

Editorial

Tacrolimus ointment: Its place in the therapy of atopic dermatitis

Atopic dermatitis (AD) is the most common inflammatory skin disease of childhood, and its incidence is increasing.¹ In developed countries, up to 20% of children are believed to be affected at some stage, and the intense itching caused by the dermatitis is distressing for the patient and disruptive for the whole family.²

Since 1952,³ corticosteroids have been the mainstay of topical treatment for AD. During these decades, many modifications have been made to the molecules and to the bases in which they have been formulated; as a result, many highly potent preparations are currently available.⁴ Despite strenuous efforts over the years to separate efficacy from side effects, there is no convincing evidence that this has been achieved: the more effective the corticosteroid, the greater the possibility of side effects. On the other hand, no pharmacologically new compounds outside this class with proven efficacy in AD have been available until recently.

Tacrolimus was first isolated in 1984,⁵ and its immunosuppressant properties were first described in 1987.⁶ Like cyclosporin, tacrolimus binds to a cytoplasmic immunophilin, and the complex inhibits the activity of the calcium-dependent phosphatase known as calcineurin. This, in turn, inhibits the translocation of the transcription factor NF-AT into the cell nucleus, blocking the initiation of NF-AT-dependent T-cell responses.⁷ Unlike cyclosporin, tacrolimus exhibits activity when applied topically.⁸

The ointment form of tacrolimus has been developed specifically for the treatment of AD. It is the first in a new class of topical macrolactam calcineurin inhibitors, and the targeted mode of action of these agents is likely to make them much more specific than any of the topical corticosteroids. The clinical development plan for tacrolimus ointment has been the largest ever in the field of dermatology. It has included more than 10,000 patients in North America, Japan, and Europe. Large, multicenter, vehicle-controlled studies in the United States and elsewhere have clearly demonstrated the efficacy and safety of the tacrolimus ointment,^{9–11} the result being that the ointment has recently been approved in

Abbreviation used

AD: Atopic dermatitis

Japan, the United States, Canada, and Europe for the treatment of AD.

Key studies in the tacrolimus ointment development plan have included short- and long-term trials—two 12-week adult trials,^{9,11} one 12-week pediatric study,¹⁰ and a 1-year pediatric study,¹² all of which were conducted in the United States and were published early in 2001. The US studies demonstrated a significantly greater efficacy for tacrolimus ointment in comparison with vehicle in patients with moderate to severe AD. On the European side, the major studies included one 3-week adult trial and one 1-year adult study.^{13,14}

Until recently, comparative studies had been lacking, so the European trials were followed by 2 large, short-term (3-week) trials—one in children and one in adults—that compared tacrolimus ointment therapy and conventional treatment with a topical corticosteroid; the results are presented by Reitamo et al^{15,16} in this issue of the Journal. In the case of the adult trial, tacrolimus was compared with the widely used moderate-to-potent topical corticosteroid hydrocortisone-17-butyrate ointment.¹⁷ In the pediatric trial, the chosen comparator was the low-potency hydrocortisone acetate ointment.

In the first of these investigations, a large, phase III, multicenter, randomized, double-blinded, parallel-group study in Europe, 0.03% tacrolimus ointment and 0.1% tacrolimus ointment were compared with 0.1% hydrocortisone butyrate ointment in the treatment of 570 adult patients with moderate to severe AD. This 3-week study demonstrated tacrolimus to be efficacious and well tolerated. The efficacy of 0.1% tacrolimus ointment was similar to that of 0.1% hydrocortisone butyrate ointment. Transient local irritation in the tacrolimus treatment groups, particularly during the first few days, was the most common adverse event. No serious safety concerns were identified.

