Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen

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Background: **A previous study with azelastine nasal spray in patients with seasonal allergic rhinitis (SAR) demonstrated that increasing the azelastine concentration from 0.1% to 0.15% allowed for once-daily dosing without increasing the incidence of adverse effects. This study evaluated the efficacy of azelastine 0.15% nasal spray administered once daily for treating symptoms of SAR.**

Methods: **In this 14-day, randomized, double-blind, placebo-controlled study, patients with moderate-to-severe SAR were randomized to azelastine 0.15% (n = 251) or placebo (n = 255), both at a dosage of 2 sprays/nostril once daily. The primary efficacy variable was change from baseline in the 12-hour reflective Total Nasal Symptom Score (TNSS). Key secondary variables were change from baseline in 24-hour instantaneous TNSS, to establish the dosing interval, and change from baseline in the Total Ocular Symptom Score (TOSS).**

Results: **The mean improvement (3.57) and percentage improvement (19.3%) in 12-hour reflective TNSS was significant ($p < 0.012$) with azelastine 0.15% compared to placebo (2.14 and 11.4%, respectively). The mean improvement in 24-hour instantaneous TNSS was also significant ($p < 0.001$) for azelastine 0.15% compared to placebo, indicating efficacy with once-daily dosing. The overall improvement and percentage improvement in TOSS was significant ($p \leq 0.012$) with azelastine 0.15% (2.21 and 16.7%, respectively) compared to placebo (1.28 and 6.0%, respectively). The overall score for the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was significantly ($p < 0.001$) improved from baseline in the azelastine group compared with the placebo group. Nasal discomfort (3.6%) and bitter taste (2.4%) were the most common adverse events. There were no reports of somnolence with azelastine.**

Conclusion: **Azelastine 0.15% was effective and well tolerated with once-daily dosing. Azelastine 0.15% nasal spray significantly improved a complex of eye symptoms compared to placebo.** © 2011 ARS-AAOA, LLC.

Key Words:
allergic rhinitis; antihistamine; clinical trial; compliance; dosing; nasal congestion; runny nose; sneezing; tolerability

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Rhinitis is one of the most common diseases in the general population. It is generally classified as allergic, either seasonal or perennial, or nonallergic, of which there are several types. In all its forms, approximately 80 to 100 million Americans may be affected annually.[1–3] The most common symptoms of allergic rhinitis are nasal congestion, sneezing, itchy nose, rhinorrhea, postnasal drip, and in many individuals, ocular symptoms such as itchy, watery, and red eyes.[1,4,5] If untreated, rhinitis may compromise quality of life by decreasing productivity at work and school, reducing participation in recreational activities, disrupting normal sleep patterns, and adversely affecting cognitive function.[5,6]

Azelastine hydrochloride is a potent histamine H_1-receptor antagonist that has demonstrated pharmacological activity other than strictly antihistaminic effects. Although the clinical relevance of these effects has not been fully established, studies performed in isolated tissues, laboratory animals, and in clinical trials in patients with allergic rhinitis have shown that azelastine inhibited the

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generation, release, and/or target tissue effects of several chemical mediators of inflammation affecting both the early and late phases of the allergic response, including histamine,[7,8] leukotrienes,[1,9] kinins,[10,11] superoxide free radicals,[12] and platelet-activating factor.[13] Azelastine also significantly decreased intercellular adhesion molecule-1 expression when incubated with nasal epithelial cells,[14] and significantly reduced interleukin-4 levels in clinical trials of patients with rhinitis.[15]

