Effects of adjuvant therapy with 0.1% olopatadine hydrochloride ophthalmic solution on quality of life in patients with allergic rhinitis using systemic or nasal therapy

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Background: Allergic rhinoconjunctivitis patients are often treated with nasal or systemic allergy therapy, forgoing therapy for ocular symptoms. This treatment regimen leaves important aspects of the allergic reaction untreated and affects quality of life (QoL). The Rhinoconjunctivitis Quality of Life Questionnaire and the Allergic Conjunctivitis Quality of Life Questionnaire quantify separate aspects of QoL.

Objective: To determine the benefit gained in QoL, measured by these questionnaires, when antiallergy eyedrops (olopatadine) were added to patients' preexisting regimens of nasal or systemic allergic rhinitis treatment.

Methods: This was a 4-week prospective, multicenter, open-label, crossover, environmental QoL study. Visit 1 randomized patients to treatment group A or B and included baseline examinations and questionnaires. Group A instilled olopatadine twice daily and concomitantly with previously prescribed nasal or systemic antiallergy medication for 2 weeks. Group B received no ocular therapy and used only previously prescribed antiallergy medication for 2 weeks. Treatment group crossover occurred at visit 2. Patients again completed the questionnaires at visits 2 and 3.

Results: Two hundred patients completed the study, 97 in group A and 103 in group B. Groups A and B experienced ocular allergic symptoms for 3.88 and 3.96 days, respectively, during the week before baseline. At visits 2 and 3, questionnaire scores were significantly improved for each group when olopatadine was added compared with the nontreatment periods. By visit 2, olopatadine improved QoL by 49% compared with 5% in the nontreated group ($P < .001$).

Conclusions: In this study, 90.5% of patients with allergic rhinitis treated nasally or systemically also had ocular allergic symptoms. Adding olopatadine to these patients' medication regimens significantly improved ocular allergic symptoms and overall QoL.

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INTRODUCTION

Seasonal allergic rhinitis is an inflammatory process induced by environmental allergens that shares several signs and symptoms with other inflammatory conditions. During an allergic reaction, mast cells in the nasal mucosa degranulate, and the released mediators induce the characteristic nasal congestion, rhinorrhea, itching of the nose and palate, and episodes of sneezing. Mast cell stabilizers, corticosteroids, leukotriene inhibitors, antihistamines, and anticholinergic agents, delivered via either systemic or nasal routes, are routinely used in rhinitis therapy.

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Allergic rhinitis can often be a component of a broader allergic condition that includes ocular allergy symptoms. The ocular allergic reaction characteristically involves the hallmark symptom of itching accompanied by signs that can include conjunctival hyperemia, tearing, lid swelling, and chemosis. These signs and symptoms are caused by the degranulation of ocular mast cells and the subsequent release of allergic mediators. The primary mediator of the early-phase nasal and ocular reactions is histamine released from the mast cell. Stimulation of histamine receptors on nerves and endothelial cells induces the itching, redness, and swelling of an allergic reaction. Antiallergy medication is most effectively delivered via topical ocular solutions; the medications available in this form are antihistamines, mast cell stabilizers, and antihistamine and mast cell stabilizer combinations (eg, 0.1% olopatadine [Patanol; Alcon Laboratories Inc, Fort Worth, TX]).[1]

The prevalence of rhinitis, estimated to be 10% to 30% in the US population,[2,3] is rising due in part to actual increases in the occurrence of the disease and in part to increases in disease awareness and diagnosis. However, actual diagnoses

may not yet accurately reflect the full scope of the condition. One study[4] estimates that up to 79.5 million people in the United States experience at least 7 days of undiagnosed nasal or ocular symptoms annually.

The economic burden of allergic rhinitis has been the subject of several studies. The annual costs, direct and indirect, associated with allergic rhinitis have been estimated to be $2.7 billion (1995 dollars),[5] $4.5 billion (1997 dollars),[6] and $5.3 billion (1996 dollars).[5] School and work absenteeism and lost productivity due to allergic rhinitis are included as indirect costs in some of these estimates. One study documented that allergic rhinitis accounts for 2 million missed school days per year.[5] Another study reported 811,000 lost workdays and 824,000 lost school days per year,[7] while another reported 3.8 million days lost from work and school combined.[8] Allergic rhinitis has also been attributed to more than 8 million visits to office-based physicians each year.[9] In many of the studies mentioned, it is probable that allergic conjunctivitis is included under the umbrella term *rhinitis* or *rhinoconjunctivitis.* There is relatively little economic research specifically of seasonal allergic conjunctivitis. One study[10] of age-matched patients with vs without seasonal allergic conjunctivitis found that those with allergic conjunctivitis had higher pain and discomfort and lower perception of health, and the combined public health care and personal out-of-pocket cost of seasonal allergic conjunctivitis per person ranged from $120 to $231 per year. In summary, these data reveal the magnitude of the impact on quality of life (QoL) and the economic costs that can be incurred by allergy.

Evaluation of the effects of QoL in patients with allergic rhinitis has historically used several types of questionnaires, including generic measures, such as the Medical Outcomes Study 36-Item Short-Form Health Survey, and specific tools, such as the 26-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ is a well-validated, disease-specific instrument that has been used in numerous studies, proving to be the most sensitive instrument for the evaluation of QoL in patients with allergic rhinitis and rhinoconjunctivitis.[11–13] The RQLQ has identified ocular symptoms among the 7 major issues in QoL for patients with allergic rhinoconjunctivitis[14]; the domains evaluated by the RQLQ also include activities, sleep, non–nose and eye symptoms, practical problems, nasal symptoms, and an emotional domain.

A separate evaluation measure, the Allergic Conjunctivitis Quality of Life Questionnaire (ACQLQ), contains 17 items grouped into 5 domains (eye symptoms, symptom-related problems, activity limitations, emotional functions, and vitality) and 2 daily efficiency questions. The ACQLQ differs from the RQLQ in that it focuses entirely on the ocular signs and symptoms of allergy.[15] Use of the RQLQ and the ACQLQ in combination is expected to yield complementary data to render a more accurate representation of the full effect of ocular and nasal allergy on patients' QoL.

