Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device

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Background: A proof-of-concept study suggested that combination therapy with commercial azelastine hydrochloride nasal spray and fluticasone propionate nasal spray significantly improved nasal symptoms of seasonal allergic rhinitis compared with either agent alone.

Objective: To compare an azelastine-fluticasone combination nasal spray administered in a single-delivery device with a commercially available azelastine nasal spray and fluticasone nasal spray.

Methods: This 14-day, multicenter, randomized, double-blind study was conducted during the Texas mountain cedar season. After a 5-day placebo lead-in, 610 patients with moderate-to-severe nasal symptoms were randomized to treatment with (1) azelastine nasal spray, (2) fluticasone nasal spray, (3) combination azelastine and fluticasone nasal spray, or (4) placebo nasal spray. All treatments were given as 1 spray per nostril twice daily. The primary efficacy variable was the change from baseline in the total nasal symptom score (TNSS), consisting of nasal congestion, runny nose, itchy nose, and sneezing.

Results: All 3 active groups were statistically superior ($P \leq .02$) to placebo, and the combination was statistically superior ($P \leq .003$) to either agent alone. The TNSS improved by 28.4% with combination azelastine-fluticasone, 20.4% with fluticasone, 16.4% with azelastine, and 11.2% with placebo. All 3 treatments were well tolerated.

Conclusions: The combination azelastine-fluticasone nasal spray provided statistically significant improvement in the TNSS and additive clinical benefit compared with either agent alone in patients with moderate-to-severe seasonal allergic rhinitis.

Trial Registration: clinicaltrials.gov Identifier: NCT00660517.

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INTRODUCTION

In a proof-of-concept study, the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray administered concomitantly significantly improved nasal symptoms of seasonal allergic rhinitis in patients with an allergy to Texas mountain cedar (*Juniperus ashei*).[1] The Joint Task Force on Practice Parameters for the diagnosis and management of rhinitis recognizes that intranasal antihistamines are appropriate for use as first-line treatment for symptoms of allergic rhinitis, and their use in combination with nasal corticosteroids may provide added benefit.[2,3] The Allergic Rhinitis and its Impact on Asthma guidelines and other expert panels also provide algorithms that include combination therapy with intranasal antihistamines and intranasal corticosteroids.[4,5]

The economic burden of allergic rhinitis is substantial and includes both direct medical costs of physician visits and medications and indirect costs related to reductions in productivity due to rhinitis symptoms or the effects of treatment. Although methods vary, the total treatment cost of rhinitis has been estimated to be as much as $7.3 billion.[6] With allergic, nonallergic, and mixed rhinitis affecting up to 60 million people in the United States annually, the costs of treatment must be viewed in light of the potential clinical benefit.[2,7] Ineffective treatment leads to patient frustration, dissatisfaction, and poor compliance. Physicians may likewise become frustrated that patients do not adhere to their prescribed treatment regimens despite their efforts to educate them.

Patients may benefit from the availability of a combination azelastine and fluticasone product in a single-delivery nasal spray device due to potential additive effects that may result from the different primary mechanisms of action of each drug and the possible improvement in adherence to therapy by delivering the 2 agents in a single device.

METHODS

Patients

The study population included males and females 12 years and older with a minimum 2-year history of allergy to Texas

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mountain cedar pollen (*J ashei*), as confirmed by a positive prick-puncture skin test result to mountain cedar pollen within the past 12 months. Before study entry, all patients or their guardians (if younger than 18 years) signed an institutional review board–approved informed consent agreement (Sterling Institutional Review Board, Atlanta, Georgia). At screening, eligible patients had to have a 12-hour reflective total nasal symptom score (TNSS) of at least 8 of a possible 12 and a congestion score of 2 or 3; by randomization, patients had to have a TNSS of at least 8 on 3 separate symptom assessments (1 of which was within 2 days of day 1 and could include the morning of day 1) during the placebo lead-in period. Patients were also required to be in general good health and free of any disease or concomitant treatment that could interfere with the interpretation of the study results as determined by the study investigator.