Azelastine 0.15% nasal spray is a new concentration of azelastine (a reformulation of Astepro® [azelastine 0.1%]; Meda Pharmaceuticals, Inc., Somerset, NJ), which delivers 50% more azelastine/spray (205.5 μg) compared to the original formulation (137 μg). The reformulated nasal spray is delivered in a sorbitol-based vehicle, with the addition of sucralose to help mask the distinctive bitter taste of the azelastine molecule. Increasing the concentration of azelastine by 50% (from 0.1% to 0.15%) allows for more drug to be delivered to the nasal mucosa when administered at 2 sprays/nostril once daily (total daily dose of azelastine: 822 μg) than the original formulation when administered at 1 spray/nostril twice daily (total daily dose of azelastine: 548 μg). In a previous study with the once-daily azelastine 0.15% formulation, superior and favorable efficacy were demonstrated when compared to placebo.[16] The objective of the current study was to evaluate the efficacy and safety of azelastine 0.15% nasal spray, administered 2 sprays/nostril once daily, for treating both nasal and ocular symptoms in patients with seasonal allergic rhinitis (SAR).

Patients and methods

Patients

The study population consisted of males and females 12 years of age and older with a minimum 2-year history of allergy to Texas mountain cedar (*Juniperus ashei*) pollen, as confirmed by a positive skin test within 12 months of screening. Prior to enrollment, written informed consent was obtained from each patient (or guardian if the patient was <18 years of age). The study protocol was approved by Sterling Institutional Review Board, Atlanta, GA. At screening, patients needed to have a 12-hour reflective Total Nasal Symptom Score (TNSS) of at least 8 out of a possible 12 and a congestion score of 2 or 3 out of a possible 3. Patients were also required to be in general good health and free of any disease that could interfere with the interpretation of the study results. Any concomitant medications that could have confounded study results were discontinued prior to enrollment and were prohibited during the study. Key exclusion criteria included: (1) the presence of nasal disease other than rhinitis; (2) the presence of any nasal mucosal erosion, nasal ulceration, or nasal septal perforation; (3) nasal or sinus surgery within the previous year; (4) chronic sinusitis; (5) a respiratory tract infection, with or without antibiotic treatment, within 14 days of Day −7; (6) persistent asthma; or (7) significant pulmonary disease.

Study design

This randomized, double-blind, placebo-controlled, parallel-group study was conducted during the 2008/2009 Texas mountain cedar allergy season at 7 investigational sites in central Texas. The study consisted of a 7-day, single-blind placebo lead-in period and a 14-day, double-blind treatment period.

During the placebo lead-in period (Day −7 to Day −1), patients were instructed to take 2 sprays/nostril of placebo nasal spray in the AM and record their symptoms twice daily (AM and PM). Symptoms for the TNSS and Total Ocular Symptom Score (TOSS) were scored on a 4-point ordinal scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms). Patients who qualified for randomization had a 12-hour reflective TNSS (AM or PM) of at least 8, and a nasal congestion score of 2 or 3, on 3 separate symptom assessments (1 of which was within 2 days of Day 1, including the AM of Day 1). Patients who met these requirements were randomized in a 1:1 ratio by a computer-generated randomization schedule to treatment with 2 sprays/nostril once daily of either azelastine 0.15% nasal spray or vehicle placebo. Patients were instructed to take study medication in the morning, record each dose taken in a diary, and to record their symptoms of TNSS and TOSS twice daily (AM and PM) in a diary. Patients returned to the clinic for an interim visit on Day 7 and a final visit on Day 14. On Days 1, 7, and 14, compliance was calculated by the amount of study medication remaining by bottle weight relative to the number of doses recorded in the diary.

The primary efficacy variable was the change from baseline to Day 14 in the 12-hour reflective TNSS, consisting of nasal congestion, runny nose, itchy nose, and sneezing. A key secondary efficacy variable was the change from baseline to Day 14 in the 24-hour instantaneous TNSS, which was calculated from symptom scores made prior to each AM dose and 24 hours after the previous dose to determine if the effect lasted for a full 24 hours. The other key secondary efficacy variable was the change from baseline in the TOSS, consisting of itchy eyes, watery eyes, and redness. Other efficacy variables included: (1) daily change from baseline in the 12-hour reflective TNSS for the entire 14-day study period, (2) daily change from baseline in the 12-hour reflective TOSS for the entire 14-day study period, and (3) change from baseline in the adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Safety and tolerability were evaluated by the frequency and severity of patient-reported adverse events, vital sign assessments, and direct visual nasal examinations.

