2011

Is Topical 1% Pimecrolimus Cream an Effective Treatment for Rosacea?

Lauren Sloan
Philadelphia College of Osteopathic Medicine, LaurenSl@pcom.edu

Is Topical 1% Pimecrolimus Cream an Effective Treatment for Rosacea?

Lauren E. Sloane, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 17, 2010

ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not topical 1% pimecrolimus cream is an effective treatment for rosacea.

STUDY DESIGN: Review of three English language primary studies published between 2007 and 2008.

DATA SOURCES: Randomized, controlled, investigator-blind clinical trials comparing topical 1% pimecrolimus application to either placebo cream or an untreated portion of the face were found using OVID, MEDLINE, and Cochrane Databases.

OUTCOMES MEASURED: Rosacea severity and improvement. Rosacea severity was assessed using the Rosacea Severity Score, set forth by the National Rosacea Society Expert Committee, which classifies the severity of erythema, papules, pustules, edema, and telangiectasia on a scale of 0 (no symptoms) to 3 (severe symptoms). Subjective severity scores were assigned using a visual analog scale (VAS) to assess rosacea severity on a scale of 0 (clear) to 5 (very severe). Rosacea severity was also assessed using a Subjective Severity Assessment (0-100 scale) and an investigators' global assessment of erythema, papules, and total inflammatory lesions.

RESULTS: Dichotomous data from the Karabulut et al. study did not show the use of topical 1% pimecrolimus cream to result in statistically significant improvement in rosacea severity, as measured by the Rosacea Severity Score, when compared to placebo cream. Dichotomous data presented by Lee et al. did not show statistically significant improvement in rosacea severity, as measured by investigators' global assessment of erythema and papules. Dichotomous data from Weissenbacher et al. did not show statistically significant improvement in severity of clinical rosacea signs (erythema, papules, scaling, and pustules) as measured by the Rosacea Severity Score and the Subjective Severity Score after use of topical 1% pimecrolimus cream.

CONCLUSIONS: Dichotomous data presented by Karabulut et al., Weissenbacher et al., and Lee et al. did not show the application of topical 1% pimecrolimus cream to cause statistically significant improvement in rosacea severity. Based on this finding, all three studies indicate that topical 1% pimecrolimus cream is not more efficacious in improving rosacea severity when compared to placebo cream or an untreated portion of the face.

KEY WORDS: Rosacea, Pimecrolimus, Elidel

INTRODUCTION

Rosacea is a common, chronic inflammatory disease affecting the face that occurs primarily between the ages of thirty and fifty. Rosacea has both a neurovascular presentation, as evidenced by erythema, telangiectasia, and flushing, as well as an acneiform presentation, manifested by the presence of papules and pustules. In addition to the neurovascular and acneiform components, certain forms of rosacea have a glandular presentation involving hyperplasia of the nasal soft tissue known as rhinophyma. Common sites of rosacea distribution are on the cheeks, nose, and chin. Rosacea is characterized by periods of remissions and relapses which are treated symptomatically, to varying degrees of success, with different topical and systemic medications and therapies.[5]

In terms of clinical relevance to Physician Assistants in practice, rosacea is a prevalent condition that is likely to be encountered by practitioners in almost all primary care settings. It is estimated that fourteen million Americans have rosacea. While the number of primary care office visits associated with rosacea each year has not be formally analyzed in the medical literature, the chronic nature of rosacea, as well as the tendency for the condition to flare and remit over an adult's lifetime, is likely associated with recurrent patient visits. Long term treatment for chronic rosacea flares can also be a costly endeavor for the patient. One study by Thomas et al. found the financial cost of standard topical rosacea medications, systemic antibiotics, isoretinoin, and topical immunomodulators to be significant, ranging from $60.90 per success using metronidazole 1% gel once daily to $152.25 per success using azelaic acid 20% cream twice daily. Furthermore, these cost estimations do not include the additional expense of office visits to the dermatologist or other primary care provider. Laser treatment for rosacea is

often considered to be a cosmetic procedure and is therefore not commonly covered by insurance, resulting in notable out-of-pocket cost for the patient.[6]

