The Use of Topical Calcineurin Inhibitors in Atopic Dermatitis

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Abstract: In recent years, two topical calcineurin inhibitors have emerged as effective alternatives to corticosteroids for the treatment of atopic dermatitis. Decisions regarding first line therapy between pimecrolimus and tacrolimus are often based on anecdotal evidence. Herein, we review the current evidence supporting the use of pimecrolimus and tacrolimus in atopic dermatitis as well as key differences in safety, tolerability, and cost between the drugs.

Keywords: Atopic dermatitis, calcineurin inhibitors, pimecrolimus, tacrolimus.

BACKGROUND

Atopic dermatitis (AD) is a chronic condition that affects 10-20% of children living in developed nations [1]. Implicated in the multifactorial etiology of AD are genetic, environmental, and immunologic factors [1,2]. In susceptible individuals, external allergens or irritants may trigger an immune response that involves T-cells, dendritic cells, mast cells, and proinflammatory cytokines [3]. The pruritic nature of AD may lead to a vicious "itch-scratch" cycle, further aggravating the flares, and leading to inflammation, infection, and scarring. Recent studies have linked the presence of null mutations of the gene encoding filaggrin, a filament-aggregation protein important to the development of a healthy epidermal barrier, to an increased susceptibility of developing AD [4].

For years, topical corticosteroids have remained the mainstay of pharmacological treatment for AD. When prescribed appropriately, cutaneous and systemic adverse effects are rare. However, chronic use, particularly of high potency topical steroids and particularly on areas such as the face, neck, and intertriginous areas, has been limited by a propensity to cause cutaneous atrophy. Topical steroids may also cause or exacerbate rosacea and perioral dermatitis [1,5,6]. Systemic side effects, such as reduced bone density and growth and hypothalamic-pituitary-adrenal axis suppression are theoretical concerns in children as their higher body surface area-to-weight ratio puts them at increased risk for systemic absorption. Additionally, risk of relapse after discontinuation of treatment and steroid tachyphylaxis must be considered when using a corticosteroid in the treatment of AD. Given the potential for these adverse effects, coupled with the high prevalence of parental "steroid phobia," there remains a need for safe and effective therapeutic alternatives for the treatment of AD.

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In recent years, two topical calcineurin inhibitors have emerged as effective alternatives to corticosteroids for the treatment of AD. Decisions regarding first line therapy between pimecrolimus and tacrolimus are often based on anecdotal evidence. Herein, we review the current evidence supporting the use of pimecrolimus and tacrolimus in atopic dermatitis as well as key differences in safety, tolerability, and cost between the drugs.

PHARMACOLOGY

Tacrolimus and pimecrolimus are classified as topical calcineurin inhibitors (TCIs). Topical application reduces inflammation by inhibition of T-cells. Both drugs bind the FK binding protein-12 (FKBP12) to inhibit calcineurin, a protein phosphatase responsible for the dephosphorylation of the nuclear factor of activated T-cells (NF-AT). Without dephosphorylation, NF-AT cannot be translocated into the nucleus, and thus the production of inflammatory interleukins is inhibited [7]. Adjunctive mechanisms of action have been proposed for tacrolimus including binding at cell surface steroid receptors, inhibition of mast cell mediator release, and downregulation of chemoattractant IL-8 receptors, intracellular adhesion molecule-1, E-selectin, and Langerhans cells IgE receptors [8-11]. Pimecrolimus has also been shown to prevent the release of pro-inflammatory mediators from both human cutaneous mast cells and rodent cell lines [7,12,13]. In addition to their effects on T-cells, NF-AT and calcineurin are involved in keratinocyte differentiation. Tacrolimus and pimecrolimus have been shown to produce sustained improvements of epidermal barrier function [14,15].