Using the ACQLQ, which exclusively examines the effects of ocular signs and symptoms experienced by patients, will add a needed component to rhinoconjunctivitis QoL evaluations, which primarily have been limited to nasal variables. Ocular complaints often go untreated; most rhinitis medications prescribed are either systemic second-generation antihistamines (accounting for 51% of prescription drug spending for rhinitis) or intranasal corticosteroids (25%).[16] In clinical trial settings using ocular or nasal allergen challenge models, it has been shown that neither systemic antihistamines nor intranasal corticosteroids achieve adequate management of the ocular component of rhinoconjunctivitis.[17–19] As a result, potential exists for the QoL of patients with rhinitis to be significantly improved by addressing the ocular component or complaint in addition to the nasal component. This study aimed to determine the extent of the benefit gained in QoL when an eyedrop treatment for ocular allergy (olopatadine) was added to patients' preexisting regimens of nasal or systemic seasonal allergic rhinitis treatment.

METHODS

Study Design

This was a 4-week prospective, multicenter, open-label, crossover, environmental model study specifically intended to evaluate QoL as the primary outcome measure. An ethical review board (IntegReview Inc, Austin, TX) approved the protocol and informed consent for this study. Six medical centers enrolled patients with seasonal allergic rhinitis undergoing systemic or nasal allergy therapy during periods when environmental airborne allergens were present in these regions. There were 2 centers in Pensacola, FL (n = 59 and n = 20) and 1 each in Miami, FL (n = 39); Mission Viejo, CA (n = 30); Orange, CA (n = 37); and Colorado Springs, CO (n = 15). Previous use of topical ophthalmic agents was allowed if the agents had been over-the-counter medications; however, to attempt to control for a historical bias, only patients with allergic rhinitis who had never been prescribed prescription topical ophthalmic antiallergy therapy were enrolled in this study.

Visit 1 Baseline Screening

Informed consent, demographic data, medical and medication histories, and visual acuity (measured with the Early Treatment Diabetic Retinopathy Study chart) were obtained from each patient. Inclusion and exclusion criteria were reviewed to ensure qualification before enrollment. Patients (aged ≥14 years) with a positive medical diagnosis and a history of seasonal or perennial allergic rhinitis were eligible for this study. Patients were required to have been currently using a prescription systemic antihistamine or topical nasal antiallergy spray at least twice a week for 1 month before enrollment. Patients who were using a topical nasal corticosteroid were required to have maintained a stable and consistent dosing regimen for at least 2 weeks before the start of the study. Patients were also required to have a corrected visual acuity logMar score of 0.70 or better using a standard Early Treatment Diabetic Retinopathy Study chart and to be able to effectively self-administer eyedrops. A urine pregnancy test was given to all women of childbearing potential. Patients

were excluded from the study if they had any active ocular or nasal infection, used any topical ophthalmic medication within 2 weeks of the study, used any new medication introduced in the 2 weeks before visit 1, underwent ocular or nasal surgery in the previous 2 months, or had a significant illness that could interfere with the study variables. Patients who qualified for the study were asked to complete an RQLQ and an ACQLQ based on their experiences during the week before visit 1.

Patients were then randomized to 1 of 2 treatment groups, A or B, in a 1:1 ratio. Patients in group A received olopatadine 0.1% ophthalmic solution twice daily (1–2 drops in each eye in the morning [within 2 hours of waking] and in the evening [approximately 8–12 hours after the morning dose]) concomitantly with their previously prescribed antiallergy medication for 2 weeks. Patients randomized to group B received no ocular therapy and used only their previously prescribed antiallergy medication for 2 weeks. All the patients were given a diary to record the number of times they used olopatadine (if applicable) and their prescribed systemic or nasal antiallergy medications for each day. Patients were instructed to use the diary once daily, after the last medication was used. All the patients were instructed not to use eyedrops other than those provided during the study. See Table 1 for the treatment design.

Visits 2 and 3

At visit 2 (14 ± 3 days after the baseline visit), medical and medication histories were updated, and visual acuity was recorded. Patients completed the RQLQ and the ACQLQ based on the week immediately before visit 2. Dosing diaries were collected from all the patients, and the study medication (olopatadine) was collected from group A. Patients who had changed their prescription medication or who had started taking a new medication were discontinued from the study. Patients who continued to qualify were given new diaries to take home to record eyedrop and prescription antiallergy medication use. Treatment group crossover occurred at visit 2 so that patients in group B were dispensed olopatadine to be instilled twice daily (as described in the previous subsection). Patients in group A were instructed to use only their previously prescribed prescription antiallergy agents.

At visit 3 (28 ± 3 days after the baseline visit), medical and medication histories were updated, and visual acuity was recorded. Patients completed the RQLQ and the ACQLQ for the previous week. Dosing diaries were collected from all the patients, and the study medication was collected from group B. Patients were then exited from the study.

Statistical Analysis

The RQLQ includes 7 domains: activities (3 questions), sleep (3 questions), non–nose and eye symptoms (7 questions), practical problems (3 questions), nasal symptoms (4 questions), eye symptoms (4 questions), and emotional (4 questions). Each question was graded on a scale from 0 to 6, with 0 being "not troubled" and 6 being "extremely troubled." A global score was calculated by averaging the scores of all the domains. The relative global QoL improvement analysis was performed using analysis of variance.

The ACQLQ is categorized into 5 domains: eye symptoms (4 questions), symptom-related problems (5 questions), activity limitations (3 questions), emotional functions (3 questions), and vitality (2 questions). In addition, there are 2 questions in a daily efficiency domain. A global score was calculated by averaging the scores of the first 5 domains. These questions were scored using a scale from 0 to 6, with 0 being "not bothered" and 6 being "extremely bothered." The 2 questions in the daily efficiency domain were based on a percentage score (of 100%). Because of this difference in scale, these questions were averaged separately and were not included in the global score. The QoL evaluations (the RQLQ and the ACQLQ) for both groups were performed at baseline, at 2 weeks (visit 2), and at 4 weeks (visit 3). For these and all other analyses, only data from patients who were properly enrolled and who completed the study were analyzed (per protocol).

