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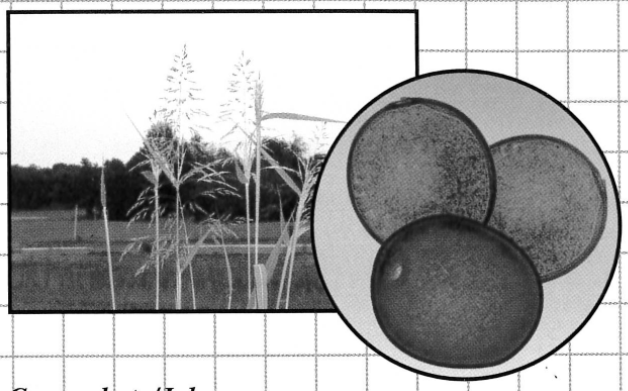

Cover photo/Johnson grass
Sorghum halepense

" Flowering is lengthy, from July through September . . ."

(refer to page A-6)

GUEST EDITORIAL

CME REVIEW ARTICLE

REVIEW ARTICLE

CLINICAL ALLERGY–IMMUNOLOGY ROUNDS

ORIGINAL ARTICLES

Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine

Craig F. LaForce, MD*; Jonathan Corren, MD†; William J. Wheeler, PhD‡; William E. Berger, MD, MBA§; and the Rhinitis Study Group

Background: Currently available oral second-generation antihistamines do not provide adequate symptom relief for many allergy patients.

Objective: To determine the ability of azelastine nasal spray to improve rhinitis symptoms in patients with seasonal allergic rhinitis who remained symptomatic after treatment with fexofenadine.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, 2-week study in patients with moderate-to-severe seasonal allergic rhinitis. The study began with a 1-week, open-label lead-in period, during which patients received fexofenadine, 60 mg twice daily. Patients who improved less than 25% to 33% with fexofenadine were randomized to treatment with (1) azelastine nasal spray, 2 sprays per nostril twice daily; (2) azelastine nasal spray, 2 sprays per nostril twice daily, plus fexofenadine, 60 mg twice daily; or (3) placebo (saline) nasal spray and placebo capsules twice daily. The primary efficacy variable was the change from baseline to day 14 in the total nasal symptom score (TNSS), consisting of runny nose, sneezing, itchy nose, and nasal congestion symptom scores.

Results: A total of 334 patients who remained symptomatic after treatment with fexofenadine were included in the efficacy analysis. After 2 weeks of treatment, azelastine nasal spray ($P = .007$) and azelastine nasal spray plus fexofenadine ($P = .003$) significantly improved the TNSS compared with placebo. Azelastine nasal spray monotherapy was as effective as the combination of azelastine nasal spray plus fexofenadine as measured by the TNSS and individual symptoms of the TNSS.

Conclusions: Azelastine nasal spray is effective monotherapy for patients who remain symptomatic after treatment with fexofenadine and should be considered in the initial management of patients with seasonal allergic rhinitis.

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INTRODUCTION

Oral and intranasal second-generation antihistamines are recommended as first-line therapy for allergic rhinitis[1]; however, patients who remain symptomatic after treatment with oral second-generation antihistamines frequently are prescribed other antihistamines, either alone or in combination regimens. In a study of drug utilization patterns in patients beginning treatment for seasonal allergic rhinitis, it was reported that nearly one third of the patients either switched drugs or added drugs during the study period, resulting in a 2-fold to 3-fold increase in the number of prescriptions compared with patients treated with monotherapy.[2] In addition, results of a survey of more than 1,400 secondary school students with allergic rhinitis indicated that 73% of the students used 2 or more rhinitis medications to treat their allergies, whereas only 27% used monotherapy.[3]

A survey sponsored by the American College of Allergy, Asthma and Immunology cited inadequate symptom relief with second-generation antihistamines as the primary reason for switching medications or for using combination therapy by 86% of allergists and 78% of primary care physicians. Additionally, it was reported that 52% of allergists and 39% of primary care physicians prescribed more than 1 oral antihistamine for their rhinitis patients.[4] These findings suggest that the currently available oral second-generation antihistamines do not provide adequate symptom relief for many patients.