PHARMACOKINETICS

Topical application of tacrolimus in pediatric and adult patients rarely produces serum tacrolimus levels in excess of 2 ng/mL. In point of fact, the AUC produced by this serum level is 30-fold below the levels seen with oral immunosuppressive doses used in transplant patients [9]. Similar results are seen in pharmocokinetic studies of adult patients on pimecrolimus, where levels above 1.4 ng/mL

1874-3722/14

were not observed after topical administration [16]. These findings were validated by a study involving 22 infants, where blood levels were below 2 ng/ml in 96% of blood samples, with the highest concentration measured at 2.26 ng/ml [17]. These levels are far below the pimecrolimus levels required for systemic immunomodulation (≥15 ng/ml) [18]. Both drugs are metabolized by the CYP3A-subfamily of metabolizing enzymes and are primarily eliminated through the feces. There are no clinically significant differences in the distribution, metabolism, and elimination of the two drugs [9,16].

INDICATIONS

Topical tacrolimus and pimecrolimus have been developed for use as short-term treatment of atopic dermatitis or intermittently as chronic therapy in adults and children over the age of 2 years. Currently, both are indicated for second-line treatment in patients who have not exhibited an adequate response to topical corticosteroid treatments or in those in which such treatments are contraindicated. The 0.03% tacrolimus ointment is FDA-approved for use in adults and children over the age of 2 years, while the 0.1% formulation is approved for adult use only [9,16].

EFFICACY

Pimecrolimus Versus Vehicle

Pimecrolimus was first shown to be effective in the short-term management of AD in a 3-week trial comparing pimecrolimus 1% cream to vehicle in 34 adults with moderate to severe AD. A twice-daily application proved to be significantly more effective than both the once-daily treatment and treatment with vehicle without any notable side effects [19]. Significant improvements in eczema area and severity index (EASI) scores along with rapid onset of action further established the usefulness of pimecrolimus in the treatment of AD in pediatric patients. In a 20-week, randomized, 3-phase trial, Kaufmann *et al.* studied twice daily pimecrolimus 1% compared to vehicle in 196 patients ages 3 months to 23 months with mild to severe atopic AD [20]. For the first 4 weeks of the trial treatment was double-blinded, followed by 12 weeks of open-label pimecrolimus. The trial concluded with a 4 week follow-up period. Treatment with pimecrolimus 1% reduced the mean EASI by 71.5% compared with an increase of 19.4% with vehicle at 4 weeks ($P < 0.001$). Differences in EASI scores between groups were significant by day four of the trial. Response to pimecrolimus was maintained throughout the 12 week open-label period without any significant difference in side effects between the two groups. After discontinuation, symptoms of atopic dermatitis gradually returned in the 4 week follow-up period.

Eichenfield and colleagues [21] performed two identical phase III, randomized, vehicle-controlled, multi-center 6 week studies evaluating the safety and efficacy of pimecrolimus 1% cream when used to treat mild to moderate AD in children and adolescents. The studies included 403 pediatric patients from 2-17 years old. At baseline, patients' EASI scores were determined, and patients were further evaluated for disease severity based on the Investigator's Global Assessment (IGA) score, pruritis severity, and subjective assessment of disease control. At study entry, 59% of patients were classified with moderate disease according to the IGA score and the mean body surface area (BSA) affected was 26%. After a seven day treatment with a basic, bland emollient cream, patients were randomized to treatment with twice daily 1% pimecrolimus or vehicle for 6 weeks. Patients were evaluated for treatment response at weekly visits, with the primary efficacy endpoint being the IGA score. Successful therapy was defined as a decrease from a score of 2 to 3 (mild to moderate) to 0 to 1 (clear to almost clear). Significant improvements in IGA score were observed at the first follow-up visit on day 8, with 12% of the pimecrolimus group being rated as clear or almost clear compared to only 2.2% of the vehicle group. Ninety-six percent of the pimecrolimus group either maintained their IGA scores or showed improvement compared to only 80% of the vehicle group.

The efficacy of pimecrolimus for long-term management of AD has been demonstrated adults, infants, and children in multiple trials ranging from 6 months to 2 years [22-27]. In a two year study, Papp *et al.* demonstrated a reduction in EASI of more than 80% at 12 months, which was sustained in the 1-year open-label follow up [28].