Key exclusion criteria included the following: (1) the presence of any nasal mucosal erosion, nasal ulceration, or nasal septal perforation (grade 1b-4) at either screening or randomization; (2) other nasal disease(s) likely to affect deposition of intranasal medication, such as sinusitis, rhinitis medicamentosa, clinically significant polyposis, or nasal structural abnormalities; (3) nasal surgery or sinus surgery within the previous year; or (4) more than 3 episodes per year of chronic sinusitis.

Study Design

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 6 investigational sites during January and February 2007 (clinicaltrials.gov identifier: NCT00660517). The study consisted of a 5-day, single-blind, placebo lead-in period during which patients were required to have a minimum symptom severity score to be eligible for double-blind treatment. The placebo lead-in period was followed by a 14-day, double-blind treatment period in which qualified patients were randomized by a computer-generated randomization schedule to treatment with (1) combination azelastine 0.1% and fluticasone, 1 spray per nostril twice daily (each metered spray of azelastine-fluticasone delivers 137 μg of azelastine hydrochloride and 50 μg of fluticasone propionate; therefore, a dosage of 1 spray per nostril twice daily delivers 548 μg of azelastine hydrochloride and 200 μg of fluticasone propionate); (2) azelastine 0.1% (Astelin; Meda Pharmaceuticals Inc, Somerset, New Jersey), 1 spray per nostril twice daily (each metered spray of Astelin delivers 137 μg of azelastine hydrochloride; therefore, a dosage of 1 spray per nostril twice daily delivers 548 μg of azelastine); (3) fluticasone (Flonase; GlaxoSmithKline, Research Triangle Park, North Carolina), 1 spray per nostril twice daily (each metered spray of Flonase delivers 50 μg of fluticasone propionate; therefore, a dosage of 1 spray per nostril twice daily delivers 200 μg of fluticasone); or (4) azelastine-fluticasone vehicle placebo, 1 spray per nostril twice daily.

Symptom severity was assessed by the 12-hour reflective TNSS, consisting of nasal congestion, runny nose, itchy nose, and sneezing, and the instantaneous TNSS recorded twice daily (morning and evening) in diary cards. The 12-hour reflective and instantaneous TNSS assessments were made before the morning and evening doses of study medication. Symptoms were scored on a scale of 0 to 3 (0 indicating no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms), such that the maximum daily symptom severity score was 24.

On the first day of the placebo lead-in period, patients were required to have a 12-hour reflective TNSS of at least 8, to have a nasal congestion score of 2 or 3, and to meet all specified study inclusion and exclusion criteria. Qualified patients then recorded 12-hour reflective and instantaneous TNSS twice daily (morning and evening) during the 5-day placebo lead-in period.

To be eligible for double-blind treatment, patients were required to have a minimum 12-hour reflective TNSS of 8 for at least 3 symptom assessments (either morning or evening) during the placebo lead-in period and have a 12-hour reflective nasal congestion score of 2 or 3 for at least 3 symptom assessments (either morning or evening). For both TNSS and nasal congestion, 1 of the 3 assessments must have occurred within 2 days of day 1.

On days 1 through 14, patients recorded 12-hour reflective and instantaneous TNSS daily (morning and evening) in diaries. Patients also recorded the severity of postnasal drip and the 12-hour reflective and instantaneous total ocular symptom score (TOSS), consisting of itchy eyes, watery eyes, and red eyes, twice daily (morning and evening) in diaries, such that the maximum daily score was 18. In addition, patients 18 years and older completed the Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) on days 1 and 14.

The primary efficacy variable was the change from baseline (day 1) to day 14 in 12-hour reflective TNSS, consisting of nasal congestion, runny nose, itchy nose, and sneezing. Baseline was the average of the combined (morning and evening) TNSS during the entire placebo lead-in period. Secondary efficacy variables included the following: (1) change from baseline to day 14 in individual symptom scores, (2) change from baseline in TNSS on each study day, (3) change from baseline to day 14 in TOSS, (4) change from baseline to day 14 in individual ocular symptom scores, and (5) change from baseline to day 14 on the RQLQ, including overall score and individual domains. Safety was assessed by patient-reported adverse events and vital sign assessments, including body temperature, blood pressure, pulse, and respiration rate, performed at baseline and study end.

