A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis

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Background: *Azelastine solution is a topically (nasal) administered antiallergy drug with a preclinical profile suggestive of efficacy in patients with allergic rhinitis.*
Objectives: *The study was designed to compare the effectiveness and safety of two dosages of azelastine nasal spray (2 sprays per nostril once daily and twice daily) with that of placebo in the treatment of patients with symptomatic seasonal allergic rhinitis.*
Methods: *Two hundred fifty-one patients (12 years of age or older) were randomized to treatment in this 2-week, double-blind, parallel-group study. Primary efficacy variables were Major Symptom Complex (nose blows, sneezes, runny nose, itchy nose, watery eyes) and Total Symptoms Complex (Major Symptom Complex plus itchy eyes/ears/throat/palate, cough, postnasal drip).*
Results: *Patients treated with azelastine had mean percent improvements in Total and Major Symptom Complex scores that were consistently superior to placebo at each evaluation point. Overall, improvements were statistically significant ($p \leq 0.05$) in the Total Symptoms Complex for both azelastine groups and in the Major Symptom Complex for the twice daily group with a trend toward statistical significance for the once daily group. Azelastine was superior to placebo in improving all individual rhinitis symptoms. Adverse experiences in the azelastine groups were minor and infrequent.*
Conclusion: *The results support the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis. (J Allergy Clin Immunol 1994;94:818-25.)*

Key words: *Azelastine nasal spray, symptomatic seasonal allergic rhinitis, Major Symptom Complex, Total Symptom Complex*

Azelastine hydrochloride is an investigational antiallergic compound that has been shown in human and animal model systems to inhibit the synthesis or target receptor activity of a broad spectrum of biologic mediators of allergy and airway hyperreactivity including histamine,[1, 2] leukotrienes,[3, 4] TAME-esterase,[5] acetylcholine,[6] serotonin,[7, 8] and bradykinin.[9] The effects of inhibiting these mediators include the inhibition of allergic reactions, interference with inflammatory processes, and modulation of airway smooth muscle response. For these reasons, azelastine should be characterized as a multifunctional antiallergic medication because it provides significant therapeutic activity in allergic hayfever and allergic asthma.[10]

Abbreviations used:
b.i.d.: Twice a day
MSC: Major Symptom Complex
NS: Nasal spray
q.d.: Once a day
SAR: Seasonal allergic rhinitis
TSC: Total Symptom Complex

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Previous short-term studies of azelastine nasal spray (Astelin NS) have shown that dosage regimens of 2 sprays per nostril once a day (q.d.) and 2 sprays per nostril twice a day (b.i.d.) are safe and effective in the treatment of seasonal allergic rhinitis (SAR).[11, 12] These studies also demonstrated that azelastine nasal spray (NS) has a rapid onset of action (within 1 to 2 hours of administration) and a long duration of effect, lasting up to 24 hours.

To alleviate the limiting factors that are often associated with SAR trials (e.g., variability and duration of the pollen counts), this study was conducted in south central Texas where pollen from the tree *Juniperus sabinoides*, commonly called mountain cedar, is an important cause of respiratory allergy. The mountain cedar pollinates heavily during the months of December, January, and February and somewhat less so in November and March, depending on yearly weather conditions. In the winter months, the pollen from the mountain cedar blows in with "northern fronts" and is the only pollen present in significant amounts in the air during this time. Mountain cedar pollen counts are higher than those observed with any other seasonal pollen. As such, it provides an excellent research model with which to evaluate the efficacy of medications in treatment of pollen-induced respiratory allergy.

In this study, conducted at four sites in south central Texas during the mountain cedar pollen season in January and February, the efficacy and safety of two dosages of azelastine NS were compared with efficacy and safety of placebo in the long-term treatment of patients with symptomatic SAR.

