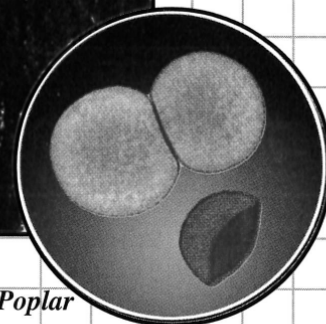


ANNALS OF Allergy, Asthma & Immunology

Official Publication of the American College of
Allergy, Asthma & Immunology

Contents of Annals of Allergy, Asthma &
Immunology Copyright © 2006 by the American
College of Allergy, Asthma & Immunology.

EDITOR: Gailen D. Marshall, MD, PhD
Annals of Allergy, Asthma & Immunology
University of Mississippi Medical Center
2500 North State Street
Jackson, MS 39216
(601) 815-5527
gmarshall@medicine.umsmed.edu



Cover Photo/Lombardy Poplar

Populus nigra

*"Sensitization to poplar pollen has been found in
allergic asthmatics, . . ."
(refer to page A6)*

VOLUME 97, SEPTEMBER, 2006

IN MEMORIAM

John C. Selner, MD, February 5, 1936, to July 20, 2006269
Gailen Marshall, MD, PhD

GUEST EDITORIAL

Specific polysaccharide antibody deficiency271
Charles H. Kirkpatrick, MD

CME REVIEW ARTICLE

Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal
necrolysis272
Barzin Khalili, MD, and Sami L. Bahna, MD, DrPH

CASE REPORTS

Lack of cross-reactivity between 5-aminosalicylic acid-based drugs: a case report and review
of the literature284
*Shiang-Ju Kung, MD; Cuckoo Choudhary, MD; Stephen J. McGeedy, MD and
John R. Cohn, MD*

Improvement of asthma control with omalizumab in 2 obese pediatric asthma patients288
Kenny Y. C. Kwong, MD, and Craig A. Jones, MD

Clustered sensitivity to fungi: anaphylactic reactions caused by ingestive allergy
to yeasts294
Kristiina Airola, MD, PhD; Leena Petman and Soili Mäkinen-Kiljunen, PhD

REVIEW

Use of the Health Plan Employer Data and Information Set for measuring and
improving the quality of asthma care298
*Erwin W. Gelfand, MD; Gene L. Colice, MD; Leonard Fromer, MD, FAAFP;
William B. Bunn III, MD, JD, MPH and Thomas J. Davies, JD, MPA*

Exhibit 1162

(Continued on page A7)

Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis

William Berger, MD*; Frank Hampel, Jr, MD†; Jonathan Bernstein, MD‡; Shailen Shah, MD§; Harry Sacks, MD¶; and Eli O. Meltzer, MD||

Background: In fall 2004, the first Azelastine Cetirizine Trial demonstrated statistically significant improvements in the total nasal symptom score (TNSS) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores with the use of azelastine nasal spray vs oral cetirizine in patients with seasonal allergic rhinitis (SAR).

Objective: To compare the effects of azelastine nasal spray vs cetirizine on the TNSS and RQLQ scores in patients with SAR.

Methods: This 2-week, double-blind, multicenter trial randomized 360 patients with moderate-to-severe SAR to azelastine, 2 sprays per nostril twice daily, or cetirizine, 10-mg tablets once daily. The primary efficacy variable was the 12-hour reflective TNSS (rhinorrhea, sneezing, itchy nose, and nasal congestion). Secondary efficacy variables were individual symptom scores and the RQLQ score.

Results: Azelastine nasal spray and cetirizine significantly improved the TNSS and individual symptoms compared with baseline ($P < .001$). The TNSS improved by a mean of 4.6 (23.9%) with azelastine nasal spray compared with 3.9 (19.6%) with cetirizine. Significant differences favoring azelastine nasal spray were seen for the individual symptoms of sneezing and nasal congestion. Improvements in the RQLQ overall ($P = .002$) and individual domain ($P \leq .02$) scores were greater with azelastine nasal spray. Both treatments were well tolerated.

Conclusions: Azelastine nasal spray and cetirizine effectively treated nasal symptoms in patients with SAR. Improvements in the TNSS and individual symptoms favored azelastine over cetirizine, with significant differences for nasal congestion and sneezing. Azelastine nasal spray significantly improved the RQLQ overall and domain scores compared with cetirizine.

Ann Allergy Asthma Immunol. 2006;97:375–381.