The current standard of treatment for rosacea is topical 0.75% to 1% metronidazole creams, lotions, and gels applied once daily. Topical 1% clindamycin, in the same vehicle forms, can be used twice daily if metronidazole is not tolerated. In patients who only exhibit a partial response to topical antibiotic treatment, sulfur-sodium sulfacetamide-containing topical treatments may be used, as well as topical benzoyl peroxide for control of persistent pustular presentations. When topical therapy proves inefficacious, systemic therapies such as tetracycline 250-500 mg orally twice daily on an empty stomach may be used. Cases that are refractory to tetracycline may be aided by the use of oral minocycline or doxycycline 50-100 mg daily to twice daily.[5]

It is known that patients with rosacea often report exacerbation of rosacea symptoms with ingestion of spicy food, hot drinks, or alcohol, exposure to sunlight, exposure to extreme heat or cold, exercise, and during emotional periods. These activities are thought to cause the release of vasoactive mediators, resulting in vasodilation and the subsequent flushing associated with rosacea. A concrete, definitive etiopathogenesis for rosacea remains unknown at the current time, but pathophysiology research on the mechanics of rosacea suggests that immune or inflammatory factors such as eicosanoids, nitric oxide, and proinflammatory cytokines may play a pivotal role in rosacea symptomatology.[2] Based on this pathophysiological research, it has been hypothesized that anti-inflammatory and/or immunomodulating agents may be effective methods of treating rosacea.

Pimecrolimus is a calcineurin inhibitor and ascomycin macrolactam derivative that has immunomodulatory and anti-inflammatory effects. Commercially marketed under the name

Elidel, pimecrolimus is administered in the form of a 1% concentration topical cream. Topical 1% pimecrolimus cream works by selecting target T-lymphocytes and mastocytes, and inhibiting the production and release of inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-1, IL-2, IL-3, IL-4, IL-5, and IL-10.[2] In addition, topical 1% pimecrolimus is thought to function by blocking expression of chemomodulators that activate inflammatory T-cells in the body. Based on the known immunomodulating effects of pimecrolimus and the suspected underlying inflammatory and immunological pathophysiology of rosacea, topical pimecrolimus has been investigated as a potential treatment to reduce the incidence and severity of rosacea symptoms.

OBJECTIVE

The objective of this systematic review is to determine whether or not, "Is topical 1% pimecrolimus cream an effective treatment for rosacea?" A 2007 Cochrane Review of existing medical literature found topical 1% pimecrolimus cream to be significantly more effective than vehicle/placebo cream in the short term (<6 weeks) and long-term (>6 weeks) treatment of atopic dermatitis.[1] Although the pathophysiology of both rosacea and atopic dermatitis is thought to involve inflammatory and immunologic responses in T-cells, a meta-analysis of the efficacy of 1% pimecrolimus on rosacea has not been performed to date.

METHODS

A detailed search was completed by the author, using the search engines MEDLINE, OVID, and the Cochrane Database of Systematic Reviews. The key words, "Pimecrolimus," "Elidel," and "Rosacea" were used in combination to search for English-language articles. All of the resulting articles from the search were published in peer-reviewed journals between 1996 and 2010. The articles were selected based on importance of the outcomes to the patient (i.e. Patient

Oriented Evidence that Matters, or POEMS). Studies that were included were those that were randomized, controlled studies, published after 1996 focusing on a patient oriented outcome for adults aged 18 or older. Excluded studies were those in which the subjects were under the age of 18 and/or articles that were published before 1996. Randomized control trials (RCTs) were searched and selected based on the evidence that they focused on a patient population over 18 years of age that had been clinically diagnosed with rosacea, as well as the evidence that the studies involved application of topical 1% pimecrolimus as the treatment intervention. Furthermore, only those articles that compared topical 1% pimecrolimus to the use of placebo cream or to the use of no cream at all were included in this review. Based on the aforementioned criteria, three investigator-blind, randomized, placebo-controlled clinical trials were selected and included in this review. Table 1 delineates the demographics of the studies included in this review.

The study by Karabulut et al. reported statistics based on the Rosacea Severity Score, Visual Analog Scale (VAS), and Total Rosacea Severity Score (i.e. sum of individual Rosacea Severity Scores). The study by Lee et al. reported statistics based on a VAS assessment as well as the investigators' global assessment of erythema, papules, total inflammatory lesion count, and proportion of affected areas after 1, 2, 4, and 8 weeks and at baseline visit. The study by Weissenbacher et al. reported statistics based on the Rosacea Severity Score, a VAS Subjective Severity Score, and a Dermatology Life Quality Index (DLQI). For this review, selected dichotomous data from the Karabulut et al. and Weissenbacher et al. studies were interpreted into numbers needed to treat (NNT), while selected dichotomous data reported in the Lee et al. study were interpreted into numbers needed to harm (NNH).

