Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis

Paul H. Ratner, MD*; Frank Hampel, MD†; Julius Van Bavel, MD‡; N. J. Amar, MD§; Pramila Daftary, MD¶; William Wheeler, PhD‖; and Harry Sacks, MD‖

Background: To our knowledge, there are no published studies that evaluated the efficacy of azelastine hydrochloride nasal spray in combination with an intranasal corticosteroid, although anecdotal reports of the use of these agents in combination are common.

Objective: To determine if greater efficacy could be achieved with the intranasal antihistamine azelastine and the intranasal corticosteroid fluticasone propionate used concurrently compared with the efficacy of each agent alone.

Methods: This randomized, 2-week, multicenter, double-blind trial was conducted during the Texas mountain cedar season. After a 5-day placebo lead-in period, 151 patients with moderate to severe nasal symptoms were randomized to treatment with the following: (1) azelastine nasal spray, 2 sprays per nostril twice daily; (2) fluticasone nasal spray, 2 sprays per nostril once daily; or (3) azelastine nasal spray, 2 sprays per nostril twice daily, plus fluticasone nasal spray, 2 sprays per nostril once daily. The primary efficacy variable was the change from baseline in the total nasal symptom score (TNSS), consisting of sneezing, itchy nose, runny nose, and nasal congestion.

Results: All 3 groups had statistically significant ($P < .001$) improvements from their baseline TNSS after 2 weeks of treatment. The TNSS improved 27.1% with fluticasone nasal spray, 24.8% with azelastine nasal spray, and 37.9% with the 2 agents in combination ($P < .05$ vs either agent alone). All 3 treatments were well tolerated.

Conclusions: The significant improvement in the TNSS with combination therapy relative to the individual agents alone is in contrast to previously published studies that found no advantage with an oral antihistamine and an intranasal corticosteroid in combination. Azelastine nasal spray and fluticasone nasal spray in combination may provide a substantial therapeutic benefit for patients with seasonal allergic rhinitis compared with therapy with either agent alone.

Ann Allergy Asthma Immunol. 2008;100:74–81.

INTRODUCTION

The most commonly used agents in the treatment of seasonal allergic rhinitis (SAR) are oral antihistamines and intranasal corticosteroids. Clinical studies[1,2] have shown that the second-generation antihistamines, cetirizine and fexofenadine, provide approximately equal therapeutic efficacy, whereas the efficacy of cetirizine seems to exceed that of loratadine.[3–5] Reviews[6,7] of well-controlled clinical trials that directly compared an intranasal corticosteroid with an oral antihistamine concluded that intranasal corticosteroids are superior to oral antihistamines for the relief of allergic rhinitis symptoms.

Azelastine hydrochloride nasal spray is the only second-generation antihistamine recommended for the treatment of SAR and nonallergic vasomotor rhinitis.[8,9] Compared with oral antihistamines, azelastine nasal spray significantly improved rhinitis symptom scores in placebo-controlled studies in patients with SAR who remained symptomatic after treatment with loratadine or fexofenadine. In these studies,[10,11] patients treated with azelastine nasal spray who received loratadine or fexofenadine concomitantly had no additional improvement when compared with treatment with azelastine nasal spray alone. In 2 direct comparative trials vs cetirizine in patients with SAR, azelastine nasal spray was significantly better than cetirizine for treating nasal symptoms in one trial,[12] numerically better than cetirizine in the second trial,[13] and significantly better than cetirizine in both trials for improving quality-of-life variables using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

In 2-week, double-blind studies with intranasal corticosteroids in patients with SAR, azelastine nasal spray at a dosage of 1 spray per nostril twice daily showed comparable efficacy

Affiliations: * Sylvana Research, San Antonio, Texas; † Central Texas Health Research, New Braunfels, Texas; ‡ Allergy and Asthma Associates Research, Austin, Texas; § Allergy and Asthma Research Institute, Waco, Texas; ¶ Allergy and Asthma Care of Waco, Waco, Texas; ‖ MedPointe Pharmaceuticals, Somerset, New Jersey.