INTRODUCTION

Allergic rhinitis (AR) is one of the most common diseases in the general population. It is estimated that AR affects more than 50 million people in the United States, which represents approximately 20% of the general population.^{1,2} The various forms of nonallergic rhinitis have been reported to affect 15 to 20 million persons in the United States.³ In addition to AR and nonallergic rhinitis, estimates suggest that 22 million to 26 million persons have mixed rhinitis, ie, seasonal AR (SAR), with exacerbations from exposure to nonallergic triggers.^{4,5}

Azelastine nasal spray is a topically administered second-generation antihistamine indicated for the treatment of SAR and nonallergic vasomotor rhinitis. Azelastine is a phthalazine derivative and represents a unique class of antihistamines. The primary mechanism of action of azelastine is

H₁-receptor antagonism. Azelastine also has demonstrated inhibitory effects on other mediators of inflammation, including leukotrienes,⁶ bradykinin and substance P,^{6,7} cytokines,⁸ intercellular adhesion molecule 1 expression,⁹ and eosinophil chemotaxis.⁹ Cetirizine hydrochloride is an oral second-generation antihistamine indicated for the treatment of SAR and perennial AR. Cetirizine also has demonstrated inhibitory effects on leukotrienes,¹⁰ prostaglandins,¹¹ intercellular adhesion molecule 1 expression,¹² and eosinophil chemotaxis.¹²

In fall 2004, the effectiveness and tolerability of azelastine, 2 sprays per nostril twice daily, were compared with those of cetirizine, 10-mg tablets once daily, in a multicenter study of 307 patients with moderate-to-severe SAR (the first Azelastine Cetirizine Trial [ACT I]).¹³ During the 2-week double-blind treatment period, azelastine nasal spray significantly improved the overall total nasal symptom score (TNSS) compared with cetirizine ($P = .02$). Azelastine nasal spray also improved all 4 symptoms of the TNSS compared with baseline, with significantly greater improvement vs cetirizine for rhinorrhea ($P = .003$) and differences that trended toward significance for itchy nose ($P = .06$) and sneezing ($P = .07$).

Differences in the TNSS between azelastine nasal spray and cetirizine were more evident as the study progressed, with statistically significant differences favoring azelastine nasal spray on study days 8 through 14. In addition, azelastine nasal spray significantly improved health-related quality of

* Southern California Research, Mission Viejo, California.

† Central Texas Health Research, New Braunfels, Texas.

‡ Bernstein Clinical Research Center, Cincinnati, Ohio.

§ Allergy and Asthma Consultants of NJ-PA PC, Collegeville, Pennsylvania.

¶ MedPointe Pharmaceuticals, Somerset, New Jersey.

|| Allergy & Asthma Medical Group & Research Center APC, San Diego, California.

Funding for this study was provided by MedPointe Pharmaceuticals.

Received for publication September 28, 2005.

Accepted for publication in revised form February 13, 2006.

life (QoL) based on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) compared with cetirizine ($P = .049$). These significant improvements over cetirizine in symptom scores and QoL variables were observed even though both treatments were highly effective compared with the baseline TNSS and RQLQ scores ($P < .001$).

Outcomes in clinical trials in rhinitis can include symptom assessments, airway patency, and nasal cytology, and all are useful in evaluating the effectiveness of pharmacologic interventions. However, effective treatment of the rhinitic patient also includes improving physical, psychological, and emotional factors that may adversely affect the patient's ability to function in daily activities.² It is becoming increasingly evident that a more comprehensive measure of health status in patients with AR requires that health-related QoL assessments are made in conjunction with clinical assessments of symptoms.¹⁴ The objective of this study was to confirm the results of the ACT I by comparing the effects of using azelastine nasal spray vs cetirizine oral tablets on the TNSS and RQLQ scores according to an identical study design in patients with moderate-to-severe SAR.

METHODS

Patients

Qualified patients were males and females 12 years and older with at least a 2-year history of SAR and a documented positive skin test reaction to ambient pollen aeroallergen during the previous year. Exclusion criteria were use of concomitant medication(s) that could affect the evaluation of efficacy; any medical or surgical condition that could affect the metabolism of the study medications; clinically significant nasal disease (other than SAR) or significant nasal structural abnormalities; respiratory tract infection or other infection requiring antibiotic drug therapy within 2 weeks of beginning the baseline screening period; a history of or current alcohol or other drug abuse; or significant pulmonary disease, including persistent asthma requiring daily controller medication. Women of childbearing potential not using an accepted method of contraception and women who were pregnant or nursing also were excluded from participation. The use of allergy medications was discontinued before beginning the open-label lead-in period; use of oral antihistamines was discontinued for a minimum of 5 days and intranasal corticosteroids for a minimum of 14 days.

Study Design

This 2-week, randomized, double-blind, parallel-group comparative trial (ACT II) was conducted during the 2005 spring allergy season at 24 investigational research centers distributed throughout the major geographic regions of the United States. The study was approved by Sterling Institutional Review Board (Atlanta, GA), and all the patients or their guardians (for patients <18 years old) signed the institutional review board–approved informed consent agreement before participation.

