Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis

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Background: A nasal spray containing the antiallergy agent olopatadine hydrochloride is being developed for the treatment of seasonal allergic rhinitis (SAR).

Objective: To evaluate the safety and efficacy of 2 concentrations of olopatadine nasal spray vs placebo in patients with SAR.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled study. After a 3- to 21-day placebo run-in, 565 patients aged 12 to 80 years were randomized to receive 0.4% or 0.6% olopatadine or placebo, 2 sprays per nostril twice daily for 2 weeks. Patients evaluated morning and evening reflective and instantaneous nasal symptoms (sneezing, stuffy nose, runny nose, and itchy nose, which compose the total nasal symptom score [TNSS]) and ocular symptoms and completed the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

Results: Olopatadine spray (0.4% and 0.6%) was significantly superior to placebo for percentage change from baseline in overall reflective ($P = .004$ and $P < .001$, respectively) and instantaneous ($P = .02$ and $P = .003$, respectively) TNSSs. Also, 0.6% olopatadine was significantly superior to placebo for reducing the reflective and instantaneous assessments of sneezing, runny and itchy nose, and itchy eyes; the instantaneous assessments of watery eyes; and the overall and all 7 domain scores of the RQLQ ($P < .05$). Olopatadine spray exhibited a safety profile comparable with that of placebo.

Conclusions: Olopatadine nasal spray (0.4% and 0.6%) provided statistically significant improvements in allergic rhinitis symptoms compared with placebo regarding TNSSs (reflective and instantaneous) and in quality-of-life variables in patients with SAR. Olopatadine nasal spray administered twice daily was safe and well tolerated in adolescents and adults.

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INTRODUCTION

Olopatadine hydrochloride is being developed in a nasal spray formulation for the treatment of seasonal allergic rhinitis (SAR). This disease is an allergen-induced inflammatory response, with an estimated incidence of 10% and 30% in the general population.[1] On exposure to a specific antigen, allergic patients exhibit a hypersensitivity response that may take minutes, or even days, to manifest. Signs and symptoms associated with SAR include sneezing, nasal congestion, rhinorrhea, ocular itching and watering, paranasal pressure, and fatigue.[2]

Olopatadine is an antiallergy agent that inhibits mast cell mediator release and possesses histamine H_1 receptor antagonist activity.[3] An ophthalmic formulation of 0.1% olopatadine solution is approved in the United States and Canada as Patanol and in Europe as Opatanol (both from Alcon Research Ltd, Fort Worth, TX) for treating the signs and symptoms of allergic conjunctivitis. The ocular pharmacology of olopatadine has been extensively reviewed.[3,4] An oral form, 2.5- and 5-mg tablets, has been approved as Allelock (Kyowa Hakko Co Ltd, Tokyo, Japan) in Japan for the treatment of allergic rhinitis, chronic urticaria, atopic dermatitis, prurigo, cutaneous pruritus, psoriasis vulgaris, and erythema exudativum multiforme.[5] The pharmacokinetics, pharmacology, and clinical trials of the oral dosage have also been reviewed.[5] Olopatadine (10 mg/kg by mouth) has also been shown to inhibit the nasal symptoms of allergic rhinitis in sensitized guinea pigs by inhibiting the release of histamine and possibly peptide leukotrienes into the nasal cavity.[6]

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This article describes the first multicenter clinical trial designed to evaluate the safety and efficacy of 0.4% and 0.6% olopatadine in the form of a nasal spray (443 and 665 μg, respectively, of olopatadine hydrochloride per spray) vs placebo spray in the treatment of patients with SAR.

MATERIALS AND METHODS

Patients

Enrolled patients were 12 years or older with a history of SAR for at least the preceding 2 years. All the patients demonstrated allergic sensitivity to a prevalent fall allergen as defined by a positive reaction on skin prick testing (a wheal size ≥3 mm greater than the diluent) or intradermal testing (a wheal size ≥7 mm greater than the diluent). The study protocol was approved by an institutional review board, and an informed consent document was signed by all the patients before participation in the study. Women of childbearing potential were enrolled if they agreed to use an acceptable method of contraception. Patients who had aberrant nasal anatomy, abnormal prestudy laboratory test results, severe obstructing congestion, recent sinusitis, or abnormal 12-lead electrocardiographic or other abnormal cardiovascular values were excluded from study participation. Medication washout times were 30 days for systemic, inhaled, and ocular corticosteroids; 14 days for intranasal corticosteroids, systemic antibiotics and antihistamines, leukotriene inhibitors, anticholinergic agents, and systemic antibiotics; 7 days for ocular antiallergy agents; 3 days for oral decongestants and nonsteroidal anti-inflammatory agents; and 1 day for nasal and ocular saline. Patients who had undergone previous immunotherapy were required to be stable for 30 days before and throughout the trial.

