Masutaka Furue
Satoshi Takeuchi
Department of Dermatology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

Abstract: Atopic dermatitis (AD) is a common, chronic, relapsing, severely pruritic, eczematous skin disease. The mainstays of treatment for AD are topical tacrolimus and topical steroids. Tacrolimus, a calcineurin inhibitor, not only complements existing treatment options but also overcomes some of the drawbacks of topical steroid therapy when given topically and thus meets the long-term needs of patients in preventing disease progression. Topical tacrolimus has been widely recognized in terms of its short- and long-term efficacies and safety, and it is also accepted as a first-line treatment for inflammation in AD. The recent proactive use of topical tacrolimus may emphasize a long-term benefit of this calcineurin inhibitor for AD treatment. To reduce possible long-term adverse effects, it is important to monitor its topical doses in daily clinics.

Keywords: atopic dermatitis, topical tacrolimus, topical steroids, dose, proactive use, adverse effects

Introduction
Atopic dermatitis (AD) is a common, chronic or chronically relapsing, severely pruritic, eczematous skin disease. In our previous Kyushu University Ishigaki Atopic Dermatitis Study cohort, 71.6% of AD patients regressed spontaneously, whereas 5.5% of non-AD individuals developed AD among nursery school children during the 3-year follow-up.1 The incidence rate of AD in Japanese elementary school students was approximately 3% from 1981 to 1983, but increased to about 6% to 7% in the 1990s.2 In recent years, the percentage of adolescent- and adult-type AD has also been increasing.3 As the first-line therapy for AD in Japan, topical steroids, topical tacrolimus and emollients are the mainstays in addition to oral antihistamines, but not topical pimecrolimus which is unavailable in Japan. The purpose of this article is to review recent research on topical tacrolimus as a treatment for AD.

Impact of topical tacrolimus on topical steroid therapy
The clinical usefulness of topically active corticosteroids must be judged in the light of their anti-inflammatory activity and propensity to cause undesirable local side effects, as well as their systemic side effects from absorption through the skin. Topical corticosteroids are generally used for patients with AD of variable clinical severity. When the disease is severely exacerbated, it is likely that patients use more creams and ointments than when it is under reasonable control. Although their frequency is low, topical corticosteroids induce various cutaneous adverse effects in locally applied
sites, such as telangiectasia, skin atrophy, hypertrichosis, perioral dermatitis, fungal/bacterial/viral infection and atrophic cutaneous striae; these side effects have long been known. On the other hand, the efficacy and safety of topical corticosteroids when used appropriately are also well-recognized. However, it is not uncommon for patients to express irrational fear and anxiety regarding the use of topical corticosteroids. This ‘steroid phobia’ may be accentuated by media publicity as well as by the common misconception that topical corticosteroids are analogous to anabolic steroids or oral steroids. Moreover, physician’s and/or pharmacist’s advice to apply topical corticosteroids ‘sparingly’ or ‘thinly’ with accompanying messages to exercise caution against steroid adverse effects usually influences patients to interpret such warnings negatively, giving rise to steroid phobia which causes poor adherence to treatment. Experience in dermatology outpatient clinics has suggested that many patients are reluctant to use even mild topical corticosteroids, which may have important implications in terms of patient compliance and subsequent response to treatment.

Before topical tacrolimus was commercially available in Japan, we collected clinical data from 1271 AD patients (210 infantile, 546 childhood, and 515 adolescent and adult AD) who had been followed for at least 6 months in outpatient clinics. All of the patients were treated with topical steroids and moisturizing emollients. The clinical severity of AD in the majority of the patients improved or remained unchanged after 6 months of conventional therapy. However, 19% of the adolescent and adult AD patients remained in a very severe or severe state or experienced exacerbation (‘uncontrolled’ group). After topical tacrolimus became commercially available in Japan in 1999, we collected clinical data from 215 patients with adolescent- and adult-type AD who had been followed by topical tacrolimus and steroid combination for at least 6 months in outpatient clinics. Very interestingly, the clinical severity of AD improved remarkably in the majority of the patients after 6 months of combination topical therapy. Only 6% of the patients with adolescent- and adult-type AD showed uncontrolled disease. In addition, a reduction in the dose of the topical steroid by add-on tacrolimus application clearly attenuated the incidence and intensity of steroid-induced side effects.