Azelastine nasal spray (Astelin; MedPointe Pharmaceuticals, Somerset, NJ) was supplied in polyethylene bottles containing 30 mL of study medication. The 10-mg cetirizine tablets (Zyrtec; Pfizer Inc, New York, NY) were enclosed in a placebo-matching capsule overfilled with lactose. Placebo nasal spray was provided in polyethylene bottles containing 30 mL of vehicle solution. Placebo capsules were filled with lactose. Each patient received either (1) active azelastine, 2 sprays per nostril twice daily, in the morning and evening, and a placebo capsule once daily in the morning or (2) active cetirizine once daily in the morning and placebo nasal spray, 2 sprays per nostril twice daily, in the morning and evening, to ensure adequate blinding of the study. The dissolution rates of 10-mg cetirizine tablets and 10-mg encapsulated cetirizine tablets overfilled with lactose were shown to be almost identical at the 20- and 30-minute (100% dissolution) points at 37°C in a comparative dissolution assay performed by McKesson Bioservices (Rockville, MD) (MedPointe Pharmaceuticals, data on file).

Patients who met the inclusion and exclusion criteria were randomized to treatment groups by means of a computer-generated randomization schedule. The randomization schedule was provided by the biostatistical group (i3 Statprobe, Ann Arbor, MI) employed by the sponsor, and access to the random code was confidential and accessible only to authorized persons who were not involved in the study. Blinding of the study was preserved at each study site until all the patients completed the study and the database was locked.

The study began with a 1-week, single-blind, placebo lead-in period, during which patients received placebo nasal spray and placebo capsules and recorded their 12-hour reflective rhinitis symptom severity scores twice daily (morning and evening) in diary cards to determine their eligibility for entry into the double-blind treatment period. Symptom severity was determined by the TNSS, which consisted of runny nose, sneezing, nasal itching, and nasal congestion scored twice daily (morning and evening) on a severity scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe), such that the maximum possible daily TNSS was 24. Patients qualified for entry into the lead-in period if they had a TNSS of at least 8 and a nasal congestion score of at least 2 during the previous 12 hours and met all the study inclusion and exclusion criteria. To be eligible for entry into the double-blind treatment period, patients must have recorded either a morning or evening TNSS of at least 8 on at least 3 days during the lead-in period and a morning or evening congestion score of 3 on at least 3 days. For TNSS and nasal congestion, 1 of the 3 days selected must have occurred within 2 days of study day 1.

Efficacy and Safety Variables

The primary efficacy variable was the change from baseline to day 14 in rhinitis symptom severity based on the combined morning and evening 12-hour reflective TNSS. Secondary efficacy variables were (1) change from baseline to day 14 in QoL variables using the RQLQ and (2) change from baseline

to day 14 in individual symptoms. Safety was evaluated by patient reports of adverse experiences and vital sign assessments, including body temperature, systolic and diastolic blood pressure, and pulse and respiration rates, which were performed at baseline and at the end of the study.

Statistical Analysis

The study sample size was based on the results of the study by Corren et al (ACT I),¹³ which was conducted in 307 patients according to a similar protocol, and on the results of a double-blind, placebo-controlled pilot study¹⁵ in which 60 patients were treated for 1 week with azelastine nasal spray, fluticasone nasal spray, cetirizine tablets, or placebo. An effect size $([\text{azelastine mean} - \text{cetirizine mean}]/\text{pooled SD})$ of 0.25 to 0.35 was identified for change in TNSS from baseline to day 14. Considering this effect size, it was determined that 150 to 175 patients per treatment group would be sufficient to detect differences between groups at the $\alpha = .05$ level of significance with 80% power. The primary analysis was an intention-to-treat (ITT) analysis that included all randomized patients with at least 1 postbaseline TNSS evaluation. Missing TNSSs in the ITT population were imputed using the last-observation-carried-forward method.

For the primary efficacy variable (change in the TNSS from baseline to day 14), the baseline score was calculated as the average of the combined morning and evening TNSSs during the placebo lead-in period. The change from baseline to day 14 was determined by subtracting the mean baseline score from the mean TNSS for the entire 14-day treatment period. Within-group comparisons were made using the paired *t* test, and between-group comparisons were made using an analysis of variance (ANOVA) model. The change from baseline in individual symptom severity scores was evaluated using a similar ANOVA model. The change in TNSS from baseline was also calculated for each individual day of the study, with baseline defined as the average of the combined morning and evening TNSSs during the lead-in period. Within- and between-group comparisons were made using the paired *t* test and ANOVA, respectively.

The QoL evaluation was performed using the self-administered RQLQ, which evaluated the following 7 domains and components: (1) activities (3 most important as identified by the patient), (2) sleep (difficulty getting to sleep, waking up during the night, lack of a good night's sleep), (3) nonnose/noneye symptoms (fatigue, thirst, reduced productivity, tiredness, poor concentration, headache, worn out), (4) practical problems (inconvenience of having to carry tissues or a handkerchief, need to rub nose/eyes, need to blow nose repeatedly), (5) nasal symptoms (stuffy/blocked, runny, sneezing, postnasal drip), (6) eye symptoms (itchy, watery, sore, swollen), and (7) emotional factors (frustrated, impatient or restless, irritable, embarrassed by symptoms). The change from baseline to day 14 in the RQLQ domain and overall scores was calculated and analyzed according to the method described by Juniper et al.¹⁶ Baseline demographics, clinical characteristics, and safety data were summarized

descriptively. The safety analysis included all the patients who received at least 1 dose of study medication and had at least 1 safety evaluation after drug administration.