Statistical Analysis

The primary efficacy variable was evaluated for the intent-to-treat population, consisting of all randomized patients with at least 1 postbaseline efficacy assessment. For each evaluation, the treatment groups were compared using an analysis of covariance model with baseline as a covariate. Missing TNSS values were imputed using the last observation carried forward method. Analyses of TOSS were performed in a manner

identical to that for TNSS. The change from day 1 to day 14 in the RQLQ score was summarized according to the method described by Juniper et al.[8] On the basis of this method, a change in the RQLQ of 0.5 units is considered clinically important. All inferential statistics were calculated at $P < .05$ level of significance.

RESULTS

Patient Disposition

A total of 610 patients were randomized to double-blind treatment. Of the 610 randomized patients, 607 had postbaseline diary data and were included in the efficacy analysis. Data for 609 randomized patients were included in the safety analysis. A total of 577 patients completed all 14 days of double-blind treatment, and 33 discontinued participation in the study. Completion rates were similar in all treatment groups. One patient in the combination group, 3 in the azelastine group, 1 in the fluticasone group, and 1 in the placebo group discontinued participation in the study because of an adverse event. The most common reason for study withdrawal was noncompliance, followed by "other," withdrawal of consent, and adverse events.

Demographic and Clinical Characteristics

The treatment groups were comparable with regard to demographic and baseline clinical characteristics (Table 1). The patients had a mean age of 39.3 years (range, 12–75 years), most patients were female (65.2%), and the average duration of allergy to Texas mountain cedar was 18.6 years (range, 2–64 years). Of the 607 patients included in the efficacy analysis, 87.0% identified themselves as white or Caucasian, 10.4% as black or African American, 1.5% as Asian or Pacific Islander, and 1.1% as other.

Efficacy

Change from baseline to day 14 in TNSS. Figure 1 shows the mean improvement in the TNSS for each treatment group. All 3 active treatment groups resulted in a statistically significant ($P < .001$) improvement from baseline. The mean

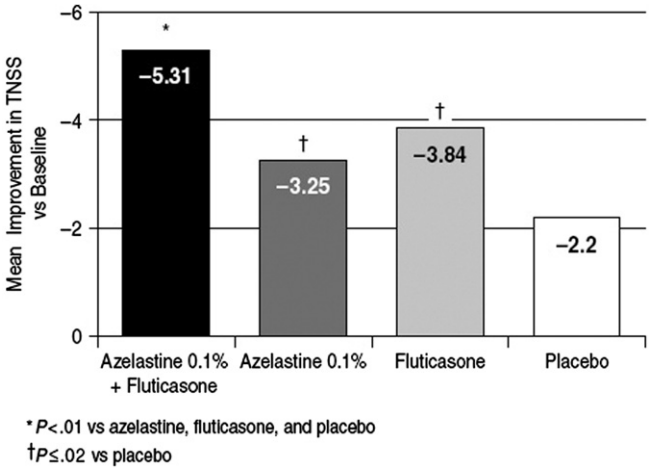


Figure 1. Mean improvement from baseline in the total nasal symptom score (TNSS) during the 14-day study period (negative values indicate improvement).

(SD) improvement from baseline TNSS was −3.25 (4.16) with azelastine, −3.84 (4.76) with fluticasone, and −5.31 (5.08) with azelastine and fluticasone in combination. The TNSS improved from baseline by 16.4% with azelastine, by 20.4% with fluticasone, and by 28.4% with the 2 agents in combination ($P < .01$ vs placebo and either agent alone). Both azelastine and fluticasone alone significantly improved the TNSS compared with placebo ($P \leq .02$).

