American Journal of Therapeutics 14, 442–446 (2007)

Reliéva, a *Mahonia Aquifolium* Extract for the Treatment of Adult Patients With Atopic Dermatitis

Howard Donsky, MD[1]* and Don Clarke, MD[2]

This clinical study was conducted to determine the efficacy and safety of Reliéva cream in adult patients with atopic dermatitis (eczema). This was an open-label trial in 42 patients with atopic dermatitis treated for 12 weeks with Reliéva cream (a homeopathic product containing Psorberine, a proprietary *Mahonia aquifolium* extract). Efficacy and safety was assessed using Eczema Area and Severity Index scores and a Subject Reported Evaluation of Treatment. The results showed significant ($P < 0.05$) improvements with respect to Eczema Area and Severity Index scores by comparison to subjects' baseline scores. In addition, subjects responding to a posttreatment evaluation questionnaire indicated a substantial benefit when rating effectiveness, itching, and appearance as a result of using the study preparation. Reliéva cream appears to be a safe and effective treatment for adult patients with atopic dermatitis (eczema).

Keywords: mahonia aquafolium, Psorberine, atopic dermatitis, eczema, Reliéva

INTRODUCTION

Atopic dermatitis is a common health problem that affects 15 million people in the United States.[1] It usually begins in infancy, affecting 10% to 17% of children.[2] Atopic dermatitis will improve in approximately 50% of these children by the time they are between 5 and 15 years of age. Other children will have some form of the disease throughout their lives.[3]

Atopic dermatitis is a pruritic, inflammatory skin disorder that is characterized by itching, eczema with lesions, dry skin, thickening of the skin, and increase in skin markings.[2] The disease often has a remitting/flaring nature that can be made worse by social, environmental, and biologic triggers.

The goal of treatment is to prevent flares. This will decrease the physical discomfort of the disease, the itching and scratching of the skin that leads to skin damage, and the social embarrassment associated with skin lesions. Current treatments consist of both oral and topical preparations, including antihistamines, steroids, immunosuppressive agents, emollients, and calcineurin inhibitors.[4–6] However, issues of effectiveness, cost, and side effect profiles limit the use of these medications.[4]

The ideal medication for the treatment of atopic dermatitis would be safe and effective for use in both children and adults with no side effects. The long-term safety of last two US Food and Drug Administration-approved medications, tacrolimus (Protopic) and pimecrolimus (Elidel), has been questioned by reports of malignancies in children.[2] There is a need for an effective and well-tolerated topical treatment for patients with atopic dermatitis. Reliéva (Apollo Pharmaceutical Inc., Oldsmar FL) topical cream (a homeopathic product) appears to be a good alternative treatment.

The active ingredient of Reliéva is Psorberine, a proprietary extract from a plant (*Mahonia aquifolium)* formulated in Novasome, a patented liposome delivery system. Psorberine has been shown to have antibacterial and antiinflammatory properties through inhibiting interleukin-8, interleukin-1β, and tumor necrosis factor-1 (Apollo Pharmaceuticals files, unpublished data). Psorberine is currently marketed as

[1]*Dermatology and Cosmetic Center of Rochester, Rochester, NY; and* [2]*Lakeside Medical Association, Glendate, CA, and Providence Holy Cross Hospital, Mission Hills, CA.*
This study was supported by Apollo Pharmaceuticals, Inc., Clearwater, Florida.
**Address for correspondence: Dermatology and Cosmetic Center, 1665 East Ridge Road, Rochester, NY 14621. E-mail: MDSkinCare@aol.com*

Reliéva, an over-the-counter homeopathic product in the United States and a natural product in Canada. Furthermore, the efficacy and safety of Reliéva in patients with mild to moderate psoriasis has been demonstrated in a 200-patient, placebo-controlled study.[7] All the known properties of *Mahonia aquifolium* and the superior pharmacologic profile of Psorberine suggested that Reliéva might also be effective in atopic dermatitis.

This article reports the results of an open-label clinical study conducted to assess the efficacy and safety of Reliéva a topical cream in adult patients with atopic dermatitis (eczema). The hypothesis to be tested was that a group of patients treated with Reliéva topical cream for 12 weeks would achieve a greater improvement in the Eczema Area and Severity Index (EASI) scores of patients with atopic dermatitis as compared with their own scores at baseline.

MATERIALS AND METHODS

Study population

The study population included adults between the ages of 18 and 80 years who had atopic dermatitis on 10% or less of their body and were in good overall health. Patients using topical atopic dermatitis medications in the past 2 weeks; systemic (oral, intravenous, intramuscular, or intradermal) medications for atopic dermatitis in the past 28 days; or any steroids, immunosuppressive medications, and cyclooxygenase-2 antiinflammatory drugs were excluded from this study. Pregnant, lactating women, women not taking medically approved birth control, or women planning to become pregnant within 30 days of the start of the study were also excluded from this study.