Azelastine nasal spray is a topically administered second-generation antihistamine with demonstrated efficacy in treating symptoms of seasonal allergic rhinitis and nonallergic vasomotor rhinitis.[5,6] In a large, prospective, open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis, 45% of 3,107 patients reported having had an unsatisfactory response to prior treatment with oral antihistamines, and 54% of these patients reported using 2 or more antihistamines during the 12 months before enrollment in the study.[7] In this study, azelastine monotherapy improved nasal symptoms of rhinitis in more than 80% of patients who reported dissatisfaction with oral antihistamine therapy.

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In a double-blind, placebo-controlled trial in patients with seasonal allergic rhinitis who remained symptomatic after 1 week of treatment with loratadine, azelastine nasal spray monotherapy significantly improved the total nasal symptom complex of rhinorrhea, sneezing, nasal itching, and nasal congestion when compared with placebo.[8] Azelastine nasal spray monotherapy was shown to be as effective as the combination of azelastine nasal spray plus loratadine for the total nasal symptom complex and for each of the individual symptoms. Forty-three percent of the patients who completed the study had used 2 or more oral antihistamines during the 12 months before enrollment. The results of this trial demonstrated that azelastine nasal spray is an effective treatment for patients with an inadequate response to loratadine and is an alternative to switching to another oral second-generation antihistamine or to using multiple antihistamines. Based on these findings, the current study was conducted to determine the ability of azelastine nasal spray to improve rhinitis symptoms in patients with seasonal allergic rhinitis who remained symptomatic after 1 week of treatment with fexofenadine.

METHODS

This was a 2-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 21 investigational sites during the 2003 spring allergy season. Male and female patients 12 years and older with a minimum 2-year history of seasonal allergic rhinitis and a documented positive allergy skin test result during the previous year were candidates for participation. Patients were excluded from participation for the following reasons: use of concomitant medications 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 seasonal allergic rhinitis or significant nasal structural abnormalities; respiratory infection or other infection that requires antibiotic therapy within 2 weeks of beginning the baseline screening period; significant pulmonary disease and/or active asthma that requires daily medication; and either a history of or current alcohol or other drug abuse.

Women of child-bearing potential were excluded from the study if they were not using an accepted method of contraception. Women who were pregnant or breast-feeding also were excluded from participation. The use of all concomitant medications was discontinued before beginning the open-label lead-in period; oral antihistamine use was discontinued for a minimum of 3 days and intranasal steroid use for a minimum of 14 days. All patients or their guardians (if the patient was younger than 18 years) signed an institutional review board–approved informed consent agreement before participation.

The study began with a 1-week, open-label lead-in period (day −7 to day 1) during which all patients were treated with fexofenadine, 60-mg tablets twice daily, and recorded their symptom severity scores and daily use of study medication in diary cards. Patients qualified for randomization into the double-blind treatment period if their total nasal symptom score (TNSS; defined as the severity score for individual symptoms of runny nose, sneezing, itchy nose, and nasal congestion) on day −7 was 8 or higher and improved by less than 25% to 33% on 3 days during the 1-week fexofenadine lead-in period. Each symptom was scored on a 4-point rating scale: 0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. One of the 3 TNSS qualification scores (either AM or PM) during the lead-in period had to be recorded within 3 days of beginning the double-blind treatment period on day 1.

Patients who did not meet the symptom qualification criteria or other study entry criteria on day 1 or who did not complete the diary as required were discontinued from the study. Patients who met the study entrance criteria were randomized to blinded treatment with (1) azelastine (Astelin; MedPointe Pharmaceuticals, Somerset, NJ) nasal spray, 2 sprays per nostril twice daily, plus placebo capsules twice daily; (2) azelastine nasal spray, 2 sprays per nostril twice daily, plus fexofenadine (Allegra; Aventis Pharmaceuticals, Bridgewater, NJ), 60 mg in capsules twice daily; or (3) placebo (saline) nasal spray, 2 sprays per nostril twice daily, plus placebo capsules twice daily. Patients were instructed to take 1 blinded capsule each morning and evening and 2 sprays per nostril from the blinded nasal spray bottles each morning and 2 sprays per nostril each evening approximately 12 hours after the morning dose.