Additionally, pimecrolimus has been shown to work particularly well for lesions on the face and neck, areas prone to adverse effects of corticosteroids [21,22,29]. Murrell *et al*. [29] compared pimecrolimus to vehicle in a 12-week trial involving 200 patients ages 12 years and older with mild to moderate head and neck AD intolerant of, or dependent on, topical corticosteroids. Compared to vehicle cream a significantly higher percentage of patients treated with pimecrolimus were cleared or almost cleared of facial AD. Notably, pimecrolimus use was associated with a reversal in skin thinning in patients with skin atrophy from prior corticosteroid use.

Tacrolimus Versus Vehicle

Tacrolimus is indicated for use in both adult and pediatric patients with moderate to severe atopic dermatitis based on the results of three randomized, double-blind, vehicle-controlled, multi-center phase III studies [30,31]. In phase III trials, patients were treated for 12 weeks with either tacrolimus ointment 0.03%, tacrolimus ointment 0.1%, or a vehicle ointment applied twice daily. The pediatric study involved 351 patients between the ages of 2 and 15 years old, and the two adult studies totaled 632 patients between the ages of 15 and 79 years old. The primary efficacy endpoint was improvement based on the physician's global evaluation of clinical response. Results were similar in all three trials; a significantly greater percentage of patients in the tacrolimus groups achieved at least 90% improvement ($P<0.001$ in both pediatric and adult studies). While the pediatric study did not provide evidence that tacrolimus 0.1% ointment was more effective than the 0.03% ointment, the adult studies suggested that the higher strength may be more effective in adult patients with more severe disease at baseline and higher BSA.

Tacrolimus has also proved useful in the long-term treatment of AD and as prophylactic treatment to prevent disease flares. Recently, a 52-week trial studied the effects of tacrolimus applied three times a week in 197 adult and

pediatric patients (>2 years old) with at least moderate AD as rated on the Physician's Static Global Assessment (PSGA) scale [32]. In phase I of the trial, patients were first randomized to double-blinded, twice-daily treatment of either tacrolimus ointment (0.03% for pediatric patients and 0.1% for adult patients) or a corticosteroid (alclometasone dipropionate ointment 0.05% for pediatric patients or triamcinolone acetonide ointment 0.1% for adult patients) for 4 days. In the next 12 weeks of phase I, patients were treated with open-label tacrolimus ointment twice daily, the strength of the ointment once again dependent on the age of the patient. Patients were eligible to enter the phase II of the trial if a PSGA scale of 0-1 (clear to almost clear) was achieved. Of the 383 patients who participated in phase I, 197 were eligible to participate in phase II. In phase II of the trial, patients were randomized to double-blind treatment of either a continuation of three-times weekly application of tacrolimus ointment or a vehicle ointment (2:1) for 40 weeks. Disease relapse (PSGA score > 2) was treated with open-label tacrolimus ointment twice daily. If a PSGA score of 0-1 was not achieved within 8 weeks of relapse, patients discontinued the trial. A significant difference between the tacrolimus group compared to the vehicle group was found for the primary efficacy endpoint in phase II: The mean number of flare-free treatment days was 177 for tacrolimus and 134 for vehicle (P=0.003). Patients treated with tacrolimus also experienced a longer time to first relapse compared to the vehicle groups (169 *vs* 43 days, respectively, P=0.037).

Topical Calcineurin Inhibitors Versus Topical Corticosteroids

Ashcroft *et al*. [33] in 2005, performed a meta-analysis comparing the efficacy and tolerability of the TCIs to that of vehicle and topical corticosteroids. Twenty-five randomized controlled trials were included in this analysis, involving 6897 adults, infants, and children. As expected, both tacrolimus and pimecrolimus were found to be superior to vehicle. When compared to betamethasone valerate 0.1%, pimecrolimus was found to be significantly less effective after three weeks of treatment (rate ratio 0.22, 0.09-0.54) on the proportion of patients determined to be clear or almost clear. Pimecrolimus was also compared to the use of a combined treatment of triamcinolone acetonide 0.1% to the trunk and hydrocortisone acetate 1% to face, neck, and intertriginous areas. The corticosteroid treatment was found to be significantly more effective after one week, three weeks, and six months, but there was no significant difference between the two groups at the end of the 12 month treatment period.