METHODS

Patients

All patients were at least 12 years old with a history and diagnosis of allergic rhinitis requiring therapy for at least the previous 2 years and a positive response to mountain cedar pollen, as confirmed by a recognized prick or scratch test within the past year. A signed informed consent document was required before the screening period. The consent document for those under the legal age of consent (18 years) was also signed by a parent or guardian.

Patients with a history of asthma could be enrolled if they had not taken long-term antiasthma medication for at least 24 consecutive months before study entrance or if they had a history of exercise-induced asthma and had used a β-agonist inhaler only in conjunction with exercise. Patients with acute exacerbations of asthma were excluded from study participation.

Pregnant and nursing women were ineligible for participation, and women of childbearing potential were included only if they used appropriate methods of contraception. Patients with an upper respiratory tract infection, with clinically significant nasal anatomic deformities, or with other significant medical conditions were excluded, as were those who experienced an episode of acute sinusitis within 60 days of participation and those receiving a changing immunotherapy regimen or beginning immunotherapy.

The following medications were restricted before the baseline evaluation: calcium channel blockers, cromolyn, β-blockers, reserpine, or monoamine oxidase inhibitors within 14 days; H_1-receptor antagonists or decongestants within 48 hours; and astemizole within 60 days. Also ineligible for study participation were those patients who had experienced a clinically significant adverse drug reaction during a previous drug study with azelastine or a similar drug.

Study design

This was a multicenter, double-blind, randomized, placebo- and positive-controlled, parallel-group study in patients with symptomatic SAR. After a 1-week single-blind placebo evaluation period, eligible patients who satisfied the minimum symptom criteria (a Major Symptom Complex [MSC] score of at least 10 on any 4 days of the baseline period with at least one symptom of moderate or greater intensity on each of the 4 days) were randomized to one of four treatment groups: azelastine NS, 2 sprays per nostril q.d. (total daily dose = 0.55 mg), azelastine NS, 2 sprays per nostril b.i.d. (total daily dose = 1.1 mg); chlorpheniramine maleate (Chlor-Trimeton Repetabs) 12 mg b.i.d.; or placebo, b.i.d. for 2 weeks of treatment.

Study medication was blinded with a double-dummy technique for both the NS and tablets. Patients received medication twice a day; at both times, they took the tablet and the NS. For the chlorpheniramine group, the NS was matching placebo, and for the azelastine groups, the tablet was matching placebo.

Rhinitis symptoms were recorded at the time of drug administration (once in the morning and once in the evening) on a diary card. For the symptoms of runny nose and sniffles; itchy nose; watery eyes; itchy eyes, ears, throat, and palate; cough; postnasal drip; and symptom stuffiness the patients used the following scale to rate severity: 0 = none; 1 = mild, symptoms barely noticeable; 2 = modest, symptoms noticeable; 3 = moderate, somewhat bothersome; 4 = moderately severe, interfered with activities; and 5 = severe, constant distraction. For nose blows and sneezes the patients used the following scale to rate the number (and severity) of their symptoms: 0 = none; 1 = 1 to 3 (mild); 2 = 4 to 6 (modest); 3 = 7 to 10 (moderate); 4 = 11 to 15 (moderately severe); 5 = more than 15 (severe).

After 1 and 2 weeks of double-blind treatment, patients returned to the study site for a physical and

TABLE I. Demographic and baseline characteristics

	Azelastine NS q.d. (*n* = 62)	Azelastine NS b.i.d. (*n* = 63)	Chlorpheniramine (*n* = 62)	Placebo (*n* = 64)
Age (yr)				
Mean	35	39	39	39
Range	12-65	12-70	13-68	13-71
Sex (%)				
Male	47	68	52	52
Female	53	32	48	48
Race (%)				
White	95	97	98	97
Other	5	3	2	3
Weight (lb)				
Mean	158.7	175.5	160.8	163.5
Range	79-237	92-270	95.5-280	90-272.5
Baseline				
Mean TSC	18.2	18.8	18.4	18.6
Mean MSC	12.1	12.5	12.4	12.2

nasal examination and a diary review. A follow-up evaluation was performed 1 week after completion or early discontinuation of double-blind therapy.