Study Design

This was a 2-week, multicenter (33 sites across the United States), randomized, double-blind, parallel-group, placebo-controlled, 3-armed study of 2 concentrations of olopatadine nasal spray and a placebo spray conducted between August 19 and November 27, 2002. Beginning with the placebo run-in period and continuing to the study exit, patients recorded in a diary the symptom severity of their itchy nose, runny nose, stuffy nose, sneezing, itchy eyes, and watery eyes using a 4-point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe).[7] The sum of scores for the 4 nasal symptoms was defined as the total nasal symptom score (TNSS). Patients evaluated their symptoms as experienced at that moment (instantaneous) and in the hours since the last dose of study medication was taken (reflective), in the morning before any other activity, and at bedtime. Each patient also completed the allergy-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[8–10] at the treatment randomization and exit visits.

During the single-blind placebo spray run-in period, patients had to have a minimum reflective TNSS of 36 of a possible 72 points on 3 of the 4 days prior to randomization to qualify for the double-blind treatment phase of the study. Patients were then randomized to receive 1 of 3 treatment regimens: two 100-μL sprays per nostril twice daily of 0.4% olopatadine nasal spray (total daily dose of 3.2 mg), 0.6% olopatadine nasal spray (total daily dose of 4.8 mg), or placebo (vehicle containing benzalkonium chloride, phosphates, edetate, povidone, sodium chloride, and water but no active ingredient) nasal spray (Alcon Research Ltd). After a week of study treatment, each patient was contacted by telephone to check protocol compliance, medication changes, potential adverse events, and diary completion. Patients returned after 2 weeks of double-blind therapy for an exit visit that included a physical examination, measurement of vital signs, laboratory analyses, completion of the RQLQ, and collection of diaries.

Statistical Methods

The primary statistical objective of this study was to demonstrate the statistical superiority of 0.4% and 0.6% olopatadine nasal sprays relative to placebo in the treatment of allergic rhinitis as evidenced by the percentage change from baseline in the TNSS. A Dunnett *t* test was used to compare changes from baseline between the olopatadine treatments and placebo for the primary and each of the secondary variables. This procedure was designed to test multiple treatments against a single control and, therefore, preserved statistical power in the presence of multiplicity.[11]

Primary and secondary conclusions were based on the intent-to-treat data set. Based on similar studies in the literature, a treatment difference of 12.5% in the TNSS change from baseline was assumed, with an approximated SD of 42%. With a projected 240 evaluable patients per group (N = 720), this study was predicted to have 90% power to detect a significant treatment difference between the olopatadine nasal sprays and placebo. All statistical tests were 2-sided, with $\alpha = .05$.

Efficacy. The primary efficacy variable was the percentage change from baseline in the reflective TNSS, defined as the average of the morning and bedtime reflective severity scores for the sum of the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing (averaged across all days). Secondary efficacy variables included the percentage change from baseline in the instantaneous TNSS, individual symptoms (ie, runny nose, itchy nose, sneezing, stuffy nose, watery eyes, and itchy eyes), and quality of life (QoL). Percentage change from baseline in the instantaneous TNSS was defined as the average of the morning and bedtime instantaneous (how the patient felt at that time) severity scores for the sum of the patients' assessments of symptoms (averaged across all days). All baseline scores were calculated using the appropriate measurements from the 3 highest days of the 4 days before randomization. These 3 days were chosen by calculating the average (mean of the awakening and bedtime assessments) for a given reflective or instantaneous symptom (TNSS or individual symptoms) for each day. The QoL was evaluated using the validated 28-item RQLQ (overall and by domain) of Juniper and Guyatt.[10] To minimize possible bias

