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Effectiveness of Azelastine Nasal Spray Compared with Oral Cetirizine in Patients with Seasonal Allergic Rhinitis

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ABSTRACT

Background: Azelastine nasal spray and oral cetirizine are selective histamine H_1-receptor antagonists that are approved in the United States for the treatment of seasonal allergic rhinitis (SAR).

Objective: The objective of the present study was to compare the efficacy and tolerability of azelastine nasal spray administered at the recommended dosage of 2 sprays per nostril twice daily with those of cetirizine in the treatment of moderate to severe SAR.

Methods: This multicenter, randomized, double-blind, parallel-group, 2-week comparative study was conducted during the 2004 fall allergy season in patients with moderate to severe SAR. After a 1-week placebo lead-in period, patients were randomized to receive azelastine nasal spray 2 sprays per nostril twice daily plus placebo tablets or cetirizine 10-mg tablets once daily plus a placebo saline nasal spray for the 2-week double-blind treatment period. The primary efficacy variables were (1) change from baseline to day 14 in the 12-hour reflective total nasal symptom score (TNSS), which combines scores for rhinorrhea, sneezing, itchy nose, and nasal congestion, and (2) onset of action, based on the instantaneous TNSS over 4 hours after the first dose of study drug. During the double-blind treatment period, patients recorded their symptom scores on diary cards twice daily (morning and evening). Patients aged ≥18 years also completed the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at baseline and on day 14.

Results: Three hundred seven patients were randomized to treatment, and 299 completed 2 weeks of study treatment. The age of the population ranged from 12 to 74 years (mean, 35 years), 62.9% were female, and 69.6% were white. Over 2 weeks of treatment, both groups had significant improvements in the TNSS compared with baseline ($P < 0.001$). The overall change in TNSS was significantly greater with azelastine nasal spray compared with cetirizine (29.3% vs 23.0% improvement, respectively; $P = 0.015$). In terms of onset of action, azelastine nasal spray significantly improved the instantaneous TNSS compared with cetirizine at 60 and 240 minutes after the initial dose (both, $P = 0.040$). Scores on each domain of the RQLQ were significantly improved in both groups compared with baseline ($P < 0.001$); the overall RQLQ score was significantly improved with azelastine nasal spray compared with cetirizine ($P = 0.049$). Both treatments were well tolerated.

Conclusion: In this 2-week study in patients with moderate to severe SAR, azelastine nasal spray was well tolerated and produced significantly greater improvements in TNSS and total RQLQ score compared with cetirizine. (*Clin Ther*. 2005;27:543–553) Copyright © 2005 Excerpta Medica, Inc.

Key words: azelastine nasal spray, cetirizine, allergic rhinitis, double-blind clinical trial.

INTRODUCTION

Azelastine nasal spray† is a topical second-generation antihistamine indicated for the treatment of seasonal

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†Trademark: Astelin® (MedPointe Pharmaceuticals, Somerset, New Jersey).

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allergic rhinitis (SAR) and nonallergic vasomotor rhinitis. The active ingredient, azelastine hydrochloride, is a high-affinity histamine H_1-receptor antagonist with potency at the H_1-receptor site ~10 times greater than that of chlorpheniramine.[1] In addition to histamine antagonism, azelastine has been shown in clinical studies to have inhibitory effects on leukotrienes,[2] bradykinin and substance P,[2,3] cytokines,[4] intercellular adhesion molecule–1 (ICAM-1) expression,[5] and eosinophil chemotaxis.[5] Cetirizine hydrochloride* is an oral second-generation antihistamine indicated for the treatment of SAR, perennial allergic rhinitis, and chronic urticaria. It is a selective H_1-receptor antagonist[6] that has been shown to inhibit leukotriene[7] and prostaglandin production,[8] as well as ICAM-1 expression and eosinophil chemotaxis.[9]

In clinical studies, cetirizine has been compared with other oral second-generation antihistamines, including loratadine and fexofenadine. In two 2-day, placebo-controlled studies in an environmental exposure unit[10,11] and in a 2-day outdoor study,[12] cetirizine 10 mg once daily was more effective than loratadine in improving nasal symptoms in patients with SAR ($P \leq 0.05$). In two 2-week, multicenter studies comparing cetirizine 10 mg once daily with fexofenadine 120 and 180 mg once daily, there were no significant differences in efficacy between cetirizine and the 2 fexofenadine doses.[13,14] However, in another environmental exposure unit study,[15] cetirizine was significantly more effective than fexofenadine during the 24-hour interval after initial administration ($P < 0.001$).

Comparative studies of azelastine nasal spray have been carried out in Europe at a dosage of 1 spray per nostril twice daily, one half the recommended adult dosage in the United States. In a 2-week, double-blind study of azelastine nasal spray and intranasal beclomethasone in patients with SAR,[16] both treatments significantly improved symptom scores compared with placebo ($P < 0.001$), and there were no significant differences between treatment groups. In a 2-week, double-blind study in patients with SAR, azelastine nasal spray and cetirizine decreased nasal symptom scores by 60% and 63%, respectively, with no significant differences between treatments.[17] In addition, the results of placebo-controlled studies have indicated that azelastine nasal spray at a dosage of 2 sprays per nostril twice daily was effective in patients who remained symptomatic after treatment with loratadine[18] or fexofenadine.[19]

Given the preceding findings, the objective of the present study was to directly compare the efficacy and tolerability of azelastine nasal spray administered at the US recommended dosage of 2 sprays per nostril twice daily with those of cetirizine in the treatment of moderate to severe SAR.