RESULTS

Patients

A total of 360 patients were randomized to double-blind treatment; however, postbaseline observations were missing for 6 patients. Therefore, data from 354 patients were included in the primary analysis of the ITT population. The evaluable patient population consisted of 342 patients who completed the 2-week study as per protocol. Nine patients discontinued before completing the 2-week treatment period: 7 in the azelastine group (4 experienced adverse events, 1 was lost to follow-up, and 2 for administrative reasons) and 2 in the cetirizine group (1 had an adverse event and 1 was lost to follow-up). Three patients completed the 2-week protocol but were not considered evaluable due to protocol violations. The treatment groups were comparable regarding demographic characteristics (Table 1). The patients ranged in age from 12 to 74 years (mean age, 35 years); 58% were female and 42% were male; and 78% were white, 7% were black, 5% were Asian, and 10% were of another racial background. The average duration of SAR was 18.4 years in the azelastine group and 18.7 years in the cetirizine group.

Primary Efficacy

The combined morning and evening 12-hour reflective TNSS was significantly improved compared with the baseline score in both treatment groups during the 2-week double-blind treatment period ($P < .001$). In the ITT population, the mean \pm SD baseline TNSS was 18.7 ± 3.1 with azelastine nasal spray ($n = 179$) and 19.1 ± 3.2 with cetirizine ($n = 175$). In the evaluable population, the mean \pm SD baseline TNSS was 18.7 ± 3.1 with azelastine nasal spray ($n = 174$) and 19.1 ± 3.1 with cetirizine ($n = 168$). In the primary analysis of the ITT population, the mean \pm SD improvement from the baseline TNSS was 4.6 ± 4.2 with azelastine nasal spray and 3.9 ± 4.3 with cetirizine ($P = .14$). The percentage change was 23.9% with azelastine nasal spray and 19.6% with cetirizine ($P = .08$). In the evaluable population, the

Table 1. Demographic Characteristics of the Study Population

Characteristic	Azelastine nasal spray group (n = 179)	Cetirizine group (n = 175)
Sex, No. (%)		
M	72 (40.2)	77 (44.0)
F	107 (59.8)	98 (56.0)
Race, No. (%)		
White	139 (77.7)	136 (77.7)
Black	9 (5.0)	15 (8.6)
Asian	9 (5.0)	7 (4.0)
Other	22 (12.3)	17 (9.7)
Age, mean (range), y	35.1 (12–64)	34.3 (12–74)

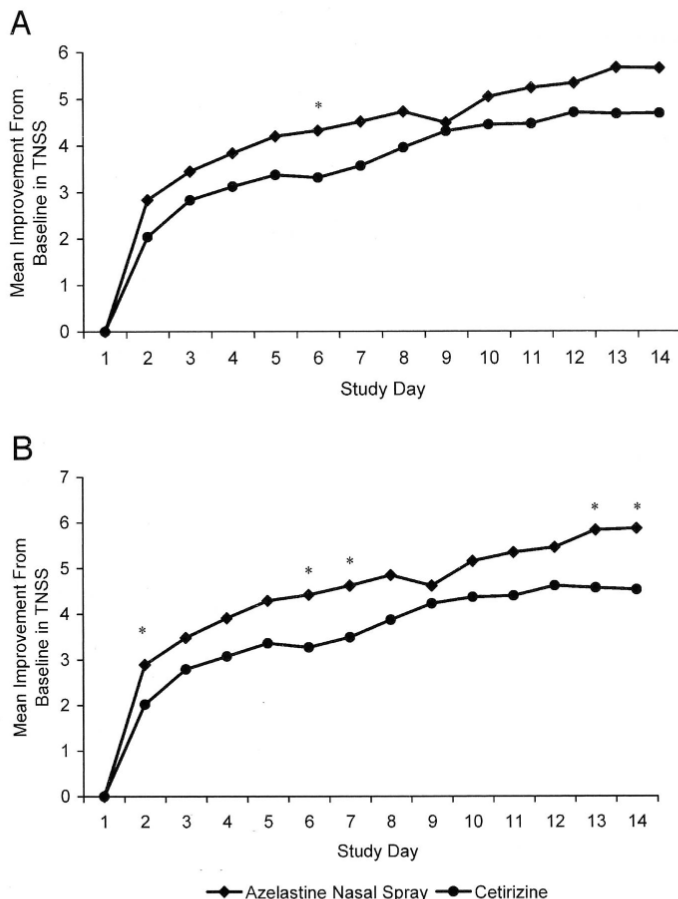


Figure 1. Mean daily improvements from baseline to day 14 in combined morning and evening 12-hour reflective total nasal symptom scores (TNSSs) in the intention-to-treat (A) and evaluable (B) patient populations. * $P < .05$ vs cetirizine (statistical significance for the entire 14 study days: intention-to-treat population, $P = .14$; evaluable population, $P = .09$).