Patients were recruited from clinical private practices, the local college student population, local newspaper advertisements, and by word of mouth. Eligibility was assessed through telephone prescreening. Patients who passed the prescreening were invited to participate in the study.

Study design

Participation began with an initial visit (day 0), which included completion of all consent forms, a screening health questionnaire, and a physical examination. Study medications were provided and patients were instructed on the application of a thin layer of Reliéva to infected areas on the skin three times per day. Patients selected to participate in the study were provided with instructions on completing the required forms. Additional visits were scheduled at 4, 8, and 12 weeks after the initiation of Reliéva treatment. At each visit, the physician evaluated the treatment area and completed an EASI form[8] for each patient. At 12 weeks, all patients completed a Subject Reported Evaluation of Treatment form and a ''side effect'' form.

Study outcomes

Baseline demographics, including sex, age at the start of the study, treatment information, and severity of disease, were tabulated. All follow-up data were compared with baseline and tabulated as change from baseline.

Eczema area and severity index

EASI is a standard form that is routinely used to evaluate atopic dermatitis.[8]

Subject reported evaluation of treatment

The Subject Reported Evaluation of Treatment form asked participants to rate the effectiveness of the treatment for itching, appearance of the rash, state of mind, social activities, work activities, and sleep. The possible ratings for each question were ''much worse,'' ''worse,'' ''same,'' ''better,'' and ''much better.''

Study preparations

The study preparation was Reliéva. Its active ingredient is Psorberine, a proprietary extract from *Mahonia aquifolium* 10% cream formulated in an emulsion cream base, for topical administration. Psorberine was prepared by Canadian Custom Packaging, Toronto, Ontario, Canada, and the cream was manufactured by IGI, Inc., Buena NJ.

Statistical analysis

SAS programming language (SAS Institute, Cary NC) was used for all analyses. EASI scores were calculated and reported as mean, standard deviation, and median (range) at baseline, 4, 8, and 12 weeks of follow up. Demographic and baseline EASI were stratified by dropout status and compared using Wilcoxon rank sum and Fisher exact test P values. Significance of EASI change from baseline to 4, 8, and 12 weeks of follow up were assessed using paired t test values. The Subject Reported Evaluation of Treatment scores were reported as percentages in each category at each time point. Significance was determined as $P < 0.05$.

RESULTS

This study enrolled 42 patients. Of these, 12 patients dropped out: right after their baseline visit, three after the 4-week follow-up visit, and one after the 8-week

follow-up visit. Per-protocol data were available for the 30 patients who completed the study and its demographic characteristics are shown in Table 1. This study group contained similar numbers of females and males with a median age of 54 years and a mean EASI score of 2.01 (moderate).

The mean (standard deviation) and median (range) for EASI scores at baseline, 4, 8, and 12 weeks for all patients in the per-protocol group (n = 30) are shown in Table 2. The EASI scores for patients with at least one follow-up measure (n = 34 at baseline and 4 weeks, n = 31 at 8 weeks, and n = 30 at 12 weeks) are also included (all patients, Table 2). The EASI scores at baseline were similar for both groups, indicating moderate levels (2.0–2.2) of eczema. With treatment, the EASI scores decreased by 75%, 91%, and 97% after 4, 8, and 12 weeks of treatment, respectively (Table 2). These statistically significant ($P < 0.0001$) decreases in EASI scores are shown in Figure 1.

At the 12-week follow-up visit, patients completed a Subject Reported Evaluation of Treatment form. The frequencies of response ratings (much worse, worse, same better, or much better) are shown in Table 3. Compared with no treatment, 93% of patients rated the effectiveness of the treatment as ''better'' or ''much better,'' 83.4% rated itching as ''better'' or ''much better,'' and 93.3% rated the appearance of rash as ''better'' or ''much better.'' No patients indicated a score of ''much worse'' and only one person (3.3%) indicated ''worse'' in response to any of the questions.

Four people reported side effects. Three patients (one female and two males) reported itching and/or burning when using the cream and dropped out of the study at weeks 1.5, 2, and 5. A fourth patient left the study because of an ear infection that was unrelated to the study preparation. All of the other people dropped out as a result of noncompliance with the medication.

Table 1. Demographic and baseline characteristics of patients in the study group.