Tacrolimus was also compared to corticosteroids. Compared to hydrocortisone acetate 1%, both tacrolimus 0.03% and 0.1% were found to be significantly more effective at three weeks of treatment (rate ratios 2.56, 1.95 to 3.36 and 3.05, 2.12-4.40, respectively). When used on the face and neck, tacrolimus 0.1% was more effective than aclometasone dipropionate 0.1% for the proportion of patients achieving at least marked improvement of greater than 75% (rate ratio 3.94, 2.21 to 7.00). Compared to more potent corticosteroids (hydrocortisone butyrate 0.1% and betamethasone valerate 0.1%), tacrolimus 0.1% was found to be equally effective at 3 weeks. Tacrolimus 0.03% was compared only to hydrocortisone butyrate 0.1% and found to be significantly less effective. Based on the results of this study, tacrolimus is more effective than pimecrolimus when compared to topical corticosteroids.

Tacrolimus Versus Pimecrolimus

In their meta-analysis, Ashcroft *et al.* confirmed the findings of previous studies, which indicated both tacrolimus and pimecrolimus are superior to vehicle. When compared to topical corticosteroids, however, tacrolimus appeared to perform better than pimecrolimus. A head-to-head trial between tacrolimus and pimecrolimus and a more recent meta-analysis validate these findings.

In 2005, Paller *et al*. [34] conducted three multicenter, investigator-blinded, 6-week studies, in which 1065 patients were randomized to twice daily treatment with either tacroliumus or pimecrolimus. Two of the studies included pediatric patients added 2 to 15 years, with one study including patients with AD classified as mild in severity by the IGA scale and the other study including patients with moderate to very severe disease. The other study included patients above the age of 16 years with mild to very severe AD. Following a 4-week washout period, patients were randomized to their study medications: Picrolimus 1%, tacrolimus 0.1%, or tacrolimus 0.03% if in the pediatric group with mild AD. Patients were to apply the medication twice daily for up to 6 weeks, or at least one week, until the affected area was completely cleared. At the end of treatment the percentage of improvement, by reduction of the EASI score, was significantly greater for tacrolimus than for pimecrolimus in adults (54.1% *vs* 34.9%, respectively; P<0.0001) in pediatric patients with moderate to very severe AD (67.2% *vs* 56.4%, respectively; P=0.04) and in the combined analysis (52.8% *vs* 39.1%, respectively; P<0.0001). At week 1 of treatment a significant difference was found in the pediatric mild AD study with a greater percentage of improvement from baseline in the tacrolimus group compared to the pimecrolimus group (39.2% *vs* 31.2%, respectively; P=0.04). Tacrolimus also showed significantly greater improvements in patients' itch scores and reductions in %BSA affected. In all three studies the most common adverse events were application site reactions. Overall, adverse event profiles were similar in both tacrolimus and pimecrolimus groups. However, in the adult study, patients treated with tacrolimus experienced more application site burning compared to patients treated with pimecrolimus (11.4% *vs* 4.9%, respectively, P=0.02). The authors concluded that tacrolimus is more effective than pimecrolimus with a similar safety profile.

A recent meta-analysis of 20 randomized clinical trials was performed to evaluate the safety and efficacy of tacrolimus and pimecrolimus for the treatment of AD in pediatric patients [35]. The 20 studies, involving 6288 patients, included 10 trials comparing the use of tacrolimus to vehicle or corticosteroids, 7 trials comparing the use of pimecrolimus to vehicle or corticosteroids, and 3 trials comparing the two calcineurin inhibitors to each other. The results of the analysis showed that, while both pimecrolimus and tacrolimus were effective in the treatment of AD in pediatric patients, tacrolimus was superior pimecrolimus.

