Therapeutic Class Overview
Topical Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review encompasses the topical immunomodulators agents used in atopic dermatitis (eczema). The two medications included in this therapeutic class are Elidel® (pimecrolimus) and Protopic® (tacrolimus).[1,2] The mechanism of action of these medications are not known, however, it has been demonstrated that both agents inhibit the phosphatase activity of calcineurin. Inhibition of calcineurin inhibits the transcription of cytokines involved in T-cell activation. Hence, these agents are referred to as calcineurin inhibitors. In addition, both agents have been shown to prevent the release of inflammatory cytokines and mediators from mast cells stimulated by antigen/immunoglobulin E.

  Both agents are Food and Drug Administration (FDA) approved as second-line therapy for the short-term and non-continuous chronic treatment of atopic dermatitis in non immunocompromised adults and children. Pimecrolimus 1% cream is approved for mild-moderate atopic dermatitis for patients two years of age and older while tacrolimus is approved for treatment of moderate to severe atopic dermatitis.[1,2]

  Consensus guidelines recommends topical corticosteroids as the standard of care for the management of atopic dermatitis.[3-6] Topical immunomodulators are considered to be an alternative to topical corticosteroids and should only be utilized if the patient is intolerant to or has failed conventional topical corticosteroid therapy.

  Concerns regarding the long-term safety of these agents have been addressed in the treatment guidelines and position papers published by medical associations. On January 19, 2006, the FDA approved updated labeling for the topical immunomodulators, pimecrolimus and tacrolimus.[7,8] This updated labeling was a result of cancer-related adverse events with the use of these medications, however position statements from several professional organizations have noted the lack of conclusive evidence linking an increase incidence of malignancies to the topical calcineurin inhibitors.[9-11]

Table 1. Current Medications Available in the Therapeutic Class[1,2,12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Pimecrolimus (Elidel®)	Second-line therapy for short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients two years of age and older who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable	Cream: 1%	-
Tacrolimus (Protopic®)	Second-line therapy for the short-term and noncontinuous chronic treatment of moderate to severe atopic dermatitis in nonimmunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable	Ointment: 0.03% 0.1%	-

Evidence-based Medicine

- The topical calcineurin inhibitors, pimecrolimus and tacrolimus are Food and Drug Administration (FDA) approved for the treatment of atopic dermatitis.
- These agents are available as pimecrolimus 1% cream (Elidel®) and tacrolimus 0.03 and 0.1% ointment (Protopic®).

- Current guidelines for the treatment of atopic dermatitis recommend the use of topical corticosteroids as first line treatment and recommend the use of topical pimecrolimus or tacrolimus in those patients intolerant or unresponsive to corticosteroids or in whom corticosteroids are contraindicated.[3-6]
- Concerns regarding the long-term safety of these agents have been addressed by the Public Health Advisory, the American College of Asthma, Allergy, and Immunology, the American Academy of Allergy, Asthma, and Immunology, the European Dermatology Forum, and the Canadian Society of Allergy and Clinical Immunology in position statements supporting the safety of these agents when used according to product labeling.[9-11]
- Clinical studies have demonstrated these two agents to be effective in treatment of atopic dermatitis compared to placebo. Compared to medium and high potency corticosteroids tacrolimus was found to be equivalent while pimecrolimus was found to be less effective compared to potent corticosteroids.[18-25]
- Limited head-to-head studies and meta-analyses comparing the efficacy of the calcineurin inhibitors have been conducted, with results favoring efficacy of tacrolimus over pimecrolimus and similar adverse effects between the groups were similar.[13-17]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[3-6]
    - Topical immunomodulators are to be used as second line therapy following failure or contraindication to topical corticosteroids.
    - Topical immunomodulators due not cause atrophy of the skin like prolonged topical corticosteroids use and may be used on body parts where atrophy is a concern or where a potent-very-high potent topical corticosteroid is not appropriate.
- Other Key Facts:
    - There are no generic agents in the class.
    - Safety concerns regarding long-term use, particularly updated with cancer-related adverse events with the use of these medications forced updates to product labeling to include black box warnings[7-8]
        - Position statements from several professional organizations have noted the lack of conclusive evidence linking an increase incidence of malignancies to the topical calcineurin inhibitors.[9-11]
    - Limited direct clinical trials between agents favor tacrolimus in efficacy in both adult and pediatric patients. [13-17]
        - Majority of trials showed that the two agents were comparable in adverse effects.
    - Pimecrolimus is approved for mild-moderate atopic dermatitis for patients two years of age and older.[1]
    - Tacrolimus is approved in children and adults with moderate-severe atopic dermatitis.
    - Dosing frequency and route of administration vary between products.[2]

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Therapeutic Class Review
Topical Immunomodulators

Overview/Summary

Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition with a prevalence of 17% in the United States.[1-2] It is one of the most common skin disorders in children with more than 85% of cases starting before the age of five.[1-2] The pathogenesis of atopic dermatitis can be explained by both, impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as cutaneous inflammatory response to environmental factors.[2] Pruritus is one of the most common symptoms of atopic dermatitis and it is an essential feature which provokes a vicious "itch-scratch" cycle that compromises the epidermal barrier which results in water loss, xerosis, microbial colonization and secondary infection.[1,3] The clinical manifestations of atopic dermatitis vary according to patient's age and disease activity and almost all patients with atopic dermatitis report dry skin.[2] The infantile and childhood stage is characterized by pruritic, red, crusted lesions and generally involves the face, neck, and extensor skin surfaces.[2] The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities.[2]

Diagnosis of atopic dermatitis is based on a constellation of clinical symptoms. There is no optimal treatment for the long-term maintenance of atopic dermatitis and there is no known cure for atopic dermatitis. The general approach to the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin's abnormal barrier function, hydrating the skin and controlling active disease with topical anti-inflammatory agents.[4] Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents.[4] Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized.[4] In contrast, lotions and creams that have high water content and low oil content should be avoided since they may trigger a flare of the disease.[4] Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation.[4] Sedating antihistamines (e.g. diphenhydramine, hydroxyzine) appear to be more effective than the non-sedating ones (e.g. fexofenadine, loratadine).[4] However, evidence supporting their use is weak due to lack of controlled trials.

Topical corticosteroids are considered to be the standard of care for the treatment for atopic dermatitis.[5] Topical corticosteroids from low-potency to high-potency are utilized one or more times daily for the treatment of acute flare of atopic dermatitis as well as for intermittent use to prevent relapse.[4] One large trial showed that twice-daily application of topical corticosteroids was no more effective than once-daily application.[1] There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents.[5] These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck.[1,4]

Topical immunomodulators are a relatively recent addition to the treatment approach for atopic dermatitis. The two medications included in this therapeutic class are Elidel® (pimecrolimus) and Protopic® (tacrolimus).[6-7] Pimecrolimus is Food and Drug Administration (FDA) approved as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non immunocompromised patients 2 years of age and older and it is available as 1% cream.[6] Tacrolimus is FDA approved as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis.[7] It is available as an ointment in two different strengths; the 0.1% formulation is appropriate initial therapy for adults and the 0.03% formulation is appropriate for children aged 2 to 15 years and for adults who cannot tolerate the higher dose.[4,7] The mechanism of action of these medications are not known, however, it has been demonstrated that both agents inhibit the phosphatase activity of calcineurin. Inhibition of calcineurin inhibits the transcription of cytokines involved in T-cell activation. Hence, these agents are referred to as calcineurin inhibitors. In addition, both agents have been shown to prevent the release of inflammatory cytokines and mediators from mast cells stimulated by antigen/immunoglobulin E.

The American Academy of Dermatology and the American College of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma and Immunology recommends topical corticosteroids as the standard of care for the management of atopic dermatitis.[8] The Primary Care Dermatology Society and the British Association of Dermatologists recommends that topical immunomodulators are considered to be an alternative to topical corticosteroids and should only be utilized if the patient is intolerant to or has failed conventional topical corticosteroid therapy and/or the application area where atrophy is a concern or the in areas where potent corticosteroid application would not be appropriate, such as the face, eyelids, genitalia, and intertriginous areas.[9]

Concerns regarding the long-term safety of these agents have been addressed in the treatment guidelines and position papers outlined in this review. On January 19, 2006, the FDA approved updated labeling for the two topical immunomodulators, pimecrolimus and tacrolimus.[10-11] This updated labeling was a result of cancer-related adverse events with the use of these medications. The new labeling includes a black box warning about a possible risk of cancer and a medication guide for patients to ensure that they are aware of this concern. The new labeling clarifies that these medications are recommended for use as a second-line treatment and are not recommended in children under two years of age. A definitive causal link between the topical immunosuppressants and the incidence of malignancy is not yet established. Until this research is concluded, both agents should be utilized appropriately.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Pimecrolimus (Elidel®)	Topical immunomodulators	-
Tacrolimus (Protopic®)	Topical immunomodulators	-

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[6-7,12]

Indication	Pimecrolimus	Tacrolimus
Second-line therapy for short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients 2 years of age and older who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable	✔	
Second-line therapy for the short-term and noncontinuous chronic treatment of moderate to severe atopic dermatitis in nonimmunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable		✔ *

*Both 0.03 and 0.1% ointment for adults and only 0.03% ointment for children two to 15 years of age.

In addition to its Food and Drug Administration (FDA)-approved indication, pimecrolimus has also been used off-label in the treatment of genital lichen planus, oral lichen planus and vitiligo. Preliminary data from a case series and short-term controlled study suggest that topical pimecrolimus may be useful as second-line treatment of steroid-resistant genital lichen planus or oral lichen planus. There is not sufficient data regarding the use of pimecrolimus in the treatment of vitiligo.[12]

Although not FDA approved, tacrolimus has also been used off-label for the treatment of genital and oral lichen planus, pyoderma gangrenosum and vitiligo. There is insufficient data to support its use in genital lichen planus and vitiligo. Initial data for use in oral lichen planus suggests a possible treatment option. Results of one trial and several case series suggest that tacrolimus may be beneficial for patients with pyoderma gangrenosum. Other possible off-label uses of tacrolimus include treatment of facial, flexural, intertriginous psoriasis, and cutaneous lupus erythematosus.[12]

Pharmacokinetics

Table 3. Pharmacokinetics[6-7,12]

Generic Name	Systemic Absorption	Distribution	Excretion (Renal)	Active Metabolites
Pimecrolimus	Minimal	Not reported	None	None
Tacrolimus	Minimal	Not reported	Not reported	Not reported

Clinical Trials

Key trials summarized in Table 4 support the Food and Drug Administration (FDA) approved indications for the topical immunomodulators in the short-term and intermittent chronic treatment of atopic dermatitis.

The FDA approval of pimecrolimus cream was based on three randomized, double-blind, vehicle-controlled, phase III studies in patients three months to 17 years of age with mild to moderate atopic dermatitis (N=589).[6] Two of these three trials support the use of pimecrolimus cream in patients two years of age and older with mild to moderate atopic dermatitis. Two other identical six week vehicle-controlled, Phase III trials were conducted in pediatric patients 2 to 17 years of age (N=403).[6] These two studies showed significant clinical response based on physician's global evaluation for pimecrolimus-treated patients compared to patients in the vehicle group.[6] These studies are outlined in the manufacturer product labeling.

The FDA approval of tacrolimus ointment was based on three randomized, double-blind, vehicle-controlled, phase III studies in patients with moderate to severe atopic dermatitis.[7] One of the studies was conducted in pediatric patients (N=351) two to 15 years of age and the other two were conducted in adult patients (N=632).[7] The primary efficacy endpoint was met by all three studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the tacrolimus group compared to the vehicle group ($P<0.001$). There was some evidence that tacrolimus 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy for the two tacrolimus strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.