Statistical analysis

In a previous study of azelastine 0.15% nasal spray administered once daily, the overall mean changes in the reflective TNSS were −4.45 and −3.03 in the azelastine and placebo groups, respectively. Using a pooled standard deviation of 4.724 and 1:1 randomization, it was

determined that a sample size of 234 patients/treatment group would be needed to detect the observed difference noted in the previous study. Allowing for a 5% dropout rate, 250 patients/treatment group were considered adequate to show a statistically significant reduction for overall change from baseline in TNSS at the 0.05 level of significance with 90% power. The primary efficacy analyses were performed on the intent-to-treat population (all randomized patients with at least 1 postbaseline efficacy observation). For each evaluation, treatment groups were compared using an analysis of covariance (ANCOVA) model with baseline as a covariate. Least-squares (LS) means were used to compare treatment groups, appropriately adjusting for the baseline effect. Missing TNSS values were imputed using the last observation carried forward method. No adjustments for multiple comparisons were made because a single primary endpoint was the only endpoint required to establish efficacy. The secondary endpoints in this study provided supportive efficacy only. The TOSS analysis was performed in a manner identical to that for the TNSS. The change from Day 1 to Day 14 in the RQLQ score was summarized according to the method described by Juniper et al.[17,18] and treatment groups were compared by ANCOVA. Safety analyses were performed on the safety population, which included all randomized patients who received at least 1 dose of study medication. Adverse events were summarized by treatment, and vital signs were examined for abnormal values and changes from baseline. Nasal examinations were performed at baseline and at Day 14.

Results

Demographic and clinical characteristics

In this study, 506 patients were randomized to double-blind treatment with either azelastine nasal spray (n = 251) or placebo nasal spray (n = 255). In total, 478 patients (94.5%) completed the study. Overall, 28 patients (5.5%) discontinued the study—9 patients (1.8%) as a result of adverse events (5 patients [2.0%] in the azelastine group and 4 patients [1.6%] in the placebo group). The treatment groups were comparable with regard to demographic and baseline clinical characteristics, including duration of SAR and baseline TNSS (Table 1). In both treatment groups, approximately 98% of patients were considered to be compliant with study medication.

Primary efficacy

The LS mean improvement from baseline in the 12-hour reflective TNSS was significantly greater in the azelastine group than in the placebo group (3.57 vs 2.14, respectively; $p < 0.001$; Fig. 1). Similarly, the LS mean percentage improvement in 12-hour reflective TNSS was significantly greater in the azelastine group vs the placebo group (19.3% vs 11.4%, respectively; $p < 0.001$).

TABLE 1. Demographic and baseline clinical characteristics (intent-to-treat population)

Characteristic	Azelastine (n = 251)	Placebo (n = 254)
Age, years, mean (range)	38.0 (12–74)	38.5 (12–75)
Gender, n (%)		
Male	94 (37.5)	104 (40.9)
Female	157 (62.5)	150 (59.1)
Race, n (%)		
Asian	2 (0.8)	0 (0.0)
Black	28 (11.2)	29 (11.4)
White	217 (86.5)	225 (88.6)
Other	4 (1.6)	0 (0.0)
Duration of SAR, years, mean (range)	17.7 (3–69)	18.7 (3–59)
TNSS* mean (range)	18.5 (8–24)	18.8 (9–24)

SAR = seasonal allergic rhinitis; TNSS = Total Nasal Symptom Score.

*Mean baseline TNSS during the 7-day lead-in period, including the AM of Day 1.

Secondary efficacy

A key secondary efficacy variable was the change from baseline in the 24-hour instantaneous TNSS (AM), to determine if efficacy was sustained over a 24-hour dosing interval. The LS mean improvement from baseline to Day 14 in the 24-hour instantaneous TNSS (AM) was 1.43 in the azelastine group and 0.83 in the placebo group ($p < 0.001$; Fig. 1).

