ANNALS OF
Allergy, Asthma
& Immunology

August 2003 • Volume 91, Number 2

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~Official Publication of~
ACAAI
American College of Allergy, Asthma & Immunology
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Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine

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Objective: To evaluate the effectiveness and safety of azelastine nasal spray, desloratadine, and the combination of azelastine nasal spray plus loratadine compared with placebo in patients with seasonal allergic rhinitis who had an unsatisfactory response to loratadine.

Methods: This was a 2-week, multicenter, placebo-controlled, randomized, double-blind study in patients with moderate-to-severe symptoms of seasonal allergic rhinitis. Following a 1-week, open-label lead-in period, during which the patients received loratadine 10 mg daily, those patients who met the symptom qualification criteria (<25% to 33% improvement taking loratadine) were randomized to treatment with azelastine nasal spray 2 sprays per nostril, twice daily, azelastine nasal spray 2 sprays per nostril, twice daily, plus loratadine 10 mg daily, desloratadine 5 mg daily plus placebo (saline) nasal spray, or placebo (saline) nasal spray/placebo capsules. The primary efficacy variable was the change from baseline to day 14 in the total nasal symptom score, consisting of runny nose, sneezing, itchy nose, and nasal congestion symptom scores recorded twice daily (AM and PM) in patient diary cards.

Results: A total of 428 patients with an unsatisfactory response to loratadine completed the double-blind treatment period. After 2 weeks of treatment, azelastine nasal spray ($P < 0.001$), azelastine nasal spray plus loratadine ($P < 0.001$), and desloratadine ($P = 0.039$) significantly improved the total nasal symptom score compared with placebo.

Conclusions: Azelastine nasal spray is an effective treatment for patients with seasonal allergic rhinitis who do not respond to loratadine and is an alternative to switching to another oral antihistamine or to using multiple antihistamines.

Ann Allergy Asthma Immunol. 2003;91:205–211.

INTRODUCTION

Azelastine nasal spray (Astelin Nasal Spray; MedPointe Pharmaceuticals, Somerset, NJ) is a topical antihistamine formulation indicated for the treatment of seasonal allergic rhinitis and nonallergic vasomotor rhinitis. The active ingredient, azelastine hydrochloride, is a selective, high-affinity, histamine H_1-receptor antagonist with structural and pharmacologic differences that distinguish it from currently available antihistamines.[1,2]

In addition to histamine antagonism, azelastine has demonstrated inhibitory effects on chemical mediators of the inflammatory response over a range of concentrations in vitro, in animal models of allergy, and in clinical trials. Azelastine prevented leukotriene generation in mast cells[3] and basophils.[4] It also inhibited the synthesis and release of leukotrienes in a dose-related manner in cultured eosinophils from patients with bronchial asthma.[5] In a double-blind, placebo-controlled clinical trial,[6] pretreatment with a single oral dose of azelastine significantly reduced levels of leukotrienes in nasal washings from patients with seasonal allergic rhinitis.

Azelastine demonstrated inhibitory effects on bradykinin-induced smooth muscle contraction in isolated tissues[1] and significantly reduced substance P levels in nasal secretions from patients with perennial allergic rhinitis[7] and allergic asthma.[8] Azelastine significantly inhibited the generation of interleukins and other cytokines in human lymphocytes[9] and significantly reduced levels of inflammatory cytokines when administered orally and intranasally to patients with allergic rhinitis.[10] In addition, in a double-blind, placebo-controlled study,[11] a single dose of azelastine nasal spray reduced levels of eosinophils and neutrophils in nasal washings and decreased levels of eosinophil cationic protein and intercellular adhesion molecule-1 expression on nasal epithelial cells in patients with seasonal allergic rhinitis.

In double-blind, placebo-controlled trials in patients with seasonal allergic rhinitis,[12,13] azelastine nasal spray was effective in treating nasal and nonnasal symptoms over 2-week study periods. Onset and duration of action assessments in patients with seasonal allergic rhinitis showed that azelastine nasal spray improved baseline symptom scores within 1 hour in the majority of patients and that these improvements reached statistical significance vs placebo saline spray within 2 to 3 hours.[14,15] In placebo-controlled, double-blind trials in patients with vasomotor rhinitis,[16] azelastine nasal spray significantly improved all symptoms of the vasomotor rhinitis symptom complex including nasal congestion during 3 weeks of treatment.