The primary efficacy variable was the change from baseline to day 14 in the TNSS, as measured by symptom scores, which were recorded twice daily (AM and PM) in the diary cards. The baseline score was defined as the average of the combined morning and evening TNSS during the lead-in period. The TNSS for each patient consisted of the combined score for all 4 symptoms (runny nose, sneezing, itchy nose, and nasal congestion). Baseline scores were subtracted from the daily TNSS to calculate the change from baseline. Change from baseline for each active treatment group during the 2-week study period was compared with placebo using a repeated-measure analysis of variance (ANOVA) according to the restricted maximum likelihood estimation for mixed-effect models. The change from baseline in individual symptom severity scores was evaluated using a similar repeated-measure ANOVA model. The primary analysis was an intent-to-treat analysis that included all patients who were randomized. Missing TNSS values in the intent-to-treat population were imputed using the last observation carried forward method. The safety analysis included all randomized patients who received at least 1 dose of study medication and had at least 1 safety evaluation following drug administration. The incidence of adverse experiences was summarized for each treatment group.

Based on the change from baseline in TNSS in previous studies with azelastine nasal spray, and assuming a .05 level of significance, 80% power, and an average difference reduction of 1.0 unit in TNSS with a standard deviation of 2.5, a sample size of approximately 100 patients per treatment group was required. All inferential statistics were calculated at the .05 level of significance.

RESULTS

Patient Disposition

A total of 443 patients were screened for participation in the trial. Three hundred thirty-four patients were randomized to double-blind treatment and had sufficient postbaseline diary data to be included in the efficacy analyses (1 patient in the placebo group was excluded because of no postbaseline diary data). Of the 108 patients who did not qualify for randomization, 54 failed to meet the inclusion and exclusion criteria at day −7, and 54 did not meet the minimum symptom score criteria at day 1. A total of 324 patients completed the 2-week, double-blind treatment period. Three patients in the azelastine monotherapy group (1 consent withdrawal, 1 treatment failure, and 1 protocol violation), 3 in the azelastine plus fexofenadine group (2 treatment failures and 1 protocol violation), and 5 in the placebo group (4 adverse events and 1 treatment failure) discontinued the study before completing 2 weeks of treatment.

Demographic and Pretreatment Characteristics

The 3 treatment groups were comparable with regard to demographic characteristics and baseline TNSS. The patients ranged in age from 12 to 80 years, with a mean age of approximately 35 years. Sixty-two percent of the patients were female, 81% were white, 11% were black, and 8% were Asian or other racial background (Table 1).

Efficacy

After 2 weeks of treatment, the mean percentage change from baseline in the overall TNSS was 18.5% with azelastine nasal spray ($P = .007$ vs placebo), 18.3% with azelastine nasal spray plus fexofenadine ($P = .003$ vs placebo), and 10.5% with placebo (saline) nasal spray (Table 2 and Figure 1). The mean absolute improvements from baseline and the relative contributions of the individual symptoms to the TNSS are shown in Figure 2.

Patients treated with azelastine nasal spray monotherapy had statistically significant improvements vs placebo for rhinorrhea (18.6% vs 9.0%; $P = .004$), sneezing (21.4% vs 9.6%; $P = .006$), and itchy nose (19.4% vs 11.4%; $P = .04$). Improvements in individual rhinitis symptoms in patients treated with azelastine nasal spray plus fexofenadine were nearly identical to those seen with azelastine nasal spray monotherapy, with statistically significant differences vs placebo for TNSS ($P = .003$), rhinorrhea ($P = .002$), sneezing ($P = .007$), and itchy nose ($P = .004$). Although nasal congestion was improved with azelastine nasal spray, the differences from placebo were not statistically significant. In the patient global evaluation, symptom improvement was rated significantly better with azelastine nasal spray ($P = .03$) and azelastine nasal spray plus fexofenadine ($P = .03$) than with placebo.