Table 1. Demographic Characteristics by Treatment Group

Characteristic	0.6% Olopatadine group (n = 184)	0.4% Olopatadine group (n = 189)	Placebo group (n = 192)
Age, y			
Range	12–71	13–67	12–80
Mean ± SD	35.6 ± 12.6	34.6 ± 12.7	35.5 ± 13.9
Sex, F/M, %	65.8/34.2	61.4/38.6	58.3/41.7
Race, No. (%)			
White	138 (75.0)	147 (77.8)	142 (74.0)
African American	16 (8.7)	26 (13.8)	23 (12.0)
Hispanic	24 (13.0)	13 (6.9)	23 (12.0)
Asian	2 (1.1)	2 (1.1)	2 (1.0)
Other	4 (2.2)	1 (0.5)	2 (1.0)

from early dropouts, efficacy variables were based on an intent-to treat approach that included all patients with at least 1 postbaseline observation regardless of the length of therapy. An overall analysis was based on the mean change for each patient using available data and carrying that data forward.

Safety. A total of 845 patients were given placebo during a 3- to 21-day run-in period; 280 patients did not qualify for randomization. The remaining 565 patients were randomized: 184 (32.6%) received 0.6% olopatadine, 189 (33.5%) received 0.4% olopatadine, and 192 (34.0%) received placebo spray. Variables evaluated were adverse events, extent of exposure, nasal examination (significant anatomic abnormalities, evidence of infection, bleeding, and ulcerations of the mucosa), clinical laboratory (hematology, blood chemistry, and urinalysis), cardiovascular (pulse, systolic and diastolic blood pressure, and electrocardiograms), and physical examination (head/eye, ear, nose, and throat; neck; cardiovascular; pulmonary; abdomen; skin and extremities; neurologic; and lymph nodes).

RESULTS

Of 845 enrolled patients, 565 met the study criteria, were randomized to treatment, and were evaluable for the safety and intent-to-treat analyses. All the data presented in this article are from the intent-to-treat data set. The 3 treatment groups were similar in terms of demographic characteristics (Table 1). The average age was 35 years (range, 12–80 years). Males composed 38.2% of the patient group; 75.6% of the patients were white, 11.5% were African American, 1.1% were Asian, 10.6% were Hispanic, and 1.2% were of other races.

Primary Efficacy: Reflective TNSS

The 0.4% and 0.6% olopatadine treatments were statistically superior to placebo use for the mean change from baseline of the overall reflective TNSS ($P = .004$ and $P < .001$, respectively) (Table 2). The average percentage reduction in TNSS from baseline was 39.2% for patients who received 0.6% olopatadine, 35.8% for patients who received 0.4% olopatadine, and 27.0% for patients who received placebo.

Secondary Efficacy

Reflective assessments of individual symptoms. The 0.4% and 0.6% olopatadine treatments were statistically superior to placebo use in reducing the reflective evaluation of the severity of runny nose ($P = .046$ and $P < .001$, respectively), itchy nose ($P = .005$ and $P = .001$, respectively), and sneezing ($P < .001$ for both concentrations) (Table 2). Although the 0.4% and 0.6% olopatadine treatments were numerically more effective than placebo use (25.7% and 24.5% decrease, respectively, vs 22.0% for placebo) for the reflective evaluation of severity for stuffy nose, the differences were not statistically significant ($P = .70$ and $P = .85$, respectively) (Table 2). The 0.4% and 0.6% olopatadine treatments were also numerically superior to placebo use in reflective severity of itchy eyes (35.2% and 41.4% decreases, respectively, vs 30.2% for placebo) and watery eyes (44.3% and 46.7% decreases, respectively, vs 37.1% for placebo), but only the 0.6% treatment reached statistical superiority for itchy eyes ($P = .02$) (Table 2).