Second-generation antihistamines are considered first-line therapy for the treatment of seasonal allergic rhinitis[17]; however, many patients do not experience adequate symptom relief with orally administered second-generation agents.[18–20]

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Supported by a grant from Medpointe Pharmaceuticals, Somerset, New Jersey.
Received for publication March 5, 2003.
Accepted for publication in revised form May 8, 2003.

The most common therapeutic options for patients with an unsatisfactory response to treatment with oral second-generation antihistamines include other oral antihistamines, azelastine nasal spray, or intranasal steroids. Azelastine nasal spray can be used either as monotherapy or in combination therapy with oral antihistamines or intranasal steroids; however, the effectiveness of azelastine nasal spray in treating patients with an unsatisfactory response to oral second-generation antihistamines has not been evaluated in a well controlled clinical trial. The primary objective of this study was to evaluate the effectiveness and safety of azelastine nasal spray, desloratadine (Clarinex; Schering, Kenilworth, NJ), and the combination of azelastine nasal spray plus loratadine (Claritin) compared with placebo in patients with seasonal allergic rhinitis who had an unsatisfactory response to treatment with loratadine.

METHODS

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 21 investigational sites during the 2002 fall allergy season in patients with seasonal allergic rhinitis. The study population consisted of male and female patients 12 years of age and older who had a minimum 2-year history of seasonal allergic rhinitis and a documented positive allergy skin test result during the previous year. Patients were excluded from participation for any of 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; having clinically significant nasal disease other than seasonal allergic rhinitis or significant nasal structural abnormalities; having respiratory infection or other infection requiring antibiotic therapy within 2 weeks of beginning the baseline screening period; having significant pulmonary disease and/or active asthma requiring daily medication; and history of or current alcohol or drug abuse. Women of childbearing potential who were not abstinent or practicing an accepted method of contraception and women who were pregnant or nursing were excluded from participation. All concomitant medications were discontinued for protocol-specified times, based on the elimination half-life of each drug, before beginning the double-blind treatment period. All patients or their guardians (if younger than 18 years of age) signed an institutional review board-approved informed consent agreement before participation.

The study consisted of 2 periods: a 1-week baseline period (day −7 to day 1) followed by a 2-week, randomized, double-blind treatment period. Patients were seen on an outpatient basis on days −7, 1, 7, and 14. Initial baseline qualification and assessments occurred on day −7, 1 week before randomization into the double-blind treatment period. Patients qualified for randomization into the double-blind treatment period when 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 lead-in period (Table 1). One of the 3 TNSS qualification scores (either AM and PM) during the lead-in period must have been recorded within 3 days of beginning the double-blind treatment period on day 1.

At day −7, patients with a TNSS score of 8 or higher over the previous 12 hours and who met the inclusion/exclusion criteria were assigned a patient number and given a 1-week supply of loratadine and a diary card in which to record symptom severity and the daily use of study medication. 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 inclusion/exclusion criteria on day 1 and who satisfied the symptom severity qualification criteria were randomized to 1 of the following 4 treatment groups: (1) azelastine nasal spray, 2 sprays per nostril twice daily, plus placebo capsule once daily; (2) desloratadine 5 mg in capsules, once daily, plus placebo saline nasal spray, 2 sprays per nostril twice daily; (3) azelastine nasal spray, 2 sprays per nostril twice daily, plus loratadine 10 mg in capsules once daily; or (4) placebo (saline) nasal spray, 2 sprays per nostril twice daily, plus placebo capsule once daily. Patients were instructed to take 1 capsule each morning, 2 sprays per nostril from the nasal spray bottle each morning, and 2 sprays per nostril each evening approximately 12 hours after the morning dose. Capsule medication was only taken in the morning. Commercially available loratadine and desloratadine were encapsulated to conceal their identity; all medications were blinded in such a manner that neither the patient nor the investigator was aware of their identity.

The primary efficacy variable was the change from baseline to day 14 in the TNSS, as measured by symptom scores recorded twice daily (AM and PM) in patient diary cards. Each individual symptom was scored using a 4-point rating scale: 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe.

Efficacy was evaluated by the change from baseline in the 12-hour reflective TNSS over 2 weeks of treatment. 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 of 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 over the 2-week

Table 1. Symptom Qualification Criteria

Day 7 TNSS qualification score	Minimum baseline TNSS
12	9
11	8
10	7
9	6
8	6

Abbreviation: TNSS, total nasal symptom score.

study period was compared with placebo using a repeated-measure analysis of variance 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 analysis of variance 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 after 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 0.05 level of significance, 80% power, and an average difference reduction of 1.0 unit in TNSS with SD of 2.5, a sample size of approximately 100 patients per treatment group was required. All inferential statistics were calculated at the 0.05 level of significance.