Disclosures: Drs Ratner, Hampel, Van Bavel, Amar, and Daftary received research grants for conducting this study, and Drs Wheeler and Sacks are employees of MedPointe Pharmaceuticals.

Sources of Funding: This study was supported by MedPointe Pharmaceuticals.

Received for publication December 20, 2006; Received in revised form July 26, 2007; Accepted for publication August 23, 2007.

to budesonide, 2 sprays per nostril twice daily (400 μg/d),[14,15] and beclomethasone (0.2 mg twice daily).[16] In a 6-week double-blind trial in patients with SAR, azelastine, 1 spray per nostril twice daily, and loratadine, 10-mg tablets once daily, significantly ($P < .05$) improved symptom scores compared with baseline, and the physician global evaluation of efficacy rated similar numbers of patients in each group with either "good" or "very good" improvement.[17] In a 2-week, double-blind trial in patients with SAR, azelastine, 1 spray per nostril twice daily, and cetirizine, 10 mg/d, produced total symptom score improvements of 61% and 67%, respectively.[18] In a 6-week, placebo-controlled study[19] in patients with perennial allergic rhinitis, a once-daily dose of 256 μg of budesonide aqueous suspension was significantly ($P < .01$) more effective than azelastine nasal spray, 1 spray per nostril twice daily, in improving the total nasal symptom score (TNSS). In a double-blind, placebo-controlled study[20] of flunisolide nasal spray and azelastine nasal spray in patients with perennial allergic rhinitis, the researchers reported little difference between the 2 treatments for the overall summary score; however, the topical corticosteroid showed a greater decrease in symptom severity compared with placebo than the antihistamine spray for all symptoms, except rhinorrhea.

Unfortunately, many patients with SAR do not achieve optimal symptom relief with single-agent therapy. In a survey conducted by the American College of Allergy, Asthma & Immunology, more than 75% of allergists and primary care physicians surveyed cited inadequate symptom relief as the reason for changing medications or prescribing combination therapy.[21] Although oral antihistamines and intranasal corticosteroids routinely are prescribed together, the weight of clinical evidence indicates that combination therapy with these agents is no more effective than the corticosteroid alone.[7,22,23] To our knowledge, there have been no published studies that evaluated the efficacy of azelastine nasal spray used in combination with an intranasal corticosteroid. We hypothesized that 2 agents with different mechanisms of action could have the potential for a greater effect when used in combination than separately. The antihistaminic effect of azelastine would be evident quickly after initial administration and sustained with regular use. The primary antihistaminic activity of azelastine could be augmented by anti-inflammatory effects of the intranasal corticosteroid during the 2-week study period. Therefore, this study was conducted to determine if greater efficacy could be achieved with the combination of intranasal azelastine and intranasal fluticasone propionate when compared with the efficacy of either agent alone in patients with SAR.

METHODS

Patients

The study population consisted of patients 12 years and older with a minimum 2-year history of allergy to Texas mountain cedar (*Juniperus ashei*) pollen, as confirmed by a positive allergy skin test result within the past year. Use of concomitant medications was discontinued for specified times, based on the elimination half-life of each drug, before patients began the double-blind treatment period. All patients or their guardians (if the patient was aged <18 years) signed an institutional review board–approved informed consent agreement (Sterling institutional review board, Atlanta, Georgia) before participation.

Study Design

This randomized, double-blind, double-dummy, parallel-group study was conducted between December 27, 2005, and February 17, 2006, at 5 investigational sites during the Texas mountain cedar season. Pollen counts were conducted at each study site to confirm the presence of mountain cedar pollen during the investigation. The objective was to determine if greater efficacy could be achieved with the combination of azelastine hydrochloride nasal spray (Astelin; MedPointe Pharmaceuticals, Somerset, New Jersey) and fluticasone propionate nasal spray (Flonase; GlaxoSmithKline, Research Triangle Park, North Carolina) compared with the efficacy of each agent alone.