TNSS during the 2-week period by day. For each of the 14 days of treatment, 0.6% olopatadine was significantly superior to placebo for percentage change from baseline in reflec-

Table 2. Percentage Change From Baseline in the Reflective Assessments of Symptoms of Seasonal Allergic Rhinitis*

Variable	0.6% Olopatadine group	*P* value†	0.4% Olopatadine group	*P* value‡	Placebo group
TNSS	−39.2 ± 26.9	<.001	−35.8 ± 28.1	.004	−27.0 ± 27.8
Runny nose	−38.5 ± 32.0	<.001	−33.0 ± 36.4	.046	−24.9 ± 36.3
Stuffy nose	−24.5 ± 77.6	.85	−25.7 ± 30.1	.70	−22.0 ± 30.5
Itchy nose	−39.5 ± 32.5	.001	−38.1 ± 33.3	.005	−27.8 ± 34.0
Sneezing	−51.7 ± 32.4	<.001	−49.5 ± 37.6	<.001	−29.0 ± 51.7
Itchy eyes	−41.4 ± 41.6	.02	−35.2 ± 43.1	.41	−30.2 ± 40.9
Watery eyes	−46.7 ± 43.1	.05	−44.3 ± 40.2	.17	−37.1 ± 39.7

Abbreviation: TNSS, total nasal symptom score.
* Data are given as mean ± SD.
† The 0.6% olopatadine group vs the placebo group.
‡ The 0.4% olopatadine group vs the placebo group.

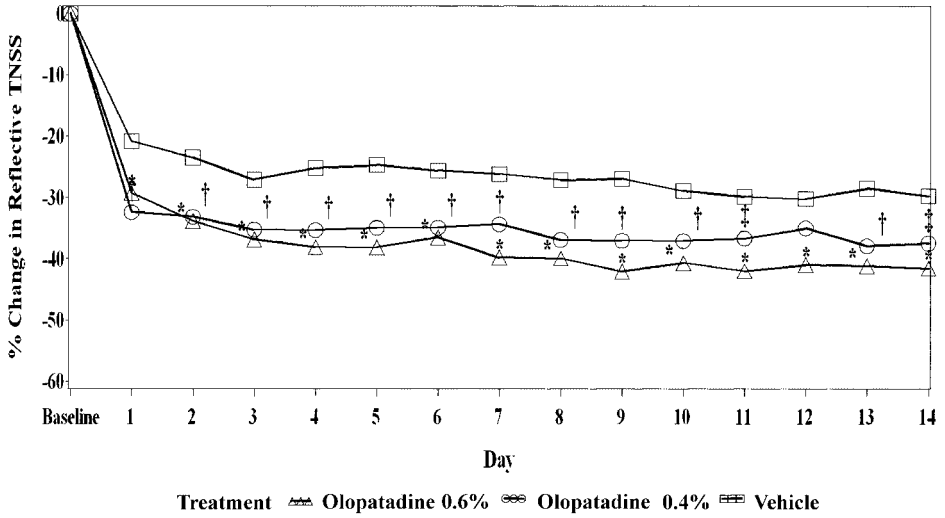

Figure 1. Intent-to-treat analysis of the percentage change in reflective total nasal symptom scores (TNSSs) by day and treatment. Asterisk indicates $P < .05$ for 0.6% olopatadine vs vehicle; dagger, $P < .05$ for 0.4% olopatadine vs vehicle; and double dagger, $P < .10$ for 0.4% olopatadine.

tive TNSS ($P < .05$); the 0.4% treatment reached significance ($P < .05$) for most days (Fig 1).

Instantaneous evaluation of the overall TNSS and individual symptoms. The 0.4% and 0.6% olopatadine treatments were statistically superior to placebo use for the percentage change from baseline in the overall instantaneous TNSS ($P = .02$ and $P = .003$, respectively) (Table 3). By instantaneous evaluation, 0.6% olopatadine treatment was significantly superior to placebo use for runny nose ($P = .009$), itchy nose ($P = .02$), sneezing ($P < .001$), itchy eyes ($P = .008$), and watery eyes ($P = .02$) but not for stuffy nose ($P = .32$) (Table 3). The 0.4% olopatadine treatment improvement was generally less than that noted for 0.6% olopatadine treatment; however, it was superior to placebo for instantaneous evaluation of all symptoms except stuffy nose ($P = .69$) and ocular symptoms ($P = .31$ for itchy eyes and $P = .44$ for watery eyes) (Table 3).