RESULTS

Patient Disposition

A total of 596 patients were screened for participation in the trial; 440 patients met the study entrance criteria and were randomized to double-blind treatment. Of the 156 patients who did not qualify for randomization, 104 failed to meet the inclusion/exclusion criteria at day −7, and 52 did not meet the minimum symptom score criteria at day 1. A total of 428 of the 440 randomized patients completed the 2-week double-blind treatment period. Of the 12 patients who did not complete the study, 4 discontinued due to an adverse event and 8 discontinued for administrative or other reasons.

Demographic and Pretreatment Characteristics

The 4 treatment groups were comparable with regard to demographic characteristics and baseline TNSS, and there were no statistically significant changes in TNSS within the treatment groups or statistically significant differences in TNSS between treatment groups during the lead-in period. The patients ranged in age from 12 to 79 years old with a mean age of approximately 35 years. Sixty-six percent of the patients were female, 80% were white, 11% were black, and 9% were Asian or other racial background (Table 2). During the 12-month period before enrollment in the study, 49% of the patients had used over-the-counter antihistamines, 30% had been treated with fexofenadine, 28% had been treated with loratadine, 17% had been treated with desloratadine, and 4% had been treated with azelastine nasal spray. In addition, 43% of the patients had been treated with 2 or more antihistamines during the 12 months before enrollment.

Efficacy

After 2 weeks of treatment, the mean percentage change from baseline in the overall TNSS was 21.9% with azelastine nasal spray ($P < 0.001$ vs placebo), 21.5% with azelastine nasal spray plus loratadine ($P < 0.001$ vs placebo), 17.5% with desloratadine ($P = 0.039$ vs placebo), and 11.1% with placebo (Table 3 and Fig 1). The mean absolute improvements from baseline and the relative contribution 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 (21.6% vs 11.0%; $P = 0.004$), sneezing (26.1% vs 7.0%; $P < 0.001$), and itchy nose (23.4% vs 12.4%; $P = 0.001$). Improvements in individual rhinitis symptoms in the azelastine nasal spray plus loratadine treatment group were virtually identical to the improvements seen with azelastine nasal spray monotherapy, with statistically significant differences for rhinorrhea ($P = 0.011$), sneezing ($P < 0.001$), and itchy nose ($P < 0.001$). In the desloratadine group, the only individual symptom that was significantly improved over placebo was sneezing ($P = 0.009$).

Table 2. Demographic Characteristics

Characteristic	Azelastine nasal spray (n = 108)		Azelastine nasal spray plus loratadine (n = 110)		Desloratadine (n = 111)		Placebo (n = 111)	
	N	%	N	%	N	%	N	%
Sex								
Male	43	39.8	36	32.7	37	33.3	34	30.6
Female	65	60.2	74	67.3	74	66.7	77	69.4
Race								
Caucasian	87	80.6	89	80.9	84	75.7	91	82.0
African-American	14	13.0	10	9.1	15	13.5	11	9.9
Asian	3	2.8	2	1.8	1	0.9	1	0.9
Other	4	3.7	9	8.2	11	9.9	8	7.2
Age (years)								
Mean (SD)	35.9		35.4		32.6		36.9	
Range	12 to 70		15 to 59		12 to 73		12 to 79	

Table 3. Change from Baseline in Mean AM and PM Total Nasal Symptom Scores and Individual Symptom Scores