For the primary analysis, Pearson correlation coefficients were calculated between visit-specific scores for corresponding questions on the RQLQ and the ACQLQ. Visit 1 scores were compared between groups A and B for each domain on the RQLQ and the ACQLQ using a 2-sample *t* test. Paired *t* tests were performed to compare changes from baseline scores for the same patients for each domain on the RQLQ and the ACQLQ. This analysis was performed separately for group A (visit 1 to visit 2) and group B (visit 1 to visit 3).

RESULTS

Two hundred eight patients were enrolled in the study, with 8 discontinuing for the following reasons: 3 were lost to follow-up, 1 discontinued based on poor medication compliance, 1 took a disallowed medication, and 3 experienced adverse events (1 patient was hospitalized for reasons unrelated to the study drug, 1 experienced exacerbated asthma symptoms, and 1 developed bacterial conjunctivitis). Two hundred patients completed the study (97 in group A and 103 in group B). Patient self-reported compliance with olopata-

Table 1. Study Treatment Design

Visit	Group A (n = 97)	Group B (n = 103)
1	Baseline	Baseline
2	After 2 weeks of twice-daily 0.1% olopatadine treatment	After 2 weeks with no topical ocular treatment
3	After 2 weeks with no topical ocular treatment	After 2 weeks of twice-daily 0.1% olopatadine treatment

dine therapy was 96.4% in group A and 93.9% in group B. The most common concomitant rhinitis medication used by patients in both randomization groups was systemic antihistamine therapy (approximately 50%). The remaining patients used combination systemic and nasal therapy (approximately 33%), nasal topical therapy (approximately 16%), and antileukotriene combination therapy (approximately 1%). No significant changes in the frequency of concomitant medication use were seen throughout the study in either group between visits 2 and 3 (group A: 18.9 vs 18.5 times; $P = .59$; group B: 18.7 vs 18.9 times; $P = .77$). No significant differences in demographic characteristics existed between the 2 groups (Table 2).

Visit 1 Baseline Screening

At the visit 1 baseline assessments, patients in groups A and B had comparable mean RQLQ global scores (2.16 and 2.17; $P = .95$). There were no statistically significant differences between randomization groups in any domain (Table 3). The baseline mean ACQLQ global scores were also comparable between groups A and B (2.04 and 2.25; $P = .25$). There were no statistically significant differences between randomization groups in any domain (Table 3). A total of 181 patients with rhinitis (90.5%) experienced at least 1 day of eye allergy symptoms during the previous week (Table 4). Thirty-seven patients (18.5%) experienced eye allergy symptoms on each of the 7 previous days (Table 4). In the baseline ACQLQ, patients in groups A and B on average experienced ocular allergy symptoms on most days of the previous week (3.88 and 3.96 days); when queried about their average effectiveness in completing daily activities during the previous week, patients in group A indicated it was 79% and those in group B indicated it was 76% (Table 3). An overall study result is shown as the measure of global QoL improvement (RQLQ) (Fig 1). The QoL measurement at 2 weeks indicates a 49% improvement from baseline in the olopatadine-treated group compared with a 5% improvement from baseline in the untreated group ($P < .001$).

Correlations Between the RQLQ and the ACQLQ

Although the 2 questionnaires evaluate nonoverlapping variables with most of their questions, some domains gather similar patient information. In these domains, correlations existed between RQLQ and ACQLQ scores. Globally, at all

Table 2. Demographic Characteristics of the Study Groups

Characteristic	Group A (n = 97)	Group B (n = 103)
Age, mean (SD), y	38.2 (13.9)	37.5 (16.4)
Sex, No. (%)		
M	33 (34)	31 (30)
F	64 (66)	72(70)
Race, No. (%)		
White	58 (60)	64 (62)
Black	15 (15)	18 (18)
Asian	0	1 (1)
Hispanic	24 (25)	20 (19)
Iris color, No. (%)		
Blue	18 (19)	25 (24)
Brown	54 (56)	48 (47)
Green	7 (7)	11 (11)
Hazel	18 (19)	18 (17)
Gray	0	1 (1)
Concomitant rhinitis medications, No. (%)		
Systemic antihistamine therapy	52 (54)	51 (50)
Combination systemic and nasal therapy	35 (36)	31 (30)
Nasal (corticosteroid or antihistamine) therapy	8 (8)	21 (20)
Antileukotriene therapy combined with systemic or nasal therapy	2 (2)	0

Table 3. Baseline RQLQ and ACQLQ Global and Domain Scores by Treatment Group*

Questionnaire and domain	Group A	Group B	*P* value
RQLQ			
Global	2.16 (1.05)	2.17 (1.16)	.95
Activities	2.51 (1.29)	2.27 (1.29)	.19
Sleep	1.86 (1.54)	2.01 (1.42)	.48
Non-nose/eye symptoms	1.95 (1.2)	1.83 (1.27)	.5
Practical problems	2.54 (1.39)	2.81 (1.58)	.21
Nasal symptoms	2.67 (1.39)	2.67 (1.50)	.99
Eye symptoms	2.22 (1.36)	2.20 (1.43)	.91
Emotional	1.66 (1.49)	1.80 (1.50)	.5
ACQLQ			
Global	2.04 (1.22)	2.25 (1.36)	.25
Eye symptoms	2.27 (1.42)	2.48 (1.63)	.34
Symptom-related problems	2.15 (1.35)	2.29 (1.45)	.48
Activity limitations	2.06 (1.44)	2.22 (1.42)	.44
Emotional functions	1.58 (1.53)	1.94 (1.51)	.10
Vitality	2.02 (1.65)	2.23 (1.64)	.37
Days in a week experiencing eye allergy symptoms, No.	3.88 (2.07)	3.96 (2.09)	.80
Efficiency, %	79.20 (17.00)	76.00 (18.30)	.24

Abbreviations: ACQLQ, Allergic Conjunctivitis Quality of Life Questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
* Data are given as mean (SD). The RQLQ and ACQLQ questions (excluding the 2 questions in the daily efficiency domain) were scored using a scale from 0 to 6 (0 = not troubled/bothered and 6 = extremely troubled/bothered).

