

Treatment of Mild to Moderate Psoriasis with Reliéva, a *Mahonia aquifolium* Extract—A Double-Blind, Placebo-Controlled Study

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Psoriasis is usually treated with local and systemic medications that have varying degrees of efficacy and safety profiles. We investigated the efficacy and safety of an alternative treatment from natural sources, *Mahonia aquifolium*, for the management of mild to moderate psoriasis. Two hundred subjects participated in a randomized, double-blind, placebo-controlled study using either the topical cream Reliéva (a homeopathic product containing a proprietary *M. aquifolium* extract) or control (placebo) twice a day for 12 weeks. Efficacy and safety were assessed using the Psoriasis Area Severity Index (PASI) and the Quality of Life Index (QLI) questionnaires at different times throughout the 12-week study. The PASI was evaluated by the physician at the beginning (week 0) and end (week 12) of the study. The QLI was assessed by patients at weeks 0, 4, 8, and 12. The results indicate statistically significant ($P < 0.05$) improvements in PASI and QLI in the *Mahonia*-treated group, compared with the control group. The side effects reported were infrequent, $< 1\%$ and minor; the most frequent side effects were rash, a burning sensation when applying the cream, and clothing stain. These data indicate that Reliéva, a proprietary form of *M. aquifolium*, is effective and well tolerated in patients with mild to moderate psoriasis.

Keywords: psoriasis, *Mahonia aquifolium*, clinical trial, efficacy, safety

INTRODUCTION

Psoriasis is a common skin disorder that affects more than 4.5 million people in North America.¹ Treatment of psoriasis is problematic because the severity and distribution of psoriatic plaques varies immensely.² Localized psoriasis can often respond to topical medications, of which steroid and vitamin D analogue creams such as calcipotriol, anthralin, coal tar, and ultraviolet light treatments are the most common. More generalized involvement of the skin may require systemic treatments with retinoids, immunosuppressives, PUVA, or biologic medications.³

M. aquifolium (Barberry, Oregon grape, Berberis) belongs to the berberidaceae family and grows wild in Europe, North and South America. *M. aquifolium* was initially used in American folk medicine as an oral medication for inflammatory skin diseases, including psoriasis and syphilis.⁴ The root and wood of *M. aquifolium* contain many isoquinoline alkaloids, of which berberine is the best characterized. The mechanism of action of the alkaloids in suppressing the inflammatory response is poorly understood; however, laboratory studies have suggested that the alkaloids may¹ inhibit DNA synthesis by blocking reverse transcriptase,² inhibit lipoxygenase and lipid peroxidation, and/or³ inhibit the cyclooxygenase-2 pathway through the reduction of prostaglandin E2. Topical application of *M. aquifolium* has been shown by immunohistochemistry to reduce the inflammatory and keratinocyte hyperproliferation markers typical of psoriasis. Several open and placebo-controlled clinical trials have supported the effectiveness of *M. aquifolium* in the treatment of psoriasis.⁵ In these

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trials, between 70% and 81% of patients improved on the basis of physician and patient assessment. Adverse events upon application of *M. aquifolium* ointment included burning and itching sensations.

The purpose of this 12-week randomized, double-blind, placebo-controlled clinical study was to assess the efficacy and safety of the topical cream, *M. aquifolium* (Reliéva), in patients with mild to moderate plaque psoriasis. We hypothesized that patients with mild to moderate psoriasis who were treated with *M. aquifolium* topical cream would achieve a greater improvement in the signs and symptoms of psoriasis compared with the control (placebo) group applying the vehicle for the same period of time. The results indicate a beneficial response in those patients using *M. aquifolium* topical cream for the treatment of psoriasis.

MATERIALS AND METHODS

Study design

A randomized, placebo-controlled, double-blind, clinical trial of Reliéva (containing a proprietary *M. aquifolium* extract known as Psorberine) was conducted at 6 sites in the United States and Canada between August 2004 and February 2005.