Pimecrolimus was also studied in two randomized clinical trials ranging from four weeks to 12 months in a younger pediatric population with a diagnosis of atopic dermatitis including infants between the ages of three and 23 months. Kapp et al showed that there was a significantly lower number of flares in the pimecrolimus group compared to the vehicle group (67.6% of patients in the pimecrolimus group had no flare at six months vs 30.4% in the vehicle group; $P<0.001$).[13] However, the *P* value at 12 months for incidence of flares of atopic dermatitis was not reported.[13] Also, Eczema Area Severity Index mean total scores and pruritus scores were not significant at month 12.[13] An open-label, extension study of Kapp et al demonstrated treatment success with pimecrolimus for an additional 12 months.[14] Staab et al showed significant improvements in all domains of a quality of life questionnaire for parents of children with atopic dermatitis.[15] There was also significant reduction in mean Eczema Area Severity Index score and severity scoring of atopic dermatitis index for the pimecrolimus group.[15] Similar efficacy results were also found in a study by Hoeger et al consisting of patients two to 11 years of age with facial atopic dermatitis who were dependent on, or intolerant of, topical corticosteroids.[16]

Pimecrolimus has been compared to tacrolimus in clinical trials that are included in this review. Kempers et al compared pimecrolimus to tacrolimus 0.03% in patients two to 17 years of age (N=141, six weeks) and found no difference in the incidence of application site reactions between the two topical immunomodulators.[17] However, itching was reported at a significantly higher rate in the tacrolimus group.[17] Fleischer et al and Abramovits et al compared tacrolimus 0.1% to pimecrolimus in adult patients for six weeks and found that tacrolimus had a significantly greater improvement in the Eczema Area Severity Index score compared to pimecrolimus.[18-19] The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the tacrolimus group.[18-19] In both studies, there were no differences in adverse events between the groups.[18-19] A meta-analysis by Paller et al of three randomized clinical trials also showed that both adults

and children in the tacrolimus-treated group had a significantly greater improvement in Eczema Area Severity Index score at week six as compared to the pimecrolimus group.[20] The most common adverse effects in all studies were local application site reactions including burning and stinging.[20] Kirsner et al conducted a subanalysis of patients enrolled in the Paller et al study[20] who were treated with topical corticosteroids within 30 days prior to enrollment and found similar results.[21] Additionally, Taneja et al conducted a cost effectiveness analysis based on the data from one of the trails include in Paller et al[20] and found the two treatments similar in estimated cost (per patient) of atopic dermatitis related drug therapy (*P* value not provided) and that for tacrolimus the expected cost of atopic dermatitis related outpatient visits was substantially lower (*P* value not provided). This cost analysis also found that the overall expected costs of atopic dermatitis-related care was lower with tacrolimus vs pimecrolimus (*P* value not reported).[22] Most recently, Yin et al conducted a meta-analysis by of four randomized clinical trials also showed that overall both adults and children in the tacrolimus-treated group had a significantly greater improvement in Investigator Global Atopic Dermatitis Assessment score at weeks three and six as well as lower rates of withdrawals due to lack of efficacy and adverse effects as compared to the pimecrolimus group.[32]

Topical tacrolimus has also been compared to topical corticosteroids. In two studies that compared tacrolimus 0.1% to a low-potency topical corticosteroid, hydrocortisone butyrate 0.1% in adult patients with moderate to severe atopic dermatitis, the response rate for tacrolimus was higher than the topical corticosteroid.[23-24] Itch and quality of sleep had improved significantly in both treatment groups.[23] In another study by Bieber et al that compared tacrolimus 0.03% to methylprednisolone aceponate 0.1% in patients two to 15 years of age with moderate to severe atopic dermatitis (N=265, three weeks) no statistical difference between the two groups in treatment success as defined by a score of clear or almost clear in Investigator's Global Assessment score was found.[25] The percentage change in Eczema Area Severity Index was statistically significant for methylprednisolone aceponate after seven and 14 days of treatment.[25] This significance was lost at day 21. Six patients in the tacrolimus group and none from the methylprednisolone aceponate group experienced adverse reactions attributed to the treatment.[25] Additionally, tacrolimus has been compared to fluticasone with varying resulst.[26-27] While one trial found no significant difference between the treatment groups another found tacrolimus to be significantly more efficacious.[26-27]

A meta-analysis by Ashcroft et al of 25 randomized controlled trials (N=6,897) showed that tacrolimus 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis.[28] Additionally, pimecrolimus was found to be less effective than potent topical corticosteroids.[28] A recently published meta-analysis and systematic review by El-Batawy assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (N=7,378).[29] In terms of overall comparison, pimecrolimus was found to be more effective than vehicle at three and six weeks.[29] However, a long-term study that was included in this review did not find any difference between these two groups at six and twelve months.[29] Also, betamethasone valerate, a potent topical corticosteroid was found to be significantly more effective in adults (three weeks) than pimecrolimus in the treatment of moderate to severe atopic dermatitis. Although, this meta-analysis showed that pimecrolimus seems to be less effective than topical corticosteroids, pimecrolimus would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds.[29] Pooled analysis of tacrolimus trials showed tacrolimus was more effective than vehicle.[29] Tacrolimus when compared to mild potency topical corticosteroid like hydrocortisone acetate was more efficacious.[29] Whereas, when compared to moderate potency topical corticosteroid, tacrolimus 0.03% was significantly less effective than topical corticosteroids and tacrolimus 0.1% was equal in effectiveness to the topical corticosteroid.[29] Overall, tacrolimus was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids.[29] A systematic review by Chen et al of 21 randomized controlled trials (N=6,288) showed that tacrolimus was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis.[30] Additionally, pimecrolimus was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis.[30] In this review three trials comparing pimecrolimus to tacrolimus were identified. While two of the trials did find tacrolimus to be significantly more efficacious, no significant difference was found in the third trial.[30]

A retrospective cohort by Hui et al evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure tacrolimus or pimecrolimus was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma (P<0.001, P=0.010). However, after the exclusion of four cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to tacrolimus and not pimecrolimus (P<0.001, P=0.086).

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kapp et al[13] Pimecrolimus 1% cream BID at first sign of flare until complete clearance of signs and symptoms vs vehicle cream BID at first sign of flare until complete clearance of signs and symptoms Patients in both groups were permitted use of moderately potent TCs to help treat flares.	DB, MC, PC, PG, RCT Infants 3 to 23 months of age with a clinical diagnosis of AD	N=251 12 months	Primary: Incidence of flares of AD at six months Secondary: IGA score, EASI, and caregiver's assessments of pruritus and overall level of disease control (pruritus was assessed by the caregiver for 24 hours prior to study visits and ranked on a scale of 0 [none] to 3 [severe], and were asked to assess the level of control over the preceding seven days on a 4-point scale; the IGA score, pruritus assessment, and caregiver assessments were dichotomized into treatment success [score of 0 or 1] or treatment failure [all other scores])	Primary: There was a significantly lower number of flares in the pimecrolimus group compared to the vehicle group (67.6% of patients in the pimecrolimus group had no flare at six months vs 30.4% in the vehicle group; *P*<0.001). At 12 months, 56.9% of patients in the pimecrolimus group had no flares compared to 28.3% of patients in the vehicle group (*P* value not reported). Baseline severity of AD did not affect the trend towards a lower incidence of flares in the pimecrolimus group. Patients in the pimecrolimus group had a significantly longer flare-free period compared to patients in the vehicle group (*P*<0.001) and the mean number of flares was lower in the pimecrolimus group compared to the control group (*P*<0.001). In the pimecrolimus group, 63.7% of patients did not require a TC during the study period, compared to 34.8% in the vehicle group and the proportion of study days on a TC was 3.2% in the pimecrolimus group compared to 6.2% in the vehicle group (*P* values not reported). Secondary: An IGA score of 0 or 1 (clear or almost clear) was achieved in 44.6% of patients in the pimecrolimus group compared to 8.7% in the vehicle group (*P*<0.001). The maximum benefit of therapy was achieved by day 22 in the pimecrolimus group compared to three months in the vehicle group and the magnitude of effect was greater in the pimecrolimus group (54.9% had achieved an IGA score of 0 or 1 by day 22 compared to 39.1% in the vehicle group; *P*=0.034). At month six, a significantly greater proportion of patients in the pimecrolimus group had clear or nearly clear skin compared to those in the vehicle group (52.9 vs 37.0%; *P*=0.03). At month 12, a higher number of patients in the pimecrolimus group had clear or nearly clear skin compared to the vehicle group, though this difference was not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				statistically significant (53.9 vs 47.8%; *P* value not reported). EASI mean total scores were significantly lower for patients in the pimecrolimus group compared to the vehicle group at day 43 (*P*<0.0001) but were not significantly different at month six, nine, or 12 (*P*>0.076). Pruritus scores were significantly lower for patients in the pimecrolimus group compared to the vehicle group at day 43, month six and nine (*P*<0.016) but were not significantly different at month 12 (*P*=0.074). A significantly higher number of patients in the pimecrolimus group had a caregiver assessment of 0 or 1 (complete or good disease control) compared to the vehicle group at day 43 and month six (*P*<0.016), but the differences were not significant at month nine or 12 (*P*>0.058).
Papp et al[14] Pimecrolimus 1% cream BID at first sign of flare until complete clearance of signs and symptoms All patients received active treatment. Patients were permitted use of moderately potent TCs to help treat flares.	ES, OL Infants 3 to 23 months of age with a clinical diagnosis of AD This was an extension of Kapp et al, above.[13]	N=91 12 months	Primary: Proportion of patients with no flares, treatment success rates (proportion of patients with clear or almost clear skin as indicated by an IGA of 0 or 1), EASI, percentage of total BSA affected by AD, course of disease (proportion of disease-free days without the use of any medication), adverse effects Secondary: Not reported	Primary: The median number of days of pimecrolimus use during the 12 months of this study was 99.0 and 27.5% of these patients required TCs during this time. Seventy-six patients used pimecrolimus for two years (original study by Kapp et al, and present study combined) and there was a progressive reduction in the mean proportion of pimecrolimus treatment days from 73.7% during the first three months of the second year to 42.3% during the last three months of the second year. The proportion of patients in this study who did not use TCs during the first year was 71.1% and this increased to 72.4% during the second year. Overall, 57.9% of patients in the pimecrolimus group did not use TCs at all during the two years. 76.9% of patients did not experience any flares during the second year and only 8.8% had a single flare. In patients on pimecrolimus for two years, the proportion experiencing no flares increased from 77.6% during the first year to 85.5% during the second year. The proportion of patients who were clear or almost clear of signs of AD increased from 36.3% at the beginning of the second year to 71.4% at the end of the second year.

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				The mean EASI score decreased from 5.8 to 2.9 and the mean percentage of total BSA affected by AD decreased from 11.3% to 6.6%. At the beginning of the first year, 75.0% of patients treated with pimecrolimus for two years had moderate or severe disease. At the end of the second year, the percentage of patients with minimal residual activity or were clear of signs of AD was 69.7%. Only 13.2% had an IGA >2. In this same group of patients, an improvement in EASI scores was already evident at three months and persisted for the remaining 21 months. The mean percentage of total BSA affected by AD decreased from 28.4% at the beginning of the first year to 7.3% at the end of the second year. The proportion of disease-free days increased from 30.0% during the first six months of the second year to 50.9% during the last two months. The majority of adverse effects reported were conditions commonly seen in childhood such as nasopharyngitis, pyrexia, cough, diarrhea, ear infection, bronchitis, rhinitis, vomiting, and gastroenteritis. There were no reports of application site reactions. Secondary: Not reported
Staab et al[15] Pimecrolimus 1% cream BID for four weeks vs placebo cream BID for four weeks	DB, MC, PC, PG, RCT Patients 3 to 23 months of age diagnosed with atopic eczema affecting some part of the face, affecting ≥5% of BSA, and having a	N=196 4 weeks (Phase I data only) Phase I: 4 weeks of treatment Phase II: 12 week OL	Primary: Parents' quality of life in five domains: psychosomatic well-being, effects on social life, confidence in medical treatment, emotional coping, and acceptance of disease, as measured by the	Primary: Significant improvements were seen in all domains of the PQoL-AD in favor of pimecrolimus (P<0.05). The most significant differences were seen in the domains of "psychosomatic well-being", "emotional coping", and "acceptance of disease". There was a significant pruritus treatment effect observed in favor of pimecrolimus by day two (P=0.018) and a significant improvement in sleep observed by day three (P=0.002). By day 29, the mean percentage change in the SCOR-AD index was -55.20% for pimecrolimus and 1.13% for the placebo group (P=0.002). Treatment success (IGA=0 [clear] or 1 [almost clear]) was observed in 53.5% of patients in the pimecrolimus group at day 29 compared to 10.6% of patients in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	baseline IGA score of mild severity or greater	extension Phase II: 4 week follow-up	PQoL-AD; pruritus and sleep loss, using the SCOR-AD; severity of disease, using IGA; degree of disease control, measured by the EASI Secondary: Not reported	placebo group (*P*<0.001). The mean EASI decreased by 71.5% in the pimecrolimus group compared to 19.4% in the placebo group by the end of the four week treatment phase (*P*<0.001). The reduction in EASI was observed as early as day four in the pimecrolimus group and it decreased by 38.5% compared to a decrease of 17.6% in the placebo group on day four (*P*<0.001). Secondary: Not reported
Hoeger et al[16] Pimecrolimus 1% cream BID vs placebo Completion of the DB phase occurred on day 43 or at the time a patient achieved a facial IGA of 0. During the OL phase patients were treated intermittently with pimecrolimus BID; treatment was discontinued when clearance occurred and was resumed upon recurrence of first signs and	DB, MC, OL, PC, RCT Patients 2 to 11 years of age with mild to moderate facial AD who were dependent on, or intolerant of, TCs	N=200 12 weeks (6 weeks DB followed by 6 weeks OL)	Primary: Efficacy (assessed by facial IGA score) Secondary: Head and neck EASI, overall EASI, pruritus severity score, time to clearance of facial AD, EDA, the amount of study drug used, safety and tolerability	Primary: A significantly greater proportion of patients treated with pimecrolimus became clear/almost clear of facial AD lesions at day 43 compared to patients in the placebo group (74.5 vs 51.0%, respectively; *P*<0.001). Statistically significant differences between groups were apparent at day 22, with 57.1% of pimecrolimus-treated patients experiencing clearance or almost clearance of their facial AD compared to 36.0% of placebo-treated patients (*P*=0.004). Improvements in facial IGA continued into the OL phase for the pimecrolimus group (87.6% at day 64 and 90.3% at day 85). A substantial improvement was also seen in patients who switched from placebo to pimecrolimus in the OL phase, of whom 79.5% at day 64 and 88.6% at day 85 achieved facial IGA scores of 0/1. Secondary: A significantly greater proportion of pimecrolimus-treated patients at day eight were EASI responders (defined as patients achieving ≥60% improvement in head and neck EASI compared with baseline) compared to placebo (37.8 vs 18.0%, respectively; *P*<0.003), rising to 77.6 vs 55.0%, respectively, at day 43 (*P*<0.001). Improvement continued into the OL phase for the pimecrolimus group and for those who switched to pimecrolimus. Overall EASI scores showed a similar trend to those for the head and neck, with significantly more overall EASI responders in the pimecrolimus group than the placebo group at day 22 (51.0 vs 27.0%, respectively; *P*<0.001) and at day 43 (71.4 vs 38.0%, respectively; *P*<0.001).