Table 4. Days During the Week Before Baseline That Patients With Rhinitis Reported Experiencing Eye Allergy Symptoms

No. of Days	Patients, No. (%) (N = 200)
0	13 (6.5)
1	10 (5.0)
2	24 (12.0)
3	41 (20.5)
4	35 (17.5)
5	23 (11.5)
6	11 (5.5)
7	37 (18.5)
Missing data	6 (3.0)

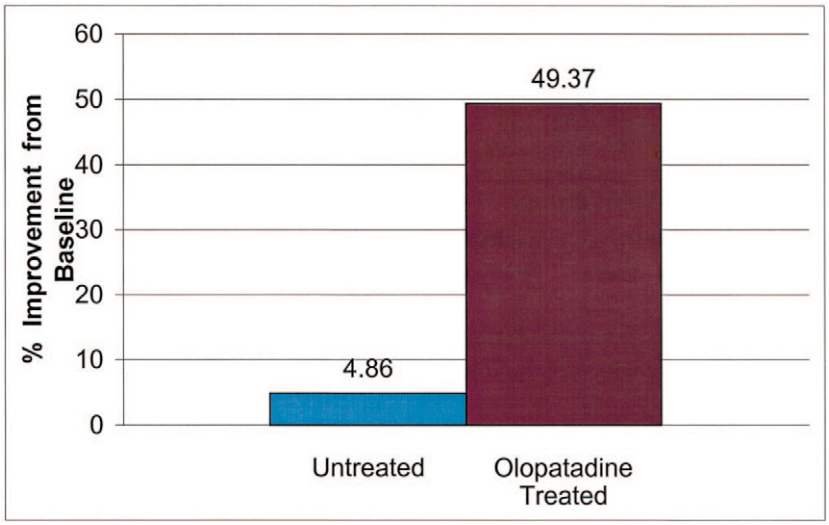

Figure 1. Relative global quality of life improvement using the Rhinoconjunctivitis Quality of Life Questionnaire. Patients who used antiallergy eyedrops (olopatadine) for the previous 2 weeks had significantly greater improvement from baseline compared with those who did not take a topical ophthalmic agent (49% improvement vs 5% improvement; $P < .001$).

3 visits, a statistically significant correlation existed between the 2 questionnaires; a significant correlation was also present in the eye symptoms and activity domains for all 3 visits (Table 5).

Visits 2 and 3

The addition of 2 weeks of olopatadine therapy to the allergic rhinitis treatment regimen of group A led to statistically and clinically significant improvements in all the RQLQ domains compared with baseline ($P < .001$) (Tables 6 and 7 and Fig 2). At visit 2, scores from the nasal symptoms and eye symptoms domains exhibited the most improvement compared with baseline in group A (-1.34 and -1.31, respectively). Visit 3 scores worsened compared with visit 2 scores after discontinuation of olopatadine therapy but remained improved from baseline scores.

Patients in group B experienced little change in mean RQLQ scores from baseline to visit 2. At visit 3, after 2 weeks of olopatadine therapy, statistically and clinically significant improvements were evident globally and in all 7 domains compared with baseline ($P < .001$) (Tables 6 and 8 and Fig 2). The greatest improvement from baseline occurred in the practical problems, nasal symptoms, and eye symptoms domains (-1.38, -1.20, and -1.12, respectively) (Fig 3).

Table 5. Correlations Between Visit-Specific Scores on Corresponding RQLQ and ACQLQ Domains*

Domain	Correlation coefficient (*R*)		
	Baseline	Visit 2	Visit 3
Global	0.84	0.9†	0.85
Eye symptoms	0.89	0.91†	0.89
Activity	0.58	0.79†	0.76‡

Abbreviations: ACQLQ, Allergic Conjunctivitis Quality of Life Questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
* $P < .001$ for all.
† Based on 199 patients.
‡ Based on 198 patients.

Table 6. RQLQ Global and Domain Scores by Visit*

Group and domain	Visit 2		Visit 3	
	Score, mean (SD)	Patients, No.	Score, mean (SD)	Patients, No.
Group A				
Global	1.09 (0.86)	97	1.47 (1.07)	97
Activities	1.33 (0.99)	97	1.62 (1.21)	96
Sleep	1.03 (1.15)	97	1.45 (1.33)	96
Non-nose/eye symptoms	1.08 (1.01)	97	1.41 (1.24)	97
Practical problems	1.32 (1.27)	97	1.68 (1.37)	97
Nasal symptoms	1.34 (1.14)	97	1.70 (1.27)	97
Eye symptoms	0.91 (0.91)	97	1.48 (1.27)	97
Emotional	0.77 (0.85)	96	1.09 (1.21)	97
Group B				
Global	2.06 (1.32)	103	1.23 (1.08)	103
Activities	2.14 (1.35)	103	1.32 (1.05)	102
Sleep	1.82 (1.48)	103	1.25 (1.33)	102
Non-nose/eye symptoms	1.79 (1.4)	103	1.22 (1.26)	103
Practical problems	2.51 (1.65)	102	1.44 (1.28)	103
Nasal symptoms	2.53 (1.55)	102	1.44 (1.28)	103
Eye symptoms	2.26 (1.59)	102	1.08 (1.08)	103
Emotional	1.68 (1.51)	101	0.92 (1.15)	103

Abbreviation: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
* Group A received treatment during visit 2 and group B received treatment during visit 3.