PATIENTS AND METHODS

This was a randomized, double-blind, parallel-group, 2-week comparative trial conducted during the 2004 fall allergy season at 20 investigational research centers distributed throughout the major geographic regions of the United States.

Inclusion and Exclusion Criteria

Study investigators selected patients from their practices and/or recruited volunteers to participate in the study. Eligible patients were male and female patients aged ≥12 years with at least a 2-year history of SAR and a documented positive allergy skin test, either intradermal or epicutaneous, during the previous year. Patients were excluded for the following reasons: use of concomitant medication(s) that could affect the assessment of efficacy of study treatment; any medical or surgical condition that could affect the metabolism of study medications; clinically significant nasal disease (other than SAR) or significant nasal structural abnormalities; respiratory infection or other infection requiring antibiotic therapy within 2 weeks of the single-blind placebo lead-in period; past or current alcohol or drug abuse; and significant pulmonary disease, including persistent asthma requiring use of controller medication. Women of childbearing potential not using an accepted method of contraception and women who were pregnant or nursing also were excluded.

Study Design

This was a randomized, double-blind, parallel-group clinical trial designed to be consistent with a draft guidance from the US Food and Drug Administration for the conduct of clinical trials in allergic rhinitis.[20] A computer-generated randomization schedule was used to assign eligible patients to the 2 treatment groups in blocks of 4. The randomization schedule was provided by a biostatistical group employed by the sponsor, and access to the code was confidential and accessible only to authorized persons not involved in the study.

*Trademark: Zyrtec® (Pfizer Inc., New York, New York).

Blinding of the study was preserved at each study site until all patients had completed the study and the database was locked.

The study began with a 1-week, single-blind lead-in period, before which all previous allergy medications were discontinued (oral antihistamines for a minimum of 5 days and intranasal steroids for a minimum of 14 days before the start of the period) and patients received placebo nasal spray and placebo capsules. Patients qualified for entry into the lead-in period if they had a total nasal symptom score (TNSS) of ≥8 and a nasal congestion score ≥2 over the previous 12 hours (12-hour reflective TNSS).[20] The TNSS is a combined measure of the severity of nasal itching, nasal congestion, runny nose, and sneezing, each rated twice daily (morning and evening) on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), with a maximum daily score of 24. Patients recorded their morning and evening 12-hour reflective symptom severity scores on diary cards for use by the investigator in determining their eligibility to enter the double-blind treatment period.

To be eligible for entry into the double-blind treatment period, patients must have recorded a morning or evening TNSS ≥8 on at least 3 days during the lead-in period and a morning or evening nasal congestion score of 3 on at least 3 days. For both the TNSS and nasal congestion score, 1 of the 3 pertinent days must have occurred within 2 days of the first day of the double-blind treatment period. In addition, because of the onset-of-action assessment (described in the following section), patients were required to have a TNSS ≥8 on the morning of randomization; patients who were not sufficiently symptomatic at that time were asked to return the next day for the onset-of-action assessment. Patients who did not meet the minimum symptom severity score at this time were not eligible for randomization. Patients who continued to meet the study inclusion criteria and met the minimum TNSS and nasal congestion criteria were randomized to receive treatment with azelastine nasal spray 2 sprays per nostril twice daily (morning and evening) plus placebo tablets (morning) or cetirizine 10-mg tablets once daily (morning) plus placebo saline nasal spray 2 sprays per nostril twice daily (morning and evening) for 2 weeks (days 1–14).

Azelastine nasal spray and placebo nasal spray were supplied by the manufacturer in spray-pump bottles of identical appearance. The placebo spray, which consisted of benzalkonium chloride, edetate disodium, hydroxypropyl methylcellulose, citric acid, dibasic sodium phosphate, and sodium chloride in purified water at pH 6.8 ± 0.3, was identical to the vehicle formulation contained in azelastine nasal spray. To mask their identity, the cetirizine 10-mg tablets were encapsulated in gelatin capsules size DB#C and overfilled with lactose. Placebo capsules were filled only with lactose. The dissolution rates of the cetirizine 10-mg tablets and encapsulated cetirizine 10-mg tablets overfilled with lactose were shown to be essentially identical at the 20- and 30-minute (100% dissolution) time points at 37°C in a comparative dissolution assay performed by McKesson Bioservices, Rockville, Maryland (MedPointe Pharmaceuticals, data on file). A placebo control group was not used in this study because both azelastine nasal spray and cetirizine have been shown to be safe and effective for the treatment of SAR.

The study was approved by Sterling Institutional Review Board, Atlanta, Georgia. All patients or their guardians (if aged <18 years) signed the approved informed consent agreement before participation.