The primary efficacy variable was the change from baseline to day 14 for the entire double-blind treatment period in the TNSS, consisting of rhinorrhea, sneezing, itchy nose, and nasal congestion. Secondary efficacy variables included the following: (1) change from baseline for each individual treatment day, (2) change from baseline to day 14 in individual symptom scores, and (3) change from baseline to day 14 in the RQLQ, including overall score and individual domains. Safety was evaluated by patient reports of adverse experiences and vital sign assessments, including body temperature, blood pressure, pulse rate, and respiration rate, performed at baseline and at the end of the study.

There were 10 symptom assessments (in the morning and evening each day) during the 5-day placebo lead-in period. To qualify for randomization to the double-blind treatment period, patients must have recorded a 12-hour reflective TNSS of at least 8 at 3 evaluation times either in the morning or in the evening (1 of which was within 48 hours of study day 1) during the lead-in period. In addition, a morning or evening nasal congestion score of 3 must have been recorded at 3 assessments (1 of which was within 48 hours of day 1).

Patients randomized to the azelastine nasal spray group received azelastine nasal spray, 2 sprays per nostril twice daily, in the morning and evening (1.1-mg azelastine) and placebo spray once daily in the morning. Patients randomized to the fluticasone group received fluticasone, 2 sprays per nostril once daily, in the morning (200-μg fluticasone) and placebo spray twice daily in the morning and evening. Patients randomized to the combination group received azelastine nasal spray, 2 sprays per nostril twice daily, in the morning and evening and fluticasone nasal spray, 2 sprays per nostril once daily, in the morning. The kits containing study drugs were assembled so that blinded azelastine nasal spray was administered before blinded fluticasone nasal

Table 1. Demographic and Baseline Characteristics

Characteristic	Azelastine hydrochloride nasal spray group (n = 49)	Fluticasone propionate nasal spray group (n = 50)	Combination azelastine nasal spray and fluticasone nasal spray group (n = 52)	Total (N = 151)
Age, y				
Mean	38.4	37.4	36.0	37.2
Range	12–73	12–72	13–70	12–73
Sex, No. (%)				
Males	22 (44.9)	15 (30.0)	19 (36.5)	56 (37.1)
Females	27 (55.1)	35 (70.0)	33 (63.5)	95 (62.9)
Race/ethnicity, No. (%)[a]				
White	36 (73.5)	32 (64.0)	41 (78.8)	109 (72.2)
Black	5 (10.2)	2 (4.0)	2 (3.8)	9 (6.0)
Asian	0	3 (6.0)	1 (1.9)	4 (2.6)
Hispanic	7 (14.3)	13 (26.0)	8 (15.4)	28 (18.5)
Other	1 (2.0)	0	0	1 (0.7)
Baseline TNSS				
Mean	19.6	19.5	19.5	19.5
SD	2.11	2.74	2.97	2.62
Range	15–24	14–24	13–24	13–24
Duration of allergy, y				
Mean	19.2	15.7	16.2	17.0
Range	3–50	3–51	4–40	3–51

Abbreviation: TNSS, total nasal symptom score.
[a] Percentages may not total 100 because of rounding.

spray. Patients were instructed to administer the morning doses of each study drug 15 to 30 minutes apart. Instruction on proper technique for administering the nasal sprays was given before starting the lead-in period and again before the double-blind treatment period, and patients were observed taking their initial dose of study medications before leaving the clinic at these visits.

The identity of the study medications was concealed through use of a device (Pharmask Inc, Medfield, Massachusetts) that prevented identification of the product but allowed for the proper administration of the nasal sprays.

During the 2-week, double-blind treatment period, the patients recorded symptom scores twice daily (morning and evening) on diary cards. Symptoms were recorded before the morning and evening doses of study medications as an evaluation of symptom severity during the previous 12 hours (12-hour reflective TNSS). Individual symptoms of the TNSS were scored on a 4-point scale, where 0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms (such that the maximum combined morning and evening TNSS was 24).