**Clinical effects of topical tacrolimus on AD**

Recent meta-analysis studies have shown the clinical efficacy of topical tacrolimus against AD. El-Batawy et al reported the results of meta-analysis from 10 papers on randomized control trials involving 2771 topical tacrolimus-treated patients and 2824 controls. It was demonstrated that topical tacrolimus was significantly more effective than the vehicle. Compared with topical steroids, both 0.1% and 0.03% tacrolimus ointments were as effective as moderate potency steroids, and more effective than a combined steroid regimen. Also, tacrolimus was more effective than mild steroids. Chronic AD lesions of the face and flexures are the most justified indications for topical tacrolimus.

In 2 randomized, double-blind studies of 632 adults with AD, Hanifin et al reported that patients treated with 0.1% and 0.03% tacrolimus ointment showed significantly greater improvement than those treated with the vehicle for all efficacy parameters evaluated, including the percentage body surface area affected, the total score and individual scores for signs of AD, the patient’s assessment of pruritus, and Eczema Area and Severity Index (EASI) score. Specifically, the 0.1% concentration was more effective than the 0.03% concentration. Although tacrolimus is a very potent immunosuppressant, its clinical potency remains limited because of its low transepidermal absorption. When applied for 1 week, 0.1% tacrolimus ointment was shown to be more potent than 0.1% alclomethasone dipropionate ointment. Both 0.03% and 0.1% tacrolimus ointments were significantly more effective than 1% hydrocortisone acetate when applied for 3 weeks in children. The efficacy of 0.1% tacrolimus ointment was similar to that of 0.1% hydrocortisone butyrate ointment and 0.12% betamethasone valerate ointment when applied for 3 weeks in adults. The continuous efficacy of topical tacrolimus has been confirmed in a previous long-term study, in which marked or excellent improvement or clearance of disease was reported in 54%, 81%, and 86% of patients at week 1, month 6, and month 12, respectively. Adverse events such as burning sensation occurred in 47% of patients but tended to occur only when initiating treatment. In a 2-year long-term application trial, marked or excellent improvement or clearance of disease was reported in 90% and 93.1% of patients at weeks 10 and 104, respectively. Adverse events such as burning sensation occurred in 79.2% (450/568) of patients within 1 year; however, the incidence of irritation side effects decreased to only 5.5% (23/418) of patients who applied the ointment for more than 1 year. Similar short-term and long-term efficacies of topical tacrolimus were previously reported in children with AD. Taken together, the important finding is that the efficacy of topical tacrolimus is not attenuated under long-term continuous application for at least 2 years. The blood concentration of absorbed tacrolimus is very low
and usually does not exceed 3 ng/mL (most patients are below the detection limit of 0.5 ng/mL).

**Adverse effects of topical tacrolimus**

The most common adverse events induced by topical tacrolimus are sensation of skin burning or irritation, especially among patients with severe or extensive disease. However, these events are usually brief and resolve during the first few days of treatment. Unlike topical corticosteroids, topical tacrolimus does not cause skin atrophy.

Bacterial and viral infections are commonly associated with AD. As tacrolimus is an immunosuppressive drug, topical tacrolimus therapy may potentially increase the risk of cutaneous infections. However, Fleischer et al reported that treatment of AD with tacrolimus ointment was not associated with an increase in cutaneous infections. A systematic review of 1554 AD patients treated with tacrolimus ointment in 5 clinical trials revealed that the 12-week adjusted incidence rates of all cutaneous infections in patients treated with the vehicle, 0.03% tacrolimus ointment, and 0.1% tacrolimus ointment were 18.0%, 24.8%, and 17.7% for adult patients, and 20.9%, 19.6%, and 23.6% for pediatric patients, respectively. The incidence of any individual cutaneous infection in the tacrolimus group was not significantly higher than that in the vehicle group, with the exception of folliculitis in adults. Several other reports also supported these findings. One of the major concerns in topical tacrolimus therapy in AD patients is the possible increase in herpes infection and subsequent Kaposi’s varicelliform eruption; however, recent long-term studies have clearly demonstrated that topical tacrolimus does not increase herpes infection.

In March 2005, the Food and Drug Administration (FDA) issued a public health advisory informing healthcare professionals and patients about the potential risk of developing cancer from the use of topical calcineurin inhibitors (http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html). This concern is based on information from animal studies, case reports in a small number of patients, and knowledge of how drugs in this class work. Specifically, in an issued statement, the FDA concluded that it may take 10 years or longer in human studies to determine if the use of topical calcineurin inhibitors is linked to cancer development. Very recently, Arellano et al have investigated the association between topical immunosuppressant therapy and development of lymphoma in 293,253 patients and found no increased risk of lymphoma in those treated with topical calcineurin inhibitors. Moreover, Margolis et al found no association between exposure to topical calcineurin inhibitors and an increased risk of non-melanoma skin cancers in 5000 adults with dermatitis.