SAFETY CONSIDERATIONS

Topical calcineurin inhibitors may be locally irritating producing burning and pruritus. Both events occur more frequently with tacrolimus [9,16,36]; however, in most cases, the burning sensations are mild and resolve within 1 to 8 days of drug use [37]. Systemically, calcineurin inhibitors produce immunosuppression, nephrotoxicity, and hypertension. However, these adverse effects are seen at serum concentration much greater than those produced from topical use.

Controversy exists regarding the use of TCIs in Netherton syndrome (NS), a syndrome in which impaired skin integrity often results in significant absorption of medications applied topically. In a small case series, 2 of 3 Netherton syndrome patients treated with tacrolimus ointment 0.1% showed marked improvement. All 3 patients demonstrated serum tacrolimus levels within the therapeutic range for organ transplant patients, however, none showed signs of tacrolimus toxicity [38]. A more recent study involving 4 patients with NS failed to validate these findings, demonstrating serum levels ranging from undetectable to 2.7 ng/ml [39]. Pimecrolimus 1% cream also proved to be effective and well tolerated in 3 children with NS. Blood levels ranged from 0.625-7.08 ng/ml, much lower than anticipated when applied to 50% of BSA [40]. In small case series, TCIs have been safe and effective treatments for NS. Larger studies are needed before even tentative conclusions regarding safety and efficacy can be made.

In 2006, the FDA approved the addition of a black box warning for the calcineurin inhibitors, tacrolimus and pimecrolimus. The warning was added because of concerns of a potential link between use of these agents and development of malignancy. These concerns were prompted by reports of cutaneous neoplasms and lymphomas in animal studies and postmarketing case reports. When used as long-term treatment as part of an immunosuppressive regimen, calcineurin inhibitors may increase the risk of developing lymphomas and non-melanotic skin cancers [41,42]. Theoretically, topical preparations could carry the same risk if absorbed sufficiently into the system; however, as evidenced by the aforementioned pharmacokinetic data, this is rarely the case. Conceivably cutaneous lymphomas, particularly cutaneous T-cell lymphoma (CTCL), may masquerade as dermatitis resulting in treatment with a TCI. Upon treatment failure, biopsy of the lesion may lead to discovery of a cutaneous lymphoma, but it would be impossible to determine if lymphoma was caused by the medication or if the condition had been initially misdiagnosed [43].

Based on this data, the FDA concluded that a casual relationship between topical calcineurin inhibitors and development of malignancy has not been established, but that continuous long-term use should be avoided, and TCIs should not be used in children under the age of 2. It is recommended by the American Academy of Dermatology Association Task Force, that tacrolimus and pimecrolimus should remain therapeutic options in AD as they are currently indicated. Although an increased risk of lymphoma with topical use is unlikely, there is potential concern if the medications are to be used on larger areas for lengthy periods of time [43].

DRUG INTERACTIONS

In light of topical administration and minimal systemic absorption, the incidence of significant drug-drug interactions is low. No formal studies have been performed on drug interactions with TCIs. Nonetheless, systemic interactions are still possible, so caution should be used when administering them with CYP3A4 inhibitors including, but not limited to, erythromycin, azole-based antifungals, calcium channel blockers and cimetidine [9,16]. It has also been reported that alcohol consumption during topical tacrolimus therapy can result in facial flushing, irritation, pruritis, and periocular edema [44].

CONTRAINDICATIONS AND PRECAUTIONS

Topical calcineurin inhibitors should be used with caution in patients with Netherton syndrome due to the potential for increased systemic absorption. Safety in patients with erythroderma has yet to be determined. Safety studies have also not been performed on either drug in patients with viral or bacterial skin infections, however, in preliminary studies, TCIs were associated with an increased risk of cutaneous bacterial and viral infections including herpetic infections. Thus, the manufacturer recommends resolution of existing infections prior to initiation of therapy. In animal photo-carcinogenicity studies, TCIs shortened the time to skin tumor formation. Thus, patients should be counseled to limit their exposure to UV radiation during treatment [9,16].