Table 7. Change From Baseline in RQLQ and ACQLQ Global and Domain Scores for Group A (Visit 2 − Visit 1)*

Questionnaire and domain	Change, mean (SE)	Patients, No.
RQLQ		
Global	−1.07 (0.09)	97
Activities	−1.18 (0.11)	97
Sleep	−0.81 (0.13)	96
Non-nose/eye symptoms	−0.87 (0.11)	97
Practical problems	−1.22 (0.18)	97
Nasal symptoms	−1.34 (0.13)	97
Eye symptoms	−1.31 (0.13)	97
Emotional	−0.91 (0.13)	96
ACQLQ		
Global	−1.2 (0.12)	97
Eye symptoms	−1.39 (0.14)	97
Symptom-related problems	−1.23 (0.13)	97
Activity limitations	−1.14 (0.14)	97
Emotional functions	−0.97 (0.16)	97
Vitality	−1.2 (0.18)	93
Days in a week with symptoms, No.	−1.8 (0.27)	89
Efficiency, %	5.13 (1.91)	80

Abbreviations: ACQLQ, Allergic Conjunctivitis Quality of Life Questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
* $P < .001$ for all except efficiency ($P = .009$).

For group A, there was clinically significant improvement in all 5 ACQLQ domain scores from baseline (Tables 7 and 9 and Fig 2). The greatest improvement occurred in the eye symptoms domain (−1.39 compared with baseline) (Fig 3). The incidence of days experiencing eye allergy symptoms during the previous week decreased by 1.7 days or 44% after olopatadine therapy (Fig 4). Compared with baseline, daily efficiency increased 5.13% after olopatadine therapy on the days when patients experienced eye allergy symptoms (Fig 5). These values (days experiencing eye allergy and daily efficiency) were gathered based on 2 specific, written questions to patients included in the ACQLQ, one regarding days with ocular symptoms and the other regarding efficiency on those days. These questions required patients to recall these values from the past 7 days.

Similar results for the ACQLQ were observed in group B. Clinically and statistically significant improvements were observed across all domains after olopatadine treatment compared with baseline (Tables 8 and 9 and Fig 2). The greatest change occurred in eye symptoms domain scores, which showed an improvement of 1.39 compared with baseline (Fig 3). After olopatadine therapy, patients experienced 1.6 fewer days (41%) with ocular symptoms during the previous week than at baseline (Fig 4). Daily efficiency on days when ocular allergic symptoms were present increased 7.07% compared with baseline (Fig 5). Baseline-corrected scores for each domain of both questionnaires showed a significant improvement during the treatment period compared with the nontreatment period (Table 10).

DISCUSSION

In this crossover study, both groups experienced meaningful improvements in QoL during periods when ocular therapy was added to their antiallergy medication regimen. At baseline, the mean number of days patients indicated being bothered by eye symptoms was 3.88 in group A and 3.96 in group B. Ninety percent of the patients with rhinitis enrolled in this study experienced at least 1 day of eye allergy symptoms during the week before the baseline visit. Approximately one-fifth of these patients experienced eye allergy symptoms every day of the previous 7 days, indicating an unmet ocular need in patients with rhinoconjunctivitis being treated only with systemic or nasal therapy. The data regarding the number of days that patients experienced eye allergies and the percentage efficiency on those days were gathered via questions to patients involving past recollections. Such information is inherently subjective, but it suggests that these patients are experiencing ocular allergy symptoms that are not adequately managed by their existing nasal or systemic therapy regimens.

The inclusion criteria of this study required patients to be receiving an existing regimen of systemic or nasal antiallergic medication at least twice a week for 1 month before enrollment. We would not consider these patients to have the most severe cases of allergy. Thus, this study represents a conservative measure of treatment effect. If more severely symptomatic or untreated patients with allergy had been enrolled, they could be expected to have more frequently bothersome eye symptoms at baseline. In addition, if more severely symptomatic patients had been enrolled it is likely that greater improvements in QoL would be evident. A previous study[20] has shown that the eyedrop solution used herein (olopatadine) has increased efficacy and treatment effect as pollen counts increase and symptoms grow more severe.

This study was designed to confer a high degree of external or real-world validity, simulating the usual care of patients who visit physicians' offices. Maintaining high external validity requires a trade-off in terms of internal validity, which is established by using study design features such as a placebo group. Although it is not possible to design a study with both high internal and external validity, in this study, effort was made to simulate the usual care conditions of a patient while also maintaining a key methodological standard randomized group assignment.

In this study, the addition of 2 weeks of olopatadine therapy yielded clinically significant improvements in QoL, as measured by the RQLQ and the ACQLQ, in all domains of each of these questionnaires. These significant improvements occurred during the period of olopatadine addition, regardless of whether it was during the first or second 2-week period of the study. With the addition of ocular therapy, ocular variables improved and significant improvements were also observed in nasal domains. These results indicate that an ocular antiallergy agent significantly contributed to nasal symptom improvement in terms of QoL. After the discontinuation of