Efficacy and Safety Variables

The coprimary efficacy variables were change from baseline to day 14 in the severity of rhinitis symptoms based on the combined morning and evening 12-hour reflective TNSS, and onset of action, based on the change from baseline in the instantaneous TNSS recorded in the physician's office immediately before the first dose of study medication and at 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes thereafter. Secondary efficacy variables were the change in TNSS from baseline to day 2 (end of the 24-hour dosing interval), and the change from baseline to day 14 in quality-of-life parameters for patients aged ≥18 years, measured using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).[21] The RQLQ assesses the domains of activities, sleep, nonnose/noneye symptoms, practical problems, nasal symptoms, eye symptoms, and emotions.

Tolerability was assessed in terms of reported adverse experiences and vital signs, which included body temperature, systolic and diastolic blood pressure, and heart and respiration rates, which were measured at baseline and at the end of the study.

Statistical Procedures

This study was designed to detect differences in TNSS and onset of action between the 2 active-treatment

groups. The sample size was based on the results of a double-blind, placebo-controlled pilot study in which 60 patients received 1 week of treatment with azelastine nasal spray, fluticasone nasal spray, cetirizine tablets, or placebo.[22] In this pilot study, an improvement in TNSS of 19.5% was observed with azelastine nasal spray, compared with 15.5% with cetirizine. A TNSS effect size of 0.25 (azelastine mean – cetirizine mean [pooled SD]) was identified for the change from baseline to the end of treatment using the same 4-point rating scale as in the present study. Based on this pilot study, it was estimated that ~150 patients per group would be sufficient to detect a difference in effect size of 0.25 between azelastine nasal spray and cetirizine for the primary efficacy variables with 80% power at the 0.05 level of significance.

The primary analysis was an intent-to-treat analysis that included all randomized patients with ≥1 postbaseline TNSS assessment. Missing TNSS values in this population were imputed using the last-observation-carried-forward method. The safety analysis included all randomized patients who received ≥1 dose of study medication and had ≥1 safety assessment after drug administration.

For the first primary efficacy variable (change in TNSS from baseline to day 14), the baseline score was calculated as the mean of the combined morning and evening TNSS during the placebo lead-in period. The change from baseline to day 14 was determined by subtracting the mean baseline score from the mean TNSS for the entire 2-week treatment period. Within-group comparisons were conducted using a paired *t* test, and between-group comparisons were conducted using an analysis-of-variance (ANOVA) model. The change from baseline in individual symptom severity scores was evaluated using a similar ANOVA model.

The second primary efficacy variable (onset of action) was determined based on the instantaneous TNSS over 4 hours. Within each treatment group, time to onset was determined using a paired *t* test on the change in TNSS from baseline. Between-group comparisons were made using the same ANOVA model as was used for change in TNSS from baseline to day 14.

The change in TNSS from baseline was also calculated for each day of the study. In assessing efficacy during the initial 24-hour treatment interval, the change in TNSS from baseline to day 2 was calculated based on the morning assessment on day 2, with baseline defined as the mean of the combined morning and evening TNSS during the lead-in period. Within- and between-group comparisons were performed using a paired *t* test and ANOVA, respectively.

Changes from baseline to day 14 in the individual RQLQ domains and the overall RQLQ score were calculated and analyzed according to the method described by Juniper at al.[21] Changes in vital signs were evaluated by comparing values before and after treatment.

All tests of significance were 2-sided. Baseline demographic and clinical characteristics were summarized descriptively.

RESULTS

Patient Disposition and Demographic Characteristics

Three hundred seven patients were randomized to receive double-blind treatment, and 299 patients completed 2 weeks of treatment (**Figure 1**). Data for all 307 patients were included in the safety assessment, and data for 306 patients were analyzed for efficacy (1 patient in the azelastine nasal spray group had no postbaseline diary data and was not included). Four patients in the azelastine group and 2 in the cetirizine group discontinued the study due to an adverse event, and 1 patient in each group was discontinued because of a protocol violation. The treatment groups were comparable in terms of demographic characteristics (**Table I**). Patients ranged in age from 12 to 74 years (mean, 35 years); 62.9% were female and 69.6% were white.

Efficacy Analyses

Change in TNSS from Baseline

During 2 weeks of treatment, both azelastine nasal spray and cetirizine significantly improved the combined morning and evening 12-hour reflective TNSS compared with baseline ($P < 0.001$). At the end of the study period, the mean improvement in TNSS was 5.56 (29.3% improvement) with azelastine nasal spray and 4.32 (23.0% improvement) with cetirizine. The overall difference in TNSS between the 2 groups across both weeks of the study significantly favored azelastine nasal spray ($P = 0.015$) (**Table II**). The improvement in daily symptom scores was significant for azelastine nasal spray compared with cetirizine on study days 8, 9, 10, 12, 13, and 14 (all, $P < 0.05$) (**Figure 2**). A per-protocol analysis that included 145 patients in the azelastine nasal spray group and 148 in the cetirizine group for whom complete data were

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