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symptoms of AD. Use of other medications that could potentially have an effect on AD (topical or systemic corticosteroids, phototherapy, topical antibiotics or oral immunosuppressants) was not permitted.				At day eight, 89.8 and 60.0% of pimecrolimus- and placebo-treated patients had no or mild pruritus of the head and neck (*P*<0.001), increasing to 93.9 vs 68.0%, respectively, at day 43 (*P*<0.001). This improvement continued into the OL phase in the pimecrolimus group, and in those who switched to pimecrolimus. Facial AD cleared twice as rapidly in patients treated with pimecrolimus compared with placebo (median time to clearance [facial IGA 0/1]: 22 vs 43 days, respectively; *P* value not reported). A higher proportion of pimecrolimus-treated patients was cleared of eyelid dermatitis at six weeks compared with placebo-treated patients (41.8 vs 31.0%, respectively; *P*=0.140). This improvement continued into the OL phase, and a marked improvement was seen in those patients who switched to pimecrolimus. Drug usage, by weight, for the head and neck was similar in the pimecrolimus and placebo groups in both the DB and OL phases. The mean±SD of total usage during the DB phase in the pimecrolimus and placebo groups were 24.2±19.5 g vs 26.9±21.9 g (*P* value not reported). In the OL phase drug usage was 19.0±15.5 g vs 21.6±18.4 g (*P* value not reported). Drug usage for the rest of the body was slightly lower in the pimecrolimus group than in the placebo group (DB phase, 45.5±28.7 vs 50.7±39.0 g; OL phase, 35.6±25.4 vs 39.0±28.5 g; *P* values not reported). Most treatment-emergent adverse events were mild to moderate in both phases of the study. Forty out of 99 (40.4%) pimecrolimus-treated patients and 34/101 (33.7%) placebo-treated patients experienced at least one adverse event during the DB phase. During the DB phase the most commonly reported adverse events were nasopharyngitis, application site irritation and pyrexia. Fewer adverse events were reported during the OL phase with the frequency of application site reactions being comparable between the two groups.
Kempers et al[17] Pimecrolimus 1% cream BID until clearing or for six weeks	MC, PG, RCT, SB Patients 2 to 17 years of age with moderate	N=141 6 week treatment phase with OL extension	Primary: Incidence of local application site reactions Secondary:	Primary: The incidence of application site reactions decreased with time in both groups, but this was more pronounced in the pimecrolimus group (*P* values not reported). Application site reactions were experienced by 24% of patients in the pimecrolimus group and 26% in the tacrolimus group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tacrolimus 0.03% ointment BID until clearing or for six weeks	AD (IGA score of 3)	(treatment data only)	Formulation attributes, safety, and efficacy (measured by IGA and patient assessment)	Erythema/irritation was reported in 8% of the pimecrolimus patients compared to 19% in the tacrolimus patients (*P*=0.039). Itching was reported in 8% of the pimecrolimus patients compared to 20% in the tacrolimus patients though this difference was not statistically significant (*P*=0.073). Warmth/stinging/burning was reported in 20% of the pimecrolimus patients compared to 17% in the tacrolimus patients though this difference was not statistically significant (*P*=0.931). The duration of application site reactions tended to be shorter in the pimecrolimus group compared to the tacrolimus group (*P* value not reported). None of the patients in the pimecrolimus group who experienced erythema/irritation reported that it lasted longer than 30 minutes, compared to 85% of patients in the tacrolimus group who reported that this lasted between 30 minutes and 12 hours (*P*<0.001). None of the patients in the pimecrolimus group who experienced warmth/burning/ stinging reported that it lasted longer than 30 minutes, compared to 67% of patients in the tacrolimus group who reported that this lasted between 30 minutes and 12 hours (*P*<0.001). The difference between the two treatment groups in the duration of itching was not significant (*P*=0.559). Secondary: A significantly higher proportion of patients/caregivers in the tacrolimus group reported that their skin felt oily compared to the pimecrolimus group (*P*<0.001). There was no significant difference in the proportion of patients who reported that their skin felt dry during treatment (*P*=0.308). At day 43, a significantly higher proportion of patients reported that pimecrolimus was suitable for use on sensitive facial skin, had a non-sticky feel, and was easy to

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				apply and rub in compared to tacrolimus (*P*<0.020). There was no significant difference in the spreadability of either product (*P*=0.06). The overall incidence of adverse effects was similar between the treatment groups: 86% of patients in the pimecrolimus group reported adverse effects compared to 84% in the tacrolimus group (*P* value not reported). There was no significant difference in IGA scores of clear/almost clear between treatment groups at any visit, though both increased compared to baseline values (*P*>0.05). On day 22, significantly more patients in the tacrolimus group reported absent or mild pruritus compared to the pimecrolimus group (*P*=0.042), though differences on all other days were not significant. On day 43, there were no significant differences between treatment groups in the proportion of patients achieving IGA or pruritus scores of 0 or 1 (*P*=0.493). IGA response rates were slightly higher in the tacrolimus group compared to the pimecrolimus group from day eight to 43, though these differences were not statistically significant (except for day 22 as mentioned above). More than 60% of patients in both groups reported absent or mild pruritus. The change from baseline in BSA affected by AD was similar in both treatment groups, though pimecrolimus tended to have a greater effect on the head and neck compared to tacrolimus which tended to have a greater effect on the legs.
Fleischer et al[18] Tacrolimus 0.1% ointment BID to all affected areas vs	CS, IB, MC, PRO, RCT Patients ≥16 years of age with moderate to very severe AD with at least 5%	N=281 6 weeks	Primary: The percent change in EASI score from baseline to week six or end of study Secondary:	Primary: The tacrolimus group had significantly greater improvement in EASI score than the pimecrolimus group (a reduction of 57 vs 39% at study end; *P*=0.0002). Secondary: Success with therapy was significantly greater with the tacrolimus group than the pimecrolimus group (40 vs 22% at study end; *P*=0.001). Significantly more tacrolimus-treated patients improved by one or more grades on the IGADA

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pimecrolimus 1% cream BID to all affected areas Both active medications were applied for up to six weeks or until one week after the affected area was completely cleared, whichever came first.	of total BSA involvement		Success of therapy based on the IGADA (success equals 'clear' or 'almost clear'), percent change from baseline in the percent BSA affected, patient's assessment of itch (visual analog scale ranging from 0 cm [no itch] to 10 cm [worst itch imaginable]), safety endpoints (incidences of all adverse events)	compared with pimecrolimus (*P*=0.001). There was a significantly greater improvement in percent BSA affected in the tacrolimus treatment group compared with the pimecrolimus group beginning with week three. The percent reduction from baseline to study end in percent BSA affected was 49% for tacrolimus and 34% for pimecrolimus (*P*=0.01). Both treatment groups had a baseline itch score of 6.7 cm and had similar improvements in patient assessment of itch (*P* value not reported). A total of 193 patients (96 tacrolimus and 97 pimecrolimus) had head and/or neck involvement at baseline. At study end, there was a 66% improvement in signs and symptoms of AD in face and neck region in the tacrolimus group compared with a 49% improvement in the pimecrolimus group (*P*=0.02). Adverse events reported were comparable for both treatment groups, and they occurred at a similar frequency (*P*=0.823). The most commonly reported adverse events were application-site burning and application-site pruritus. Two tacrolimus-treated patients and four pimecrolimus-treated patients discontinued study due to adverse effects (*P*=0.447). For patients with moderate disease at baseline the percent reduction in EASI score from baseline for 188 patients was significantly greater for tacrolimus than pimecrolimus beginning at week one and continuing to the study end (59 vs 43%; *P*=0.01). Tacrolimus-treated patients improved significantly more than pimecrolimus-treated patients by one or more grades on the IGADA (79 vs 62%; *P*=0.016). Treatment discontinuation due to lack of efficacy occurred in 0% of tacrolimus-treated patients and in 5.6% of pimecrolimus-treated patients (*P*=0.024).
Abramovits et al[19] Tacrolimus 0.1% ointment BID to all affected areas	CS, IB, MC, PRO, RCT Patients ≥16 years of age	N=188 6 weeks	Primary: The percent change in EASI score from baseline to end of study	Primary: Tacrolimus-treated patients had significantly greater improvement in EASI score compared with pimecrolimus-treated patients at the end of study (59 vs 43% reduction; *P*=0.01). The percent improvement from baseline in EASI score was also significantly greater for the tacrolimus group than the pimecrolimus group at weeks