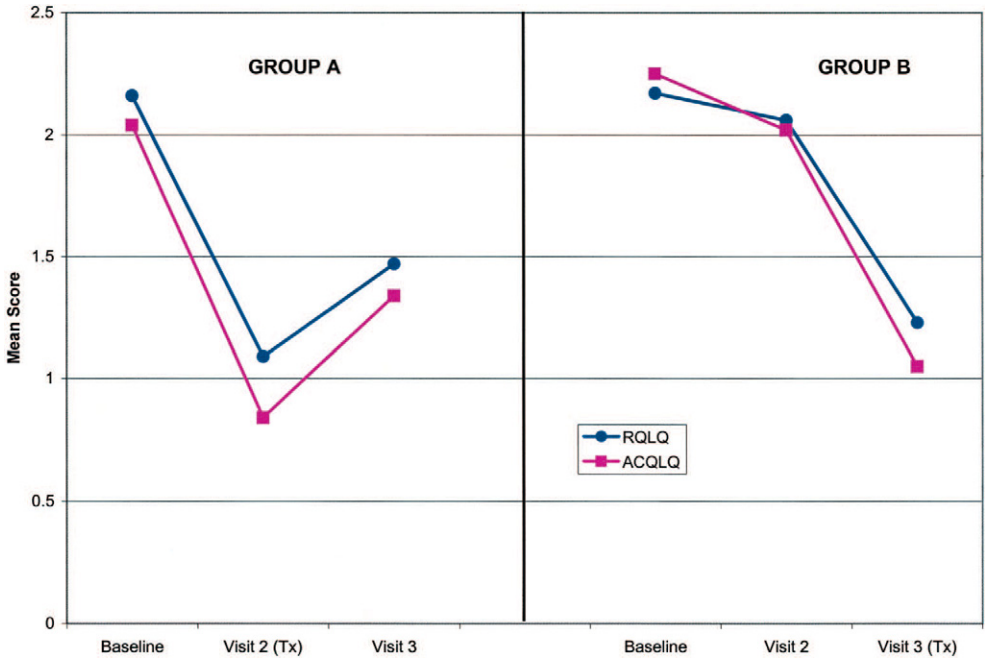

Figure 2. Mean Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Allergic Conjunctivitis Quality of Life Questionnaire (ACQLQ) global scores by visit for group A (n = 97) and group B (n = 103). Each question was graded on a scale from 0 to 6, with 0 being "not troubled/bothered" and 6 being "extremely troubled/bothered." Significant improvements compared with baseline were evident in each group after 2 weeks of olopatadine treatment ($P < .001$). Tx indicates treatment.

Table 8. Change From Baseline in RQLQ and ACQLQ Global and Domain Scores for Group B (Visit 3 − Visit 1)*

Questionnaire and domain	Change, mean (SE)	Patients, No.
RQLQ		
Global	−0.94 (0.10)	103
Activities	−0.94 (0.13)	102
Sleep	−0.77 (0.13)	102
Non-nose/eye symptoms	−0.62 (0.11)	103
Practical problems	−1.38 (0.16)	103
Nasal symptoms	−1.20 (0.14)	103
Eye symptoms	−1.12 (0.13)	103
Emotional	−0.90 (0.12)	103
ACQLQ		
Global	−1.20 (0.13)	103
Eye symptoms	−1.39 (0.15)	103
Symptom-related problems	−1.22 (0.14)	103
Activity limitations	−1.13 (0.14)	103
Emotional functions	−1.04 (0.14)	103
Vitality	−1.12 (0.15)	103
Days in a week with symptoms, No.	−1.60 (0.24)	91
Efficiency, %	7.07 (2.67)	82

Abbreviations: ACQLQ, Allergic Conjunctivitis Quality of Life Questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
* $P < .001$ for all except efficiency ($P = .01$).

olopatadine therapy for 2 weeks, patients in group A experienced an increase in mean scores in all domains at visit 3; however, these scores did not reach the same levels as the baseline scores. This finding may be due to a carryover effect of olopatadine during the subsequent 2 weeks. A common component of allergy clinical trials is a washout period of 2 weeks for antihistamines and mast cell stabilizers. Because the visit 3 questionnaire reflected the experiences of the patients during the previous week, it is possible that continuing effects of olopatadine improved the QoL compared with baseline. This area should be explored in future clinical trials. In addition, consistent with the improvements seen in nasal domains with the addition of eyedrops, there was a corresponding worsening of nasal variables when ocular treatment was withdrawn.

Although most information gathered in the RQLQ and the ACQLQ does not overlap, some domains cover similar aspects of the patient's QoL. For example, the eye symptoms domains of the RQLQ and the ACQLQ exhibited the greatest level of clinically significant improvement with the addition of olopatadine therapy, indicating that these patients meaningfully benefit from adding ocular therapy to preexisting systemic or nasal medication regimens.

Many previous studies have evaluated systemic nonsedating or lesser-sedating antihistamines compared with placebo or other systemic antihistamines. Similarly, QoL studies have evaluated nasal corticosteroids compared with placebo and other medications of this category. These studies have indicated that significant improvements in QoL are evident with the use of systemic antihistamines or nasal corticosteroids compared with placebo.[21–23] In addition, use of the RQLQ has

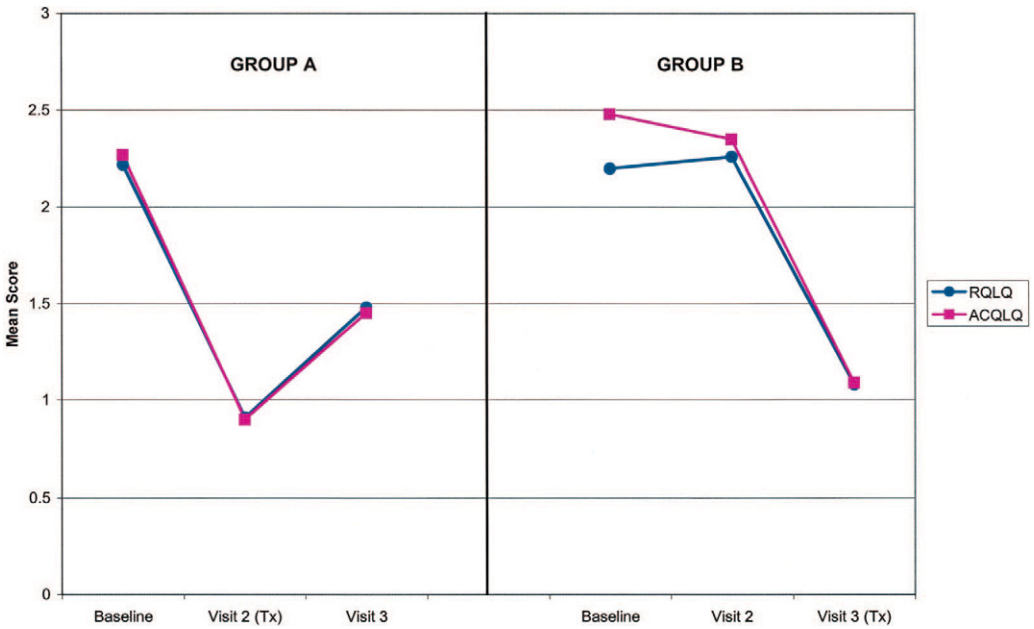

Figure 3. Mean Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Allergic Conjunctivitis Quality of Life Questionnaire (ACQLQ) eye symptom domain scores by visit for group A (n = 97) and group B (n = 103). Each question was graded on a scale from 0 to 6, with 0 being "not troubled/bothered" and 6 being "extremely troubled/bothered." This domain exhibited the greatest magnitude of change for both groups on the ACQLQ and was 1 of the 3 most changed domains on RQLQ measurements. Significant improvements compared with baseline were evident in each group after 2 weeks of olopatadine treatment ($P < .001$). Tx indicates treatment.