The primary efficacy parameters consisted of the Total Symptom Complex (TSC) and MSC severity scores. In general, the TSC consists of the symptoms that are typically part of the rhinitis profile, and the MSC consists of those symptoms most dominant in the rhinitis symptom profile. Five individual symptom scores (runny nose, itchy nose, sneezing, nose blows, and watery eyes) were summed to form the MSC severity score and three additional symptoms (postnasal drip, cough, and itchy eyes/ear/throat/palate) were summed with the MSC to form the TSC severity score.

The changes from baseline for the TSC and MSC severity scores were based on the daily average mean scores. For each evaluation period (at the end of weeks 1 and 2 and at the end of study), the mean for all the morning individual rhinitis symptom scores and the mean for all the evening individual rhinitis symptom scores were calculated for the respective periods. The overall daily average was then calculated on the basis of the mean of the two means. The TSC and MSC severity scores were determined by summing the daily average severity scores for the appropriate individual rhinitis symptoms at baseline and at each evaluation period.

Secondary efficacy parameters consisted of changes in individual symptoms, changes in the TSC severity score that included the additional symptom of stuffiness, the investigators' and patients' global evaluations, the investigators' assessment of rhinitis symptoms, and nasal examination findings. Safety parameters consisted of physical examinations, measurements of vital signs and body weights, clinical laboratory assessments, and adverse experience reports.

The study protocol was approved by a national institutional review board.

Statistical analysis

Previous azelastine investigations showed that 61 patients per group would be sufficient to detect a difference of 45% between the azelastine mean change and placebo mean change for the TSC severity score with an alpha level of 0.05 and a power of 80%.

The primary analysis was an intent-to-treat analysis, performed with all available patient-response data at each weekly evaluation period. In addition, an end-point analysis, based on each patient's last daily average score during double-blind treatment carried forward, and an overall analysis, based on each patient's average of all available responses during double-blind treatment, were also performed. The mean percent and mean absolute changes from baseline for the TSC and MSC severity scores were analyzed by analysis of covariance, incorporating effects of treatments, center, and their interaction plus the baseline as a covariate. Underlying assumptions such as normality and homoscedasticity of the analysis of covariance model were tested and met.

Treatments were compared by use of two-tailed *t* tests, with the mean square error from the covariance analysis. Treatment differences for global evaluations (investigators' and patients') and changes in nasal examination findings were analyzed by the Cochran-Mantel-Haenszel test.

Within each treatment group, the change from baseline after each week of double-blind treatment was calculated for vital signs, body weights, and laboratory parameters and analyzed by a two-tailed *t* test. Treatment group comparisons were based on an analysis of

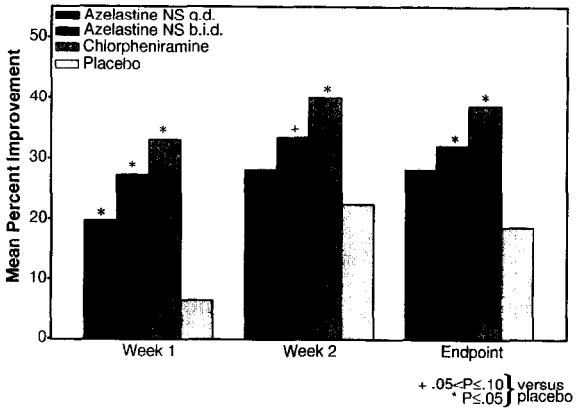

FIG. 1. Mean percent improvement in the TSC severity scores during weeks 1 and 2 and at end point.