Similarly, a large, randomized, double-blinded, parallel-group, phase III European/Canadian study compared 0.03% and 0.1% tacrolimus ointment with 1% hydrocortisone acetate ointment treatment in children 2 to 15 years old with moderate to severe AD.¹⁶ The results of this 560-patient study showed 0.03% and 0.1% tacrolimus to be significantly more effective than 1% hydrocortisone acetate and demonstrated a clear trend for 0.1% tacrolimus to be more effective than 0.03% tacrolimus. When the results are averaged over the 3-week course of treatment, it is seen that patients had a

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median improvement from baseline of 55.2% with 0.03% tacrolimus, of 60.2% with 0.1% tacrolimus, and of 36.0% with hydrocortisone acetate. This higher efficacy of tacrolimus ointment was observed without resulting compromises in the safety profile. Transient skin burning was the only adverse event that showed a significantly higher incidence in the tacrolimus treatment groups than in the hydrocortisone acetate group. The occurrence of skin infections, especially herpes-related infections, was similar in all groups. The study confirmed earlier results that had demonstrated low systemic absorption of tacrolimus.

Topical corticosteroids are very effective in the short-term treatment of AD. However, because of the well-documented local side effects that are associated with their use over prolonged periods, such as skin atrophy and striae, long-term studies involving continuous use of topical corticosteroids are not regarded as ethical, and none have been conducted. Topical corticosteroids also carry the potential to cause systemic side effects, though these are less frequently seen; they include hypothalamic-pituitary-adrenal suppression, and infants and small children, with their high skin surface-area/body-mass ratio, are most at risk. Thus, high-potency topical corticosteroids are indicated only for short periods with a limited area of treatment. Weak topical corticosteroids are preferred for regions of skin where penetration is high, such as the face and the flexures. The intermittent use of potent corticosteroids might improve the safety profile, and combining their use with mild corticosteroids might reduce the degree of relapse; however, these approaches have not achieved the ultimate goal of providing long-term control.

As a result of these constraints, the maximum double-blinded treatment period in the trials reported by Reitano et al^{15,16} was limited to 3 weeks, but patients were allowed to treat all areas of the body. These problems are being addressed in a double-blinded study in adults, currently under way, in which tacrolimus ointment alone is being compared with treatment with corticosteroids of different potencies over a period of up to 6 months.

Experience with topical corticosteroids over the last 50 years has shown that they do not provide effective monotherapy for AD. The efficacy of corticosteroids is most marked during the first days of treatment, and if continued use is necessary, there tends to be a plateau after 1 or 2 weeks. This was clearly shown after the first week of treatment in the European/Canadian pediatric study. The usual regimen for the use of topical corticosteroids for AD has been to control symptoms with a preparation of acceptable efficacy and then stop and wait until the next episode arises. The fear of corticosteroid-induced local side effects is widespread^{18,19} and not ill-founded. Patients are also often confused about the potency of the corticosteroid that they are using.¹⁹ With a "stop and go" treatment schedule, the potential for corticosteroid-induced side effects is reduced but certainly not eliminated.

Given the comparable short-term efficacies seen with tacrolimus ointment and conventional corticosteroids in the European study with adult patients with AD, why use tacrolimus? Although this new class of topical immuno-

modulators is not licensed for maintenance therapy, there is the possibility of treating patients for prolonged periods, or on repeated occasions, without the fear of the cumulative damage, such as skin atrophy, corticosteroid dermatoses, or telangiectasia, that is associated with corticosteroids. Tacrolimus ointment, in contrast to corticosteroids, can be used over the whole body, including such vulnerable areas as the face (including the eyelids and periorbital area) and the flexures. It thus offers the possibility of effective monotherapy.

A long-term (1-year), single-arm study in adults showed an increasing percentage of patients categorized as having marked improvement or clearance over a 1-year period.¹³ Although the percentage of patients in those categories after the first few weeks of treatment was no different from that for the short-term trials, a steadily increasing number of patients reached those categories on longer follow-up (54%, 81%, and 86% of patients at week 1, month 6, and month 12, respectively). The rebound effect sometimes seen after topical corticosteroid withdrawal was not seen after tacrolimus therapy was stopped. In this study, patients applied 0.1% tacrolimus ointment until 7 days after improvement of the lesions and then restarted therapy whenever new lesions occurred.