Patient eligibility was assessed through a telephone prescreening visit before entry into the study. During the initial visit (week 0), subjects were evaluated for eligibility, and informed consent and bill of rights forms were obtained. In addition, all subjects completed a screening health questionnaire and a brief physical examination. Qualified participants (n=200) were randomized into 1 of 2 treatment groups: active (*M. aquifolium*, 10%; n=100) or placebo (control excipients, n=100). The active product group received active ingredients (*M. aquifolium*, 10%), and the placebo product group received the same formulation without active ingredient. Subjects in both groups applied the product twice a day to the selected area. The selected area was a 4.0 cm × 4.0 cm area of skin that typified the patient's psoriasis. This area was selected by the investigator, using a precut template.

Study preparations

The active group was treated with a study preparation that contained Reliéva (IGI, Inc, NJ; Canadian Custom Packaging, Canada), a homeopathic product. Its active ingredient is a highly concentrated, proprietary extract of *M. aquifolium* 10% known as Psorber-

ine, in Novasome, a patented liposome preparation from IGI, Inc, and formulated in an emulsion cream base for topical administration. Matching placebo preparations were prepared with excipients but no active components (IGI, Inc, NJ; Canadian Custom Packaging, Canada).

Study protocol

The study protocol required 4 patient visits, including the initial visit. At the initial visit (week 0), a Psoriasis Area Severity Index (PASI) evaluation was performed by the physician and each patient completed the Quality of Life Index (QLI) Questionnaire. Participants then returned at 4, 8, and 12 weeks after the start of treatment. At each visit, patients completed the QLI. The physician conducted a second PASI evaluation at week 12. Study medications were provided at the time of visits to the study site, and compliance was monitored via telephone calls. Assistance was provided as needed.

PASI

The PASI evaluation is used to indicate the severity of psoriasis and was selected as the primary efficacy end point. A higher score indicates more active disease.⁶

PASI was evaluated using a 4.0 cm × 4.0 cm template on a selected area of skin that was typical of the patient's psoriasis involvement. The selected area was evaluated on the basis of the amount of skin in the template affected (0% to 100%). Erythema (redness), infiltration (thickness), and desquamation (scaliness) were assessed as none, minimal, mild, moderate, or severe and translated into a number (0 to 4) for each time point. The PASI score was calculated using the following equation: PASI = % affected × (erythema + infiltration + desquamation). Maximum PASI = 100% × (4 + 4 + 4) = 12.

QLI questionnaire

The QLI questionnaire was selected as a secondary end point and used to assess the patient's quality of life and adverse events. It included 12 questions that reflect impairment in the quality of life of the patient during the previous month. Each question was quantified from "not at all" to "very much" using a number from 0 to 10. The maximum possible score of 120 is correlated with very active disease, and the minimum score of zero indicated no quality of life impact.

The change in QLI was calculated at the end of study by subtracting the week 12 score from the QLI

score at baseline. A decreasing score indicated a positive treatment benefit.

Study participants

All male or female participants between the ages of 18 to 80 years, in good overall health with current mild to moderate plaque psoriasis covering less than 10% to 15% of the body, were eligible for this study. Subjects were recruited from the clinical private practice setting, local college student population, local newspaper ads, and word of mouth.

Exclusion criteria included painful or inflamed lesions, intertriginous psoriasis, extremely hypertrophic lesions, and severe psoriasis. Patients using topical psoriasis medications within the past 2 weeks, and those taking systemic (oral, intravenous, intramuscular, or intradermal) medications for psoriasis in the past 28 days, those using steroids, immunosuppressive medications, and cyclooxygenase-2 anti-inflammatory drugs, and those using any medication conflicting with the product ingredients were also excluded from this study. Women planning to become pregnant within 90 days of the start of the study and pregnant or lactating women or women not taking medically approved birth control were also excluded.

Statistical analysis

Mean and standard deviations (SD), median, and minimum and maximum changes (min and max) were reported for continuous variables. Frequencies and percentages were reported for categorical variables. Independent sample *t* tests were used to compare differences between groups for continuous variables, and Fisher exact tests were used to test between group differences for categorical variables. The difference in PASI and QLI scores, pretreatment

and posttreatment, was performed by subtracting the score determined posttreatment from the score at baseline. The change in score was analyzed using the Wilcoxon rank sum test.

The accepted level of significance for all tests was $\alpha = 0.05$. All analyses were performed using SAS (SAS Institute, Cary, NC). A per protocol analysis and an intent-to-treat analysis were performed.