Symptoms	Azelastine nasal spray (n = 106)*				Azelastine nasal spray plus loratadine (n = 108)*				Desloratadine (n = 111)				Placebo (n = 110)*		
	Mean baseline	Mean improv.	% Improv.	P value†	Mean baseline	Mean improv.	% Improv.	P value†	Mean baseline	Mean improv.	% Improv.	P value†	Mean baseline	Mean improv.	% Improv.
TNSS	17.70	3.88	21.9	<0.001	18.04	3.88	21.5	<0.001	17.67	3.10	17.5	0.039	16.79	1.87	11.1
AM	8.93	1.87	20.9	0.003	9.15	1.91	20.9	0.002	8.96	1.50	16.7	0.081	8.54	0.98	11.5
PM	8.78	2.02	23.0	<0.001	8.88	1.96	22.1	0.001	8.72	1.60	18.3	0.031	8.27	0.92	11.1
Rhinorrhea	4.63	1.00	21.6	0.004	4.61	0.93	20.2	0.011	4.66	0.78	16.7	0.087	4.36	0.48	11.0
AM	2.33	0.46	19.7	0.019	2.37	0.47	19.8	0.014	2.37	0.36	15.2	0.195	2.24	0.25	11.2
PM	2.30	0.53	23.0	0.002	2.24	0.45	20.1	0.022	2.29	0.41	17.9	0.064	2.13	0.24	11.3
Sneezing	3.60	0.94	26.1	<0.001	3.79	0.94	24.8	<0.001	3.57	0.71	19.9	0.009	3.43	0.24	7.0
AM	1.81	0.48	26.5	<0.001	1.86	0.45	24.2	0.001	1.78	0.37	20.8	0.014	1.70	0.14	8.2
PM	1.80	0.47	26.1	<0.001	1.92	0.49	25.5	<0.001	1.80	0.35	19.4	0.014	1.74	0.11	6.3
Itchy nose	4.40	1.03	23.4	0.001	4.47	1.05	23.5	<0.001	4.31	0.78	18.1	0.084	4.02	0.50	12.4
AM	2.20	0.48	21.8	0.022	2.25	0.51	22.7	0.008	2.20	0.40	18.2	0.167	2.04	0.28	13.7
PM	2.20	0.55	25.0	<0.001	2.22	0.53	23.9	<0.001	2.12	0.39	18.4	0.079	1.99	0.24	12.1
Congestion	5.07	0.90	17.8	0.151	5.15	0.95	18.4	0.080	5.12	0.82	16.0	0.326	4.98	0.67	13.5
AM	2.59	0.44	17.0	0.145	2.66	0.48	18.0	0.056	2.61	0.37	14.2	0.505	2.57	0.32	12.5
PM	2.48	0.46	18.5	0.190	2.50	0.48	19.2	0.133	2.51	0.45	17.9	0.243	2.41	0.35	14.5

Abbreviation: TNSS, total nasal symptom score.

* Two patients in the azelastine nasal spray group, 2 patients in the azelastine nasal spray plus loratadine group, and 1 patient in the placebo group had no postbaseline diary data and were not included in the efficacy analysis.

† Statistical significance vs placebo.

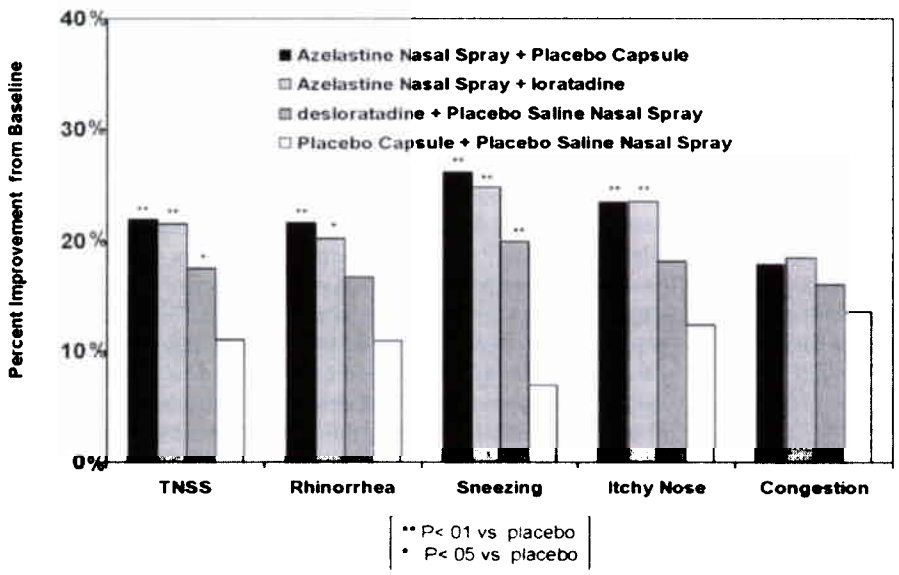

Figure 1. Mean percent improvement from baseline in total nasal symptom score (TNSS) and individual symptom scores.