The 1-year follow-up did not reveal any safety issues. The incidence of skin infections was similar to that seen overall in the AD population. Systemic absorption of tacrolimus was minimal; consequently, any systemic immunosuppression seems unlikely. Immunocompetence, as measured by the Recall Antigen Test, which was used to assess delayed-type hypersensitivity reactions as an indirect measure of cellular immune response (Multitest CMI, Institut Mérieux, Lyon, France), showed a patient population with depressed cell-mediated immunity at baseline but with no notable changes after prolonged treatment. This is the first study in which topical corticosteroids were withheld from patients with AD for a prolonged period.

Similarly, the long-term US pediatric safety study showed no indication that the effectiveness of tacrolimus ointment decreases over time.¹² Improvements in disease status, as demonstrated by reductions in eczema area and severity index scores, percent body surface area affected, individual signs and symptoms of AD, and the patient's assessment of pruritus, generally occurred during the first week of treatment and were maintained throughout the study. Given the promising results seen in these 2 noncomparative studies, it will be interesting to learn whether the results of the ongoing 6-month comparative study described above confirm the benefits of therapy over prolonged treatment periods.

With the introduction of any new class of drugs, such as the topical macrolactam calcineurin inhibitors, questions about potential long-term side effects are bound to arise, though it might not be possible to answer some of these for many decades. The issue of UV light exposure is a case in point. A clinical study conducted with healthy human volunteers found no evidence of phototoxicity when tacrolimus ointment was used at concentrations of up to 0.3%.²⁰ Results obtained in a mouse photocarcino-

genicity model system suggested that tacrolimus ointment at exaggerated dosing levels modestly reduced the latency period of UV light-induced skin tumor development.²¹ This outcome was anticipated and is similar to results obtained with other common topical preparations for which sun exposure is not contraindicated. Moreover, the clinical relevance of these findings is not known. This model, which uses albino hairless mice and is designed to cause tumors in all animals (even those not treated with study drug), has yet to be proved as a basis for estimating risks in human beings. However, as a precaution, patients are advised to protect treated areas of skin from concomitant sunlight or other UV light sources. This measure has also been adopted with other dermatologic products associated with similar findings. Importantly, up to 3 years of therapy with tacrolimus ointment has so far failed to reveal any signs of increased risk of skin malignancies, though more experience will clearly be required to address this issue conclusively.

The incidence rates for other potential side effects, such as skin infections (in particular, viral infections, including herpes simplex and molluscum contagiosum), have not proved to be higher than in the general AD population, and there is no reason to expect the picture here to change. Indeed, reduced levels of staphylococcal colonization have been reported²² with prolonged treatment.

On certain regions of the body, the use of topical corticosteroids must be severely restricted. Localization of AD to the eyelids is common, but the use of corticosteroids around the eyes has been associated with the development of glaucoma and cataracts as well as with local cutaneous side effects, such as atrophy and telangiectasia. In an open-label trial, 20 patients with eyelid dermatitis were treated with tacrolimus ointment twice daily for up to 8 weeks.²³ The severity of eyelid dermatitis was assessed at baseline, at regular intervals throughout the treatment period, and at 2 weeks after treatment. Four eye examinations, which included intraocular pressure measurements, were performed before, during, and after treatment without showing significant change, which provides evidence of the safety of tacrolimus ointment in treating this area.

CONCLUSIONS

The results presented in this issue of the Journal provide further information on the contribution that tacrolimus ointment is likely to make in the overall management of AD, and they allow us to make a more focussed assessment of its position in therapy. Taken in conjunction with the results from the United States, they make it clear that tacrolimus ointment constitutes a major new development in the treatment of the disease. Short- and long-term trials have demonstrated a clear, positive risk-benefit ratio in the treatment of this chronic, relapsing disease that affects the quality of life of many families. The safety profile of tacrolimus ointment has indicated that these patients have not been exposed to any new or significant adverse effects, though as with the introduction of any other novel agent we should remain alert to the possibility that long-term use

in large numbers of patients could reveal hazards not identified in the extensive trials to date. Tacrolimus ointment introduces the potential for long-term intermittent monotherapy in the treatment of moderate to severe AD, and its introduction is likely to change the approach that we use to manage the disease.

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