Table 1. Characteristics of Studies Included in Systematic Review of the Efficacy of 1% Topical Pimecrolimus Cream Versus Placebo in the Treatment of Rosacea							
Study	Type	# of Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Karabulut, 2008 (1)	RCT (Investigator blind, randomized placebo controlled, split-face trial)	25	23-60 y.o.	Adult rosacea patients w/ bilateral papulopustular rosacea lesions	No extrafacial/ocular lesions, pregnant or breastfeeding, hypersensitivity to Elidel, viral or malignant disease, severe ocular rosacea or severe flare-up reaction in the past, previous rosacea tx 4 weeks prior entry of into study	N/A	Split-face application of 1% topical pimecrolimus cream (Elidel) for 4 weeks
Lee, 2008 (2)	RCT (Investigator blind, randomized, split-face trial)	18	Mean age 43.9 y.o. +/- 15.9 yrs.	At least 18 y.o., diagnosed with steroid-induced rosacea, previous hx of topical corticosteroid use for >2 weeks	No severe skin lesions requiring systemic tx other than antihistamine, acne vulgaris, debilitating medical disorders, use of HRT or oral corticosteroid, previous facial laser tx or surgical procedures 4 weeks prior to study enrollment, pregnant and lactating women	3	Use of 1% pimecrolimus cream on one half of the subject's face for 2 weeks (2x/day) followed by 6 weeks of 1% pimecrolimus cream application on the whole face (2x/day)
Weissenbacher, 2007 (3)	RCT (Randomized vehicle-controlled, double-blind trial)	40	36-76 y.o.	Pts with papulopustular rosacea	Specific exclusion guidelines were not delineated in paper	N/A	Daily application of a 1% pimecrolimus cream to the face B/L for tx of papulopustular rosacea

OUTCOMES MEASURED

The primary outcomes measured in all three studies were rosacea severity and improvement as quantified by the National Rosacea Society Expert Committee's Rosacea Severity Score system.[8] The Rosacea Severity Score assesses the severity of four key rosacea symptoms (i.e. erythema, papules, scaling, pustules) and rates them on a scale of 0 to 3, with 0 representing a complete absence of symptoms, 1 representing mild symptoms, 2 representing moderate symptoms, and 3 representing severe symptoms. Karabulut et al. also examined Total Rosacea Severity Score by analyzing the sum of various individual severity assessments.

All three studies involved Subjective Severity Assessment of rosacea using some form of a Visual Analog Scale (VAS). Karabulut et al. performed a subjective severity assessment of each subject's rosacea severity using VAS on a 0 to 10 mm scale. The study by Lee et al. had each subject conduct his/her own VAS assessment of the severity of his/her facial lesions and pruritus on a 0 to 100 scale (where 0 is absence of symptoms and 100 is severe). Weissenbacher et al. performed a subjective severity assessment using a VAS on a scale of 0 mm to 100 mm (where 0 is "no skin changes" and 100 is "very severe skin changes"). Rosacea severity and improvement were also measured via an assessment of erythema, papules, total inflammatory lesion count, and proportion of affected areas after 1, 2, 4, and 8 weeks and at baseline visit via Investigators' Global Assessment of Severity.[3]

RESULTS

The results, as they pertain to the measured outcomes, were presented primarily as dichotomous data in each of the three studies and analyzed as dichotomous data. While three participants withdrew from the Lee et al. study, and one participant withdrew from the Karabulut et al. study, the data from each study were presented as an intention to treat analysis.

Karabulut et al. reported rates of rosacea severity improvement as 0.5416% and 0.125% in the experimental and control group respectively. This difference was not statistically significant as p-values were not provided for this data. The relative benefit increase (RBI) was calculated to be 3.33%, while the absolute benefit increase (ABI) was calculated as 0.4166%. Based on these calculations, the number needed to treat (NNT) for this study was 2.4 using topical 1% pimecrolimus cream. This is clinically important in that, for every 2.4 patients treated with 1% pimecrolimus cream, 1 more patient had improved rosacea as compared to the control group (Table 2).

