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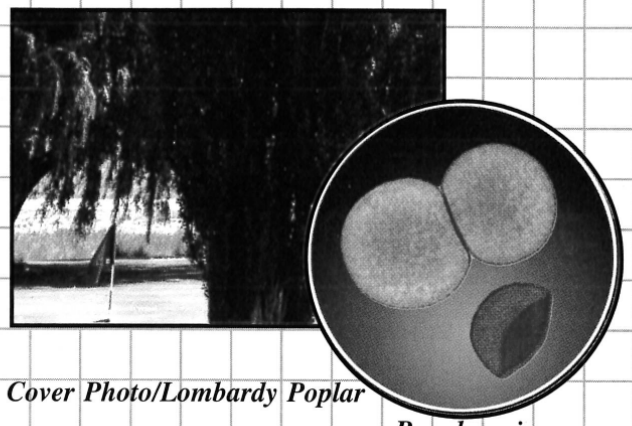

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Populus nigra

"Sensitization to poplar pollen has been found in allergic asthmatics, . . ."
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REVIEW

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

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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.

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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 phthalazinone derivative and represents a unique class of antihistamines. The primary mechanism of action of azelastine is H_1-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

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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 study[15] in which 60 patients were treated for 1 week with azelastine nasal spray, fluticasone nasal spray, cetirizine tablets, or placebo. An effect size ([azelastine mean – cetirizine mean]/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 ± 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 ± 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 ± 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)

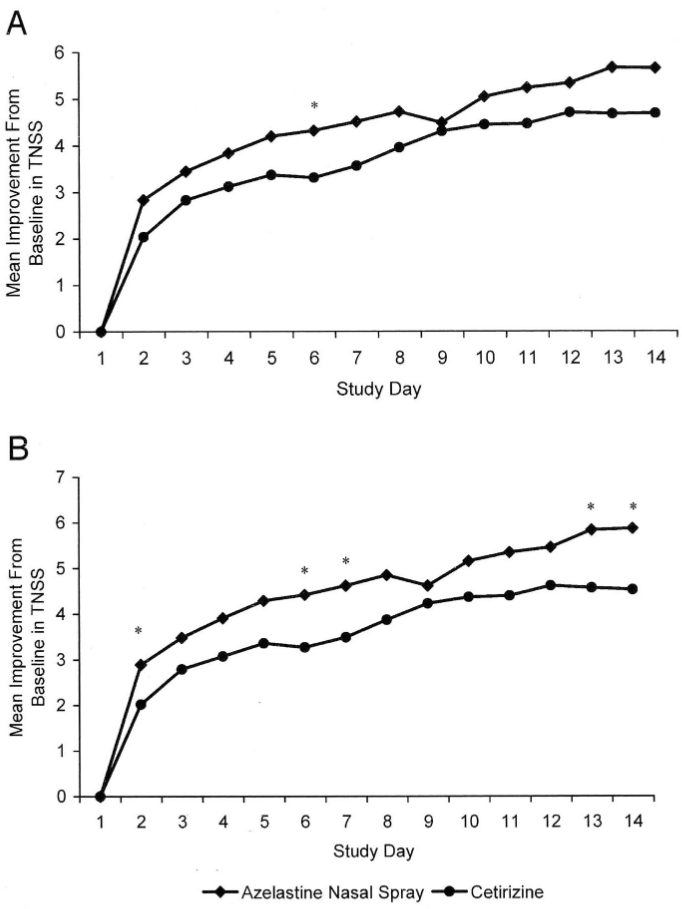

Figure 1. Mean daily improvements from baseline to day 14 in combined morning and evening 12-hour reflective total nasal symptom scores (TNSSs) in the intention-to-treat (A) and evaluable (B) patient populations. *$P < .05$ vs cetirizine (statistical significance for the entire 14 study days: intention-to-treat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

mean ± 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

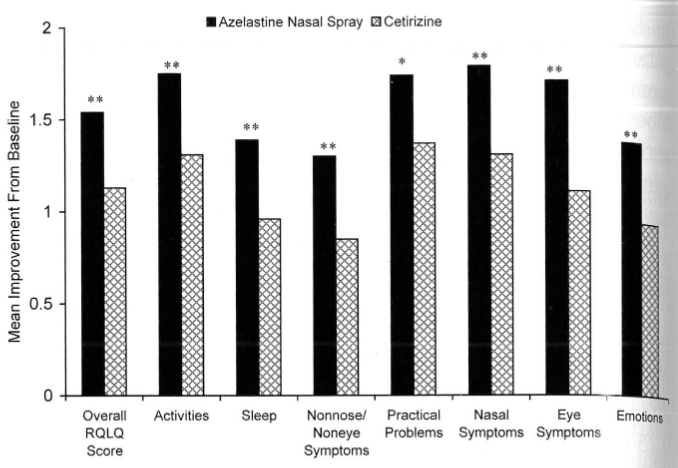

Figure 2. Mean improvement from baseline to day 14 in overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score and individual RQLQ domain scores (intention-to-treat population). *$P \leq .05$ vs cetirizine. **$P < .01$ vs cetirizine.

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

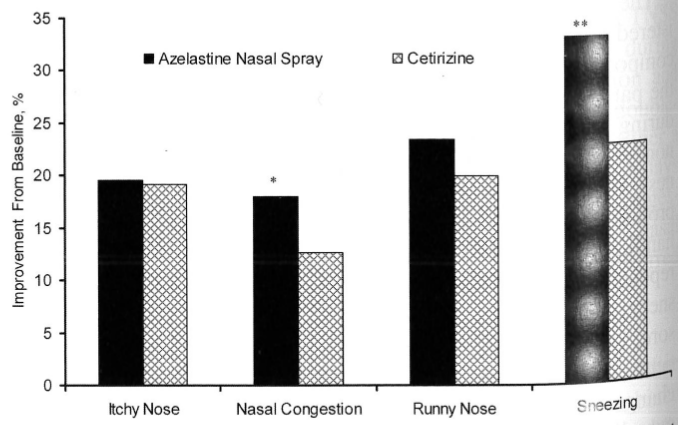

Figure 3. Percentage improvement from baseline to day 14 in individual symptom scores (intention-to-treat population). *$P = .049$ vs cetirizine. **$P = .01$ vs cetirizine.

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