Statistical Analysis

Patients were randomized to treatment by a computer-generated randomization schedule, which was accessible only to authorized persons who were not involved in the study. The primary efficacy analyses were performed on an intent-to-treat population consisting of all randomized patients with at least 1 postbaseline observation. Missing TNSS values were imputed using the last-observation-carried-forward method. Safety analyses were performed on all randomized patients who received at least 1 dose of study medication.

The effects of treatment were determined at each day of the study and after 14 days based on change from baseline in the TNSS. Baseline TNSS was defined as the average of all TNSS scores during the 5-day placebo lead-in-period. The treatment groups were compared using an analysis of variance model with baseline as a covariate. The data from this study were tested for homogeneity and were normally distributed. No site-related effects were identified. The TNSS was analyzed as the mean change from baseline during the entire 14-day study period. Additional analyses included the mean change from baseline in TNSS for individual study days and individual symptoms and the mean percentage change from baseline during the entire 14-day study period.

The quality-of-life evaluation was performed using the self-administered RQLQ, which evaluated the following 7 domains: (1) activities, (2) sleep, (3) non–nose/eye symptoms, (4) practical problems, (5) nasal symptoms, (6) eye symptoms, and (7) emotional factors. The change from baseline to day 14 in the RQLQ domains and overall score was calculated and analyzed according to the method described by Juniper at al.[24]

The incidence of adverse events was summarized by body system, severity, and relationship to study drug. Vital sign measurements, including oral body temperature, systolic and diastolic blood pressure, pulse rate, and respiration rate, were examined for abnormal values and changes from baseline.

Table 2. Data for the TNSS

Variable[a]	Baseline data		Change from baseline TNSS data			% Change from baseline TNSS data		
	LS Mean	SD	LS Mean	SD	*P* value[b]	% change LS mean	SD	*P* value[b]
TNSS								
Azelastine hydrochloride nasal spray plus fluticasone propionate nasal spray	19.5	3.0	7.4	5.6	NA	37.9	27.7	NA
Azelastine nasal spray alone	19.7	2.1	4.8	4.3	.008	24.8	22.2	.01
Fluticasone nasal spray alone[c]	19.6	2.7	5.2	4.6	.03	27.1	24.5	.04
Itchy nose								
Azelastine nasal spray plus fluticasone nasal spray	4.7	1.0	1.9	1.7	NA	39.9	39.0	NA
Azelastine nasal spray alone	4.8	0.8	1.1	1.4	.009	25.4	29.7	.03
Fluticasone nasal spray alone	4.8	1.3	1.3	1.5	.02	25.5	32.9	.04
Congestion								
Azelastine nasal spray plus fluticasone nasal spray	5.4	0.6	1.7	1.4	NA	31.2	25.7	NA
Azelastine nasal spray alone	5.5	0.5	1.1	1.5	.02	19.2	26.6	.02
Fluticasone nasal spray alone	5.5	0.4	1.1	1.2	.04	21.1	23.4	.04
Runny nose								
Azelastine nasal spray plus fluticasone nasal spray	4.9	1.0	1.7	1.6	NA	36.4	32.9	NA
Azelastine nasal spray alone	4.9	0.8	1.1	1.4	.02	20.5	27.6	.05
Fluticasone nasal spray alone	5.0	1.0	1.3	1.2	.19	23.0	53.4	.09
Sneezing								
Azelastine nasal spray plus fluticasone nasal spray	4.5	1.2	2.1	1.7	NA	46.4	37.2	NA
Azelastine nasal spray alone	4.5	1.1	1.5	1.0	.04	34.2	25.8	.08
Fluticasone nasal spray alone	4.3	1.3	1.5	1.5	.05	31.8	38.1	.04

Abbreviations: LS, least squares; NA, data not applicable; TNSS, total nasal symptom score.
[a] Data were available for 52 patients in the combination therapy group, 49 in the azelastine nasal spray group, and 49 in the fluticasone nasal spray group.
[b] Statistical significance of azelastine nasal spray plus fluticasone nasal spray vs the individual agent.
[c] One patient had no postbaseline efficacy assessment and was not included in the analysis.