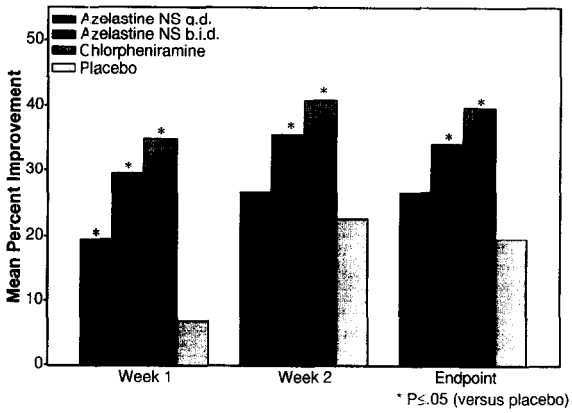

FIG. 2. Mean percent improvement in the MSC severity scores during weeks 1 and 2 and at end point.

variance, including effects of centers, treatments, and center-by-treatment interaction. The proportions of patients with the most frequently reported individual adverse experiences were compared across the treatment groups by chi square tests. The level of significance for all tests was set at $p = 0.05$.

RESULTS

Two hundred fifty-one patients, ages 12 to 71 years, satisfied the inclusion criteria and were randomized to double-blind treatment. One patient, however, was lost to follow-up, and another patient withdrew before taking any double-blind medication. Thus data from 250 patients were avaialble for the analyses of safety, and data from 249 patients were included in the analyses of efficacy. The patients were randomized in equal numbers to the four treatment groups, and, with the exception of a higher mean baseline body weight in the azelastine NS b.i.d. group, there were no significant differences among the treatment groups for the demographic parameters (Table I).

All 251 patients met the study entry criterion of a minimum MSC severity score. There were no statistically significant differences among the treatment groups at baseline in the mean TSC and MSC values (Table I). The average daily pollen counts for each week during double-blind therapy were very high throughout the study period (≥ 1200 grains/m^3).

Primary efficacy parameters

The mean percent improvement in the TSC and MSC severity scores for the active-treatment groups were superior to those for the placebo

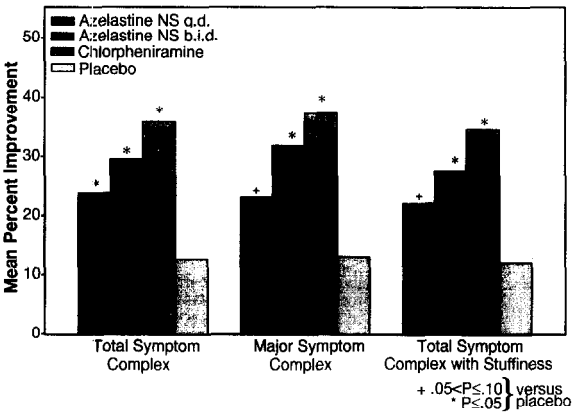

FIG. 3. The overall mean percent improvement in the TSC and MSC severity scores and in the TSC score including the additional symptom of stuffiness.

group at each evaluation point (Figs. 1 and 2). After 1 week of treatment, the mean percent improvements in the TSC and the MSC severity scores for the azelastine NS q.d. (20% for both scores) and azelastine NS b.i.d. (27% and 30%, respectively) groups were statistically significantly ($p \leq 0.05$) greater than that observed for the placebo group (7% for both scores).

During week 2, statistical significance versus placebo was maintained for the azelastine NS b.i.d. group for the MSC severity score (36%) and approached statistical significance ($p \leq 0.10$) for the TSC severity score (34%). The mean percent improvements for the azelastine NS q.d. group during week 2 exceeded those for placebo in the TSC and MSC severity scores but were not statistically significant.