Weissenbacher et al. reported rates of rosacea severity improvement as 0.32% and 0.37% in the experimental and control group respectively. This difference was not statistically significant as p-values were not provided for this data. The relative benefit increase (RBI) was calculated to be 0.135%, while the absolute benefit increase (ABI) was calculated to be -0.05%. Based on these calculations, the number needed to treat (NNT) for this study was -20.0. This is clinically significant in that, for every 20 patients treated with the 1% pimecrolimus cream, 1 patient fewer had improved rosacea compared to the control (Table 2).

Lee et al. reported rates of rosacea severity improvement as 0.2% and 0.0% in the experimental and control group respectively. The difference was not statistically significant as p-values were not provided for this data. The relative risk increase (RRI) was calculated to be 0.0%, while the absolute risk increase (ARI) was calculated to be 0.2%. Based on these calculations, the number needed to harm (NNH) for this study was 5. This is clinically important because for every 5 patients treated with 1% pimecrolimus cream, 1 more patient had worsened rosacea symptoms as compared to the control group (Table 3). The study by Lee et al. was unique in that it specifically analyzed the effect of 1% topical pimecrolimus on steroid-induced

rosacea as opposed to idiopathic rosacea. It is also important to note that there were pieces of

continuous data discussed in the Lee et al. study (i.e. results of the investigator's global

assessment of erythema and papules, lesion counts of papules and pustules, and percentage of

facial areas involved measured at 1, 2, 4, and 8 weeks from baseline) that may suggest a

significant therapeutic role for 1% pimecrolimus in the treatment of steroid-induced rosacea.

However, the aforementioned pieces of continuous data could not be converted to dichotomous

data for the purpose of this review and were therefore not included in the analysis.

Table 2. Efficacy of Topical 1% Pimecrolimus in Improvement of Rosacea - NNT					
Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)
Karabulut, 2008	0.125%	0.5416%	3.33%	0.4166%	2.40
Weissenbacher, 2007	0.37%	0.32%	0.135%	-0.05%	-20.0*

* This negative value for NNT indicates that for every 20 patients treated with the experimental treatment (i.e. topical 1% pimecrolimus cream), 1 patient fewer had improved rosacea compared to the control. P-values and 95% CI were not provided for the dichotomous data presented in the studies.

Table 3. Efficacy of Topical 1% Pimecrolimus in Improvement of Rosacea - NNH					
Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Numbers Needed to Harm (NNH)
Lee, 2008	0%	0.2%	0%	0.2%	5*

* P-values and 95% CI were not provided for the dichotomous data presented in the study.

In terms of adverse effects encountered by subjects in the studies included in this

analysis, Lee et al. reported that 20% of subjects (i.e. three of the fifteen subjects involved in the

study) experienced side-effects like burning or stinging at the site of pimecrolimus application or

hyperpigmentation of an initially inflamed area of skin prior to pimecrolimus application.

Notably, no patients participating in the Lee et al. study reported an exacerbation of their rosacea

signs after application of the pimecrolimus. Side effects associated with treatment in the

Karabulut et al. study included mild and transient local irritation of the skin. Three patients in this study complained of transient stinging/burning/itching of the skin lasting 5 to 10 minutes after application of pimecrolimus during the first 5 to 7 days of the trial. Two patients complained of lip dryness during the trial. One patient ultimately withdrew from the study at the second week due to a "severe flare up reaction."[2] In the Weissenbacher et al. study, one patient complained of facial skin tightness and another patient complained of pruritus.

DISCUSSION

Pimecrolimus is a topical calcineurin inhibitor and immunomodulator. Clinically indicated for the treatment of atopic dermatitis by the U.S. Food and Drug Administration, pimecrolimus acts by penetrating the inflamed epidermal layer of the skin and inhibits the transcription and activation of proinflammatory cytokines including IL-2, IL-4, IL-10, and interferon gamma. This ultimately prevents the immunologic activation of T-cells. Adverse reactions to the drug include headache, burning at the site of application, and nasopharyngitis. According to the U.S. Black Box warning, topical calcineurin inhibitors have been associated with rare cases of skin malignancy and lymphoma, and should therefore be used only in short-term and intermittent treatment regimens with application to limited surface areas. Further, pimecrolimus is not recommended for use in children under the age of 2 years. Contraindications for use of the drug include hypersensitivity to pimecrolimus or any other components in its formulation.[4]

