

Topical Immune Modulators
Topical Calcineurin Inhibitors Oregon Drug Class Review, October 2008
University of Utah College of Pharmacy Executive Summary

Introduction

Currently two Topical Calcineurin Inhibitors are available for use in the United States: pimecrolimus and tacrolimus.^{1,2} The topical calcineurin inhibitors are indicated in the treatment of atopic dermatitis. The Oregon Drug Class Review on the Topical Calcineurin Inhibitors was published in 2008.³ The Oregon Report reviews the safety and efficacy of the two topical agents. For a comparison of the mechanisms of action, indications and dosing information for pimecrolimus and tacrolimus see Table 1 beginning on page 9 of the Oregon Report also available in the appendix of this executive summary document. A summary of the safety and efficacy data published following the Oregon Report is included at the end of this document.

Disease Overview

Atopic dermatitis (AD) is a common, recurring inflammatory skin disease.³⁻⁶ AD is considered a minor dermatologic disorder but it is associated with substantial costs and morbidity.⁷ In the United States, the cost of illness for AD by third-party payers reaches up to \$3.8 billion annually.⁷ The prevalence of AD has increased 3-fold since 1970 and is still on the rise, especially in children.^{3,7} AD affects up to 30% of children and about 2-10% of adults worldwide.^{3,7} In addition, patients with AD experience more atopic manifestations including asthma, allergic conjunctivitis, allergic rhinitis and food allergies which can increase the costs and morbidity associated with AD.⁷

Atopic dermatitis is a chronic skin disorder characterized by pruritus, eczematous dermatitis, allergic shiners, facial pallor, rash and dryness.⁸ Diagnosis of atopic dermatitis is based on these symptoms and other skin disorders (i.e. contact dermatitis, seborrheic dermatitis, scabies, psoriasis, etc.) should be ruled out before a diagnosis of AD is made.³⁻⁸ In AD, a complex set of interactions between genetic susceptibility genes results in skin barrier dysfunction, defects in the innate immune system and immunoglobulin E hyper-reactivity.⁸ Those with a personal or family history of AD are at increased risk for developing allergic rhinitis or asthma. Other complications associated with the disease include eyelid dermatitis, chronic blepharitis and skin infections.⁸

Pruritus is the principal symptom of AD and control of this symptom is important as irritation from scratching can induce inflammatory mediators and lead to a vicious scratch-itch cycle, prolonging the disease.^{4,8,9} Guidelines for Care for Atopic Dermatitis from the American Academy of Dermatology (2004) recommend treatment with topical corticosteroids as the standard of care in AD.^{4,9} Complications associated with topical corticosteroid use, including striae, atrophy and tachyphylaxis, limit the long-term use of these agents. The calcineurin inhibitors, pimecrolimus and tacrolimus, are recommended to reduce the severity of symptoms associated with AD. Long-term (>1 year) safety for these agents is unknown and concerns regarding immunosuppression and malignancy

limit their use. Emollients, tar, and antihistamines (topical and systemic) are listed as steroid-sparing options for the prevention and treatment of AD.^{4,9}

Key Questions in the Oregon Report

- 1. Are there any differences in effectiveness between the calcineurin inhibitors?**
- 2. Are there any differences in safety between the calcineurin inhibitors?**
- 3. Are there any differences in safety or effectiveness between the calcineurin inhibitors in special populations?**

Clinical Efficacy³

The Oregon Evidence-based Practice Center at the Oregon Health & Science University conducted a literature search to identify comparative clinical trials evaluating the topical immune modulators in the treatment of atopic dermatitis or eczema in children and adults. Trials comparing pimecrolimus to tacrolimus or one of the active agents to placebo or topical corticosteroids were included in the review. Case reports, case series, and single-arm extension trials were excluded. Outcomes used to determine effectiveness included frequency of rebound flare-ups, reduction in symptom severity, duration of effectiveness, quality of life, and treatment failure. Overall, 47 trials were included in the analysis; including 3 systematic reviews, 2 head-to-head trials, 10 active-control trials (compared to topical corticosteroid agents), 17 placebo vehicle controlled trials, and a number of observational and quality-of-life trials.

Mild to Moderate Disease (OR)

Twelve studies, including two head-to-head studies, were available for evaluation of treatment of mild to moderate disease. The two head-to-head trials found tacrolimus 0.03% ointment was as effective as pimecrolimus 1% cream in treating atopic dermatitis and reducing pruritus (pooled relative risk, 1.19, 95% CI 0.98-1.45). An indirect analysis of 4 vehicle-controlled trials found no difference in effectiveness between tacrolimus and pimecrolimus (pooled relative risk 0.97, 95% CI 0.63-1.48). Overall, the available evidence suggests lower strength tacrolimus ointment and pimecrolimus cream are equally efficacious in treating atopic dermatitis in patients with mild to moderate disease.