Parameter	Study group (n = 30)
Age (years)	
Mean (SD)	49.2 (15.4)
Median (range)	54 (21–71)
Gender	
Female	17 (56.7%)
Male	13 (43.3%)
EASI* at baseline	
Mean (SD)	2.01 (1.54)
Median (range)	1.5 (0.5,6.4)

SD, standard deviation; EASI, Eczema Area and Severity Index.
*EASI scores are rated as follows: 3, severe; 2, moderate; 1, mild; and 0, none.[8]

Table 2. Eczema area and severity index* (EASI) scores for all patients in the study.

Time point (N)	Mean (SD)	Median (range)	Comparison to baseline paired *t* test *P* value
Per protocol			
Baseline 30	2.01 (1.54)	1.50 (0.5–5.6)	
4 weeks 30	0.50 (0.84)	0.20 (0–4.0)	<0.0001
8 weeks 30	0.16 (0.43)	0.0 (0–2.0)	<0.0001
12 weeks 30	0.06 (0.18)	0.0 (0–0.8)	<0.0001
All patients†			
Baseline 34	2.16 (1.52)	1.70 (0.5–6.4)	
4 weeks 34	0.58 (0.90)	0.25 (0–4.0)	<0.0001
8 weeks 31	0.19 (0.46)	0.0 (0–2.0)	<0.0001
12 weeks 30	0.06 (0.18)	0.0 (0–0.8)	<0.0001

SD, standard deviation.
*EASI scores are rated as follows: 3, severe; 2, moderate; 1, mild; and 0, none.[8]
†Three subjects had follow up only at 4 weeks and one subject had follow up at 4 and 8 weeks only.

DISCUSSION

This study was designed to determine the efficacy and safety of Reliéva for the treatment of adult patients with atopic dermatitis (eczema). Patients treated with Reliéva showed significant improvement in atopic dermatitis during both short- (4 weeks) and long- (12 weeks) term periods of time. Significant improvement was measured by comparing EASI scores before treatment (baseline) with EASI scores at 4, 8, and 12 weeks of treatment and by patient responses to a posttreatment evaluation questionnaire. Patient

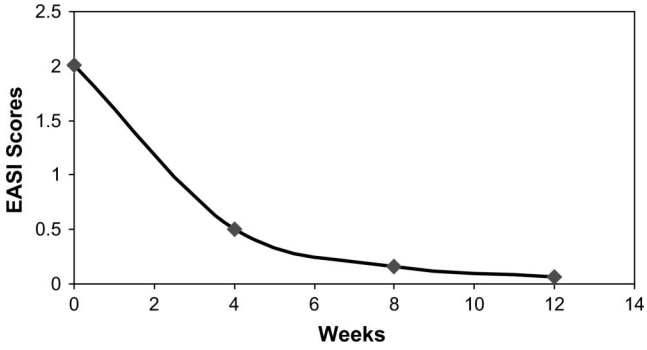

FIGURE 1. The responses of Eczema Area and Severity Index (EASI) scores of patients treated with *Mahonia aquifolium* for 12 weeks.

Table 3. Patient responses to the subject reported evaluation of treatment form completed after 12 weeks of treatment with *Mahonia aquifolium.*

Rate each question	Much worse	Worse	Same	Better	Much better	Better and much better
Effectiveness of the treatment	0 (0%)	0 (0%)	2 (6.7%)	9 (30%)	19 (63.3%)	28 (93.3)
Itching from treatment	0 (0%)	0 (0%)	5 (16.7%)	11 (36.7%)	14 (46.7%)	25 (83.4)
Appearance of rash from treatment	0 (0%)	1 (3.3%)	1 (3.3%)	10 (33.3%)	18 (60%)	28 (93.3)
Your state of mind from treatment	0 (0%)	1 (3.3%)	12 (40%)	7 (23.3%)	10 (33.3%)	17 (66.6)
Your social activities from treatment	0 (0%)	1 (3.3%)	22 (73.3%)	3 (10%)	4 (13.3%)	7 (23.3)
Your work activities from treatment	0 (0%)	1 (3.3%)	20 (66.7%)	5 (16.7%)	4 (13.3%)	9 (30%)
Sleep from treatment	0 (0%)	1 (3.3%)	16 (53.3%)	7 (23.3%)	6 (20%)	13 (43.7)

responses to the posttreatment questionnaire indicated substantial benefit when rating effectiveness, itching, and appearance as a result of using the study preparation. Few side effects were reported; none of them were serious.

Mahonia aquifolium is known for its antiinflammatory properties[9,10] and has been used for the treatment of psoriasis.[11,12] The present study preparation used was Reliéva. The active ingredient is Psorberine, a proprietary extract from the natural compound *Mahonia aquifolium* formulated in Novasome, a patented liposome delivery system. This formulation was shown in a placebo-controlled trial to be effective and well tolerated for the treatment of patients with mild to moderate plaque psoriasis.[7] This study demonstrates the application of Psorberine, the proprietary extract from *Mahonia aquifolium,* for adult patients with atopic dermatitis.