Safety

Bitter taste was the most commonly reported adverse experience among patients treated with azelastine nasal spray monotherapy (11%) and azelastine nasal spray plus loratadine (4%). Headache (3%) and pharyngitis (4%) were the most commonly reported adverse events with desloratadine, whereas headache (7%) was the most commonly reported adverse event in the placebo group. Somnolence was reported by 2% of the patients treated with azelastine nasal spray compared with 1% for patients treated with azelastine nasal spray plus loratadine, 1% for patients treated with desloratadine, and 1% for patients treated with placebo.

Two patients treated with azelastine nasal spray monotherapy discontinued the study due to an adverse event: one patient had moderate chest pain and the other experienced lightheadedness. One patient in the desloratadine group (headache and nausea) and 1 patient in the placebo group (rash) also discontinued due to an adverse event. None of these

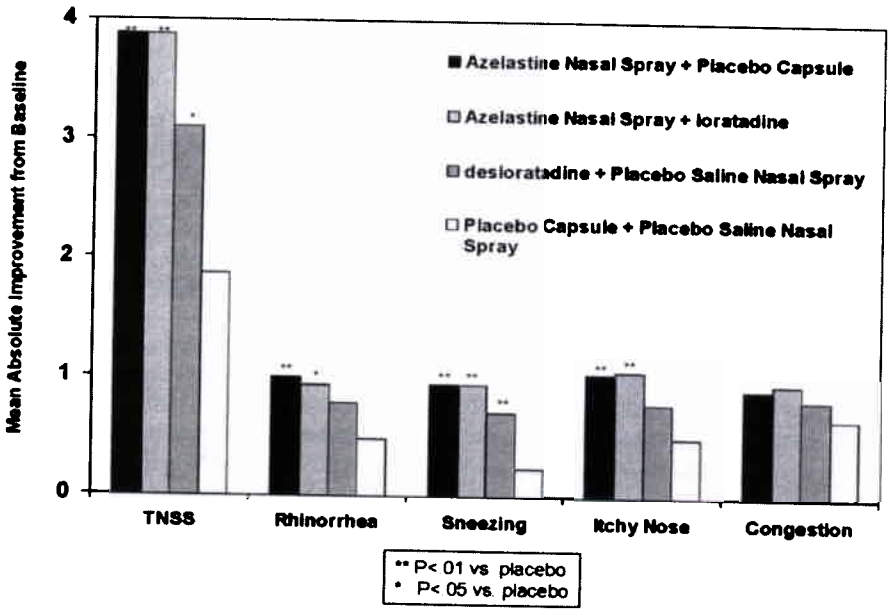

Figure 2. Mean absolute improvement from baseline in total nasal symptom score (TNSS) and individual symptom scores.

events were considered serious, and all of the patients recovered fully upon discontinuation of the study medications.

DISCUSSION

This double-blind, placebo-controlled study demonstrated that azelastine nasal spray was an effective therapy for seasonal allergic rhinitis patients who had an unsatisfactory response to loratadine. The patients enrolled in this study had moderate-to-severe rhinitis symptoms that improved by less than 25% to 33% compared with their baseline symptom scores when treated with loratadine for 7 days. After 2 weeks of treatment, patients in the azelastine nasal spray group had a statistically significant ($P < 0.001$) mean improvement in the TNSS that was approximately twofold greater than the improvement in the placebo group. Patients treated with azelastine nasal spray in combination with loratadine also had statistically significant ($P < 0.001$) improvement in the TNSS compared with placebo; however, this combination regimen resulted in the same improvement as seen with azelastine nasal spray alone. Patients treated with desloratadine had statistically significant ($P = 0.039$) improvement vs placebo in the TNSS, although the magnitude of improvement was approximately 40% less than that seen with azelastine nasal spray.

The overall improvement in the TNSS with azelastine nasal spray monotherapy was the result of statistically significant improvements over placebo in 3 of the 4 individual symptoms making up the TNSS. The combination of azelastine nasal spray with loratadine resulted in the same degree of improvement for each individual symptom as seen with azelastine nasal spray alone, which suggests that the improvements in rhinitis symptoms with this combination therapy regimen were attributable to azelastine nasal spray. In contrast, the overall improvement in the TNSS with desloratadine was primarily due to the effect on sneezing, the only individual symptom for which desloratadine demonstrated a significant improvement over placebo.