Quality of life. The 0.4% and 0.6% olopatadine treatments improved the overall RQLQ score from baseline significantly greater than placebo ($P = .02$ and $P < .001$, respectively) (Fig 2). The 0.6% olopatadine treatment was superior to placebo for all 7 domains: activities ($P < .001$), sleep ($P < .001$), non-nose/eye symptoms ($P = .004$), practical problems ($P < .001$), nasal symptoms ($P = .004$), eye symptoms ($P = .02$), and emotional aspects ($P = .001$). The 0.4% olopatadine treatment was superior to placebo for 4 of the 7 domains ($P < .05$) but did not reach significance on the sleep ($P = .13$), non-nose/eye symptoms ($P = .08$), and emotional ($P = .16$) subscales.

Safety Results

No serious adverse events, related or unrelated to therapy, were reported during the study. Nonserious adverse events in the overall safety populations were usually mild to moderate,

Table 3. Percentage Change From Baseline in the Instantaneous Assessments of Symptoms of Seasonal Allergic Rhinitis*

Variable	0.6% Olopatadine group	*P* value†	0.4% Olopatadine group	*P* value‡	Placebo group
TNSS	−33.3 ± 27.9	.003	−31.6 ± 27.6	.02	−23.6 ± 32.0
Runny nose	−32.5 ± 34.2	.009	−30.2 ± 34.3	.02	−14.9 ± 90.7
Stuffy nose	−22.7 ± 33.9	.32	−20.7 ± 29.2	.69	−18.4 ± 31.5
Itchy nose	−34.2 ± 33.6	.02	−33.8 ± 34.9	.02	−24.0 ± 43.8
Sneezing	−46.4 ± 46.7	<.001	−45.7 ± 41.8	<.001	−23.5 ± 77.2
Itchy eyes	−39.4 ± 36.2	.008	−32.8 ± 41.0	.31	−27.2 ± 43.7
Watery eyes	−44.0 ± 42.2	.02	−37.6 ± 43.9	.44	−32.5 ± 42.8

Abbreviation: TNSS, total nasal symptom score.
* Data are given as mean ± SD.
† The 0.6% olopatadine group vs the placebo group.
‡ The 0.4% olopatadine group vs the placebo group.

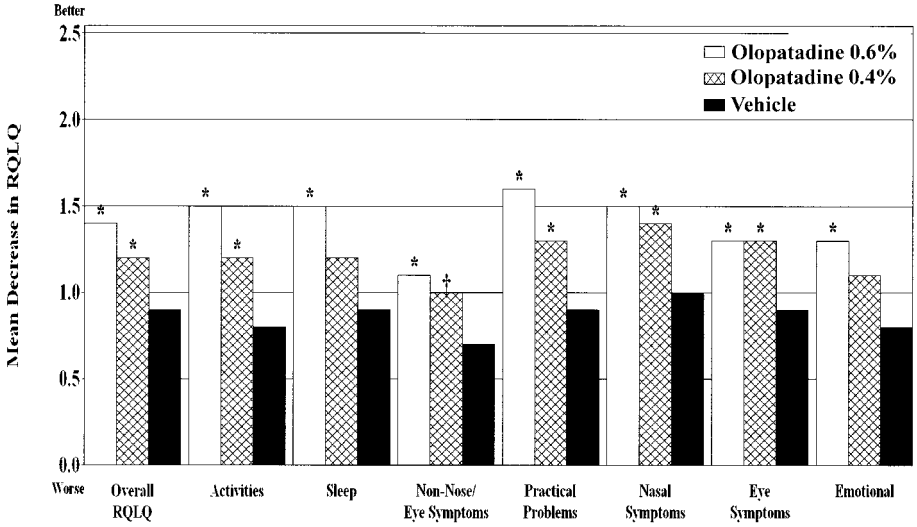

Figure 2. Intent-to-treat analysis of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) by domain and treatment. Asterisk indicates $P < .05$; dagger, $P < .10$.

usually resolved with or without treatment, and generally did not interrupt patient continuation in the study. Eleven patients discontinued the treatment phase of the study owing to adverse events (Table 4). Causality assessments revealed that only 4 of 11 of these patients' adverse events were related to therapy. No safety issues were identified and no treatment-related changes were observed in the laboratory test results of hematology, blood chemistry, and urinalysis. The evaluation of cardiovascular variables showed that olopatadine nasal spray administered twice daily was safe and well tolerated. There also were no clinically relevant mean or individual changes in physical (including nasal) examinations for any of the treatment arms during this study. The most common adverse event was bitter taste, and it seemed to be dose related (Table 5). The incidence of somnolence was negligible (0.5% for 0.4% and 0.6% olopatadine and 0% for placebo) (Table 5).