Irrational fear of drugs always hampers patients’ adherence and compliance to therapy. McNeill and Koo stated that animal and human studies suggest that topical tacrolimus is a safe alternative to topical steroids, with only transient burning sensation as the major known adverse effect compared with those of topical steroids, including long-term side effects. Therefore, currently available data do not suggest that ‘unknown risks’ of topical tacrolimus need be any more concerning than the known side-effects of the topical steroids.

**Recent topics on topical tacrolimus**

Fleischer et al compared the efficacy and safety of 0.1% tacrolimus ointment and 1% pimecrolimus cream in adult patients with moderate to very severe AD. In their study, 281 patients (141 treated with tacrolimus and 140 treated with pimecrolimus) were randomized to a multicenter, investigator-blinded, 6-week study. Tacrolimus-treated patients had significantly greater improvements in EASI score than pimecrolimus-treated patients (mean % reduction from baseline to study end: 57% vs 39%, respectively; \(P = 0.0002\)). Treatment success rate was also significantly higher among the tacrolimus-treated patients than among the pimecrolimus-treated patients (40% vs 22% at study end; \(P = 0.001\)), as well as improvement in the percentage of total body surface area affected (a reduction of 49% vs 34% at study end; \(P = 0.01\)).

With regard to itch sensation, Hon et al evaluated the clinical efficacy of topical tacrolimus for itch reduction in children with AD. Seven children (3 and 4 girls) with AD were treated with topical tacrolimus for a consecutive 2-week period after a 1-week run-in. The clinical severity of AD was assessed using the SCORing Atopic Dermatitis scale. Sleep disturbance, as reported by the patients, and nocturnal scratching documented by a wrist movement monitor (DigiTrac), were evaluated at baseline and throughout treatment. Itch and sleep disturbance scores were reduced. Moreover, scratching activity, as documented by the DigiTrac movement recorder, was reduced from 115.0 g/min (64.8–215.5) to 71.5 g/min (51.0–118.0) \((P = 0.028)\) after 2 weeks of treatment, showing that tacrolimus is effective in relieving itch in children with AD. In another study, the efficacy and safety of tacrolimus ointment for pediatric patients with AD was evaluated by meta-analysis. In this previous study, topical tacrolimus
induced remission of pediatric AD, and the effects of 0.03% and 0.1% tacrolimus ointment were better than those of 1% hydrocortisone acetate and 1% pimecrolimus. However, no significant difference was found between the 0.03% tacrolimus group and the 0.1% tacrolimus group.