RESULTS

Patient demographics and baseline disease characteristics

The 200 patients (100 active patients, 100 control patients) who entered the study constituted the intent-to-treat population. Of these, 171 patients (97 active group, 74 control group) completed the study, had no significant protocol deviation, and constituted an evaluable population used for the per-protocol analysis.

Intent-to-treat population

The demographics and patient characteristics (age, sex, PASI, QLI) of the intent-to-treat population indicate no differences among the 2 treatment groups (Table 1). Mean PASI scores (6.93 ± 2.6 in the active group; 6.85 ± 2.9 in the control group) and QLI scores (60.9 ± 32 in the active group; 56.6 ± 31 in the control group) were comparable among the 2 treatment groups. Eighty-one patients (41%) had a PASI score between 0 and 6, and 119 (59%) had a PASI > 6.

Discontinuation of treatment

The intent-to-treat population that entered the study consisted of 100 patients in the active group and 100

Table 1. Patient demographics and baseline disease characteristics.

	Active (N = 100)	Placebo (N = 100)	* <i>P</i>
Mean age, years (SD)	48.3 (± 13.7)	48.3 (± 14.0)	0.49 [†]
Sex			
Males, N (%)	51 (51%)	42 (42%)	0.26 [‡]
Females, N (%)	49 (49%)	58 (58%)	
Psoriasis area severity index at baseline (mean \pm)	6.93 (± 2.6)	6.85 (± 2.9)	>0.1 [§]
Quality of life index at baseline (mean \pm)	60.9 (± 32)	56.6 (± 31)	>0.1 [§]

[†]Independent samples *t* test *P* value.

[‡]Fisher exact test *P* value.

[§]Wilcoxon rank sum *P* value.

^{||}N = 99; 1 patient in the active treatment group did not have baseline scores available for analysis and was excluded from all analyses.

Table 2. PASI scores intent-to-treat population.*

		N	Active	N	Placebo	P [†]
PASI	Baseline	100	6.93 (\pm 2.6)	100	6.85 (\pm 2.9)	0.0095
	Average [‡]	100	-3.39 (3.59 SD)	100	-0.09 (4.85 SD)	
	Median [‡]	100	-3 (-11/3 min/max)	100	0.0 (-12/12 min/max)	

*Using all randomized patients; 3 in the active and 26 in the placebo group received worst-case scores.

[†]Wilcoxon rank sum *P* value.

[‡]Reduction from baseline at week 12.

Table 3. QLI intent-to-treat population.*

		N	Active	N	Placebo	P [†]
QLI	Baseline	99	60.2	100	54.7	> 0.1
	Average [‡]	99	23.6 (31.3 SD)	100	-3.88 (41.71 SD)	
	Median [‡]	99	20 (-98/98 min/max)	100	7.5 (-113/81 min/max)	0.0001

*Using all randomized patients; 1 patient in the active treatment group did not have baseline scores available for analysis and was excluded from all analyses.

[†]Wilcoxon rank sum *P* value.

[‡]Reduction from baseline.

patients in the control group. The most frequent causes of discontinuation were no response, which occurred in 2 patients in the active group and 11 in the control group; product caused burning, which occurred in 1 patient in the control group; rash developed in 1 patient in the control group. Two patients in the control group moved out of state and 11 patients in the control group discontinued therapy because of noncompliance. One subject in the active group died for non-treatment-related reasons.

Efficacy analysis

Intent-to-treat population

An intent-to-treat analysis was performed on all patients who entered the study. For PASI, a score of 12 (worst case score) was imputed at the 12-week visit for all patients who dropped from the study. Of the 100 patients in each group who began the study, 3 patients in the active group and 26 patients in the placebo group received worst-case scores. In this analysis, a statistically ($P=0.0095$) significant improvement from baseline was observed between the active and control groups for PASI (Table 2).

A similar analysis was performed on the quality of life assessments (QLI) measured at baseline and at the end of study (week 12). One patient in the active treatment group did not have baseline scores and was excluded. The average QLI change score in the active group was 25.5 (SD=28.8) and 15.1 in the placebo

group (SD=22.5). Statistical analysis of the data indicates a statistically ($P=0.0001$) significant improvement from baseline for the active group compared with the control group for QLI. This indicates that the active group and the placebo group were not similar with respect to the change in QLI from the beginning to the end of the study (Table 3).