DISCUSSION

In this study, treatment with 0.4% and 0.6% olopatadine, 2 sprays per nostril twice daily, provided significant relief from allergy symptoms compared with placebo spray during the 2-week trial. In this clinical trial, the TNSS was defined as a combination score for the 4 major symptoms of allergic rhinitis: sneezing, runny nose, itchy nose, and stuffy nose. Use of the TNSS as the primary efficacy variable is appropriate for an allergic rhinitis study with the goal of assessing a medication's overall impact on the rhinitis symptoms

Table 4. Summary of 11 Patients Who Discontinued During the Randomized Treatment Phase Because of Nonserious Adverse Events

Patient age, y	Treatment	Coded adverse event	Outcome of event	CA
33	0.6% Olopatadine	Headache	Resolved w/Tx	R
57	0.6% Olopatadine	Sinusitis	Resolved w/Tx	R
33	0.6% Olopatadine	Pneumonia	Resolved w/Tx	NR
36	0.4% Olopatadine	Dizziness	Resolved wo/Tx	R
		Dyspepsia	Resolved wo/Tx	R
		Headache	Resolved wo/Tx	R
33	0.4% Olopatadine	Pharyngitis	Resolved w/Tx	NR
27	0.4% Olopatadine	Bronchitis	Resolved w/Tx	NR
40	0.4% Olopatadine	Infection	Resolved w/Tx	NR
50	0.4% Olopatadine	Dermatitis lichen	Resolved w/Tx	NR
30	0.4% Olopatadine	Sinusitis	Resolved w/Tx	NR
14	Placebo	Headache	Resolved wo/Tx	R
22	Placebo	Bronchitis	Lost to follow-up	NR
		Nausea	Resolved wo/Tx	NR
		Vomiting	Resolved wo/Tx	NR

Abbreviations: CA, causality assessment; NR, not related; R, related; w/Tx, with treatment; wo/Tx, without treatment.

Table 5. Related Adverse Events by Treatment Group*

Adverse event	0.6% Olopatadine group	0.4% Olopatadine group	Placebo group
Bitter taste	9.2	5.8	0
Headache	2.2	2.6	1.0
Epistaxis	3.8	1.1	1.0
Pharyngitis	1.6	0.5	0.5
Somnolence	0.5	0.5	0

* Data are given as percentages.

(symptom complex) as the best indicator of its therapeutic effect. Treatment with 0.6% olopatadine was statistically significantly greater than placebo therapy for improving TNSSs and each individual symptom score, except stuffy nose. Comparisons of 0.4% olopatadine with placebo also reached statistical significance except for ocular symptoms and 3 RQLQ domains (sleep, non-nose/eye symptoms, and emotional). Although both concentrations of olopatadine were slightly numerically greater than placebo spray for reducing congestion, there were no statistically significant differences. In addition, no patients dropped out of the study because of congestion.

Both concentrations of olopatadine provided numerically greater reductions in ocular symptoms (itchy and watery eyes) vs placebo. The 0.6% olopatadine treatment reached statistical significance for instantaneous and reflective evaluation of itchy eyes and for instantaneous (but not reflective) evaluation of watery eyes. The effect of olopatadine on ocular symptoms may have been systemic. Tamura et al[12] observed that oral administration of 0.1% and 1 mg/kg of olopatadine significantly inhibited passive anaphylaxis reaction–induced vascular hyperpermeability of the conjunctiva in a rat model of allergic conjunctivitis, suggesting a systemic effect on ocular symptoms.

Vehicle nasal spray was used as the placebo. The placebo spray, not surprisingly, produced beneficial effects. It reduced the symptom scores for every variable (Tables 2 and 3) and improved QoL (Fig 2). The placebo response to a nasal spray can be even more confounding than the response to an oral formulation because the nasal spray can possibly clear allergens from nasal passages, thereby reducing the dose of allergen exposure and, hence, the allergic response.