There was a significant ($p < 0.001$) improvement in the 12-hour reflective TOSS in the azelastine group (2.21 and 16.7%) compared to the placebo group (1.28 and 6.0%; Fig. 2).

The LS mean daily change from baseline in the 12-hour reflective TNSS (AM and PM combined) was significantly ($p < 0.05$) greater for azelastine vs placebo on all study days (Fig. 3). The mean daily change from baseline in

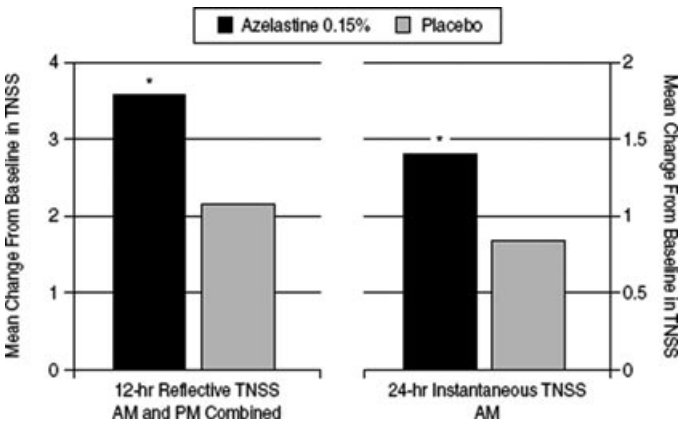

FIGURE 1. Mean improvement from baseline in the 12-hour reflective and 24-hour instantaneous TNSS (intent-to-treat population). *$p < 0.001$ vs placebo. (Maximum daily reflective TNSS = 24; maximum daily instantaneous TNSS = 12). TNSS = Total Nasal Symptom Score.

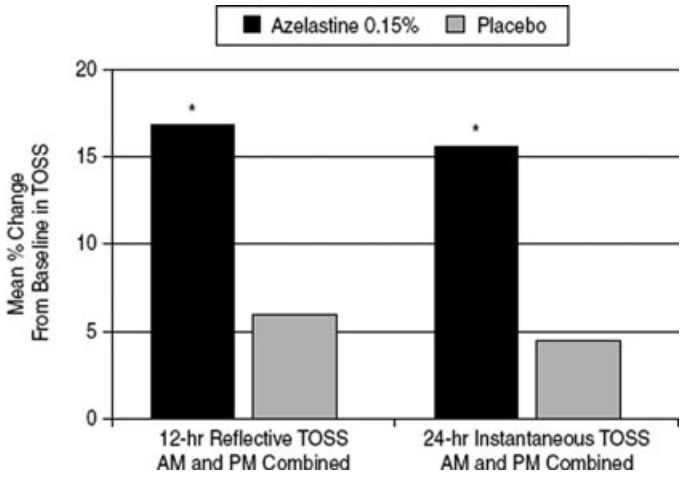

FIGURE 2. Mean percent improvement from baseline in the 12-hour reflective and 24-hour instantaneous TOSS (intent-to-treat population). *$p \leq 0.012$ vs placebo. TOSS = Total Ocular Symptom Score.

the 24-hour instantaneous TNSS (AM) was significantly ($p < 0.05$) greater for azelastine vs placebo on all study days, except for Day 6 and Day 9 (Fig. 4).

The LS mean change from baseline in the 12-hour reflective (AM and PM combined) individual nasal symptom scores was significant ($p < 0.01$) for all individual symptoms (nasal congestion, runny nose, itchy nose, and sneezing) in the azelastine group compared with the placebo group (Fig. 5).

The overall score for the RQLQ was significantly ($p < 0.001$) improved from baseline in the azelastine group (1.12) compared with the placebo group (0.74).