mean \pm SD improvement from baseline was 4.6 ± 4.2 with azelastine nasal spray and 3.8 ± 4.3 with cetirizine ($P = .09$), and the percentage improvement was 24.2% with azelastine nasal spray and 19.2% with cetirizine ($P = .046$). Patients in both treatment groups experienced increasing improvements in the TNSS as the study progressed. Individual daily improvements for the ITT and evaluable patient populations are shown in Figure 1.

Secondary Efficacy

Change from baseline to day 14 in RQLQ scores. Each individual RQLQ domain score and the overall RQLQ score were significantly improved from baseline in both treatment groups ($P < .001$). Azelastine nasal spray significantly improved each domain of the RQLQ, including the nasal symptoms domain ($P \leq .05$), and the overall RQLQ score ($P = .002$) compared with cetirizine (Fig 2).

Change from baseline to day 14 in individual symptoms. In the ITT population, the 4 individual symptoms of the TNSS were significantly improved during the 14-day study with

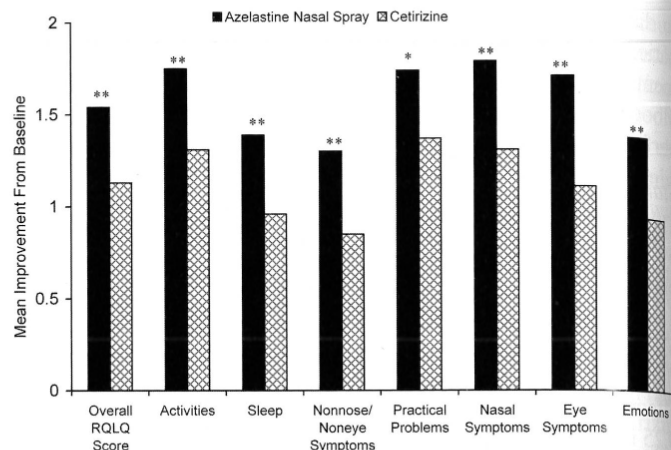


Figure 2. Mean improvement from baseline to day 14 in overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score and individual RQLQ domain scores (intention-to-treat population). * $P \leq .05$ vs cetirizine. ** $P < .01$ vs cetirizine.

both treatments compared with baseline scores ($P \leq .03$). Improvements in the 4 symptoms of the TNSS favored azelastine nasal spray over cetirizine, and statistically significant improvements in favor of azelastine nasal spray were observed for nasal congestion ($P = .049$) and sneezing ($P = .01$) (Fig 3).

Safety

Azelastine nasal spray and cetirizine were well tolerated in this study. The most common adverse event with azelastine nasal spray was bitter taste (7.7%). All other adverse events in both treatment groups, including somnolence, headache, epistaxis, and pharyngolaryngeal pain, occurred with an incidence of less than 2%. Four patients in the azelastine group discontinued the study because of adverse events (headache and fatigue, unexpected pregnancy, elevated blood pressure, and cough). One patient in the cetirizine group discontinued because of vomiting and gastrointestinal distress. There were

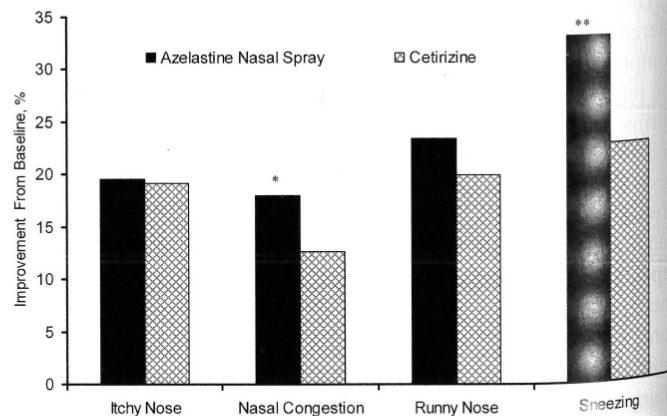


Figure 3. Percentage improvement from baseline to day 14 in individual symptom scores (intention-to-treat population). * $P = .049$ vs cetirizine. ** $P = .01$ vs cetirizine.

no clinically significant pretreatment to posttreatment changes in vital signs in either treatment group.