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vs pimecrolimus 1% cream BID to all affected areas Both active medications were applied for up to six weeks or until one week after the affected area was completely cleared, whichever came first.	with mild to very severe AD according to IGADA with at least >5% of total BSA involvement		Secondary: Success of therapy based on the IGADA (success equals 'clear' or 'almost clear'), percent change from baseline in the percent BSA affected as estimated from four designated body regions, patient's assessment of itch (visual analog scale ranging from 0 cm [no itch] to 10 cm [worst itch imaginable]), safety endpoints (incidences of all adverse events)	one and three (*P*=0.05 and *P*=0.03 respectively). Secondary: Success of therapy on the IGADA was significantly greater for tacrolimus than pimecrolimus at week one (*P*<0.02), week three (*P*=0.03), and end of study (*P*<0.02). Similarly, a significantly greater proportion of tacrolimus-treated patients achieved treatment success at week three (*P*=0.03) and end of study (*P*=0.04) than pimecrolimus-treated patients. For treatment of the head and neck region, the tacrolimus group had significantly greater improvement for the signs and symptoms score than the pimecrolimus group (*P*=0.05 at week three and *P*=0.04 at end of study). Although, there was no significant difference between the groups in the percent of BSA affected at week one, three or end of study, there was a trend towards greater improvement in the tacrolimus group (*P*=0.42, *P*=0.16 and *P*=0.10 respectively). Patient's assessment of itch decreased by half in the tacrolimus ointment group from a baseline value of 6 to 3 cm and a similar decrease was also observed with pimecrolimus cream (*P* value not reported and data not shown). Overall, there were no significant differences in adverse events between the groups (*P*=0.19). However, there was a trend towards a higher frequency of the most common adverse events in the tacrolimus group. The most common adverse events were application-site burning and application-site itching for both treatment groups (*P*=0.33 and *P*=0.41).
Paller et al[20] Tacrolimus 0.03% ointment or 0.1% ointment BID for six weeks or until seven days after clearance vs	MA Patients 2 years of age and older with mild to severe AD	N=1,065 6 weeks	Primary: Change from baseline in EASI score at week six Secondary: IGADA (success means clear or almost clear), percent BSA	Primary: The change in baseline in EASI score at week six was significantly greater in the tacrolimus groups compared to the pimecrolimus groups in adults (54.1 and 34.9%, respectively; *P*<0.0001), children with moderate to severe disease (67.2 and 56.4%, respectively; *P*=0.04), and in the combined analysis (52.8 and 39.1%, respectively; *P*<0.0001). In the study evaluating pediatric patients with mild AD, there was a significant difference in EASI score favoring tacrolimus at week one (*P*=0.04), and a trend toward advantage with tacrolimus at week six, but this difference was not significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pimecrolimus 1% cream BID for six weeks or until seven days after clearance			affected, patient's assessment of itch, and safety endpoints (overall incidences of all adverse events and individual incidence rates of application site adverse events)	(*P*=0.07). In all patients with moderate disease, the percentage reduction in EASI score at week six was significantly higher in the tacrolimus group compared to the pimecrolimus group (*P*=0.003). In patients with head and neck involvement, the percentage reduction in EASI score at week six was greater in the tacrolimus group compared with the pimecrolimus group (57.0 and 42.0% respectively; *P*=0.01). Secondary: IGADA scores were significantly better at six weeks for tacrolimus compared to pimecrolimus in the adult patient group, in the children with moderate to very severe disease, and in the combined analysis (all $P \leq 0.01$) but this difference was not significant in the pediatric patients with mild disease (*P* value not reported). At six weeks, there was a significantly greater reduction with tacrolimus compared to pimecrolimus in percentage of BSA affected for the adult patients, for the pediatric patients with moderate to very severe disease, and in the combined analysis (all $P \leq 0.001$), and this difference was observed as early as week three ($P \leq 0.01$). In pediatric patients with mild disease, a significant difference in favor of tacrolimus was observed at week one (*P*=0.02) but this difference was not significant at week six (*P*=0.15). At week six in all three studies, the reduction in itch score was significantly greater in all the tacrolimus groups compared to the pimecrolimus groups ($P \leq 0.01$) and significant differences in favor of tacrolimus were observed as early as week one in both pediatric studies ($P \leq 0.05$). The most common adverse effects in all studies were local application site reactions including burning and stinging. In both pediatric studies, there were no significant differences observed in adverse effects between the tacrolimus and pimecrolimus groups (*P* values not reported). In the adult study, application site burning occurred more frequently in the

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				tacrolimus group compared to the pimecrolimus group (*P*=0.02) early in treatment, but by week one there were no significant differences observed between the groups (*P* value not reported). In the pediatric study of patients with mild AD, significantly more patients withdrew from the study due to an adverse effect in the pimecrolimus group compared to the tacrolimus group (*P*=0.002).
Kirsner et al[21] Tacrolimus 0.03% ointment or 0.1% ointment BID for six weeks or until seven days after clearance vs pimecrolimus 1% cream BID for six weeks or until seven days after clearance	MA Patients 2 years of age and older with mild to severe AD treated with TCs within 30 days prior to enrollment (subanalysis of patients in Paller et al, above[20])	N=347 6 weeks	Primary: Change from baseline in EASI score at week six Secondary: IGADA (success means clear or almost clear), percent BSA affected, patient's assessment of itch, and safety endpoints (overall incidences of all adverse events and individual incidence rates of application site adverse events)	Primary: Compared to baseline there was significantly greater mean percent improvement in EASI score for patients treated with tacrolimus compared to pimecrolimus (53.2 vs 33.7%; *P*=0.0002). Additionally, the improvement with pimecrolimus at end of study was less than at day 22 (33.7 vs 39.8%; *P* value not reported). Secondary: At end of study more patients treated with tacrolimus achieved treatment success (clear or almost clear) compared with pimecrolimus (*P*=0.0007). By Day 22 study end point was achieved by 24.0% of patients treated with tacrolimus compared with 15.3% of patients treated with pimecrolimus (*P*=0.04). Significantly more patients with mild, moderate or severe/very severe AD at baseline had an improvement of one or more grades on the IGDA with tacrolimus treatment compared to pimecrolimus treatment (*P*=0.0006). Significantly more patients with moderate AD at baseline had an improvement of one or more grades on the IGDA with tacrolimus treatment (76.9%) compared to pimecrolimus treatment (49.0%) (*P*=0.0006). Compared to baseline the percent BSA affected was significantly greater with tacrolimus compared to pimecrolimus (*P*=0.002). Patients assessment of itch was significantly improved in the tacrolimus group compared to the pimecrolimus group a difference that was sustained till the end of the study (*P*=0.002). Adverse events were reported at similar rates in both treatment groups (tacrolimus,