Safety

There was a low incidence of adverse events in this study (Table 3). Bitter taste was reported by 10.7% of the patients treated with azelastine nasal spray monotherapy and by 9.8% of the patients treated with azelastine nasal spray plus fexofenadine. Nasal passage irritation was reported by 4.5% of the patients treated with azelastine nasal spray monotherapy and by 3.6% of the patients treated with azelastine nasal spray plus fexofenadine. Somnolence was reported by 1 patient (0.9%) in each of the azelastine treatment groups. All of the discontinuations due to adverse experiences were in the placebo (saline) group.

DISCUSSION

In view of the role of inflammatory mediators in allergic rhinitis, histamine antagonists, such as azelastine, that have additional antiallergic or anti-inflammatory properties have advantages in the treatment of allergic rhinitis.[9] In addition to histamine antagonism, azelastine has demonstrated inhibitory effects on other chemical mediators of the inflammatory response, including leukotrienes,[10–13] kinins and substance P,[14–16] inflammatory cytokines,[17,18] and intercellular adhesion molecule 1.[19] Further, the higher local concentrations of antihistamine in the nasopharynx that can be achieved with topical administration may enhance any antiallergic or anti-inflammatory activity, resulting in a rapid onset of action and a lower incidence of systemic adverse effects than with oral administration.[20]

The clinical versatility of azelastine nasal spray has been demonstrated in several well-controlled clinical trials. In double-blind, placebo-controlled trials in patients with seasonal allergic rhinitis, azelastine nasal spray significantly improved

Table 1. Demographic Characteristics

Characteristic	Azelastine nasal spray (n = 112)	Azelastine nasal spray plus fexofenadine (n = 112)	Placebo (n = 111)
Sex, no. (%)			
Male	46 (41.1)	40 (35.7)	42 (37.8)
Female	66 (58.9)	72 (64.3)	69 (62.2)
Race, no. (%)			
White	91 (81.3)	90 (80.4)	89 (80.2)
Black	11 (9.8)	11 (9.8)	16 (14.4)
Asian	5 (4.5)	6 (5.4)	2 (1.8)
Other	5 (4.5)	5 (4.5)	4 (3.6)
Age, mean (range), y	34.5 (12–80)	35.1 (12–75)	35.2 (12–68)

Table 2. Change From Baseline in Mean AM and PM Total Nasal Symptom Scores (TNSS) and Individual Symptom Scores

	Azelastine nasal spray (n = 112)				Azelastine nasal spray plus fexofenadine (n = 112)				Placebo (n = 110)*		
	Mean baseline	Mean improvement	% improvement	*P* value	Mean baseline	Mean improvement	% improvement	*P* value	Mean baseline	Mean improvement	% improvement
TNSS											
Mean	17.86	3.31	18.5	.007	18.69	3.42	18.3	.003	17.95	1.89	10.5
AM	8.91	1.61	18.1	.008	9.38	1.73	18.4	.002	9.02	0.90	10.0
PM	8.94	1.70	19.0	.014	9.30	1.68	18.1	.017	8.97	1.02	11.4
Rhinorrhea											
Mean	4.62	0.86	18.6	.004	4.72	0.89	18.9	.002	4.42	0.40	9.0
AM	2.29	0.38	16.6	.028	2.36	0.45	19.1	.003	2.22	0.19	8.6
PM	2.32	0.49	21.1	.002	2.37	0.44	18.6	.007	2.21	0.22	10.0
Sneezing											
Mean	3.92	0.84	21.4	.006	3.99	0.83	20.8	.007	4.07	0.39	9.6
AM	1.92	0.41	21.3	.013	1.97	0.42	21.3	.010	2.02	0.19	9.4
PM	1.99	0.43	21.6	.013	2.01	0.41	20.4	.024	2.06	0.21	10.2
Itchy nose											
Mean	4.34	0.84	19.4	.041	4.69	0.98	20.9	.004	4.40	0.50	11.4
AM	2.17	0.43	19.8	.018	2.34	0.50	21.4	.001	2.19	0.22	10.0
PM	2.19	0.42	19.2	.111	2.35	0.48	20.4	.028	2.21	0.29	13.1
Congestion											
Mean	4.98	0.76	15.3	.214	5.29	0.72	13.6	.372	5.08	0.59	11.6
AM	2.53	0.39	15.4	.153	2.71	0.36	13.3	.344	2.60	0.29	11.2
PM	2.45	0.37	15.1	.439	2.57	0.35	13.6	.554	2.49	0.31	12.5