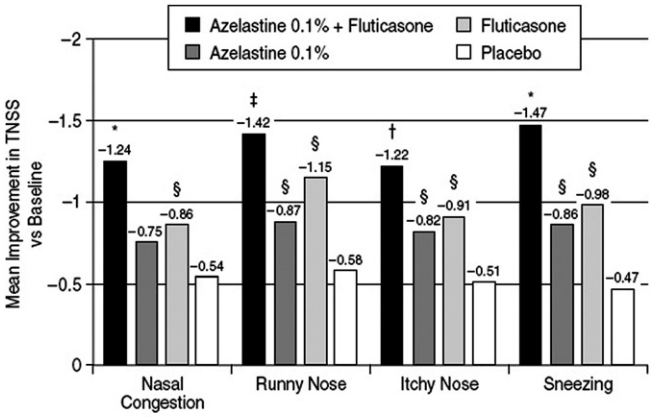
Change from baseline to day 14 in individual symptoms. Combination therapy significantly ($P < .05$) improved the individual TNSS symptoms of nasal congestion, itchy nose, and sneezing compared with azelastine, fluticasone, or placebo (Figure 2). Combination therapy significantly ($P < .01$) improved the individual TNSS symptoms of runny nose compared with azelastine or placebo but not fluticasone.

Change from baseline to day 14 in TNSS on individual study days. Figure 3 shows the mean daily improvement in TNSS in each treatment group. The combination of azelastine

Table 1. Demographic and Baseline Clinical Characteristics (Intent-to-Treat Population)

Characteristic	Azelastine 0.1% and fluticasone (n = 153)	Azelastine 0.1% (n = 152)	Fluticasone (n = 151)	Placebo (n = 151)
Age, mean (range), y	39.5 (12–73)	39.5 (12–74)	38.1 (12–74)	39.9 (12–75)
Sex, No. (%)				
Male	56 (36.6)	55 (36.2)	51 (33.8)	49 (32.5)
Female	97 (63.4)	97 (63.8)	100 (66.2)	102 (67.5)
Race, No. (%)				
White	132 (86.3)	135 (88.8)	130 (86.1)	131 (86.8)
Black	15 (9.8)	15 (9.9)	16 (10.6)	17 (11.3)
Asian	4 (2.6)	0 (0.0)	3 (2.0)	2 (1.3)
Other	2 (1.3)	2 (1.3)	2 (1.3)	1 (0.7)
TNSS, mean (range)[a]	18.8 (9–24)	18.1 (10–24)	18.3 (8–24)	18.7 (10–24)
Duration of SAR, mean (range), y	18.7 (3–64)	19.0 (2–61)	18.4 (3–57)	18.1 (3–56)

Abbreviations: SAR, seasonal allergic rhinitis; TNSS, Total Nasal Symptom Score.
[a] Mean baseline TNSS during 5-day lead-in period, including the morning of day 1.



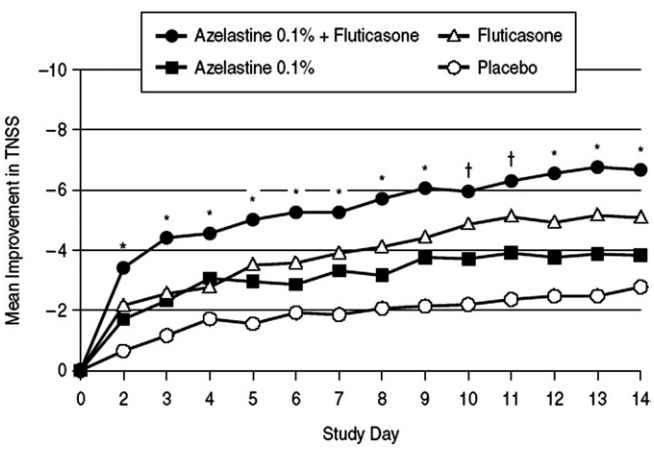
*P <.01 vs azelastine, fluticasone, and placebo
†P <.05 vs azelastine, fluticasone, and placebo
‡P <.01 vs azelastine and placebo
§P <.05 vs placebo

Figure 2. Mean improvement from baseline in the severity of individual nasal symptoms. TNSS indicates total nasal symptom score.

and fluticasone was statistically superior ($P \leq .01$) compared with azelastine or placebo on each day of the study, and the combination was statistically superior ($P \leq .01$) to fluticasone on every study day except days 10 and 11.