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				24.0% vs pimecrolimus, 25.6%; *P* value not reported). Application site burning (tacrolimus, 9.9% vs pimecrolimus, 14.2%; *P*=0.3), and application site itching (tacrolimus, 7.0% vs pimecrolimus, 10.2%; *P*=0.3) were the most common adverse events reported. Skin infection and folliculitis were each reported once in the tacrolimus group. Infected dermatitis was reported once and skin infection was reported four times in the pimecrolimus group.
Taneja et al[22] Tacrolimus 0.1% ointment BID for six weeks or until seven days after clearance vs pimecrolimus 1% cream BID for six weeks or until seven days after clearance	Cost-effectiveness Patients ≥16 years of age with mild to severe AD Cost effectiveness analysis based on data from one of the MC, PRO, R, six weeks trails include in Paller et al.[20]	N=not reported 6 weeks	Primary: Expected number of days with resolved AD over six weeks, cost of AD-related care (drug therapy and outpatient visits) Secondary: Not reported	Primary: It was estimated that compared to pimecrolimus, tacrolimus resulted in 4.9 fewer days with AD (30.0 vs 34.9; difference, 4.9; *P* value not reported). It was estimated that compared to pimecrolimus, faster resolution of AD with tacrolimus would result in two fewer days of therapy (38.9 vs 36.7; *P* value not reported). The two treatments were similar in estimated cost (per patient) of AD related drug therapy (tacrolimus, $214.31 vs pimecrolimus, $216.02; *P* value not provided). For tacrolimus the expected cost of AD related outpatient visits was substantially lower (tacrolimus, $286.96 vs pimecrolimus, $330.12; *P* value not provided). Overall expected costs of AD-related care was lower with tacrolimus vs pimecrolimus ($501.27 vs $546.14; difference, $44.87; *P* value not reported). Secondary: Not reported
Reitamo et al[23] Tacrolimus 0.1% ointment BID to affected areas until clear and then for seven more days	CS, DB, MC, RCT Patients 18 years of age and older with a diagnosis of AD with a severity	N=972 6 months	Primary: Response rate at month three (proportion of patients with at least 60% improvement in mEASI	Primary: At month three, 72.6% of patients in the tacrolimus group responded to treatment compared to 52.3% of patients in the TC group (*P*<0.001). Secondary: The tacrolimus group had a higher response rate at all other time points throughout the six months compared to the TC group (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs hydrocortisone butyrate 0.1% ointment BID to affected areas until clear and then for seven more days (trunk and extremities) and hydrocortisone acetate 1% ointment BID to affected areas until clear and then for seven more days (head and neck)	grading of moderate to severe		Secondary: Response rate at time points other than three months, mEASI, EASI, physician's global evaluation of clinical response, patient's assessment of global response, physician's assessment of individual signs, affected BSA, patient's assessment of itch and quality of sleep, and the number of days on treatment as a percentage of days in the study	A significant improvement in mEASI was observed as early as day eight in both treatment groups and increased up to the six-month point. At month six, the median percentage change in mEASI was -87.7% in the tacrolimus group and -82.5% in the TC group ($P<0.008$). The improvement in EASI and affected BSA followed the same trend. For EASI, the median percentage change was -85.0% in the tacrolimus group and -81.5% in the TC group ($P=0.01$). For the BSA, the median percentage change was -88.2% for the tacrolimus group and -80.3% in the TC group ($P=0.001$). Physicians' global assessments of clinical response was higher in the tacrolimus group compared to the TC group ($P<0.001$). There was a greater reduction in individual signs of AD in the tacrolimus group compared to the TC group and more patients in the tacrolimus group experienced clearance or excellent improvement (at month six, 61.3% of tacrolimus patients and 46.4% of TC patients had clearance or excellent improvement; $P<0.001$). Patients' assessments were significantly higher in the tacrolimus group compared to the TC group. At six months, 86.6% of patients in the tacrolimus group rated their AD as much better or better compared with 71.8% of patients in the TC group ($P<0.001$). Itch and quality of sleep improved significantly in both treatment groups (*P* value not reported). Patients in the tacrolimus group remained in the study longer compared to the TC group and had a lower number of treatment days as a percentage of days in the study (*P* values not reported).
Mandelin et al[24] Tacrolimus 0.1% ointment BID to affected areas until clear and then for seven more days	CS, DB, MC, RCT Patients 18 years of age and older with a diagnosis of AD	N=80 12 months	Primary: Response rate at month three (proportion of patients with at least 60% improvement in	Primary: At month 3, 77.5% of patients in the tacrolimus group responded to treatment compared to 72.5% of patients in the TC group ($P<0.001$). Secondary: Affected BSA, mEASI, EASI, and transepidermal water loss improved over baseline in both treatment groups ($P\leq0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs hydrocortisone butyrate 0.1% ointment BID to affected areas until clear and then for seven more days (trunk and extremities) and hydrocortisone acetate 1% ointment twice daily to affected areas until clear and then for 7 more days (head and neck)	with a severity grading of moderate to severe Some of the efficacy and safety data were reported in Reitamo et al.[23]		mEASI Secondary: Affected BSA, mEASI, EASI, physician and patient assessment of global response, transepidermal water loss, antigen testing, adverse events	With the exception of transepidermal water loss of the trunk and limbs (*P* value not provided) improvement in affected BSA, mEASI, EASI, and transepidermal water loss in the tacrolimus group was significantly greater at six months compared to the TC group ($P \leq 0.05$, ≤ 0.001). No significant difference was observed between treatment groups in these measures at month 12 (*P* value not provided). A significant difference in the EASI score was seen with tacrolimus vs TC when the head and neck area were analyzed separately (month six; $P \leq 0.01$; month 12; $P \leq 0.05$). At month 12 there was an improvement in median affected BSA of 91.0% in the tacrolimus vs 79.0% in the TC group, a difference that was not significant (*P* value not provided). No significant difference was found in the number of patients who were rated by their physician as having a "cleared or excellent' response (tacrolimus, 57.5% vs TC, 42.5%; $P=0.26$). However, when specifically looking at the head and neck area a significant difference was found (tacrolimus, 60.0% vs TC, 30.0%; $P=0.01$). No significant difference between the treatment groups was found in the number of antigens at month 12 ($P=0.46$). An adverse event was reported by 100% of patients in the tacrolimus group vs 85.0% of patients in the TC group ($P=0.03$). Commonly reported adverse events included application-site skin burning, flu syndrome, and folliculitis. No serious adverse events were reported in either treatment arm.
Bieber et al[25] Tacrolimus 0.03% ointment BID to all affected BSA vs methylprednisolone aceponate (MPA)	CS, DB, MC, RCT Patients 2-15 years of age with a history of moderate to severe AD for at least 1 year experiencing	N=265 3 weeks	Primary: Treatment success (defined as a score of clear or almost clear in the static IGA score) Secondary: The percentage change in EASI	Primary: In both groups, treatment was successful in the majority of patients by the end of treatment: MPA, 66.6%; tacrolimus, 66.9%. The difference between treatment groups was not statistically significant ($P=0.9314$). At day 14 the success rate was 50.3% for MPA vs 41.1% for tacrolimus. The number of patients cleared at the end of treatment was 37.2% for MPA and 29.4% for tacrolimus. All patients in the MPA groups and 97.1% in the tacrolimus group reported an improved IGA score at the end of treatment (*P* values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
0.1% ointment in the evening (vehicle ointment was applied in the morning)	acute flare of AD according to IGA (≥4) with at least 5% of total BSA involvement		and patient's assessment of itch and sleep, Children's Dermatology Life Quality Index, patient's assessment of global response, affected BSA and medication costs	Substantial improvement in EASI was noted at days four and seven for both treatment groups. However, there was a greater mean percentage change from baseline for EASI with MPA compared with tacrolimus during the study. At the end of treatment the mean percentage change from baseline for EASI was 89.7% in the MPA group compared with 85.3% in the tacrolimus group. The difference between the two groups was significant after seven days of treatment (*P*=0.0352) and after 14 days of treatment (*P*=0.0214) but not at day 21 (*P*=0.0667). The percentage of affected BSA decreased from approximately 29.0% at baseline for both treatment groups to 6.8% in the MPA group compared with 7.7% in the tacrolimus group at the end of the study. The mean intensity of itching declined substantially from baseline to end of treatment and was particularly pronounced in the MPA group. The change in assessment of itch was statistically significant for MPA by day four (day four; *P*=0.026; day seven; *P*=0.0006; day 14; *P*=0.0007; day 21; *P*=0.0004). The improvement in quality of sleep with MPA was significantly better than tacrolimus at day 14 (*P*=0.0409) and at the end of treatment (*P*=0.0094). Medication cost comparison between MPA and tacrolimus were significant for MPA (*P*=0.0001). Six patients in the tacrolimus group and none from the MPA group experienced adverse reactions including pruritus, erythema, skin burning and hot flushes that were attributed to treatment. A total of four patients (all in the tacrolimus group) discontinued the study due to adverse events. No patients in the MPA group and two patients in the tacrolimus group reported a worsening of the disease compared with baseline.
Doss N, Reitamo S, et al[26] Tacrolimus 0.1% ointment BID vs	DB, IN, MC, Phase IV, RCT Patients ≥16 years of age with moderate to severe facial AD	N=568 6 weeks	Primary: Response rate Secondary: mEASI, presence of facial erythema, patient and	Primary: Response rates (defined as patients achieving ≥60.0% reduction in the mLEASI from baseline to day 21) in the FAS was 93.3% with tacrolimus and 87.8% with fluticasone (95% CI, 0.65 to 10.29%; *P*=0.026) establishing the superiority of tacrolimus. This result was confirmed in the PPS (lower limit of 95% CI, 0.09%; *P*=0.046).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone 0.005% ointment BID Patients treated facial AD lesions for three weeks or until clearance. After day 21, patients entered a second 21 day period with the option of continuing without study treatment if facial lesions had cleared, continuing to apply the same ointment QD if residual facial lesions persisted or switching medication to that of the other group BID if patient and physician were not satisfied with the improvement of facial lesions. Patients treated non-facial AD lesions with OL fluticasone 0.005% ointment.	covering ≥10% of the face (head, neck, cleavage and nape), had experienced >2 flares on the face in the 12 months prior to enrollment and who inadequately responded to or who were intolerant to conventional therapies		physician assessed global clinical response with respect to facial lesions, the number of patients who required a switch to the alternative treatment, safety and tolerability	Secondary: Facial erythema and patients' assessment of facial pruritus decreased in both groups during treatment. Improvement was slightly more pronounced in the tacrolimus ointment group, but between group differences were not statistically significant at day 21 or end of treatment (*P* values not reported). The physicians' global assessment of clinical response for the facial region was significantly different between the two groups (*P*=0.043). Eighty eight percent (250/283) of patients in the tacrolimus group and 79% (220/279) in the fluticasone group showed marked or excellent improvement, or clearance of lesions. Similar results were obtained for patients' global assessment of clinical response (*P*=0.014). At day 21, more patients in the fluticasone group (24/259, 9.0%) switched to tacrolimus than switched from tacrolimus to fluticasone (12/267, 4.5%; *P*=0.095). In the first 21 days, 105 (37%) and 74 (26%) patients in the tacrolimus and fluticasone groups experienced at least one adverse event. Most were application site reactions; the most commonly occurring were skin burning sensation and pruritus. Other facial application site adverse events of interest included herpes infection (4 patients vs 1 patient) and lymphadenopathy (0 patients vs 1 patient). The only serious adverse event was a facial reaction considered to be related to tacrolimus. Discontinuation resulting from adverse events occurred in 7 (2%) and eight (3%) patients. In the second 21 days, the incidence of facial application site adverse events was much lower than in the first period, occurring in 12/253 (5%) who received tacrolimus in both phases, 4/29 (14%) who switched from fluticasone, 6/228 (3%) who received fluticasone in both phases and none of the 15 patients who switched from tacrolimus.
Doss N, Kamoun MR et al[27] Tacrolimus 0.03% ointment BID	DB, NI, RCT Patients 2 to 15 years of age with moderate to severe AD, a	N=479 6 weeks	Primary: Response rate Secondary: mEASI score at each visit,	Primary: Response rates (defined as patients achieving ≥60.0% improvement in mEASI at week three vs day one) in the PPS were high in both treatment groups, with 86.3 and 91.5% of patients in the tacrolimus and fluticasone groups, respectively (95% CI, -11.8 to 1.2). The NI of tacrolimus vs fluticasone was demonstrated. Similar results were obtained in the FAS.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone 0.005% ointment BID Patients applied treatment to all lesions (except on the eyelids) until clearance (up to a maximum of three weeks). Patients in whom treatment was considered ineffective were discontinued at day 21. The remaining patients were followed up for an additional three weeks, those who had residual persisting lesions at day 21 could continue QD treatment during this period.	Rajka and Langeland score ≥4.5 and an inadequate response to TCs		percentage change vs day one severity of pruritus and sleep quality at each visit, global assessment of clinical response by physician and patient or parents at each visit after day one and adverse events	Secondary: Assessment of mEASI at each visit showed that changes were similar in both treatment groups. The overall mean (±SD) percentage change in total mEASI score was -79.5±26.6% in tacrolimus-treated patients and -82.3±33.6% in the fluticasone-treated patients, with similar decreases in each of the four body regions (post hoc analysis data not reported). Patients' assessment of pruritus improved substantially in those receiving tacrolimus, with median change at day 21 of -84.0%. In patients receiving fluticasone, the median change was -91.5% (*P*=0.008). Quality of sleep improved in both treatment groups, with no significant differences between them. In patients two to six years of age, there was little difference in median change between tacrolimus (-87.0%) and fluticasone (-90.0%). In children seven to fifteen years of age, the difference was more marked (-81.0 vs -93.0%). When stratified by pruritus score, the respective percentages of patients were very similar in the tacrolimus and fluticasone groups, with approximately 60.0% of patients benefiting from treatment (data not reported). The percentages of patients with moderate or better improvement on the physicians' global assessment of clinical response were 93.6 and 92.4% in the tacrolimus and fluticasone groups, respectively (*P*=0.050). Patients/parents considered global condition to have improved or greatly improved in 86.9% of patients receiving tacrolimus and 88.6% of patients receiving fluticasone (FAS; *P*=0.047, PPS; *P* value not significant). Other than the well-known application site skin burning sensation in the tacrolimus group, the incidence of adverse events was similar between the two treatments groups. Skin burning sensation was the most common event in both treatment groups, followed by pruritus. Herpes infections were reported in five patients (2.1%) receiving tacrolimus and two patients (0.8%) receiving fluticasone during the first three week period, and by a third patient receiving fluticasone during the second three week period. Folliculitis was reported in four patients (1.7%) receiving tacrolimus and two (0.8%) receiving fluticasone (all cases reported during the first three week period).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ashcroft et al[28] Pimecrolimus 1% cream vs tacrolimus vs vehicle vs TCs	MA Children, adolescents, and adults diagnosed with AD	N=6,897 1 week to 12 months	Primary: Proportion of patients rated by the investigator as clear or almost clear (for pimecrolimus), proportion of patients achieving at least 90% improvement from baseline (for tacrolimus) Secondary: Patients' global assessments of feeling better or much better, proportion of patients with flares of atopic dermatitis, improvements in quality of life, tolerability assessed by overall rates of withdrawal, withdrawal due to adverse effects, proportion of patients with burning of the skin and skin infections	Primary: In five trials evaluating pimecrolimus vs vehicle, pimecrolimus was significantly more effective than vehicle at three weeks (P<0.0001), and three of these found that pimecrolimus retained this efficacy at six weeks (P<0.0001). Another trial found no significant difference at six months between pimecrolimus and vehicle. In three vehicle-controlled trials, there were significantly fewer flares at six months in the pimecrolimus group compared to the vehicle group, and remained more effective at preventing flares at 12 months (P value not reported). One trial evaluated pimecrolimus and a potent TC and found that betamethasone valerate 0.1% was significantly more effective than pimecrolimus after three weeks of treatment when evaluating the proportion of patients who were clear or almost clear (P=0.0008). One study evaluated pimecrolimus vs a potent TC on the trunk and a mild TC on the face and found that the combination of TCs was significantly more effective than pimecrolimus (when evaluating the proportion of patients moderately clear or better) at one week, three weeks, and six months but found no difference at 12 months (P value not reported). One direct comparison of pimecrolimus 1% cream and tacrolimus 0.03% ointment found no difference in the proportion of patients (children) who were clear or almost clear at six weeks (P=0.15). One study evaluating pimecrolimus four times daily compared to pimecrolimus BID found no difference in the proportion of patients clear or almost clear at the end of three weeks (P value not reported). One trial compared tacrolimus 0.03%, tacrolimus 0.1%, and vehicle and found that the 0.03% strength was significantly more effective compared to vehicle when evaluating the proportion of patients clear or achieving excellent improvement (P=0.006), but that the 0.1% strength did not differ from vehicle (P=0.13) at three weeks. When evaluating patients' assessments of improvement as better or much better, both strengths proved significantly better than vehicle. Three other trials reported the same outcomes as described above after 12 weeks and found both

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				strengths to be significantly more effective than vehicle (*P*<0.0001). Two trials compared tacrolimus 0.03% and 0.1% vs hydrocortisone 1% and found that tacrolimus was significantly more effective than hydrocortisone when evaluating the proportion of patients clear or achieving excellent improvement at three weeks (*P*<0.0001). One trial compared tacrolimus 0.1% and alclometasone 0.1% and found that tacrolimus was significantly more effective than alclometasone for treating facial dermatitis (*P* value not reported). One trial compared tacrolimus 0.03% and 0.1% and hydrocortisone butyrate 0.1% (a potent TC) and found that the 0.03% tacrolimus was significantly less effective than the hydrocortisone butyrate judged by the proportion of patients clear or achieving excellent improvement at three weeks (*P*=0.008); but no significant difference was seen between the 0.1% strength of tacrolimus and the hydrocortisone butyrate (*P*=0.65). Two trials compared tacrolimus 0.1% with betamethasone valerate 0.1% or hydrocortisone butyrate 0.1% and found that the tacrolimus was as effective as the TCs in the proportion of patients achieving at least marked improvement (*P* value not reported). One trial compared tacrolimus 0.1% with a regimen of hydrocortisone butyrate 0.1% on the trunk and extremities and hydrocortisone acetate 1% on the head and neck. It found that tacrolimus was significantly more effective than the combined TC regimen when evaluating the proportion of patients clear or achieving excellent improvement at 12 weeks (*P*<0.0001). Six trials compared tacrolimus 0.1 and 0.03%. Three trials found no difference in proportion of patients clear or achieving excellent response at three weeks between the two strengths (*P*=0.44) and the remaining three found tacrolimus 0.1% to be significantly more effective than the 0.03% strength (*P*=0.04) at 12 weeks. Secondary: Significantly more patients withdrew from treatment in the vehicle groups than with either pimecrolimus or tacrolimus (*P*<0.05). Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus group compared to the vehicle group but was significantly higher in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the tacrolimus group compared to the vehicle group (*P* values not reported). Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus or tacrolimus groups compared to topical TCs, nor did rates when comparing tacrolimus 0.03 to 0.1% (*P* values not reported). Skin irritation and skin burning did not differ significantly between pimecrolimus groups and vehicle (*P*=0.257), but the rate was significantly higher with pimecrolimus compared to betamethasone valerate 0.1% or a combined regimen of triamcinolone acetonide 0.1% and hydrocortisone acetate 1% (*P* value not reported). Both strengths of tacrolimus were more likely to cause skin burning compared to vehicle (*P*=0.010) and mild or potent TCs (*P* values not reported). Quality of life was difficult to measure and different outcome measures were used in the studies. In two studies, parents judged quality of life to be improved in patients taking pimecrolimus compared to placebo, and three trials showed increases in quality of life in patients taking tacrolimus 0.03 and 0.1% compared to placebo (*P* values not reported). Tacrolimus 0.1% was found to have a significantly greater improvement on quality of life in adults compared to the 0.03% strength, but no significant differences were found in infants and children (*P* values not reported). No quality of life assessments were found comparing pimecrolimus and tacrolimus to topical TCs (*P* values not reported).
El-Batawy et al[29] Pimecrolimus or tacrolimus vs TCs	MA of 19 RCTs Patients of all ages with AD	N=7,378 3 weeks to 6 months	Primary: Treatment success as defined by proportion of patients who were rated by the investigator as clear or almost clear (equivalent to	Primary: Pimecrolimus was found to be significantly more effective than vehicle at three weeks (*P*=0.005) and six weeks (*P*<0.00001) as measured by IGA. One trial of infants with mild to very severe AD found no significant difference between both groups at six months (*P*=0.08) and 12 months (*P*=0.47) as measured by IGA. Only one trial compared pimecrolimus cream 1% with betamethasone-17-valerate 0.1% cream, with the TC found to be significantly more effective than pimecrolimus (RR, 0.22; 95% CI, 0.09 to 0.54; *P*=0.0008), as measured by IGA of AD at three