RESULTS

Disposition of Patients

A total of 151 patients were randomized to double-blind treatment at 5 study centers. Of the 151 randomized patients, 150 had postbaseline diary data and were included in the efficacy analysis. Data for all 151 randomized patients were included in the safety analysis. A total of 147 patients completed all 14 days of the double-blind treatment period. All of the patients in the azelastine nasal spray group completed 14 study days. In the fluticasone group, 1 patient withdrew consent and 1 withdrew for lack of efficacy. In the combination group, 2 patients were withdrawn for noncompliance with the protocol.

Demographic Characteristics

The treatment groups were comparable for baseline demographic and clinical characteristics (Table 1). The patients were a mean age of 37.2 years (range, 12–73 years), most were female, and the average duration of allergy to Texas mountain cedar was 17 years.

Primary Efficacy

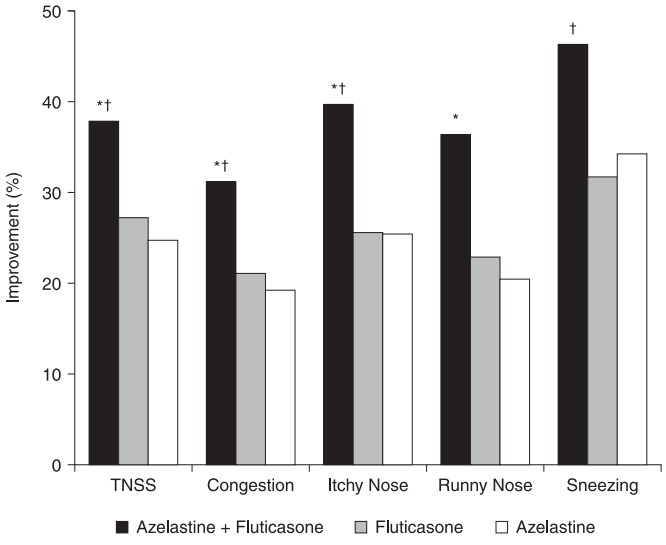
Primary efficacy was change from baseline to day 14 in TNSS. Table 2 provides the mean improvements in the TNSS and individual symptoms for the 3 treatment groups. The treatment groups were comparable for baseline symptom scores, and all 3 treatments resulted in statistically significant ($P < .001$) improvements from baseline. The mean $\pm$ SD improvement from the baseline TNSS was 4.8 $\pm$ 4.3 with azelastine nasal spray, 5.2 $\pm$ 4.6 with fluticasone nasal spray, and 7.4 $\pm$ 5.6 with the 2 agents in combination. The TNSS improved from baseline by 27.1% with intranasal fluticasone, by 24.8% with azelastine nasal spray, and by 37.9% with the 2 agents in combination ($P < .05$ vs either agent alone); there were absolute improvements of 11% and 13% with combination therapy compared with intranasal azelastine and fluticasone, respectively. These absolute improvements represent greater than 40% relative improvement compared with either agent alone ($P = .007$ vs azelastine and $P = .02$ vs fluticasone).

Secondary Efficacy

Change from baseline to day 14 in individual symptoms. Combination therapy improved all individual TNSS symptoms compared with the individual agents (Fig 1). Combination therapy provided 48% more relief from nasal congestion and 56% more relief from nasal itching than fluticasone alone, and the combination was statistically superior to both azelastine and fluticasone. Combination therapy provided 58% more relief from runny nose than fluticasone alone, and the combination was statically superior to azelastine. Combination therapy provided 46% more relief from sneezing than fluticasone alone, and the combination was statistically superior to fluticasone.