Table 9. ACQLQ Global and Domain Scores by Visit*

Group and domain	Visit 2		Visit 3	
	Score, mean (SD)	Patients, No.	Score, mean (SD)	Patients, No.
Group A				
Global	0.84 (0.76)	97	1.34 (1.08)	97
Eye symptoms	0.9 (0.95)	97	1.45 (1.2)	97
Symptom-related problems	0.93 (0.88)	97	1.48 (1.28)	97
Activity limitations	0.93 (0.94)	97	1.33 (1.21)	97
Emotional functions	0.62 (0.74)	97	1.10 (1.18)	97
Vitality	0.85 (1.00)	94	1.28 (1.30)	94
Days of week	2.21 (1.77)	90	3.32 (2.17)	84
Efficiency, %	83.4 (17.5)	90	80.7 (16.7)	92
Group B				
Global	2.02 (1.36)	102	1.05 (1.08)	103
Eye symptoms	2.35 (1.55)	102	1.09 (1.17)	103
Symptom-related problems	2.04 (1.43)	102	1.10 (1.16)	103
Activity limitations	1.99 (1.47)	102	1.08 (1.19)	103
Emotional functions	1.71 (1.58)	102	0.89 (1.26)	103
Vitality	1.82 (1.63)	102	1.11 (1.39)	103
Days in a week with symptoms, No.	3.96 (2.15)	95	2.35 (1.96)	94
Efficiency, %	76.8 (18)	100	84.1 (17.5)	99

Abbreviations: ACQLQ, Allergic Conjunctivitis Quality of Life Questionnaire.

* Group A received treatment during visit 2 and group B received treatment during visit 3.

yielded significant differences between medications of the same category compared with each other in terms of QoL.[24,25] In comparing systemic antihistamines with intranasal corticosteroids, the RQLQ scores indicated that greater QoL benefit was gained with the use of intranasal corticosteroids, significantly in the nasal symptom scores.[26] It has also been established in the RQLQ that a 0.5-point change is considered the minimum clinically meaningful difference (ie, the smallest difference that patients perceive as beneficial).[27,28]

Although numerous other studies have used the RQLQ to evaluate the effects of antiallergy medications on QoL (as described later herein), to our knowledge, the RQLQ has not been used previously to evaluate the addition of an eyedrop to systemic or nasal therapy, as in the present study. This study is also unique in its employment of the ACQLQ and the RQLQ. The simultaneous use of these 2 instruments in the same study has not previously been evaluated. The results indicate that the 2 questionnaires significantly correlate on global (all domain) scores and on comparable individual domains (eye symptoms and activity) at all visits. The ACQLQ complements the RQLQ with questions specific to eye allergy symptoms and with additional queries regarding daily efficiency that are unique to this questionnaire. The benefit of using the ACQLQ in this study was the survey instrument's focus on ocular symptoms, the frequency of these symptoms, and their effect on QoL. In cases in which allergic conjunctivitis is the primary consideration under evaluation, the ACQLQ was demonstrated, in 8 categories, to be signifi-

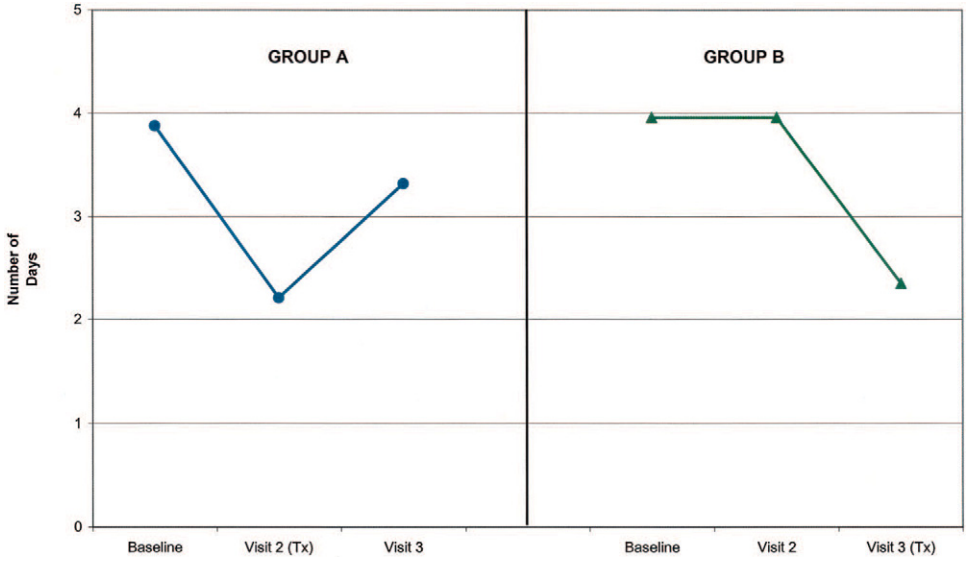

Figure 4. Mean number of days experiencing eye allergy symptoms during the previous week as reported by the patients. After olopatadine therapy, patients in groups A (n = 97) and B (n = 103) experienced 1.7 (44%) and 1.6 (41%) fewer days, respectively, with ocular symptoms during the previous week than at baseline. Tx indicates treatment.