DISCUSSION

Previous comparative studies^{17,18} of oral antihistamines in SAR generally have not shown significant differences between agents when evaluated across 14-day study periods. For ACT I,¹³ it was hypothesized that an intranasally administered antihistamine should have a greater effect on symptoms than an oral second-generation antihistamine, due in part to greater local concentrations of active drug in the nasal mucosa. In that study, it was shown that azelastine nasal spray was significantly more effective than oral cetirizine for treating nasal symptoms and for improving the overall RQLQ score in patients with moderate-to-severe SAR.

In the present study, azelastine nasal spray and cetirizine significantly improved the TNSS and individual symptoms of the TNSS compared with baseline scores overall and on each day of the study. Rapid relief of rhinitis symptoms was evident in both groups at the first evaluation after initial administration. Azelastine nasal spray continuously improved the TNSS during the 14 study days, with the greatest degree of improvement during the second week of treatment. Differences in the TNSS between azelastine nasal spray and cetirizine were not statistically significant; however, the magnitude of improvement favored azelastine nasal spray over cetirizine on each of the 14 study days. In addition, there was a statistically significant difference favoring azelastine nasal spray for overall percentage improvement in the TNSS in the evaluable patient population. Although there were no differences between treatment groups in TNSS, a statistically significant difference favoring azelastine nasal spray over cetirizine was seen in the nasal symptoms domain of the RQLQ, which reflects improvement in the severity of nasal symptoms on the last day of the 14-day study.

Regarding individual symptoms, azelastine nasal spray significantly improved sneezing and nasal congestion compared with cetirizine. The positive effect of azelastine nasal spray on congestion was observed despite the fact that the cetirizine group had the added benefit of daily use of a placebo saline spray. Based on data from ACT I and ACT II, nasal congestion seems to be the most difficult symptom to treat in the rhinitis symptom complex. In ACT I, the improvement in nasal congestion with azelastine nasal spray was 21.1% compared with a placebo response of 18.1%, whereas in ACT II, the improvement in nasal congestion with azelastine nasal spray was 18.0% compared with a placebo response of 12.6%. It seems that the failure to demonstrate a statistical difference between treatments in ACT I was due to the high placebo response rate in that study.

The ability of azelastine nasal spray to improve nasal congestion has previously been reported in multicenter placebo-controlled trials in SAR¹⁹ and nonallergic vasomotor rhinitis.²⁰ The importance of effectively treating nasal congestion was demonstrated in a large open-label trial²¹ involving more than 4,000 patients with SAR, nonallergic vasomo-

tor rhinitis, or mixed rhinitis (seasonal allergies with sensitivity to nonallergic triggers) in which nasal congestion was reported as the most bothersome rhinitis symptom by 52% of the patients. In this trial, azelastine nasal spray was reported to control all rhinitis symptoms, including nasal congestion, regardless of rhinitis diagnosis, and patients with mixed rhinitis were identified as a subgroup most likely to respond to treatment with azelastine nasal spray.

The RQLQ is a standardized disease-specific questionnaire that was developed to measure physical, emotional, and social problems that are troublesome to patients with rhinoconjunctivitis.²² The RQLQ has been methodologically validated, is reproducible in patients with stable rhinitis, and has been determined to be capable of detecting clinically meaningful changes in QoL variables.¹⁶ As in ACT I, in the present study, all the individual domains of the RQLQ and the overall RQLQ score were significantly improved from baseline in both treatment groups. Although oral cetirizine significantly improved RQLQ scores, patients treated with azelastine nasal spray reported additional statistically significant improvement beyond that reported with cetirizine for each individual RQLQ domain, including the nasal symptoms domain, and for the overall RQLQ score. Although it is often assumed that patients prefer oral medications to sprays, in ACT I and ACT II, patients reported superior improvements in QoL variables with azelastine nasal spray compared with oral cetirizine. The clinical benefits of topical therapy with azelastine are evident in the consistent outcomes of ACT I and ACT II. In both trials, there were no times during the 14-day TNSS evaluation periods, no individual symptom assessments, and no individual domains of the RQLQ where azelastine nasal spray was not numerically or statistically better than cetirizine.

Rhinitis is a significant cause of widespread morbidity, and although often incorrectly viewed as a nuisance disease, the symptoms of rhinitis can have a major impact on the patient's QoL by interfering with sleep, causing fatigue, and impairing daily activities and cognitive function.¹ Although individual symptoms of AR may be particularly bothersome, it is often the impact of these symptoms on daily activity and well-being that causes the patient to seek medical care.²³ As an example of the magnitude of this effect, in a study of patients with perennial AR, Bousquet et al²⁴ reported that QoL tended to be worse in 7 of 9 health-related domains among patients with rhinitis compared with those with asthma.

The Joint Task Force on Allergy Practice and Parameters advises that improving the negative impact on daily life in patients with rhinitis defines successful treatment as much as providing symptom relief.¹ The value of health-related QoL assessments in rhinitis is the emphasis that is placed on the patient's perspective in assessing the functional effects of the illness and the therapy.²⁵ As recommended by Juniper,²⁶ for most patients with rhinitis, and in particular for patients with SAR, improving patient well-being and QoL should be the primary goal of treatment.