Although nasal congestion was not significantly improved in the active treatment groups, well controlled studies have shown that both azelastine nasal spray and desloratadine can improve nasal congestion in patients with rhinitis. For azelastine nasal spray, statistically significant improvements in nasal congestion have been reported in patients with seasonal allergic rhinitis[13] and nonallergic vasomotor rhinitis[16] and have been demonstrated objectively by anterior rhinomanometry in patients with seasonal allergic rhinitis.[21] Desloratadine was shown to significantly improve nasal congestion in patients with allergic rhinitis and asthma[22] and to improve nasal inspiratory flow rates in patients with seasonal allergic rhinitis.[23] In the current study, the improvement in the placebo group for the individual symptoms of the TNSS was greatest for nasal congestion, and the failure to detect statistically significant differences between active treatments and placebo may be due to the nasal irrigation provided by the placebo saline nasal spray. In future studies, it would be useful to include objective measurements of nasal airflow to more accurately determine the effect of second-generation antihistamines on nasal congestion.

As expected, the incidence of adverse experiences was low in the 3 active treatment arms of this study. Bitter taste (11%) of the medication was the most commonly reported adverse event with azelastine nasal spray. The incidence of somnolence with azelastine (2%) was similar to that with desloratadine (1%), a nonsedating antihistamine, and placebo (1%). Although azelastine is not considered a nonsedating antihistamine, studies using positron emission tomography to ana-

lyze histamine receptor binding in the human brain demonstrated that the degree of penetration of the blood-brain barrier and the extent of histamine receptor occupancy with azelastine was significantly less than that of first-generation antihistamines and comparable with that of nonsedating second-generation antihistamines.[24]

The selection of patients with an inadequate response to an oral antihistamine for inclusion in this study addresses a common treatment outcome in patients with allergic rhinitis. Antihistamines are considered first-line therapy for allergic rhinitis; however, many patients treated with oral second-generation antihistamines do not achieve an optimal therapeutic response and are often treated with other antihistamines or intranasal steroids either alone or in various combination regimens. In a study of 1,458 secondary school students with allergic rhinitis,[18] 73% of the students reported using 2 or more rhinitis medications, whereas only 27% reported using monotherapy. In a study of drug utilization patterns in more than 60,000 patients initiating treatment for seasonal allergic rhinitis, nearly one third of the patients either added or switched drugs during the study period, which resulted in a threefold and twofold increase, respectively, in the number of prescriptions for these patients compared with patients treated with monotherapy.[19] In addition, a survey conducted by the American College of Allergy, Asthma, and Immunology reported that 52% of allergists and 39% of primary care physicians surveyed prescribed more than 1 oral antihistamine, and more than 75% of allergists and primary care physicians cited inadequate symptom relief as the reason for switching medications or using combination therapy regimens.[20] Consistent with these findings, 43% of the patients in the current study had used 2 or more antihistamines during the 12 months before enrollment in the double-blind treatment period.

CONCLUSION

This study demonstrated that azelastine nasal spray was an effective treatment for patients with seasonal allergic rhinitis who had an unsatisfactory response to loratadine. In addition, compared with treatment with azelastine nasal spray monotherapy, no additional therapeutic benefit was achieved by adding loratadine in combination therapy with azelastine nasal spray. For rhinitis patients who experience limited clinical improvement with oral antihistamines, azelastine nasal spray is an alternative to switching to another oral antihistamine or to using multiple antihistamines.

ACKNOWLEDGMENTS

The authors thank William J. Wheeler, PhD for contributions to the design of the study and assistance in preparation of the manuscript.

‡ Members of the Rhinitis Study Group are: Dean Atkinson, MD, Oklahoma City, OK; Charles Banov, MD, Charleston, SC; David Bernstein, MD, Cincinnati, OH; Jimmy Chevalier, MD, Glendale, AZ; David Cook, MD, Danville, CA; Jonathan Corren, MD, Los Angeles, CA; Albert Finn, MD, Charleston, SC; David Gossage, MD, Knoxville, TN; Frank Hampel, MD, New Braunfels, TX; Melvin Haysman, MD, Savannah, GA; Craig LaForce, MD, Raleigh, NC; Dennis Ledford, MD, Tampa, FL; William Lumry, MD, Dallas, TX; Jonathan Matz, MD, Baltimore, MD; John Morris, MD, Louisville, KY; Paul Ratner, MD, San Antonio, TX; Eric Schenkel, MD, Easton, PA; Julius Van Bavel, MD, Austin, TX; and Michael Welch, MD, San Diego, CA.

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