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs vehicle			IGA score 0 or 1) (pimecrolimus), treatment success as defined as proportion of patients who achieved at least 90% improvement from baseline, as rated by PGE score (tacrolimus) Secondary: Patient Global assessment of feeling better, PSS, frequency of flares of AD and steroid sparing effect	weeks. Tacrolimus 0.03% ointment was found to be more effective than vehicle (RR, 2.13; 95% CI, 1.24 to 3.68; *P*=0.006), but this was not the case for the 0.1% ointment (*P*=0.13). Two other studies compared both tacrolimus concentrations to vehicle for 12 weeks. Tacrolimus 0.03 and 0.1% were both significantly more effective than placebo (RR, 3.6; 95% CI, 2.26 to 5.72; *P*=0.00001). Two studies compared tacrolimus 0.03% and 0.1% ointments with 1% hydrocortisone acetate and found they were significantly more effective than the mild TC at three weeks (RR, 2.56; 95% CI, 1.95 to 3.36 and RR, 3.09; 95% CI, 2.14 to 4.45; *P*=0.00001 for both). Secondary: Pimecrolimus cream 1% was found significantly more effective than vehicle as assessed by the PSS at three weeks (RR, 2.10; 95% CI, 1.70 to 2.58; *P*<0.00001) and six weeks (RR, 1.84; 95% CI, 1.44 to 2.36; *P*<0.00001). Pimecrolimus cream 1% used regularly for six months resulted in significantly fewer flares of AD and a significant decrease in the use of TCs vs vehicle with allowed TCs in case of flares (RR, 1.90; 95% CI, 1.50 to 2.41; *P*<0.00001 and RR, 1.83; 95% CI, 1.52 to 2.19; *P*<0.00001), as demonstrated by two long term studies. Only one trial compared pimecrolimus cream 1% with a combined treatment regimen of triamcinolone acetonide 0.1% cream (on trunk and limbs), and hydrocortisone acetate 1% cream (on face and flexures). The combined TCs regimen was found to be significantly more effective than pimecrolimus after one week (*P*<0.00001), three weeks (*P*<0.00001), and six months (*P*=0.003) of treatment, but treatment groups did not differ significantly at the end of treatment at 12 months (RR, 0.77; 95% CI, 0.63 to 0.93; *P*=0.008). One study compared tacrolimus 0.03% and 0.1% ointments with 0.1% hydrocortisone butyrate ointments. Tacrolimus 0.03% was significantly less effective than the TC (RR, 0.74; 95% CI, 0.59 to 0.93; *P*=0.01) and tacrolimus 0.1% was as effective as the TC (*P*=0.72).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In one study, tacrolimus 0.1% was superior to a combined TCs regimen of 0.1% hydrocortisone butyrate ointment applied to the trunk and arms, and 1% hydrocortisone acetate ointment applied to the face and flexures (*P* value not reported).
Chen et al[30] Tacrolimus applied locally vs pimecrolimus applied locally vs placebo or TCs	SR Published DB, RCTs of patients <18 years of age with a diagnosis of AD	N=6,288 (21 articles) Duration not reported	Primary: IGA or PGE Secondary: EASI or mEASI, quality of life and adverse events	Primary: *Tacrolimus 0.03% ointment vs tacrolimus 0.1% ointment:* Two of the three trials found no significant difference between the two treatments on the proportions of patients with a PGE ≥90% at three weeks (pooled OR, 1.04; 95% CI, 0.39 to 2.80). The third trial found no significant difference between the strengths on the proportions of patients with an IGA ≤1 at 12 weeks (OR, 0.82; 95% CI, 0.48 to 1.48). *Tacrolimus vs placebo:* Two of the four trials reported on the proportion of patients with a PGE ≥90% at three weeks (OR, 4.98; 95% CI, 2.58 to 9.61) and another reported on the proportion of patients with an IGA ≤1 at six weeks (OR, 2.95; 95% CI, 1.84 to 4.74). One trial reported on the proportion of patients with a PGE ≥90% at 12 weeks (OR, 7.56; 95% CI, 3.36 to 17.02), with tacrolimus 0.03% being significantly more effective than placebo. Two trials directly compared tacrolimus 0.03 and 0.1%, and placebo with one trial reporting on the proportion of patients with a PGE ≥90% at three weeks (OR, 2.00; 95% CI, 0.84 to 4.78) and the other reporting on the proportion of patients with an IGA ≤1 at 12 weeks (OR, 9.26; 95% CI, 4.13 to 20.74). Tacrolimus 0.1% was significantly more effective than placebo. *Tacrolimus ointment vs mild TCs:* Two trials compared tacrolimus 0.03 and 0.1% to hydrocortisone acetate 1% (N=1,161). Both strengths of tacrolimus were significantly more effective than hydrocortisone acetate on the basis of the proportion of patients with a PGE ≥90% or an IGA ≤1 at three weeks (ORs, 3.49; 95% CI, 2.47 to 4.94 and 4.94; 95% CI, 3.02 to 8.05). *Pimecrolimus 1% cream vs placebo:* Pimecrolimus 1% was significantly more effective than placebo in six trials (OR, 3.21; 95% CI, 2.48 to 4.14), with four trials reporting that pimecrolimus 1%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				remained significantly more effective after six weeks (OR, 2.80; 95% CI, 2.11 to 3.73). Another trial found a significant difference between the proportions of patients IGA ≤1 at four weeks (OR, 9.69; 95% CI, 4.12 to 22.83). The most recent trials found a significant difference between the proportions of patients with an IGA ≤1 at one week (OR, 2.78; 95% CI, 1.18 to 6.54), and pimecrolimus resulted in significantly fewer children with flare of AD at six months (51.9%). *Pimecrolimus 1% cream vs potent TCs (trunk) and mild TCs (face):* Two trials comparing pimecrolimus 1% with combined treatment with triamcinolone acetonide 1% (trunk) and hydrocortisone acetate 1% (face) demonstrated that pimecrolimus 1% was no more significantly effective than hydrocortisone acetate 1% on the basis of the proportion of patients with an IGA ≤1 at six months. The corresponding OR at 12 months were 1.59 (95% CI, 1.20 to 2.11) and 1.31 (95% CI, 0.97 to 1.77). *Pimecrolimus 1% cream vs tacrolimus 0.03 and 0.1% ointment:* One trial showed no significant difference in the proportion of children with an IGA ≤1 at four weeks (OR, 1.28; 95% CI, 0.78 to 1.88). Another trial found a significant difference in the proportion of children with an IGA ≤1 at six weeks (OR, 2.05; 95% CI, 1.05 to 4.01). In the most recent trial, there was also a significant difference in the proportion of children with an IGA ≤1 at six weeks (OR, 2.20; 95% CI, 1.18 to 4.12). Secondary: *Tacrolimus vs placebo:* Four articles reported that the improvement percentage from baseline (by reduction in EASI score) was significantly greater for the tacrolimus-treated patients compared to placebo ($P<0.001$). Tacrolimus 0.1% exhibited statistically significant improvements from baseline at the end of treatment compared to placebo for all quality of life scores in children and toddlers ($P<0.05$). The effects of tacrolimus were substantial in the aspects of symptoms and feelings, sleep and treatment. Tacrolimus 0.03% demonstrated significant quality of life improvements in both children and toddlers at the end of treatment compared with placebo for all quality of life scores ($P<0.05$), except personal relationships scales in children (*P* value not reported). Differences

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				between tacrolimus groups were found to not be significantly different between children and toddlers; however, one trial reported that there was a difference. *Tacrolimus ointment vs mild TCs:* Two articles reported that the improvement percentage from baseline (by reduction in EASI score) was significantly greater for the tacrolimus-treated patients than for the hydrocortisone acetate (*P*<0.001). Another trial demonstrated similar efficacy results regarding treatment success, with significant advantages observed for EASI, itch and sleep with methylprednisolone aceponate 0.1%. *Pimecrolimus 1% cream vs placebo:* Five articles reported that improvement percentage from baseline (by reduction in EASI score) was significantly greater for the pimecrolimus-treated patients than for placebo (*P*<0.001). In a trial with infants with mild to severe atopic eczema, after four weeks of treatment, there was an increase in the mean percentage change from baseline in the eczema area and severity index of 71.5 vs 19.4% with placebo (*P* value not reported). The increased efficacy was paralleled by the following mean percentage changes from baseline in the five domains of the questionnaire: psychosomatic well-being; 14.6 vs 6.2%, effects on social life; 6.7 vs 2.3%, confidence in medical treatment; 10.0 vs 3.7%, emotional coping; 16.1 vs 6.5% and acceptance of disease; 19.6 vs 7.0% (*P* values not reported). *Pimecrolimus 1% cream vs tacrolimus 0.03 and 0.1% ointment:* One article reported that the improvement percentage from baseline (by reduction in EASI score) was significantly greater for the tacrolimus-treated patients compared to pimecrolimus (*P*=0.04). The incidence of adverse events with tacrolimus 0.03% was 15 to 84%, with 29 patients withdrawing because of adverse events. The incidence of adverse events with tacrolimus 0.1% was 13 to 39%, with 11 patients withdrawing because of adverse events. The incidence of adverse events with pimecrolimus 1% was 5 to 86%, with 27 patients withdrawing because of adverse events. The major adverse events included burning and pruritus.
Hui et al[31] Exposure to	Retrospective cohort	N=953,064 Patients	Primary: Initial cancer diagnosis	Primary: A total of 11,961 unique cases of cancer were reported in the cohort, with the most common being breast (21%), prostate (15%) and lung cancer (9%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tacrolimus alone (n=11,898), pimecrolimus alone (n=22,716),or both (n=4,068)	Any plan member with a diagnosis of AD or eczema between January 2001 and December 2004; patients with a history of any cancer were excluded	followed until initial cancer diagnosis, disenrollment from health plan, death or end of study (December 31, 2005), whichever was first	Secondary: Not reported	Compared to unexposed the age and sex adjusted cancer HR's were 0.93 (95% CI, 0.81 to 1.07; *P*=0.306) for patients exposed to tacrolimus and 1.15 (95% CI, 0.99 to 1.31; *P*=0.054) for patients exposed to pimecrolimus. Compared to the unexposed group the HR for melanoma was 0.32 (95% CI, 0.12 to 0.84; *P*=0.021) for subjects exposed to tacrolimus and the HR for lung cancer was 0.52 (95% CI, 0.28 to 0.94; *P*=0.030) for patients exposed to pimecrolimus. With the exception of T-cell lymphoma no other significant differences were found between the treatment and unexposed groups (*P*=0.059 to 0.966). For T-cell lymphoma the HR's were 5.04 (95% CI, 2.39 to 10.63; *P*<0.001) for patients exposed to tacrolimus and 3.76 (95% CI, 1.71 to 8.28; *P*=0.010) for patients exposed to pimecrolimus. After the exclusion of four cases (physician suspected T-cell lymphoma prior to exposure), there were 12 unique cases of T-cell lymphoma documented (tacrolimus only, seven; pimecrolimus only, three; exposed to both, two). The exclusion of the four cases changed the HR to 5.44 (95% CI, 2.51 to 11.79; *P*<0.001) for patients exposed to tacrolimus and 2.32 (95% CI, 0.89 to 6.07; *P*=0.086) for those exposed to pimecrolimus. The median time for T-cell lymphoma diagnosis was 1.4 and 1.5 years for tacrolimus and pimecrolimus exposure respectively. A significant increase in the risk of T-cell lymphoma was also observed with exposure to systemic immunosuppressants (HR, 2.65; 95% CI, 1.75 to 4.00; *P*<0.001) or psoriasis therapy (HR, 7.54; 95% CI, 4.15 to 13.71; *P*<0.001). Secondary: Not reported
Yin et al et al[32] Tacrolimus 0.03% ointment or 0.1% ointment BID for six	MA Patients adult and pediatric patients with	N=1,834 6 weeks or until seven days after	Primary: IGADA at week one, three and six or end of study (success means	Primary: IGADA scores were significantly better at six weeks for tacrolimus 0.1% compared to pimecrolimus 1% in the adult patient group at week three (RR, 0.55; 95% CI, 0.42 to 0.73) and week six/end of study (RR, 0.58; 95% CI, 0.46 to 0.72).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks or until seven days after clearance vs pimecrolimus 1% cream BID for six weeks or until seven days after clearance	mild to severe AD	clearance	clear or almost clear) for pediatric and adult patients based on severity of AD Secondary: Safety endpoints (overall incidences of all adverse events) and withdrawals due adverse events and lack of efficacy	In the children with moderate to very severe disease, significantly better IGADA scores were significantly better at six weeks/end of study (RR, 0.55; 95% CI, 0.34 to 0.88). The combined analysis of efficacy show that tacrolimus was more effective than pimecrolimus at week three and at week six/end of study(three weeks RR, 0.67; 95% CI, 0.56 to 0.80; six weeks RR, 0.65; 95% CI, 0.57 to 0.75). There was no significant difference in IGADA scores for pediatric patients with mild disease taking 0.03% tacrolimus or 1% pimecrolimus. Secondary: In adults, incidence of adverse events (most often reported as application site reactions) occurred more frequently in the tacrolimus 0.1% group compared to the pimecrolimus group (RR, 1.30; 95% CI, 1.02 to 1.66). In pediatric patients with mild-moderate AD, there were no significant differences observed in adverse effects between the tacrolimus 0.3% and pimecrolimus. In pediatric patients with moderate-very severe AD, there were no significant differences observed in adverse effects between the tacrolimus 0.1% and pimecrolimus. Fewer pediatric patients with mild AD treated with 0.03% tacrolimus withdrew due to lack of efficacy than 1% pimecrolimus (RR, 0.05; 95% CI, 0.00 to 0.84). There was no difference in withdrawals between 0.03% tacrolimus and 1% pimecrolimus in pediatric patients with moderate AD. There was no difference in withdrawals between 0.1% tacrolimus and1% pimecrolimus in the treatment of adult patients or moderate to very severe pediatric patients. Combined analyses of withdrawal showed that fewer tacrolimus-treated patients withdrew because of a lack of efficacy (RR, 0.32; 95% CI, 0.19 to 0.53) or adverse event (RR, 0.43; 95% CI, 0.24 to 0.75), compared with pimecrolimus-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients.