The beneficial effects of Psorberine can be explained by its pharmacologic profile determined by recent in vitro experiments (Apollo Pharmaceuticals files, unpublished data). It was found that Psorberine inhibits the release of the proinflammatory cytokines interleukin-8, tumor necrosis factor-α, and interleukin-1β as well as the inflammatory cytokine interleukin-2. This effect of Psorberine may contribute to its antiinflammatory activity. It also inhibits the chemotaxis of T cells toward chemokines, an activity that is important for any antiinflammatory compound. Furthermore, Psorberine may promote the proliferation of T cells but may sequester them away from the sites of inflammation. Therefore, Psorberine is a potent antiinflammatory molecule. Because T cells are not the sole inflammatory cells, it remains to be seen whether Psorberine has any effect on other inflammatory cells such as neutrophils, dendritic cells, T helper 1, and natural killer cells. The effect on other cell types is a topic for future investigation.

Current treatments for eczema consist of both oral and topical preparations, including antihistamines, steroids, and immunosuppressive agents.[4–6] However, issues of effectiveness, cost, and side effect profiles limit the use of these medications. Recently, calcineurin inhibitors (tacrolimus, Protopic; pimecrolimus, Elidel) became available for the treatment of inflammatory skin disease.[2] These inhibitors do not have the risks of topical corticosteroids and were believed to be safe and effective. However, long-term safety has been questioned by reports of malignancies in children.[2]

In contrast to these medications, this report suggests that Reliéva is efficacious and safe for the treatment of adult patients with atopic dermatitis. This is a natural product formulated in a liposome system that can help millions of people worldwide, including approximately 15 million people in the United States alone who have atopic dermatitis.[1]

ACKNOWLEDGMENTS

We thank Global Clinicals, Inc., and its staff for performing this study, Laurie LaBree, MS, for the statistical evaluation, and Andrea Gwosdow, PhD, for assistance in preparing the manuscript.

REFERENCES

1. Williams H, Robertson C, Stewart A, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. *J Allergy Clin Immunol*. 1999;103:125–138.

2. Ellis CN, Kahler KH, Grueger J, et al. Cost effectiveness of management of mild-to-moderate atopic dermatitis with 1% pimecrolimus cream in children and adolescents 2–17 years of age. *Am J Clin Dermatol*. 2006;7:133–139.
3. What is eczema? A comprehensive eczema resource at *EczemaNet*. Available at: www.skincarephysicians.com/eczemanet/whatis.html#difference. Accessed April 25, 2007.
4. Williams HC. Atopic dermatitis. *N Engl J Med*. 2005;352:2314–2324.
5. Kass DA, Sinert R, Ghidorzi AJ. Dermatitis, atopic, E-Medicine from *Web MD*, June 5, 2006. Available at: www.emedicine.com/EMERG/topic130.htm#section~follow-up. Accessed April 25, 2007.
6. Krafchik BR. Atopic dermatitis, E-Medicine from *Web MD*, April 7, 2006. Available at: www.emedicine.com/derm/topic38.htm#section~workup. Accessed April 25, 2007.
7. Bernstein S, Donsky H, Gulliver W, et al. Treatment of mild to moderate psoriasis with Relieva, a *Mahonia aquifolium* extract—a double-blind, placebo-controlled study. *Am J Ther*. 2006;13:121–126.
8. Hanifin JM, Thurston M, Omoto M, et al. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. *Exp Dermatol*. 2001;10:11–18.
9. Mueller K, Ziereis K. The antipsoriatic *Mahonia aquifolium* and its active constituents; I. Pro- and antioxidant properties and inhibition of 5-lipoxygenase. *Planta Med*. 1994;60:421–424.
10. Bezakova L, Misik V, Malekova L. Lipoxygenase inhibition and antioxidant properties of bisbenzylisoquinoline alkaloids isolated from *Mahonia aquifolium*. *Pharmazie*. 1996;51:758–761.
11. Muller K, Ziereis K, Gawlik I, The antipsoriatic *Mahonia aquifolium* and its active constituents; II. Antiproliferative activity against cell growth of human keratinocytes. *Planta Med*. 1995;61:74–75.
12. Augustin M, Andrees U, Grimme H, et al. Effects of *Mahonia aquifolium* ointment on the expression of adhesion, proliferation, and activation markers in the skin of patients with psoriasis. *Forsch Komplementarmed*. 1999;(Suppl 2):19–21.