Taken together, the PASI and QLI data clearly indicate a greater clinical improvement in patients receiving Reliéva compared with patients receiving placebo.

Evaluable population (per-protocol analysis)

Ninety-seven active patients and 74 placebo patients were included in the per-protocol analysis.

The average PASI change in the active group was -3.58 (SD=3.47, median = -3, and min = -11, max = 3) and -2.22 in the placebo group (SD=3.25, median = -1.6, and min = -11.9, max = 4). Testing the median PASI change between active and placebo patients gives a significant *P* value of 0.0095 using a 2-sided Wilcoxon rank sum test, indicating that the active group and the placebo group are not similar with respect to the outcome.

A similar analysis was performed on the quality of life assessments (QLI) measured at baseline and at the end of study (week 12). The average QLI change score in the active group was 25.5 (SD=28.76, median = 21, and min = -41, max = 98) and 15.1 in the placebo group (SD=22.45, median = 12.5, and min = -31,

max = 81). Testing the median change scores between active and placebo patients gives a significant *P* value of 0.0186 using a 2-sided Wilcoxon rank sum test, indicating that the active group and the placebo group are not similar with respect to the change in QLI score from baseline to end of study.

Side effects

No significant side effects were reported by either group. One patient in the active group complained of staining from the cream. In the control (placebo) group, 1 patient reported a rash and 2 others reported a burning sensation when applying the cream.

DISCUSSION

Psoriasis is a difficult disorder to treat because of the severity and distribution of psoriatic plaques varying greatly, and some of the side effects of the current medications. The present study was conducted to determine if the use of Reliéva, a proprietary formulation of *M. aquifolium*, a natural preparation from a plant source, could provide effective treatment for psoriasis without serious side effects. The study found that patients with mild to moderate psoriasis who were treated with Reliéva topical cream achieved a significantly greater improvement in the signs and symptoms of psoriasis compared with the control group.

One reason for the effectiveness of Reliéva may be found from the study by Augustin.⁷ This author used immunohistochemistry to stain psoriatic plaques treated with either topical application of *M. aquifolium* or conventional treatment (dithranol). The study demonstrated marked reduction in the inflammatory and keratinocyte hyperproliferation markers typically seen in psoriasis. This author⁷ reported that both treatments were effective, although greater reductions were seen in dithranol-treated plaques.

Similar reports of the clinical effectiveness and safety of *M. aquifolium* for mild to severe psoriasis are found in the literature in placebo-controlled, open clinical trials and observational studies.^{5,7-11} All of these studies reported improvement in psoriatic plaques treated with *M. aquifolium* cream. A recent review of all of these studies was conducted by Gulliver and Donsky.⁵

Our study reports similar results from a double-blind, placebo-controlled clinical trial. The efficacy of Reliéva was measured by changes in the PASI and QLI scores. For the PASI score, the Reliéva-treated active group showed a significantly greater reduction

in the PASI score compared with the control (placebo) group. A similar greater reduction was reported for the QLI scores for the active compared with the control group.

The significant improvements of the active group might also be reflected in the dropout rate of the study. More patients in the control (placebo) group dropped out of the study because of lack of response and noncompliance than the active treatment group (control group: 22 patients; active group: 3 patients).

The tolerability of the active *M. aquifolium* (Reliéva) topical cream was excellent. The side effects reported were minor and reported in few patients. The most frequent side effects were rash, a burning sensation when applying the cream, and clothing stain. Clothing stains were removed with a simple wash.

Similar side effects were reported by Weisenauer and Ludtke,¹⁰ who evaluated the safety of *M. aquifolium* cream and concluded that *M. aquifolium* was a potent and safe therapy for moderately severe cases of psoriasis. A low side effect profile was also reported by others.^{7,9}

CONCLUSIONS

This randomized, double-blind, placebo-controlled study demonstrated that Reliéva topical cream is a safe and effective treatment for mild to moderate plaque psoriasis. This was demonstrated by the statistically significant improvement of the signs and symptoms of mild to moderate plaque psoriasis compared with patients receiving placebo. Reliéva is well tolerated when applied to the affected areas twice a day for 12 weeks.

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