Safety

The most common adverse event in the azelastine group was nasal discomfort (3.6%; Table 2). In the placebo group,

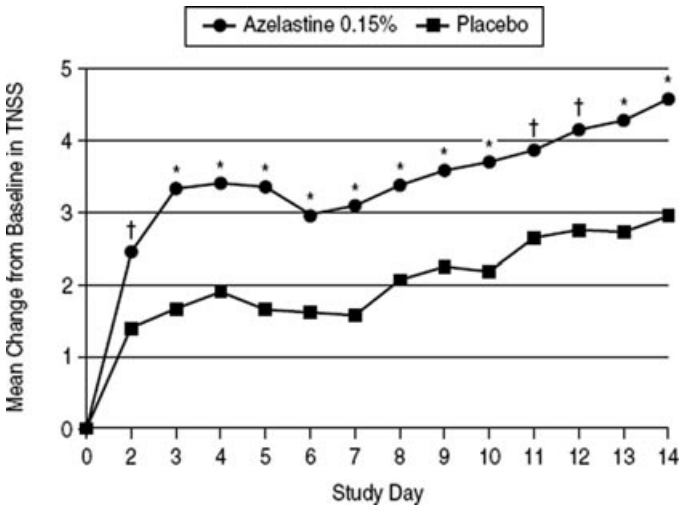

FIGURE 3. Mean improvement from baseline in the 12-hour reflective TNSS (AM and PM combined; intent-to-treat population). *$p < 0.001$ vs placebo; †$p \leq 0.01$ vs placebo. TNSS = Total Nasal Symptom Score.

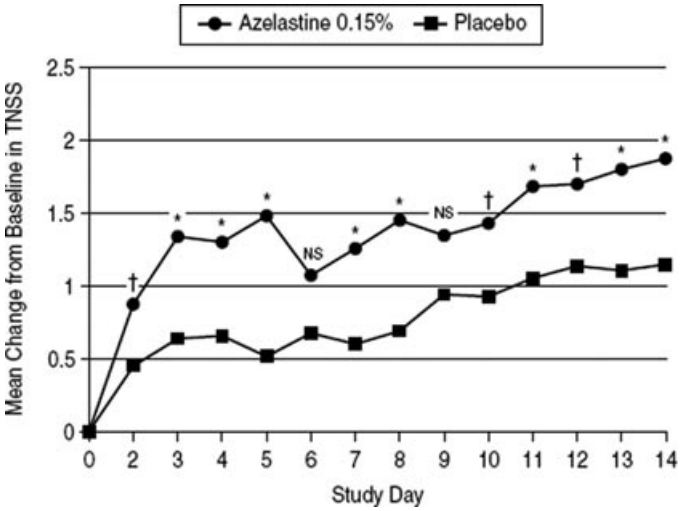

FIGURE 4. Mean improvement from baseline in the 24-hour instantaneous TNSS (AM; intent-to-treat population). *$p < 0.01$ vs placebo; †$p < 0.05$ vs placebo. NS = not statistically significant; TNSS = Total Nasal Symptom Score.

the most common adverse event was mild epistaxis (1.6%). All other adverse events in the azelastine group had an incidence of less than 3%. There were no serious adverse events reported during the study. In total, 5 patients (2.0%) in the azelastine group and 4 patients (1.6%) in the placebo group discontinued the study due to an adverse event. There were no clinically important changes in vital signs, and no reports of moderate or severe epistaxis, nasal irritation, or mucosal bleeding during the study.

Discussion

This study is the second of 2 well-controlled studies in patients with allergy to Texas mountain cedar pollen designed to obtain approval from the U.S. Food and Drug