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: CI=confidence interval, CS=comparative study, DB=double-blind, ES=extension study, FAS=full analysis set, HR=hazard ratio, IB=investigator-blinded, IN=international, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PPS=per protocol set, PRO=prospective, R=randomized, RCT=randomized controlled trial, RR=relative risk, SB=single blind, SD-standard deviation, SR=systematic review
Miscellaneous abbreviations: AD=atopic dermatitis, BSA=body surface area, EASI=Eczema Area and Severity Index, EDA=Eyelid Dermatitis Assessment, IGA=Investigator's Global Assessment, IGADA=Investigator Global Atopic Dermatitis Assessment, mEASI=Modified Eczema Area and Severity Index, mLEASI=Modified Localized Eczema Area and Severity Index, PGE=Physician Global Evaluation score, PQoL-AD=Quality-of-Life Questionnaire for Parents of Children with Atopic Dermatitis, PSS= Pruritus severity score, RR=relative risk, SCOR-AD=Severity Scoring of Atopic Dermatitis, TCs=Topical corticosteroids

Special Populations

Table 5. Special Populations[6-7,12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Pimecrolimus	Safety and efficacy in the elderly have not been established. Not indicated for use in children <2 years of age.	Not studied in patients with renal dysfunction.	Not studied in patients with hepatic dysfunction.	C	Unknown
Tacrolimus	No dosage adjustment is required in the elderly. Not indicated for use in children <2 years of age.	Not studied in patients with renal dysfunction.	Not studied in patients with hepatic dysfunction.	C	Yes

Adverse Drug Events

The following table depicts the adverse events that occurred in >5% of the study population for both, pimecrolimus cream and tacrolimus ointment. Post-marketing adverse events common to both medications in this class include lymphomas, basal cell carcinoma, squamous cell carcinoma and malignant melanoma.[6-7] Post-marketing adverse drug events specifically related to pimecrolimus cream include anaphylactic reactions, ocular irritation after application of cream near the eyes, angioneurotic edema, facial edema, skin flushing associated with alcohol use and skin discoloration.[6] Post-marketing adverse drug events for tacrolimus ointment include seizures, bullous impetigo, osteomyelitis, septicemia, rosacea, renal impairment and acute renal failure in patients with or without Netherton's syndrome.[7]

Table 6. Adverse Drug Events (%)[6-7]

Adverse Event(s)	Pimecrolimus (%)		Tacrolimus (%)	
	Adults	Pediatrics	Adults	Pediatrics
Central Nervous System				
Headache	7	11 to 25	13 to 20	5 to 9
Hyperesthesia	-	-	2 to 7	-
Dermatological				
Acne	-	-	3 to 7	0 to 2
Application site irritation	6	<1 to 3	-	-
Application site reaction	14	2 to 3	-	-
Erythema	-	-	12 to 28	7 to 12
Folliculitis	6	<2	4 to 6	2
Pruritus	5	<1 to 2	25 to 46	19 to 41
Pustular rash	-	-	2 to 4	2 to 7
Skin burning	25	1 to 10	28 to 58	20 to 43
Skin infection	6	<5	5 to 12	10 to 16
Skin tingling	-	-	2 to 8	1 to 2
Viral infection	-	<1 to 6	-	-
Gastrointestinal				
Abdominal pain	<1	3 to 5	-	-
Diarrhea	2	<1 to 7	2 to 4	4 to 5
Gastroenteritis	1	<1 to 7	-	-
Vomiting	<1	3 to 6	1	4 to 6
Respiratory				
Asthma	-	-	4 to 6	6 to 13
Bronchitis	2	<1 to 10	-	-

Adverse Event(s)	Pimecrolimus (%)		Tacrolimus (%)	
	Adults	Pediatrics	Adults	Pediatrics
Cough	2	9 to 15	1 to 3	10 to 18
Nasopharyngitis	7	10 to 26	-	-
Pharyngitis	<1	<1 to 8	3 to 4	6 to 12
Rhinitis	-	-	2 to 3	4 to 6
Sinusitis	-	-	2 to 6	3 to 7
Sore throat	3	3 to 8	-	-
Upper respiratory infection	<5	4 to 19	-	-
Other				
Accidental injury	-	-	3 to 6	6 to 8
Alcohol intolerance	-	-	3 to 7	-
Allergic reaction	-	-	6 to 12	4 to 13
Fever	1	7 to 12	1 to 4	14 to 21
Flu symptoms	-	-	22 to 31	28 to 34
Hypersensitivity	3	4 to 5	-	-
Infection	-	-	1 to 6	7 to 10
Influenza	9	3 to 13	-	-
Lack of drug effect	-	-	0 to 6	1 to 6
Otitis media	-	-	0 to 2	11 to 12
Tonsillitis	<1	<1 to 6	-	-
Urticaria	-	-	3 to 6	4 to 5

- Event not reported.

Contraindications/Precautions[6-7,10-11]

Pimecrolimus cream and tacrolimus ointment are contraindicated in patients with a history of hypersensitivity to the medication or any component of the cream or ointment.

On January 19, 2006, the Food and Drug Administration (FDA) approved updated labeling for the two topical immunomodulators, pimecrolimus and tacrolimus. This updated labeling was a result of cancer-related adverse events with the use of these medications. As of December 2004, the FDA received 19 reports of cancer-related adverse events linked with tacrolimus use (3 cases in pediatric patients <16 years of age).[10-11] Two deaths in adults related to complications of the cancers and eight hospitalizations were reported (two pediatric). For pimecrolimus, 10 reports linked to cancer-related adverse events were received (four pediatric patients, three in patients <6 years of age).[10-11] The product labeling now includes a black box warning about a possible risk of cancer and a medication guide to be distributed to patients to ensure they are aware of the possible risk. The new labeling clarifies that these medications are recommended for use as second-line treatments and are not recommended in children under two years of age.

A definitive causal link between the topical immunosuppressants and the incidence of malignancy is not yet established. Clinical studies are being conducted by the manufacturers of both Elidel® cream and Protopic® ointment, Novartis Pharmaceuticals Corp. and Astellas Pharm Inc., respectively. As reported by Astellas Pharm Inc., in February 2007, there have been no reports of malignancies to date in one thousand patients enrolled (mean cumulative tacrolimus ointment administration 2.5 years per patient).[33] According to the FDA, it may take human studies of ten years or longer before the actual risk of cancer is determined. Until this research is concluded, both agents should be utilized only as recommended.

The American Academy of Dermatology recommends that topical corticosteroids remain the standard of care for the management of atopic dermatitis. Despite the rare cases of cancer that have been reported with topical immunomodulators, their recommendation is that these agents remain available for use but reserved based on reasonable clinical criteria.

The American College of Asthma, Allergy, and Immunology and the American Academy of Allergy, Asthma, and Immunology released a report in June 2005 suggesting that there is no evidence of systemic

immunosuppression or an increased incidence of lymphoma with the short-term or intermittent long-term use of topical pimecrolimus or tacrolimus.[34] Also in June of 2005, the European Dermatology Forum, a non-profit organization made up of leading European dermatologists reviewed the potential photo-carcinogenicity of topical calcineurin inhibitors. They concluded in their position statement that there is no conclusive evidence from rodent trials to indicate that the long-term application of topical calcineurin inhibitors is photo-carcinogenic and that there is a need for long-term studies in patients to further evaluate any potential photocarcinogenicity.[35] Most recently, the Canadian Society of Allergy and Clinical Immunology released a position statement in July 2013 reiterating that despite the FDA Black Box warnings, no evidence has been published linking an increase incidence of malignancies to the topical calcineurin inhibitors in children or adults, but recognize that while long-term studies are in progress, the safety and efficacy of these agents should be weighed against their theoretical risk. [36]

Black Box Warning for the Topical Immunomodulators[6-7]

WARNING
Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy (i.e., skin cancer and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including pimecrolimus and/or tacrolimus ointment. Therefore: • Avoid continuous long-term use of topical calcineurin inhibitors, including pimecrolimus and/or tacrolimus ointment, in any age group, and limit application to areas of involvement with atopic dermatitis. • Pimecrolimus cream and/or tacrolimus ointment is not indicated for use in children less than 2 years of age. Of the tacrolimus topical dosage forms, only tacrolimus 0.03% ointment is indicated for use in children 2 to 15 years of age.

Pimecrolimus and tacrolimus use should be avoided in patients with malignant and pre-malignant skin conditions.[6,7] These medications should not be used in patients with Netherton's syndrome or other skin diseases where there is potential for increased systemic absorption.[6,7] There is a lack of safety and efficacy data for the use of these medications in immunocompromised patients and should be avoided.[6,7]

Drug Interactions[6-7,12]

Due to limited systemic absorption with immunomodulators applied topically, drug interactions with other systemically absorbed drugs are unlikely to occur and none are documented with these agents. There have been no formal drug interaction studies conducted with pimecrolimus and/or tacrolimus; however, they cannot be ruled out. For this reason, concomitant administration of topical immunomodulators with known CYP3A4 inhibitors (e.g. erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, and cimetidine) in patients with widespread or erythrodermic disease should be done with caution.

Dosage and Administration

Table 7. Dosing and Administration[6-7]

Generic Name	Usual Adult Dose*	Usual Pediatric Dose*	Availability
Pimecrolimus	Apply a thin layer to the affected skin and rub in completely twice daily until signs and symptoms of atopic dermatitis resolve	Not indicated for use in children <2 years of age.	Cream: 1%
Tacrolimus	Apply a thin layer ointment to the affected skin and rub in completely twice daily until signs and symptoms of atopic dermatitis resolve	Not indicated for use in children <2 years of age. Children ≥2 years of age: Apply a thin layer of the 0.03%	Ointment: 0.03% 0.1%

Generic Name	Usual Adult Dose*	Usual Pediatric Dose*	Availability
		ointment to the affected skin and rub in completely twice daily until signs and symptoms of atopic dermatitis resolve	

*If signs and symptoms (e.g., itch, rash, and redness) do not improve within six weeks, patients should be re-examined by the prescriber to confirm diagnosis of atopic dermatitis. Continuous long-term use of these agents should be avoided and application should be limited to areas of involvement with atopic dermatitis. Pimecrolimus cream and tacrolimus ointment should not be used with occlusive dressings since occlusive dressings may promote systemic exposure of the medication.