The long-term safety of topical tacrolimus was previously assessed by Reitamo et al using an open-label study, with the incidence of adverse events being the primary end-point. In the study, 466 children with AD aged 2 to 15 years applied 0.03% or 0.1% tacrolimus ointment twice daily for up to 29.5 months. The most common application site events were skin burning and pruritus, but their prevalence decreased over time. There was no increase in viral infections or other adverse events over time, and laboratory profiles were consistent with those reported in atopic populations. Substantial improvement in all efficacy end-points was observed by week 2 and was maintained throughout the study. Reitamo et al conducted a 4-year follow-up study of AD therapy with 0.1% tacrolimus ointment where both children and adults applied the ointment continuously or intermittently twice daily during episodes of active disease plus an additional week after remission over a follow-up period of up to 4 years. The intent-to-treat population comprised 782 patients (median age, 22 years; range 2–72) who remained in the study for up to 4 years. Approximately half of the patients discontinued the study prematurely; the median follow-up period was 1422 days. The median tacrolimus ointment use during the first week was 31.2 g, and ointment use decreased during the first year and then remained stable for the remainder period of the study. The median cumulative tacrolimus use was 271.5 g at month 6, 462.5 g at month 12, 739.9 g at month 24, 1029.3 g at month 36 and 1320.8 g at month 48. Altogether 51.8% of the patients discontinued prematurely and the main reasons were withdrawal of consent (13.3%), loss to follow-up (11.3%) and lack of efficacy (9.4%). Adverse events led to discontinuation in 3.7% of the patients. The most frequent application site events were skin burning and pruritus most commonly occurring in adult patients during the initial treatment period; prevalence decreased after the first week and remained at a low level throughout the study. In general, calculated daily hazard rates showed no indication of increased risk of adverse events with prolonged treatment. The total affected body surface area decreased substantially upon treatment onset, and treatment efficacy was maintained until the end of the study with smaller but continuous improvements throughout the follow-up period. Overall, 75% of the patients and 76% of the investigators rated their satisfaction with the treatment as excellent, very good or good at the end of the study or at the time of premature discontinuation. The safety profile of the intermittent or continuous long-term application of 0.1% tacrolimus ointment for up to 4 years was consistent with that established from shorter studies and implied no cause for concern. In addition, 0.1% tacrolimus ointment demonstrated sustained efficacy as reflected by the expression of high satisfaction with the treatment by both patients and investigators. In another study, the long-term safety of tacrolimus was evaluated by Krueger et al who reviewed its pharmacokinetics after topical application in adult and pediatric patients with moderate to severe AD from all clinical trials in which tacrolimus blood levels were obtained. In their study, 0.03% or 0.1% tacrolimus ointment was applied twice daily. During the 12 clinical efficacy trials of tacrolimus ointment, single blood samples were obtained at various times relative to tacrolimus ointment application. In the pharmacokinetic studies, the concentration of 89% to 95% of tacrolimus whole blood samples was <1 ng/mL; the mean maximum concentrations ranged from 0.2 to 1.6 ng/mL and the mean area under the blood concentration-time curves (0–12 hours) ranged from 1.4 to 13.1 ng x h/mL. Likewise, in the clinical efficacy trials, the concentration of the majority (85%–99%) of tacrolimus samples was <1 ng/mL. Furthermore, Krueger et al showed that tacrolimus ointment is associated with minimal systemic absorption and no evidence of systemic accumulation in patients with moderate to severe AD.

One of the recent topics on topical tacrolimus is that proactive intermittent low-dose application can control acute disease and prevent exacerbations. For example, a 12-month European multicenter randomized study previously demonstrated that the proactive, twice-weekly application of 0.03% tacrolimus ointment can maintain AD in remission and reduce the incidence of disease exacerbation (DE) in children with AD. During the initial open-label period, 267 children with AD applied 0.03% tacrolimus ointment twice daily for up to 6 weeks to all affected areas. When an Investigator Global Assessment (IGA) score of ≤2 was achieved, the patient entered the disease control period (DCP) and was randomized to receive tacrolimus (n = 125) or vehicle ointment (n = 125) twice weekly for 12 months. Exacerbations were treated with 0.03% tacrolimus ointment twice daily until an IGA ≤ 2 was regained, then randomized treatment was restarted. The outcome measure was the number of DEs during the DCP that required substantial therapeutic intervention. Proactive application of 0.03% tacrolimus ointment significantly reduced the number of DEs during the DCP that required substantial...
therapeutic intervention and the percentage of DE treatment days, and increased the time to first DE requiring intervention. Furthermore, similar beneficial clinical effects by this type of proactive treatment with 0.1% tacrolimus ointment have been reported in patients with adult AD.21

Breneman et al also evaluated the long-term efficacy and safety of 3-times-weekly use of tacrolimus ointment for preventing AD relapse. Adult and pediatric patients with moderate to severe AD who were clear of the disease after up to 16 weeks of treatment with tacrolimus ointment were randomized in a double-blind fashion to 3-times-weekly treatment with either tacrolimus ointment (0.03% or 0.1%) or vehicle for 40 weeks. The number of flare-free treatment days was considered as the primary end-point. A total of 125 patients were randomized to tacrolimus and 72 patients to vehicle. The mean number of flare-free treatment days was 177 for tacrolimus and 134 for vehicle (P = 0.003). The median time to first relapse was 169 days for tacrolimus and 43 days for vehicle (P = 0.037). Maintenance therapy with tacrolimus ointment was associated with significantly more flare-free days than vehicle treatment, as well as a significantly longer time until first relapse.44

Conclusions
The major side effect of topical tacrolimus is a transient burning sensation which usually subsides within several days of continuous application. Topical tacrolimus has already been commercially available for 10 years in Japan, and so far there have been no case reports on the development of internal and cutaneous malignancies due to topical tacrolimus. Topical tacrolimus is presently considered a safe and beneficial drug, and in conjunction with topical steroids, plays a major role in the management of AD. Careful follow-up and dose monitoring are however essential in order to foster this life-changing drug in dermatology-related medical fields.

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Disclosures
The authors disclose no conflicts of interest.

References