TABLE II. Contribution of the individual rhinitis symptoms to the MSC and TSC severity scores at baseline and end point

Symptom	Azelastine NS q.d. (n = 62)			Azelastine NS b.i.d. (n = 63)		
	Mean (%) baseline	Mean (%) end point	Percent improvement	Mean (%) baseline	Mean (%) end point	Percent improvement
Runny nose/sniffles	2.80 (15.4)	2.06 (15.8)	26.4	2.84 (15.1)	1.87 (15.0)	34.2
Nose blows	2.65 (14.5)	1.91 (14.6)	27.9	3.05 (16.2)	2.13 (17.1)	30.2
Sneezes	2.45 (13.4)	1.78 (13.6)	27.3	2.55 (13.5)	1.72 (13.8)	32.5
Itchy nose	2.26 (12.4)	1.62 (12.4)	28.3	2.10 (11.2)	1.35 (10.9)	35.7
Watery eyes	1.96 (10.8)	1.38 (10.6)	29.5	1.95 (10.4)	1.03 (8.3)	47.2
MSC	12.12 (66.5)	8.75 (66.9)	27.8	12.49 (66.4)	8.10 (65.2)	35.0
Itchy eyes/ears/throat/palate	2.48 (13.6)	1.62 (12.4)	30.2	2.38 (12.6)	1.48 (11.9)	37.8
Cough	1.18 (6.5)	0.82 (6.3)	30.5	1.57 (8.3)	1.12 (9.0)	28.7
Postnasal drip	2.45 (13.4)	1.88 (14.4)	23.2	2.38 (12.6)	1.73 (13.9)	27.3
TSC	18.23 (100)	13.07 (100)	28.3	18.82 (100)	12.43 (100)	33.9

For the end-point analysis, the mean percent improvements in the TSC and MSC severity scores, respectively, for the azelastine NS q.d. group (28% and 27%) and the azelastine NS b.i.d. group (32% and 34%) exceeded those for placebo (19% and 20%) and were statistically significant (vs placebo) for the azelastine NS b.i.d. group.

Overall, when both treatment weeks were combined (Fig. 3), the mean percent improvements in the TSC (30%), MSC (32%), and TSC with stuffiness (28%) were statistically significant for the azelastine NS b.i.d. group versus placebo (12% to 13%). For the azelastine NS q.d. group, the overall mean percent improvement across both weeks was statistically significant for the TSC severity score (24%) and approached statistical significance for both the MSC severity score (23%) and TSC with stuffiness severity score (22%) versus placebo.

Treatment with 12 mg of chlorpheniramine maleate also resulted in improvements in the TSC and MSC severity scores that were statistically significantly greater than those for placebo after each week of treatment, overall across both weeks, and for the end-point analysis.

Secondary efficacy parameters

Results of the analyses for the secondary efficacy variables were generally consistent with the pattern of therapeutic responses for the mean percent improvements in the TSC and MSC severity scores. Treatment with azelastine resulted in improvements in all individual symptoms of the TSC severity score. For both azelastine NS groups, the percentage of each symptom's contribution to the total severity score at the end point of the study was similar to its percent contribution at baseline (Table II). Therefore the magnitude of each symptom's improvement for the azelastine NS q.d. and b.i.d. groups was proportional to its contribution to the TSC severity score at baseline.

In addition, across both weeks of treatment, investigators rated a greater majority of patients in the azelastine NS b.i.d. group (84%; $p \leq 0.05$) and the azelastine NS q.d. group (73%) as therapeutically improved when compared with patients in the placebo group (66%). A greater majority of patients in the azelastine NS q.d. and b.i.d. groups (86% and 82%, respectively) also rated their therapetic response as improved when compared with the placebo group (77%).

Safety parameters

There were no clinically meaningful within-group changes or between-group differences for any of the treatment groups in vital signs and body weight. Pre- and posttreatment physical examination results were unremarkable. There were no differences between the azelastine NS groups and the placebo group in the percentage of patients who had a change in the nasal examination parameters (nasal secretion and turbinate mucosa). In addition, there were no meaningful between-treatment differences in the pretreatment and end-of-treatment mean laboratory values for adult patients.

Azelastine NS was well tolerated, and only two patients treated with azelastine (both from the azelastine NS b.i.d. treatment group) discontinued therapy because of an adverse experience

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