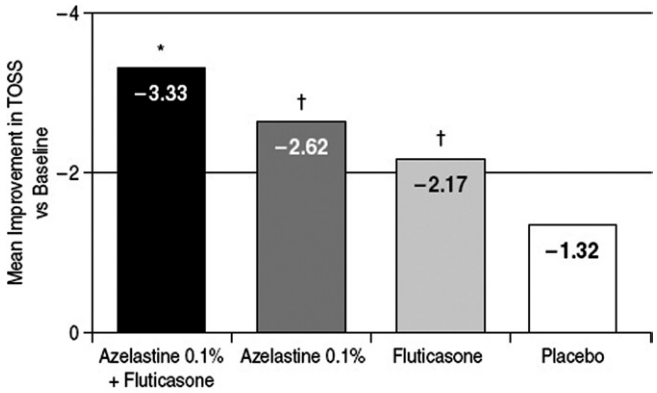
Change from baseline to day 14 in TOSS. Combination therapy significantly ($P < .01$) improved the overall TOSS compared with either fluticasone or placebo but not azelastine (Figure 4). The percentage improvement in TOSS was 21.2% for azelastine, 17.5% for fluticasone, 26.6% for the combination, and 10.5% for placebo.

Change from baseline to day 14 in individual ocular symptoms. Combination therapy significantly ($P < .05$) improved all individual ocular symptoms compared with azelastine, fluticasone, or placebo, with the exception of azelastine for watery eyes (Figure 5). In addition, each component of the combination was significantly ($P < .05$) better than placebo for each individual symptom of the TOSS.



*$P \leq .01$ vs azelastine, fluticasone, and placebo
†P <.01 vs azelastine and placebo

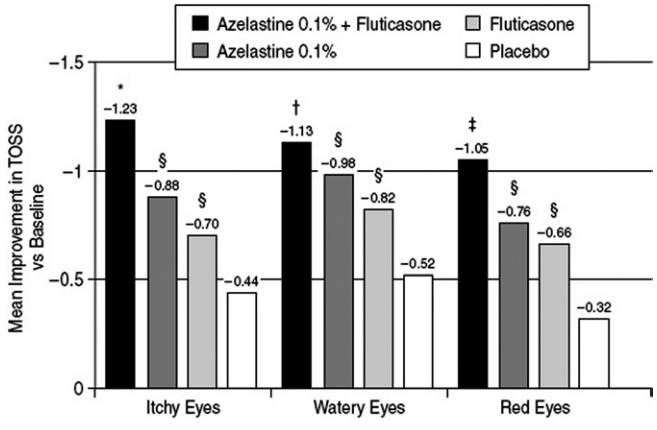
Figure 3. Mean improvement from baseline in the total nasal symptom score (TNSS) on individual study days.



*P <.01 vs fluticasone and placebo
†$P \leq .012$ vs placebo

Figure 4. Mean improvement from baseline in the total ocular symptom score (TOSS) during the 14-day study period.

Change from baseline to day 14 in RQLQ scores. All 3 treatments produced a statistically significant ($P < .001$) improvement from baseline, both for overall score and for each individual domain of the RQLQ. The mean change from baseline in the overall RQLQ score was 1.17 with azelastine, 1.43 with fluticasone, 1.60 with azelastine-fluticasone combination therapy, and 1.01 with placebo. The combination of azelastine and fluticasone significantly improved the overall RQLQ score compared with azelastine ($P = .005$) and placebo ($P < .001$) but not fluticasone ($P = .29$). The change from day 1 to day 14 in the overall RQLQ score was clini-



*$P \leq .01$ vs azelastine, fluticasone and placebo
†P <.05 vs fluticasone and placebo
‡P <.05 vs azelastine, fluticasone and placebo
§P <.05 vs placebo

Figure 5. Mean improvement from baseline in the severity of individual ocular symptoms. TOSS indicates total ocular symptom score.