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Academy of Dermatology, Clinical Guidelines Task Force: **Guidelines of Care for Atopic Dermatitis (2004)**[5#]	• Topical corticosteroids are the standard of care to which other treatments are compared. • Cutaneous adverse effects including striae, skin atrophy, and telangiectasia limit the long-term use of topical corticosteroids. • Data regarding the optimal strength, concentration, duration, and frequency of application is lacking. • Noncutaneous adverse effects associated with long term use of topical corticosteroids are not well documented. • The use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies. • Calcineurin inhibitors (pimecrolimus and tacrolimus) have demonstrated efficacy in reducing the severity, extent and symptoms of atopic dermatitis (AD) in adults and children. The long-term safety of these agents is unknown, including the potential for malignancy and immunosuppression. • Oral antihistamines have limited usefulness. There is limited evidence to support the efficacy of these agents in controlling itch or urticaria associated with atopic dermatitis.
Joint Task Force on Practice Parameters in Collaboration with the American College of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma and Immunology: **Atopic Dermatitis: A Practice Parameter Update 2012**[8]	• The intensity of management and treatment of AD is dictated by the severity of illness, which relates to the effect of AD on the quality of life of the patient and his or her family. • The clinician should establish treatment goals with the patient. These can include reduction in number and severity of flares and increase in disease-free periods. • Clinicians should use a systematic, multipronged approach that includes skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of exacerbating factors. Clinicians should evaluate the success of the approach and modify the treatment plan, if needed. • The clinician should be aware that AD is characterized by reduced skin barrier function, which leads to enhanced water loss and dry skin; therefore the clinician should recommend hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer. • Moisturizers should be recommended as first-line therapy. • If AD is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. • Clinicians should not prescribe potent fluorinated corticosteroids for use on the face, eyelids, genitalia, and intertriginous areas or in young infants.

Clinical Guideline	Recommendation(s)
	• Clinicians should recommend ultrahigh-potency corticosteroids only for very short periods (one to two weeks) and in nonfacial nonskinfold areas. • When prescribing topical steroids, clinicians should remember that the degree of corticosteroid absorption through the skin and hence the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. • Clinicians can consider the use of tacrolimus ointment, which has been shown to be effective and safe in both adults and children older than two years for the treatment of AD, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Clinicians should consider the use of tacrolimus ointment, which, unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds that, is unresponsive to low-potency topical steroids. • Clinicians must counsel patients that transient localized burning and itching can occur during the first week of topical tacrolimus. This might limit its usefulness in certain patients. • Once a flare is controlled, the clinician might consider prescribing tacrolimus ointment twice daily, twice weekly to eczema-prone areas to prevent future flares. • Clinicians should consider the use of topical pimecrolimus cream, which is a calcineurin inhibitor that safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus. • Although tar preparations are widely used in the treatment of AD, there are no randomized controlled studies that have demonstrated their efficacy. • Newer coal tar products have been developed that are more cosmetically acceptable, with respect to odor and staining of clothes, than some older products. • Clinicians should not recommend tar preparations for acutely inflamed skin because this might result in additional skin irritation. • Some patients might benefit from the use of antihistamines for the relief of pruritus associated with AD. • Treatment of AD with topical antihistamines is generally not recommended because of potential cutaneous sensitization. • Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. • Clinicians should consider the addition of dilute bleach baths twice weekly to reduce the severity of AD, especially in patients with recurrent skin infections.
Primary Care Dermatology Society and the British Association of Dermatologists: **Guidelines for the Management of Atopic Eczema (2006; reviewed, January 2010)**[9]	• Patients should be educated on the disease state, how to avoid exacerbating factors and how to keep skin hydrated. <u>Use of emollients</u> • Patients should be educated about the proper use of emollients. • Emollients should be applied as liberally and frequently as possible, ideally every four hours or at least three to four times per day. • Intensive emollient use will reduce the need for topical steroids; emollient use should exceed steroid use by 10:1 in terms of quantities used. • A surfactant such as lauromacrogols may be added to the emollient to help break the scratch-itch cycle.

Clinical Guideline	Recommendation(s)
	Principles of treatment with topical steroids • Topical steroids provide symptomatic relief and are safe in the short term. • Topical steroid potency should be matched to the disease severity and the affected site (weaker corticosteroids should be used on the face and flexures). • Topical steroids should be limited to a few days to a week for acute eczema and up to four to six weeks to gain initial remission for chronic eczema. • The weakest topical steroid that is effective should be chosen. • Potent topical steroids should not be used without specialist advice in infants. • Patients using moderate and potent topical steroids must be kept under review for both local and systemic side-effects. • Very potent corticosteroids may be used on rare occasions in resistant severe disease. Immunomodulatory treatments • Topical immunomodulators (pimecrolimus and tacrolimus) are an alternative to corticosteroids and should only be used if the patient is intolerant to or has failed conventional corticosteroid therapy. These agents should not usually be considered first-line treatments unless there is a specific reason to avoid or reduce the use of topical corticosteroids. • Topical immunomodulators should only be initiated by physicians with a special interest and experience in dermatology, after careful discussion with the patient about potential risks and benefits. Other treatments • Sedating antihistamines may be used to reduce itch and scratch; non-sedating antihistamines have very limited benefit.
European Dermatology Forum; European Academy of Dermatology and Venereology; European Federation of Allergy; European Task Force on Atopic Dermatitis; European Society of Pediatric Dermatology; Global Allergy and Asthma European Network: **Guidelines for Treatment of Atopic Eczema (2012)**[37]	Skin care • Emollients should be prescribed in adequate amounts and these should be used liberally and frequently, e.g. for emollient cream/ointment a minimum of 250 g per week. Emollient bath oils and soap substitutes should also be used. In winter time more lipid ingredients are preferable. • A regular use of emollient has a short- and long-term steroid sparing effect in mild to moderate atopic eczema. An induction of remission with topical corticosteroids is required first. • The rapid progress in better molecular and biochemical knowledge on the predisposing atopic eczema background should provide access to scientifically designed barrier improving topical agents, which indeed correspond to a major part of the etiologic treatment of the disease and are not limited to a mere symptomatic one. Topical anti-inflammatory therapy • Topical steroids o Topical corticosteroids are important anti-inflammatory drugs to be used in atopic eczema, especially in the acute phase. o Topical corticosteroids have a significant effect improving skin lesions compared to placebo. o Topical corticosteroids with an improved risk-benefit ratio are recommended in atopic eczema. o The efficacy of topical glucocorticosteroids can be increased by using wet wraps.

Clinical Guideline	Recommendation(s)
	o Proactive 'therapy', e.g. twice weekly application in the long-term follow-up may help to reduce relapses • Topical calcineurin inhibitors o Topical calcineurin inhibitors are important anti-inflammatory drugs to be used in atopic eczema. o Topical calcineurin inhibitors have a significant effect compared to placebo in short-term and long-term treatment of atopic eczema. o Topical calcineurin inhibitors are especially indicated in problem areas (face, intertrignous sites, anogenital area). o Proactive therapy with twice weekly application of tacrolimus ointment may reduce relapses. o Effective sun protection should be recommended in patients treated with Topical calcineurin inhibitors. • Antipruritic therapy o There is evidence that topical corticosteroids can be used in the initial phase of atopic eczema exacerbation to control pruritus. o There is evidence that systemic interferon gamma influences atopic eczema itch, however, therapeutic use was not further investigated following initial trials. o There is evidence that topical calcineurin inhibitors can be used in atopic eczema until clearance of eczema to control pruritus. o There is evidence that UV-therapy can be used in atopic eczema to relieve pruritus. Narrow band UVB seems to be most preferable. o Although there is evidence that short-term application of topical local anaesthetics may reduce itch sensation in atopic eczema, routine clinical use in atopic eczema cannot be recommended as an adjuvant antipruritic therapy in atopic eczema. o There is preliminary evidence that topical N-palmitoylethanolamin may be effective as an adjuvant antipruritic therapy in atopic eczema, but further trials are needed before an evidence based recommendation can be given. o There is preliminary evidence that capsaicin is useful in the treatment of atopic eczema itch but further trials are needed before an evidence based recommendation can be given. o At the moment there is not enough randomized controlled trial evidence to support the use of doxepin in the treatment of atopic eczema itch. o At the moment there is not enough randomized controlled trial evidence to support the use of mast cell stabilizers in the treatment of atopic eczema itch. o At the moment there is not enough randomized controlled trial evidence to support the safe use of leukotriene receptor antagonists in the treatment of atopic eczema itch. o Although there is evidence that opioid receptor antagonists naltrexone and nalmefene† may reduce atopic eczema itch, there is insufficient data to recommend routine use of these substances in atopic eczema. o At the moment there is not enough randomized controlled trial evidence to support the use of selective serotonin reuptake inhibitors paroxetine and fluvoxamine in the treatment of atopic eczema itch.

Clinical Guideline	Recommendation(s)
	• Antihistamines o There is not enough evidence to support the general use of both first and second generation antihistamines (H1-antagonists) for treatment of pruritus in atopic eczema. • Antimicrobial therapy o Oral antibiotics have no benefit on the skin condition in atopic eczema as long as skin lesions are not obviously superinfected. o A short-term treatment with systemic antibiotics may be beneficial if the skin is obviously superinfected with bacteria. o There is evidence from open observational studies only that antiseptic substances are beneficial for the treatment of atopic eczema. o An antimycotic therapy may be efficient in atopic eczema patients suffering from the 'head and neck' variant. o Topical glucocorticosteroids or calcineurin inhibitors reduce the colonization rate of Staphylococcus aureus in atopic eczema. o Antiseptic textiles have a moderate clinical effect on atopic eczema. o The long-term application of topical antibiotics is not recommend due to the risk of increasing resistances and sensitizations (the latter being relevant for a subgroup of topical antibiotics only). o Eczema herpeticum should be treated without delay using systemic antiviral therapy, such as systemic acyclovir.

* American Academy of Dermatology evidence-based guidelines are sunset five years from the date of publication as they are perceived to be no longer current. This guideline was sunset in 2009. An evidenced based guideline is in development. Estimated publication date for diagnosis and assessment is December 2013 while topical and systemic treatment guidance is anticipated for February 2014.[38]
†Not available in the United States.

Conclusions

The two topical calcineurin inhibitors, pimecrolimus and tacrolimus that are Food and Drug Administration (FDA) approved for the treatment of atopic dermatitis are discussed in this review. They are available as pimecrolimus 1% cream (Elidel®) and tacrolimus 0.03 and 0.1% ointment (Protopic®). Current guidelines for the treatment of atopic dermatitis recommend the use of topical corticosteroids as first line treatment and recommend the use of topical pimecrolimus or tacrolimus in those patients intolerant or unresponsive to corticosteroids or in whom corticosteroids are contraindicated.[5,8-9] Concerns regarding the long-term safety of these agents have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the potential risk of cancer of these two products to healthcare providers and patients. The FDA has advised that Protopic® and Elidel® be used only as labeled and asked providers and patients to consider these agents only as second-line therapies; new labeling was approved in early 2006.[10-11] In response to the Public Health Advisory, the American College of Asthma, Allergy, and Immunology, the American Academy of Allergy, Asthma, and Immunology and the European Dermatology Forum released reports supporting the safety of these agents when used according to product labeling.[34,35] Currently, there is no data to suggest a causal relationship between the use of topical calcineurin inhibitors and an increased incidence of photo carcinogenicity, lymphoma, or cancer. Further studies are needed to fully evaluate the long-term safety of these agents.

Several head-to-head studies comparing the efficacy of these two calcineurin inhibitors have been summarized here. A meta-analysis of three studies directly comparing pimecrolimus and tacrolimus conducted by Paller et al evaluated the change from baseline in Eczema Area and Severity Index score at week six of treatment.[20] Results favored treatment with tacrolimus and adverse effects between the groups were similar.[20] Another meta-analysis by Ashcroft et al. evaluating pimecrolimus, tacrolimus, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in Eczema Area and Severity Index Score in patients using tacrolimus compared to patients using pimecrolimus in

addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease, though only one direct comparison of these agents was represented in the meta-analysis.[28] A recently published meta-analysis and systematic review by El-Batawy et al showed that pimecrolimus was found to be more effective than vehicle.[29] A long-term study that was included in this review did not find any difference between these two groups at six and twelve months.[29] Pooled analysis of tacrolimus trials showed tacrolimus was more effective than vehicle.[29] Overall, tacrolimus was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids.[29]

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