial involving 10 children between 1 and 4 years of age.[14] Patients were treated with 1% pimecrolimus twice daily for 3 weeks to assess efficacy and systemic absorption. Eight of the children showed a positive clinical response to pimecrolimus, with EASI scores improving by 8

to 89%. Two patients experienced a disease flare during treatment. Blood pimecrolimus concentrations remained at low levels during the trial, with 63% of concentrations below the 0.5 ng/ml level of detection. The maximum concentration observed was 1.8 ng/ml.

In last month's *Journal of the American Academy of Dermatology*, Eichenfield and coworkers published the results of the first large-scale clinical trial of pimecrolimus cream in children.[15] This paper presents pooled data from two independent 6-week multicenter, randomized trials. A total of 403 patients (1-17 years of age) were enrolled. Patients were randomized to receive twice daily applications of either 1% pimecrolimus or vehicle alone. IGA and EASI scores were used to assess efficacy, as well as pruritus and self/caregiver assessments. At the final visit, 34.8% of the pimecrolimus group were rated as clear or almost clear of disease, compared to 18.4% of the patients in the vehicle group. Improved IGA scores were observed in 59.9% of the pimecrolimus group, versus 33.1% of the vehicle group. EASI scores reflected a similar degree of efficacy. Improvement was noted for most pimecrolimus patients by day 8. Pruritus was reduced, and self/caregiver assessments were higher with pimecrolimus. The authors concluded that 1% pimecrolimus cream was safe and effective for the treatment of atopic dermatitis in children and adolescents.

Adverse Effects

Topical application of tacrolimus or pimecrolimus may cause local reactions such as a burning sensation, stinging, soreness, or pruritus in up to 26% of patients. The effects typically last no more than 15 to 20 minutes, although some patients may exhibit a prolonged response, especially within the first week of treatment. Less common adverse effects include acne, infected hair follicles, headache, increased sensitivity of the skin to temperature changes, nausea, arthralgias, or flu-like symptoms.[4-6]

Topical immunomodulators may also be associated with a slightly higher risk of skin infections, including staphylococcal impetigo, varicella, eczema herpeticum, and molluscum contagiosum. Establishing the incidence of infection is difficult, as patients with atopic dermatitis are already at greater risk. In the Paller study, children treated with 0.03% tacrolimus ointment had a significantly higher incidence of varicella than children receiving vehicle alone (4.8% versus 0%); however, this increase has not been seen in all clinical trials.[5,10] Despite the minimal systemic absorption shown in these trials, there remains concern about the potential for toxicity resulting from absorption through excoriated skin. Patients and families should be instructed to report any signs of serious infection to their health care provider.

Although no cases of phototoxicity have been reported in humans, animal studies revealed a shortened time to skin tumor formation with tacrolimus use. Patients using either product should be instructed to minimize sun exposure and avoid tanning beds. Protective clothing and the use of sunblock should also be discussed with the patient and family.[5,6]

Lymphadenopathy has been reported in a small number of patients treated with tacrolimus ointment (0.8%). These cases were felt to be related to other infections and cleared with antibiotics. Because the systemic use of these agents has been linked to a higher risk for lymphoma, patients receiving topical immunomodulators should be closely observed and the need to discontinue therapy considered when lymphadenopathy is present.[4]

Drug Interactions

At this time, no specific drug interactions have been reported with topical tacrolimus or pimecrolimus. Because both drugs undergo metabolism through the cytochrome P450 3A4 enzyme system (CYP3A4), there is a theoretical potential for drug interactions through this pathway. Patients receiving concurrent therapy with drugs which inhibit CYP3A4, such as erythromycin, itraconazole, ketoconazole, fluconazole, cimetidine, or calcium channel blockers, should be monitored closely. It is possible that even minimal systemic absorption, coupled with impaired metabolism, could lead to serum concentrations high enough to cause immunosuppression or toxicity.[4]

Dosing Recommendations

Tacrolimus ointment (Protopic®; Fujisawa) is available in both 0.03% and 0.1% strengths, in 30 and 60 gram tubes. It is recommended that the lower strength be used in children less than 16 years of age.[5] Pimecrolimus (Elidel®; Novartis) is available as a 1% cream, in 15, 30, and 100 gram tubes.[6] Either product should be applied in a thin layer over the affected skin twice daily. A pea-size amount typically covers an area about the size of a 2-inch circle. The ointment or cream should be rubbed in gently and completely. The use of occlusive dressings is not recommended. Treatment should be continued until the skin clears.[5,6]

Cost

The cost of therapy for the macrolactam immunomodulators is considerably greater than traditional therapy, since many steroid products are available in generic form (Table). The increased price of these agents may be offset, in part, by their improved safety profile.

Table. Cost of therapy

Drug	Strength	Size	Price
Protopic®	0.03%	30 gram	$ 59.95
	0.03%	60 gram	119.90
	0.1%	30 gram	64.09
	0.1%	60 gram	128.16
Elidel®	1%	15 gram	25.02
	1%	30 gram	47.52
	1%	100 gram	150.00

(average wholesale price, 2002 Drug Topics Red Book)

Summary

The macrolactam immunomodulators, tacrolimus and pimecrolimus, provide a new treatment option for children with atopic dermatitis. Unlike corticosteroids, these products do not produce skin atrophy. Although post-marketing experience is still limited, clinical trials have shown the macrolactams to have minimal systemic toxicity and few significant adverse effects, making them a useful addition to standard therapies.

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Pharmacology Literature Review

Saquinavir disposition in children

The pharmacokinetic and pharmacodynamic profiles of saquinavir, a protease inhibitor, were evaluated in children with HIV in this two-part study. Area under the concentration-time curve (AUC) data were found to be lower in children than adults, reflecting a higher clearance or reduced bioavailability. Concomitant administration with nelfinavir, a second protease inhibitor, increased AUC values, presumably by inhibiting metabolism. Grub S, et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. **Clin Pharmacol Ther 2002;71:122-30.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/3/02:

1. Digoxin immune Fab (ovine) (DigiFab®) was added to the Formulary for binding digoxin after overdose. This product replaces Digibind®.
2. Zoledronic acid (Zometa®) , a bisphosphonate for the treatment of hypercalcemia of malignancy, was added for outpatients requiring parenteral therapy.
3. The restriction for nesiritide was amended to include use by emergency medicine prescribers.
4. The restriction for rituximab was amended to include first-line therapy for elderly patients with diffuse large B cell lymphoma.

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