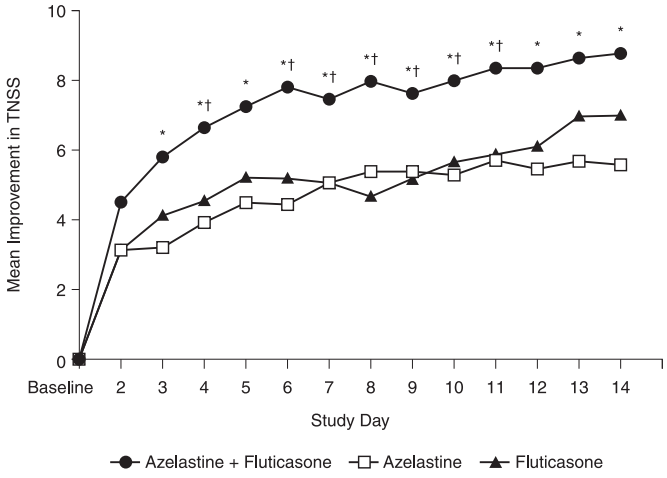
Change from baseline to day 14 in TNSS on individual study days. Figure 2 shows the improvement in the 3 treatment groups on each individual day of the study. The combination of azelastine and fluticasone was statistically superior to azelastine alone on study days 3 through 14, and the combination was statistically superior to fluticasone alone on days 4 and 6 through 11.

Change from baseline to day 14 in RQLQ scores. All 3 treatments produced statistically significant ($P < .001$) improvements from their respective baseline RQLQ scores for overall score and for each individual domain of the RQLQ (Table 3). The mean change from baseline in the overall RQLQ score was 1.21 in the azelastine nasal spray group, 1.47 in the fluticasone group, and 1.92 in the combination group, which was statistically significant compared with azelastine and approached significance compared with fluticasone.



*Azelastine + Fluticasone; $P<.05$ vs Fluticasone
†Azelastine + Fluticasone; $P<.05$ vs Azelastine

Figure 1. Total nasal symptom score (TNSS) and individual symptoms. The asterisk indicates $P < .05$ for azelastine hydrochloride plus fluticasone propionate vs fluticasone alone; dagger, $P < .05$ for azelastine plus fluticasone vs azelastine alone.



*$P<.05$ vs Azelastine
†$P<.05$ vs Fluticasone

Figure 2. Total nasal symptom score (TNSS) daily improvements. The asterisk indicates $P < .05$ for azelastine hydrochloride plus fluticasone propionate vs azelastine alone; dagger, $P < .05$ for azelastine plus fluticasone vs fluticasone alone.

Safety

All 3 treatments were well tolerated. The most common adverse event was the bitter taste associated with azelastine (8.2% in the azelastine group, 2.0% in the fluticasone group, and 13.5% in the combination group). Headache was reported by 4.1% of patients in the azelastine group, by 4.0% of patients in the fluticasone group, and by 5.8% of patients in the combination group. No other adverse event was reported by more than 1 patient. There were no significant changes from baseline to the end of the study in vital sign assessments.

DISCUSSION

In this study, significantly greater efficacy was achieved by combination therapy with an antihistamine nasal spray and an intranasal corticosteroid spray, when compared with either agent alone.

Azelastine nasal spray plus fluticasone nasal spray provided greater than 40% relief of the TNSS relative to fluticasone alone and greater than 48% relief of nasal congestion relative to fluticasone alone. All of the individual symptoms of the TNSS were improved with combination therapy when compared with either fluticasone or azelastine alone. This improvement reached statistical significance compared with azelastine on day 3 and compared with both fluticasone and azelastine on day 4, and the improvement in TNSS steadily increased with combination therapy during the 14-day study period.

The combination regimen was well tolerated by the patients in this study. Compliance was evaluated by patient diary entries and confirmed by bottle weights measured before and after the double-blind treatment period. Compliance

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.