The use of topical therapy is appropriate in the treatment of SAR. Delivering medication directly to the site of allergic

inflammation has an inherent advantage over oral therapy. The higher concentrations of antihistamines that can be achieved in the nasal mucosa by topical as opposed to oral administration should enhance the antiallergic and potential anti-inflammatory effects of these agents, making targeted delivery to the site of inflammation an important consideration in selecting therapy for rhinitis. In addition, topical administration should minimize the risk of interactions with concomitant medications.²⁷ The benefits of topical antihistamine therapy have been demonstrated in placebo-controlled clinical studies with oral antihistamines in which azelastine nasal spray was effective in treating patients who remained symptomatic after treatment with oral loratadine²⁸ or fexofenadine.²⁹ In these studies, no additional clinical benefit was seen with azelastine nasal spray combined with oral agents compared with treatment with the nasal spray alone.

This study was double-blinded such that each patient received either an identity-concealed bottle of azelastine nasal spray plus placebo capsules or encapsulated cetirizine tablets plus placebo/saline nasal spray. The beneficial effect of intranasal saline on chemical mediators of inflammation and symptoms of rhinitis has been documented in clinical trials.^{30,31} In effect, patients in the cetirizine group were taking an active second therapeutic agent (saline nasal spray) in addition to the oral antihistamine. The use of a saline spray placebo in the cetirizine group might reduce the difference between the 2 groups, thereby making it more difficult to achieve a statistically significant separation between treatments. As such, the difference in the TNSS between azelastine nasal spray and cetirizine oral tablets may in fact be greater than the difference observed in this study.

Azelastine nasal spray and cetirizine were well tolerated in this study. Although relatively high incidences of somnolence and bitter taste were reported in early trials^{19,32–35} with azelastine nasal spray, subsequent trials in patients with vasomotor rhinitis²⁰ and postmarketing studies in patients who remained symptomatic after treatment with loratadine²⁸ or fexofenadine²⁹ reported somnolence rates with azelastine nasal spray that were similar to those with placebo. The lower incidence of azelastine-related adverse events in the later trials is most likely due to using a proper dosing technique, in which the drug is administered without tipping the head backward or deeply inhaling the spray, thereby minimizing the potential for systemic absorption, which could result in bitter taste and somnolence.

CONCLUSIONS

This study was conducted to compare the use of azelastine nasal spray vs cetirizine oral tablets for improving nasal symptoms and health-related QoL variables in patients with SAR. Azelastine nasal spray and cetirizine were effective in treating nasal symptoms in patients with moderate-to-severe SAR. In the primary analysis, although not achieving statistical significance, improvement in the TNSS and individual symptom scores favored azelastine nasal spray over cetirizine, and statistically significant differences favoring azelas-

tine nasal spray were seen for the individual symptoms of nasal congestion and sneezing. In addition, azelastine nasal spray significantly improved QoL compared with cetirizine oral tablets in the overall RQLQ score and for each individual RQLQ domain.

ACKNOWLEDGMENTS

We thank William Wheeler, PhD, for his contributions to the design of the study and preparation of the manuscript and Carrie D'Andrea, MS, for clinical trial management.

Members of the ACT II Study Group include the following: Niranjana J. Amar, MD, Waco, TX; Jonathan Corren, MD, Los Angeles, CA; Bruce DeCotis, MD, Brick, NJ; David Graft, MD, Minneapolis, MN; Harold B. Kaiser, MD, Minneapolis, MN; John Klimas, MD, Charlotte, NC; Craig F. LaForce, MD, Raleigh, NC; Dennis K. Ledford, MD, Tampa, FL; William R. Lumry, MD, Dallas, TX; S. David Miller, MD, North Dartmouth, MA; Anjali S. Nayak, MD, Normal, IL; Andrew J. Pedinoff, MD, Skillman, NJ; Bruce M. Prenner, MD, San Diego, CA; Paul H. Ratner, MD, San Antonio, TX; Ellen Sher, MD, Ocean, NJ; David L. Schneider, MD, Metairie, LA; William W. Storms, MD, Colorado Springs, CO; Ashley J. Tatum, MD, Seattle, WA; and John A. Zora, MD, Woodstock, GA.