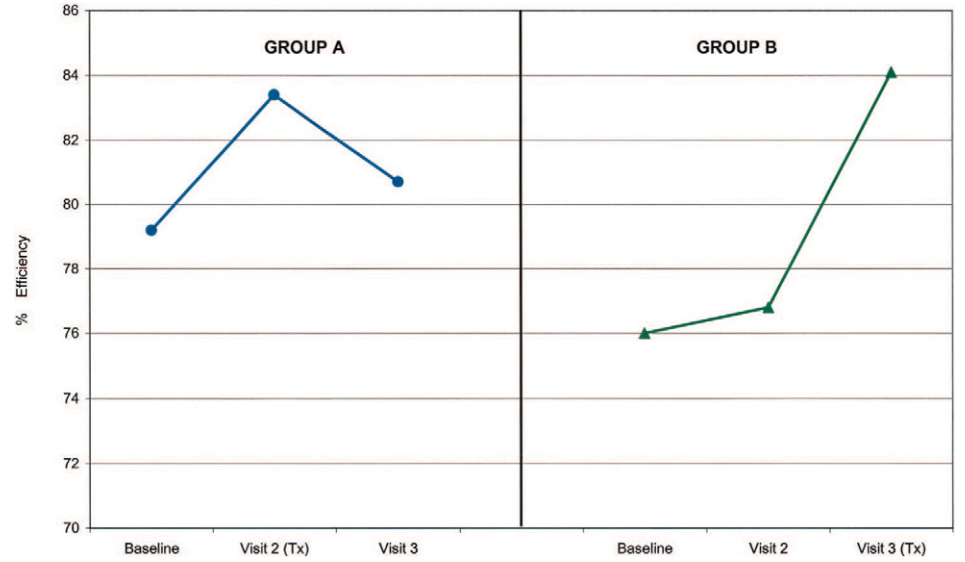

Figure 5. Mean percentage efficiency, as self-evaluated by study patients, on days when experiencing eye allergy symptoms. In groups A (n = 97) and B (n = 103), compared with baseline, daily efficiency increased 5.13% and 7.07%, respectively, after olopatadine therapy on the days when patients experienced eye allergy symptoms. Tx indicates treatment.

cantly modifiable by therapy. Although further testing is required to officially validate this questionnaire and to determine the value of the minimum clinically meaningful difference, it is a promising new tool with which to approach, evaluate, and compare various drugs, therapeutic modalities, classes, or concentrations.

In terms of safety and efficacy, previous studies have evaluated the addition of ocular therapy to systemic or nasal therapy. One study[18] comparing a fully topical regimen (olopatadine eyedrops and fluticasone nasal spray) with a topical and systemic regimen (fluticasone nasal spray and fexofenadine pill) revealed that the use of an eyedrop and nasal spray offered more effective overall treatment of the signs and symptoms of allergic rhinoconjunctivitis. An additional study[19] compared the efficacy of separate routes of medication administration for allergic rhinoconjunctivitis: ocular (olopatadine), nasal (mometasone), and systemic (fexofenadine). Results indicated that topical symptoms were best

Table 10. Change From Baseline by Phase in RQLQ and ACQLQ Global and Domain Scores*

Questionnaire and domain	Group A		Group B	
	No ocular treatment	Ocular treatment	No ocular treatment	Ocular treatment
RQLQ				
Global	−0.69 (0.11)	−1.07 (0.09)	−0.11 (0.08)	−0.94 (0.10)
Activities	−0.89 (0.14)	−1.18 (0.11)	−0.14 (0.11)	−0.94 (0.13)
Sleep	−0.43 (0.14)	−0.81 (0.13)	−0.21 (0.13)	−0.77 (0.13)
Non-nose/eye symptoms	−0.55 (0.13)	−0.87 (0.11)	−0.06 (0.09)	−0.62 (0.11)
Practical problems	−0.87 (0.14)	−1.22 (0.18)	−0.35 (0.12)	−1.38 (0.16)
Nasal symptoms	−0.97 (0.15)	−1.34 (0.13)	−0.13 (0.12)	−1.20 (0.14)
Eye symptoms	−0.73 (0.15)	−1.31 (0.13)	0.05 (0.11)	−1.12 (0.13)
Emotional	−0.57 (0.13)	−0.91 (0.13)	−0.12 (0.10)	−0.90 (0.12)
ACQLQ				
Global	−0.70 (0.12)	−1.20 (0.12)	−0.24 (0.10)	−1.20 (0.13)
Eye symptoms	−0.82 (0.13)	−1.39 (0.14)	−0.14 (0.12)	−1.39 (0.15)
Symptom-related problems	−0.68 (0.14)	−1.23 (0.13)	−0.26 (0.12)	−1.22 (0.14)
Activity limitations	−0.75 (0.15)	−1.14 (0.14)	−0.26 (0.12)	−1.13 (0.14)
Emotional functions	−0.48 (0.14)	−0.97 (0.16)	−0.24 (0.13)	−1.04 (0.14)
Vitality	−0.72 (0.17)	−1.20 (0.18)	−0.42 (0.13)	−1.12 (0.15)
Days in a week experiencing eye allergy symptoms, No.	−0.57 (0.24)	−1.80 (0.27)	−0.04 (0.21)	−1.60 (0.24)
Efficiency, %	1.76 (1.97)	5.13 (1.91)	1.98 (1.60)	7.07 (2.67)

Abbreviations: ACQLQ, Allergic Conjunctivitis Quality of Life Questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
* Data are given as mean (SD). $P < .001$ for all.

treated topically (ie, ocular symptoms with a topical ocular agent and nasal symptoms with a nasal spray) and that eyedrop use can lend added benefit to treating nasal signs and symptoms.[19] In addition, an environmental study of olopatadine alone has shown that olopatadine can decrease the severity and frequency of ocular allergy signs and symptoms.[20]

The present study's evaluation of health-related QoL can be of assistance in therapy selection for practitioners in particular because it reveals that the addition of topical ocular antiallergy therapy to patients' antiallergy medication regimens can have a significant positive impact on QoL. The results of this study are highly applicable to the general population of patients with allergy because the inclusion and exclusion criteria allowed for the participation of a broad population of patients with allergy taking systemic or nasal medications.

CONCLUSION

In this study, it was revealed that 90.5% of patients with allergic rhinitis being treated nasally or systemically also had ocular allergic symptoms. For these patients, QoL was impaired, and the addition of an efficacious antiallergy eyedrop resulted in beneficial effects on patient QoL. The addition of olopatadine eyedrops improved patient QoL from baseline by 49% compared to 5% improvement in the nontreatment group ($P < .001$), as measured by the well-validated RQLQ. In addition, the ACQLQ can become an important tool for furthering our understanding of therapeutic modulation and its impact on QoL in patients with ocular allergy.

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