The studies chosen for analysis had several limitations. Each study assessed the qualitative severity of rosacea via the National Rosacea Society Expert Committee guidelines. However, due to the uncontrollable triggers of rosacea (i.e. stress, sunlight, menstruation, hot environments), the therapeutic impacts of the pimecrolimus may have been altered, which in turn

may have affected the rosacea severity of each patient and his/her Rosacea Severity Score. In the study by Lee et al., subjects were given the opportunity to assess their own rosacea severity via a visual analog scale. Based on the subjective nature of self-assessment, these visual analog scale scores may not have been well-standardized or controlled. In the Lee et al. study, three subjects experienced adverse effects (i.e. burning, stinging) and one patient complained of postinflammatory hyperpigmentation, and three subjects dropped out early in the study for reasons including noncompliance, loss of follow-up, and protocol violations. This change in subject enrollment may have impacted the accuracy of the study outcomes. The study by Weissenbacher et al. also utilized a placebo cream for the control group that may have had emollient properties to reduce skin scaling and dryness. The therapeutic effects of this placebo vehicle cream may have caused improvement in rosacea severity symptoms, thereby impacting the significance of the rosacea severity improvement in the experimental group.

CONCLUSION

The studies reviewed demonstrate that the topical application of 1% pimecrolimus cream is not an effective treatment for rosacea in that it is not shown to cause a statistically significant improvement in the severity of rosacea. There were multiple methods used to assess rosacea severity in each of the studies analyzed, including the Rosacea Severity Score set forth by the National Rosacea Society Expert Committee, Visual Analog Scores with differing numerical scales and means of assessment (i.e. self-assessment and investigator assessment), and an investigator assessments of global rosacea severity. The use of such a variety of assessment tools makes it difficult to do side-by-side comparisons of results (i.e. improvement in rosacea severity) from multiple studies as rosacea severity is qualitatively and quantitatively analyzed by differing parameters. Future studies evaluating the efficacy of pimecrolimus in reduction of

rosacea symptoms should use one central method of assessment, such as the Rosacea Severity Score set forth by the National Rosacea Society Expert Committee, to evaluate results. Future investigations may be warranted in the investigation of the effects of 1% pimecrolimus cream on steroid-induced rosacea as compared to the effects of 1% pimecrolimus cream on rosacea occurring in non-steroid users. In addition, future tests may focus experimental methods on the split-face method of experimental control, so as to evaluate the effects of pimecrolimus versus placebo on the same face with the same baseline severity of rosacea symptoms.

REFERENCES

1. Ashcroft DM, Chen LC, Garside R, Stein K, Williams HC. Topical pimecrolimus for eczema. *Cochrane Database Syst Rev.* 2007;(4):CD005500. DOI:10.1002/14651858.CD005500.pub2.
2. Karabulut AA, Izol Serel B, Eksiolgu HM. A randomized, single-blind, placebo-controlled, split-face study with pimecrolimus cream 1% for papulopustular rosacea. *J Eur Acad Dermatol Venereol.* 2008;22(6):729-734.
3. Lee DH, Li K, Suh DH. Pimecrolimus 1% cream for the treatment of steroid-induced rosacea: an 8 week split-face clinical trial. *Br J Dermatol.* 2008;158(5):1069-1076.
4. Lexi-Comp ONLINE [database online]. Hudson, OH: Lexi-Comp Inc; 2010. http://online.lexi.com. Accessed November 21, 2010.
5. McPhee SJ, Papadakis MA, eds. Current Medical Diagnosis & Treatment 2010. 49th ed. New York, NY: McGraw-Hill Medical; 2010.
6. Thomas K, Yelverton CB, Yentzer BA, et al. The cost-effectiveness of rosacea treatments. *J Dermatol Treatment*. 2009;20(2):72-75.
7. Weissenbacher S, Merkl J, Hildebrandt B, et al. Pimecrolimus cream 1% for papulopustular rosacea: a randomized vehicle-controlled double-blind trial. *Br J Dermatol*. 2007;156(4):728-732.
8. Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2004;50(6):901-912.