* One patient in the placebo group had no postbaseline diary data and was not included in the efficacy analysis.

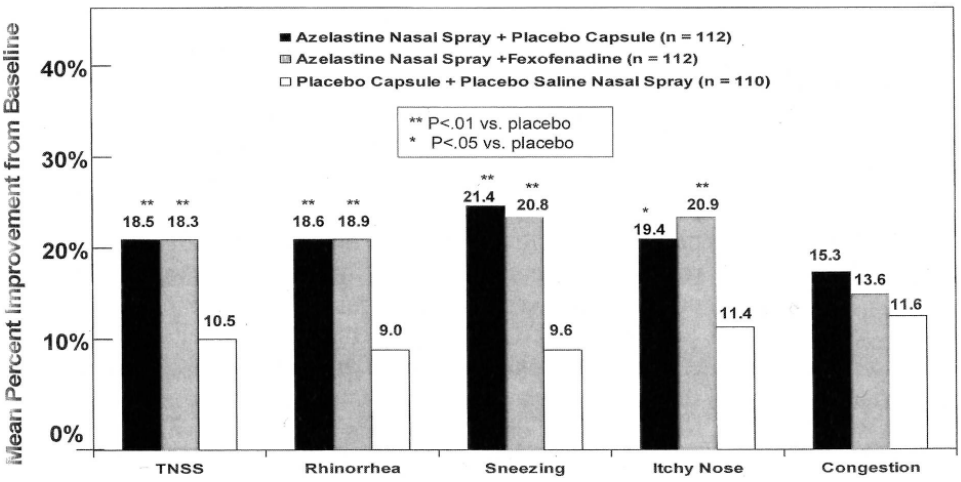

Figure 1. Mean percent improvement from baseline in total nasal symptom score (TNSS) and individual symptom scores.

nasal and nonnasal symptoms in short-term models[21,22] and over 2- and 4-week study periods.[5,23,24] In the placebo-controlled trial of seasonal rhinitis patients who remained symptomatic after 1 week of treatment with loratadine, azelastine nasal spray monotherapy was statistically superior to placebo in treating the total nasal symptom complex and was similar to combination therapy with azelastine nasal spray plus loratadine.[8] In addition, 2 placebo-controlled, double-blind trials in patients with nonallergic vasomotor rhinitis demonstrated that azelastine nasal spray significantly improved all symptoms of the vasomotor rhinitis symptom complex, including nasal congestion during 3 weeks of treatment.[6]

In the current study, 86% of the patients treated with fexofenadine for 1 week during the lead-in period remained at least moderately symptomatic based on the specified study entrance criteria. Statistically significant ($P < .01$) improvement in the TNSS and statistically significant ($P < .05$) improvements in 3 of the 4 individual symptoms making up the TNSS were observed when these patients were switched to treatment with azelastine nasal spray for 2 weeks. Further, no additional clinical benefit was achieved by combining fexofenadine with azelastine nasal spray when compared with azelastine nasal spray as monotherapy. As anticipated, bitter taste was the most common adverse event, reported by approximately 10% of the patients

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