Table 2. Commonly Reported Adverse Events (Safety Population)[a]

Adverse event	Adverse events, No. (%)			
	Azelastine 0.1% and fluticasone (n = 153)	Azelastine 0.1% (n = 152)	Fluticasone (n = 153)	Placebo (n = 151)
Dysgeusia (bitter taste)	11 (7.2)	3 (2.0)	0 (0.0)	0 (0.0)
Epistaxis	6 (3.9)	4 (2.6)	6 (3.9)	5 (3.3)
Headache	4 (2.6)	2 (1.3)	6 (3.9)	2 (1.3)
Pharyngolaryngeal pain	2 (1.3)	1 (0.7)	0 (0.0)	1 (0.7)
Nasal discomfort	2 (1.3)	0 (0.0)	1 (0.7)	0 (0.0)
Nausea	1 (0.7)	2 (1.3)	0 (0.0)	2 (1.3)
Mucosal erosion	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)
Somnolence	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)

[a] A patient with multiple adverse events is counted only once in any row. Adverse events were coded using the *Medical Dictionary for Regulatory Activities*.

cally important (>0.5 units) in the combination group compared with the placebo group.

Safety and Tolerability

All 3 treatments were well tolerated (Table 2). The most common adverse event was bitter taste (2.0% with azelastine, 0.0% with fluticasone, and 7.2% with combination therapy). There were no significant findings based on assessment of vital signs.

DISCUSSION

Allergic rhinitis is a global problem that is increasing in prevalence. It is 1 of the most common illnesses in the general population, with prevalence estimates ranging from 3% to 19% in the population of the United States.[3] Untreated rhinitis has been shown to significantly reduce work and school productivity ($P < .05$), impair sleep, and reduce quality of life and cognitive function and should not be underestimated as a health care problem.[9]

There is still a need for effective rhinitis therapy, especially for patients with severe or difficult-to-treat symptoms. A nationwide survey indicated that a significant proportion of patients with rhinitis experience poor symptom control with either an intranasal antihistamine or an intranasal steroid.[10] The combination of azelastine and fluticasone in a single-delivery device should benefit a proportion of patients with symptoms that are not controlled by either agent alone.

Patients who cannot avoid allergen exposure and/or do not adequately respond to multiple pharmacologic interventions may be offered the option of allergen immunotherapy. Immunotherapy is an important treatment option; however, many patients refuse this avenue for various reasons, including inconvenience, cost, lack of efficacy, and adverse effects.[11,12] For example, immunotherapy patients are recommended to undergo treatment for at least 5 years, and although some patients may remain in sustained remission after treatment, others may relapse. There are no specific tests or clinical markers that will distinguish between patients who will relapse compared with those who will remain in long-term clinical remission.[13]

Virtually all patients seen in allergy specialty practice have tried at least 1 allergy medication without success, and many patients require more than 1 medication to achieve a satisfactory degree of symptom control. Although combination therapy is frequently prescribed, there are a relatively small number of published clinical studies that have evaluated combination therapies for allergic rhinitis. Nielsen and Dahl[14] analyzed pertinent medical literature published between 1966 and 2001 and reported no difference in efficacy among the intranasal steroids for treating allergic rhinitis and no clinical evidence to support the practice of combining an intranasal steroid with an oral antihistamine. Review articles by Akerlund et al[15] and Howarth et al[16] also reported no evidence to suggest that a clinical benefit can be achieved by combining an intranasal steroid and an oral antihistamine in the treatment of allergic rhinitis.

In the current study, combination therapy with azelastine and fluticasone provided significantly greater improvement in the TNSS compared with placebo. All of the individual symptoms of the TNSS were improved with combination therapy when compared with either azelastine or fluticasone. This improvement in TNSS with combination therapy reached statistical significance compared with each individual agent on day 2 and continued during the 14-day study period. In addition to the TNSS improvements seen in this study, the ocular symptom complex was also significantly improved with combination therapy compared with fluticasone and placebo. The difference in improvement with combination therapy compared with azelastine monotherapy was not significant. The antihistaminic effect of azelastine may provide more relief of ocular symptoms than fluticasone; however, no definitive conclusion with regard to this outcome can be made without a direct comparative study. Although it is speculation, the original azelastine (Astelin) labeling included data from studies in which the administration technique for the nasal spray was not uniform. Some patients appeared to have inhaled and swallowed substantial amounts of medication such that the incidence of bitter taste and somnolence was substantially higher than in subsequent stud-

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