PATIENT MONITORING GUIDELINES

Patients should be regularly evaluated for clinical improvement. If there is not adequate improvement after six weeks of therapy, then a reassessment of diagnosis and therapy choice is recommended. Patients that develop lymphadenopathy should be monitored for the resolution of this condition [9,16].

DRUG DOSING AND ADMINISTRATION

Table **1** lists manufacturer recommended drug dosing and administration guidelines. When applying either drug, patients should rub the drug in gently and completely to clean, dry skin. Patients should not use occlusive dressings as they may promote systemic absorption. Tacrolimus and pimecrolimus should be discontinued upon clearance of active disease [9,16].

PRODUCT AVAILABILITY AND AVERAGE WHOLESALE PRICE

Table **2** lists the average wholesale price (AWP) for Protopic (tacrolimus) and Elidel (pimecrolimus). Although daily cost calculations can be complicated by the variability of the size of affected areas and amount applied to those areas, it can be reasonably predicted that a one-gram dose is sufficient for the average patient. Using the FDA-approved twice-daily dosing, a 60 gram tube would constitute a month's supply. Thus, the predicted daily cost of Elidel and Protopic is $16.52 and $16.99, respectively. Using the 60 gram

Table 1. Dosing and Administration of TCIs

Tacrolimus [9]	Pimecrolimus [16]
Adults: Apply a minimal amount of 0.03% or 0.1% ointment to the affected area twice daily. Pediatric patients (≥2 yo): Use only the 0.03% ointment twice daily.	Adults and Pediatric (≥ 2 yo) patients: Apply a thin layer of 1% cream to the affected area twice daily.

Table 2. AWP of TCIs

AWP as of April 2010 [45]	Protopic 0.03%	Protopic 0.1%	Elidel 1%
30 g tube	$254.87	$254.87	$247.79
60 g tube	$509.75	$509.75	$495.57
100 g tube	$849.58	$849.58	$825.94

tube as a reference, the Protopic products are 3% more expensive than Elidel.

SUMMARY AND FINAL RECOMMENDATION

Topical corticosteroids are the established gold standard for the treatment of atopic dermatitis. But given an unfavorable side effect profile when used improperly, coupled with the high prevalence of parental "steroid phobia," there remains a need for safe and effective therapeutic alternatives. In recent years, two topical calcineurin inhibitors have emerged as safe and effective alternatives to corticosteroids for the treatment of AD. Topical calcineurin inhibitors are particularly useful for patients intolerant of or dependant on corticosteroids. It is the authors' opinion that given the high cost of therapy compared to corticosteroids, TCIs should not be considered first line therapy for most patients with AD. However, they should be strongly considered when presented with a patient with existing steroid atrophy or a parent with a level of "steroid phobia" likely to result in non-compliance.

In clinical efficacy trials, tacrolimus was found to be more effective than pimecrolimus when compared to vehicle, representative corticosteroids, and pimecrolimus. For both drugs, twice daily treatment was superior to once daily application. Despite greater efficacy with the oil-based tacrolimus, the water-based pimecrolimus was better tolerated by patients. Furthermore, the predicted cost of pimecrolimus is 3% less than that of tacrolimus. To ensure treatment compliance, decisions regarding first line therapy between pimecrolimus and tacrolimus should be made on a case-by-case basis, considering cost and tolerability issues. One might consider using pimecrolimus during the day and tacrolimus at night for those patients who prefer a water-based cream but respond best to tacrolimus.

With regards to safety, the FDA has issued black box warning for a possible increased risk of lymphomas in patients treated with TCIs. It should be noted that lymphomas were seen in animal studies with high serum concentration of drug. Theoretically, topical preparations could carry the same risk with sufficient systemic absorption; however, serum concentrations are very low with topical application. Although an increased risk of lymphoma with topical use is unlikely, there is potential concern if the medications are to be used on larger areas for lengthy periods of time. Thus, the clinician should be vigilant in this setting. While preliminary data regarding safety and efficacy in NS shows promise, long-term data in larger patient populations is necessary before even tentative conclusions can be made.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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Received: February 7, 2014 Revised: March 26, 2014 Accepted: March 26, 2014