REFERENCES

1. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol.* 1998;81:478–518.
2. Thompson A, Juniper E, Meltzer E. Quality of life in patients with allergic rhinitis. *Ann Allergy Asthma Immunol.* 2000;85:338–348.
3. Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. *Allergy Asthma Proc.* 2001;22:185–189.
4. Settipane RA, Lieberman P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol.* 2001;86:494–508.
5. Settipane RA, Settipane GA. Nonallergic rhinitis. In: Kaliner MA, ed. *Current Review of Allergic Diseases*. Philadelphia, PA: Current Medicine Inc; 2002:53–66.
6. Shin MH, Baroody F, Proud D, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. The effect of azelastine on the early allergic response. *Clin Exp Allergy.* 1992;22:289–295.
7. Shinoda M, Watanabe N, Suko T, Mogi G, Takeyama M. Effects of anti-allergic drugs on substance P (SP) and vasoactive intestinal peptide (VIP) in nasal secretions. *Am J Rhinol.* 1997;11:237–241.
8. Ito H, Nakamura Y, Takagi S, Sakai K. Effects of azelastine on the level of serum interleukin-4 and soluble CD23 antigen in the treatment of nasal allergy. *Arzneim-Forsch.* 1998;48:1143–1147.
9. Ciprandi G, Pronzato C, Passalacqua G, et al. Topical azelastine reduces eosinophil activation and intercellular adhesion molecule-1 expression on nasal epithelial cells: an antiallergic activity. *J Allergy Clin Immunol.* 1996;98:1088–1096.
10. Cheria-Sammari S, Aloui R, Gormand B, et al. Leukotriene B₄ production by blood neutrophils in allergic rhinitis: effects of cetirizine. *Clin Exp Allergy.* 1995;25:729–736.

11. Charlesworth EN, Kagey-Sobotka A, Norman PS, Lichenstein LM. Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. *J Allergy Clin Immunol.* 1989;83:905-912.
12. Ciprandi G, Buscaglia S, Pesce G, et al. Cetirizine reduces inflammatory cell recruitment and ICAM-1 (or CD54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge. *J Allergy Clin Immunol.* 1995;95:612-621.
13. Corren J, Storms W, Bernstein J, et al. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther.* 2005;27:543-553.
14. Meltzer EO, Tyrell RJ, Rich D, Wood CC. A pharmacologic continuum in the treatment of rhinorrhea: the clinician as economist. *J Allergy Clin Immunol.* 1995;95:1147-1152.
15. Corren J, Sacks H, Nayak A. Efficacy of azelastine nasal spray, cetirizine tablets, fluticasone nasal spray, and placebo in patients with seasonal allergic rhinitis [abstract]. *Ann Allergy Asthma Immunol.* 2005;94:197.
16. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol.* 1999;104:364-369.
17. Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1999;104:927-933.
18. Hampel F, Ratner P, Mansfield L, et al. Fexofenadine hydrochloride, 180 mg, exhibits equivalent efficacy to cetirizine, 10 mg, with less drowsiness in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2003;91:354-361.
19. Storms WW, Pearlman DS, Chervinsky P, et al. Effectiveness of azelastine nasal solution in seasonal allergic rhinitis. *ENT J.* 1994;73:382-389.
20. Banov CH, Lieberman P. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol.* 2001;86:28-35.
21. Lieberman P, Kaliner MA, Wheeler WJ. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. *Curr Med Res Opin.* 2005;21:611-618.
22. 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.
23. Juniper EF. Rhinitis management: the patient's perspective. *Clin Exp Allergy.* 1998;28:34-38.
24. Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial rhinitis with the French version of the SF-36 health status questionnaire. *J Allergy Clin Immunol.* 1994;94:182-188.
25. Schipper H, Clinch J, Powell V. Definitions and conceptual issues. In: Spilker B, ed. *Quality of Life Assessment in Clinical Trials.* New York, NY: Raven Press Ltd; 1990:11-24.
26. Juniper EF. Measuring health-related quality of life in rhinitis. *J Allergy Clin Immunol.* 1997;99:S742-S749.
27. Davies RJ, Bagnall AC, McCabe RN, et al. Antihistamines: topical vs oral administration. *Clin Exp Allergy.* 1996;26:S11-S17.
28. Berger WE, White MV. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. *Ann Allergy Asthma Immunol.* 2003;91:205-211.
29. LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. *Ann Allergy Asthma Immunol.* 2004;93:154-159.
30. Georgitis J. Nasal hyperthermia and simple irrigation for perennial rhinitis changes in inflammatory mediators. *Chest.* 1994;106:1487-1492.
31. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. *Laryngoscope.* 2000;11:1189-1193.
32. Weiler JM, Meltzer EO, Benson PM, Weiler K, Widlitz MD, Freitag J. A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model. *J Allergy Clin Immunol.* 1994;94:972-980.
33. Meltzer EO, Weiler JM, Dockhorn RJ, Widlitz MD, Freitag JJ. Azelastine nasal spray in the management of seasonal allergic rhinitis. *Ann Allergy.* 1994;72:354-359.
34. Ratner PH, Findlay SR, Hampel F, van Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1994;94:818-825.
35. LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1996;76:181-188.

Requests for reprints should be addressed to:
 William Berger, MD
 Southern California Research
 27800 Medical Center Rd
 Suite 240
 Mission Viejo, CA 92691
 E-mail: weberger@uci.edu