Moderate to Severe Disease

Twenty-two studies, including one small head-to-head trial, were available for evaluation of treatment of moderate to severe disease. Clinical evidence comparing higher strength tacrolimus 0.1% ointment to pimecrolimus 1% cream in patients with moderate to severe disease reported conflicting evidence. In the small head-to-head trial of 139 patients with moderate to severe atopic dermatitis, tacrolimus 0.1% ointment was more effective in achieving treatment success (relative risk 1.83, 95% CI 1.13 to 2.96) and relieving pruritus (-3.7 cm compared with -2.0 cm, $P \leq 0.01$) than pimecrolimus 1% cream at 6 weeks. Indirect comparison of 3 tacrolimus trials and 1 pimecrolimus trial demonstrates no statistically significant differences in treatment success or change in pruritus score. Limited evidence comparing lower strength tacrolimus 0.03% ointment to pimecrolimus cream also showed no statistically significant differences in achieving treatment success

or improving pruritus scores. Overall, the available evidence suggests similar rates of efficacy in improving treatment success rates and disease symptoms between the topical immune modulators in moderate to severe atopic dermatitis.

Maintenance or prevention (24 to 52 weeks)

No head-to-head trials comparing tacrolimus to pimecrolimus in maintenance or preventative therapy are available. No tacrolimus trials were long in duration and indirect comparative assessments could not be conducted. Five pimecrolimus vehicle-controlled trials are available for evaluation. Of these, one trial evaluated pimecrolimus therapy in adults and four in infants and children. Three trials evaluated patients with mild to moderate disease and 2 trials evaluated patients with moderate to severe disease. Four of the pimecrolimus trials demonstrated efficacy in favor of pimecrolimus cream in preventing flares and reducing topical steroid use over 24 to 52 weeks. Overall, no evidence is available for topical tacrolimus therapy in the maintenance or prevention of atopic dermatitis. Evidence for pimecrolimus in the maintenance or prevention of atopic dermatitis suggests improved efficacy compared to placebo.

Safety³

In general, the topical immune modulators are well tolerated. The most frequent adverse events reported with topical immune modulator therapy include application site reactions (burning, stinging, erythema, and irritation). In the two head-to-head trials, both total withdrawal rate and treatment-related withdrawal rate were not significantly different between both strengths of tacrolimus (0.03%, 0.1%) ointment and pimecrolimus 1% cream. Indirect meta-analysis demonstrated similar rates of adverse events between the agents. Application site reactions, such as burning and stinging, were reported more frequently in patients treatment with immune modulators than patients treated with placebo vehicle or topical corticosteroids (49-52% compared with 29-35%). In addition, total withdrawal rates were slightly higher in the tacrolimus and pimecrolimus treatment groups compared to the topical steroid treatment groups in 4 active-control trials.

More serious adverse events may be associated with long-term topical immune modulator therapy. Both topical calcineurin inhibitors have a Food and Drug Administration (FDA) Black Box Warning for rare cases of malignancy (including skin and lymphoma) associated with topical calcineurin inhibitor therapy. The warning states treatment with topical calcineurin inhibitors is limited to short-term and intermittent treatment using the minimum amount necessary. Good-quality, long-term evidence evaluating serious harms associated with topical immune modulator therapy is lacking. One small observational study reported a low risk of the development lymphoma in patients with up to 4 years exposure of topical immune modulator therapy. There is also insufficient evidence evaluating the risk of serious viral skin infections with tacrolimus and pimecrolimus therapy and none of the clinical trials evaluated in the Oregon Review reported skin atrophy, telangiectasia, or adrenal suppression with topical calcineurin inhibitor use.

Special Populations³

Overall, no comparative clinical evidence in subgroup populations based on age, gender, race, and comorbidities for tacrolimus and pimecrolimus is available for evaluation. Most subgroup analyses were performed for either tacrolimus or pimecrolimus in vehicle-controlled trials and no significant differences in treatment effect between gender, age or white and multiracial (black, Asian, Hispanic) patients were found.