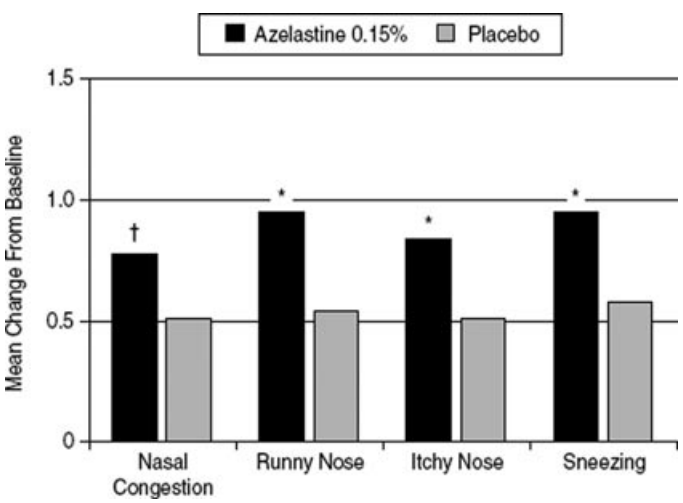

FIGURE 5. Mean improvement from baseline in the 12-hour reflective individual nasal symptom scores (AM and PM combined; intent-to-treat population). *$p < 0.001$ vs placebo; †$p < 0.01$ vs placebo.

TABLE 2. Common adverse events (safety population)

Adverse event, n (%)	Azelastine (n = 251)	Placebo (n = 255)
Nasal discomfort	9 (3.6)	0 (0.0)
Bitter taste	6 (2.4)	2 (0.8)
Headache	5 (2.0)	0 (0.0)
Sneezing	5 (2.0)	0 (0.0)
Epistaxis	4 (1.6)	4 (1.6)

Administration for a once-daily dosage regimen of the azelastine 0.15% nasal spray formulation. The LS mean improvement in the primary efficacy variable, 12-hour reflective TNSS, was similar in this study (3.57 with azelastine vs 2.14 with placebo; $p < 0.001$) and in the first study (3.53 vs 1.97; $p < 0.001$).[16] The LS mean improvement in the 24-hour instantaneous TNSS was also statistically significant ($p < 0.001$) with azelastine compared with placebo in both studies.[16] Together, these 2 studies confirmed the efficacy of azelastine 0.15% nasal spray when administered once daily in patients with SAR. In addition to the improvements in the reflective and instantaneous TNSS, there were significant ($p \leq 0.01$) improvements with azelastine compared to placebo for all individual symptoms of the TNSS, including nasal congestion.

In the van Bavel et al.[16] study, a key secondary efficacy variable was the change from baseline in a secondary complex score (SSCS) that included assessments of postnasal drip, itchy eyes, cough, and headache. The SSCS, including the individual symptom of itchy eyes, was significantly ($p \leq .05$) improved with azelastine 0.15% nasal spray compared with placebo.[16] In the current study, a key secondary efficacy variable was the TOSS, and both the 12-hour reflective score and the 24-hour instantaneous score were significantly ($p \leq 0.012$) improved with azelastine compared to placebo.

Fluticasone furoate,[19] fluticasone propionate,[20] and mometasone furoate[21] have been reported to improve ocular symptoms of allergic rhinitis. The mechanisms by which the intranasal antihistamines and the intranasal corticosteroids improve ocular symptoms are not determined with certainty but may involve both neural pathways and local anatomical relationships with vascular transfer of medication from nasal passages to the lacrimal duct.[22]

Most adverse events in this study were mild or moderate in intensity, with nasal discomfort being the most common in the azelastine group. There were no reports of sedation is this study. Although somnolence was not reported in this study, as indicated in the azelastine 0.15% product labeling, the clinical development program included seven placebo-controlled studies in which 1544 patients were treated with azelastine 0.15% nasal spray. Of the 1544 patients treated with azelastine 0.15% nasal spray, 11 (<1%) reported somnolence compared to 1 of 1339 patients treated with placebo.

This study confirms that azelastine 0.15% nasal spray can be administered in an effective and well-tolerated once-daily regimen, providing the potential for improved compliance with nasal spray therapy for SAR.

Conclusion

The results of this study demonstrate that azelastine 0.15% nasal spray administered at a dosage of 2 sprays/nostril once daily was effective in treating nasal symptoms related to SAR. Furthermore, these results confirm that azelastine 0.15% nasal spray can be administered in an effective and well-tolerated once-daily regimen, providing the potential for improved compliance with nasal spray therapy.

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