As an additional measure of efficacy, QoL evaluation was also used in this study. Issues of QoL have been used extensively in evaluating the considerable health-related consequences of allergic rhinitis.[13] Use of 0.6% olopatadine significantly improved each of the 7 individual domains during treatment compared with baseline. Treatment with 0.4% olopatadine was superior on 4 domains compared with baseline but was not statistically significantly different on the sleep, non-nose/eye symptoms, and emotional subscales.

The incidence of bitter taste reported in this study was dose related (9.2% for 0.6% olopatadine vs 5.8% for 0.4% olopatadine vs 0% for placebo) (Table 5). However, no patients discontinued treatment because of bitter taste (Table 4). Other adverse events were only slightly greater (not statistically) than placebo. Somnolence was not a significant adverse effect of olopatadine nasal spray. In this study, somnolence was only 0.5% for 0.4% and 0.6% olopatadine vs 0% for placebo. This observation is reassuring because somnolence (drowsiness) was the most common adverse event reported in the Japanese-approved label for the oral dosage form of olopatadine (Allelock, 2.5- and 5-mg tablets).[14]

In conclusion, olopatadine nasal spray, 2 sprays per nostril twice daily, elicited significant improvements in allergic rhinitis symptoms during the entire 2 weeks of treatment that were greater than those observed in the placebo nasal spray group based on either standard symptom scores (TNSS) or QoL assessments. Both 0.4% and 0.6% olopatadine were well tolerated in this study. These data support the use of olopatadine nasal spray as an effective and safe antiallergy agent for the treatment of symptoms of allergic rhinitis.

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REFERENCES

1. Salzano FA, d'Angelo L, Motta S, et al. Allergic rhinoconjunctivitis: diagnostic and clinical assessment. *Rhinology*. 1992;30:265–275.
2. Hollingsworth HM. Allergic rhinoconjunctivitis: current therapy. *Hosp Pract (Off Ed)*. 1996;31:61–62, 65–67, 71–73.
3. Yanni JM, Stephens DJ, Miller ST, et al. The in vitro and in vivo ocular pharmacology of olopatadine (AL-4943A), an effective anti-allergy/antihistaminic agent. *J Ocul Pharmacol Ther*. 1996;12:256–267.
4. Sharif NA, Xu SU, Miller ST, et al. Characterization of the ocular antiallergic and antihistaminic effects of olopatadine (AL-4943A), a novel drug for treating ocular allergic diseases. *J Pharmacol Exp Ther*. 1996;278:1252–1261.
5. Ohmori K, Hayashi K, Kaise T, et al. Pharmacological, pharmacokinetic and clinical properties of olopatadine hydro-

chloride, a new antiallergic drug. *Jpn J Pharmacol*. 2002;88: 379–397.
6. Miyake K, Horikoshi K, Ikeda Y, Ishii A, Karasawa A. Effects of olopatadine hydrochloride on the increase of histamine and peptide-leukotrienes concentrations in nasal lavage fluid following the antigen-antibody reaction in actively sensitized guinea pigs. *Jpn J Pharmacol*. 2001;85:453–456.
7. Food and Drug Administration. Guidance for industry: allergic rhinitis: clinical development programs for drug products (draft guidelines). Available at: http://www.fda.gov/cder/guidance/2718dft.htm. Accessed July 7, 2005.
8. Guyatt GH, Kirshner B, Jaeschke R. Measuring health status: what are the necessary measurement properties? *J Clin Epidemiol*. 1992;45:1341–1345.
9. Juniper EF, Guyatt GH, Jaeschke R. How to develop and validate a new quality of life instrument. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*. 2nd Ed. New York, NY: Raven Press Ltd; 1995:49–56.
10. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. 1991;21:77–83.
11. Westfall PH, Tobias RD, Rom D, et al. Concepts and basic methods for multiple comparisons and tests. In: *Multiple Comparisons and Multiple Tests Using the SAS System.* Cary, NC: SAS Institute Inc; 1999:13–40.
12. Tamura T, Sato H, Miki I, et al. Effects of orally administered olopatadine hydrochloride on the ocular allergic reaction in rats. *Allergol Int*. 2003;52:77–83.
13. Schoenwetter WF, Dupclay L, Appajosyula S, et al. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin*. 2004;20:304–317.
14. Allelock [package insert]. Tokyo, Japan: Kyowa Hakko Kogyo Co Ltd; April 2004.

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