2013 Update

One systematic review and one comparative analysis published since the Oregon Report are available for evaluation.^{10, 11} Topical pimecrolimus was compared to other topical treatments for eczema in one systematic review published in 2009.¹⁰ Thirty-one randomized controlled trials, involving over 8000 patients, were included in the analysis. Pimecrolimus therapy was significantly more efficacious and well-tolerated than cream base vehicle in short-term (<6 weeks) and long-term (>6 weeks) trials. Pimecrolimus therapy was less efficacious than treatment with either topical tacrolimus or topical corticosteroid therapy according to the investigators' global assessment. In addition, more patients withdrew from pimecrolimus therapy due to lack of efficacy compared to other active treatment groups. No differences in adverse events were reported between treatment groups.

A review of three randomized control trials comparing tacrolimus ointment to pimecrolimus cream was published in 2010.¹¹ A total of 347 adult and pediatric patients were included in the analysis. Topical tacrolimus was significantly more efficacious and well-tolerated than topical pimecrolimus according to the Eczema Area and Severity Index score, Investigator's Global Atopic Dermatitis Assessment, and patient assessment ($p = 0.0002$). No differences in adverse events were reported between treatment groups.

Summary

Pimecrolimus and tacrolimus are two topical calcineurin inhibitors currently available for use in the US. Topical calcineurin inhibitors are indicated in the treatment of atopic dermatitis. The Oregon Drug Class Review on the Topical Calcineurin Inhibitors was published in 2008. According to the review, the two agents are more effective than placebo and demonstrate similar rates of safety and efficacy in the treatment of atopic dermatitis in adult and pediatric patients. Two reviews of comparative clinical evidence published after the Oregon Report demonstrate superiority for topical tacrolimus compared to topical pimecrolimus. No differences in safety were reported between the agents in the Oregon Report or in any of the reviews following the Oregon Report. Overall, both topical pimecrolimus and tacrolimus are effective in the treatment of atopic dermatitis in pediatric and adult patients. Some evidence suggests topical tacrolimus may be more efficacious than topical pimecrolimus. In general, topical calcineurin inhibitor use should be limited to short-term and intermittent treatment using the minimum amount necessary.

References

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Appendix

Table 1 taken from the Oregon Report³

Table 1. Characteristics of tacrolimus and pimecrolimus

Scientific name	Tacrolimus	Pimecrolimus
Brand	Protopic®	Elidel®
Chemical structure	Macrolide	Ascomycin derivative
Manufacturer	Astellas Pharma	Novartis
Approval date	December 8, 2000	December 13, 2001
Country	US, Canada	US, Canada
Dose	0.03%, 0.1%	1%
How supplied	Ointment	Cream
	Children (2 to 15 years): 0.03% Adults: 0.03%, 0.1%	Children (2 to 15 years) and Adults: 1%
FDA Indication	Indicated as <i>second-line therapy</i> for the short-term and noncontinuous chronic treatment of <i>moderate to severe</i> atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable. Not indicated for children younger than 2 years of age.	Indicated as <i>second-line therapy</i> for the short-term and noncontinuous chronic treatment of <i>mild to moderate</i> atopic dermatitis in unimmunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. Not indicated for use in children less than 2 years of age.
Black box warning	Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including pimecrolimus and tacrolimus. Therefore, continuous long-term use of topical calcineurin inhibitors in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.	
Precautions	Should be avoided on malignant or premalignant skin conditions. Malignant or premalignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), can present as dermatitis.	
Contraindications	Contraindicated in individuals with a history of hypersensitivity to tacrolimus or pimecrolimus or any of the components of the cream or ointment.	
Mechanism of action	The mechanism of action of tacrolimus in atopic dermatitis is not known. Tacrolimus has been shown to inhibit T-lymphocyte activation by first binding to intracellular protein macrophilin-12 (also known as FKBP-12). A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as IL-2 and gamma interferon). Tacrolimus also inhibits transcription of genes encoding IL-3, IL-4, IL-5, GM-CSF, and TNF- α , all of which are involved in the early stages of T-cell activation. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils, and to down regulate the expression of Fc ϵ RI on Langerhans cells.	The mechanism of action of pimecrolimus in atopic dermatitis is not known. Pimecrolimus has been shown to bind with high affinity to macrophilin-12 (also known as FKBP-12) and inhibit calcineurin. As a consequence, it inhibits T cell activation by blocking transcription of early cytokines. In particular, nanomolar concentrations of pimecrolimus inhibit synthesis of IL-2 and interferon gamma (Th1-type) and IL-4 and IL-10 (Th2-type) cytokine synthesis in human T cells. In addition, pimecrolimus prevents release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE.

Abbreviations: GM-CSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; TNF, tumor necrosis factor.