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Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis

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Background: Azelastine hydrochloride is an H_1-receptor antagonist with anti-inflammatory properties that is available in the US as Astelin Nasal Spray for the treatment of seasonal allergic rhinitis. The symptoms of seasonal allergic rhinitis can initially be treated with monotherapy using either an antihistamine or an intranasal corticosteroid. Patients whose symptoms do not respond adequately are often prescribed a combination of both an antihistamine and an intranasal corticosteroid.

Objective: Three multicenter, randomized, double-blind studies were conducted to determine whether patients with moderate-to-severe symptoms of seasonal allergic rhinitis who had responded inadequately to monotherapy with either an oral antihistamine or an intranasal corticosteroid, and who were candidates for combination therapy with both an oral antihistamine and an intranasal corticosteroid, could be effectively treated with azelastine nasal spray monotherapy.

Methods: Following a 1- to 2-week washout period, patients were randomized to 7 days of double-blind treatment with either azelastine nasal spray (2 sprays per nostril bid, 1.1 mg/day) monotherapy or combination therapy with oral loratadine (Claritin, one 10-mg tablet/day) plus intranasal beclomethasone dipropionate monohydrate (Beconase AQ, 2 sprays per nostril bid, 336 μg/day). Efficacy was determined at the end of the study by both a physician assessment of the need for additional anti-rhinitis medication and a patient global evaluation of therapeutic effectiveness. The three studies were conducted at 71 investigational sites during the 1998 spring allergy season. Three separate studies were conducted to verify the reproducibility of the new study design.

Results: In all three studies a total of 1,070 patients were randomized to double-blind treatment. There were no statistically significant differences in the percentage of patients treated with azelastine nasal spray versus patients treated with a combination of loratadine tablets and beclomethasone nasal spray who did not require additional anti-rhinitis medication (32% to 45% and 39% to 46%, respectively). The patient global evaluation indicated that 77% to 84% of the patients treated with azelastine nasal spray had symptomatic improvement and 85% to 90% of the patients treated with loratadine tablets and beclomethasone nasal spray had symptomatic improvement. The most commonly reported adverse experience with azelastine nasal spray was a transient aftertaste (8%), while the most commonly reported adverse experience with loratadine tablets and beclomethasone nasal spray in combination was headache (6%).

Conclusions: Based on the percentage of patients not requiring additional anti-rhinitis medication and the patient assessment of efficacy, azelastine nasal spray monotherapy was as effective as the combination of oral loratadine plus intranasal beclomethasone in treating moderate-to-severe symptoms of seasonal allergic rhinitis.

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INTRODUCTION

Azelastine hydrochloride, a phthalazinone derivative, is a high-affinity histamine H_1-receptor antagonist[1] administered as a nasal spray for the treatment of seasonal allergic rhinitis. In addition to H_1-receptor antagonism, azelastine also affects cells and chemical mediators of the inflammatory response as shown in in vitro studies[2–7] and in animal models of allergic inflammation.[8–10] In clinical trials in patients with seasonal allergic rhinitis, azelastine reduced levels of leukotrienes and kinins following nasal allergen challenge[11] and downregulated intercellular adhesion molecule-1 (ICAM-1) expression while reducing eosinophil and neutrophil infiltration in both the early- and late-phase of the allergic response.[12]

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In United States clinical trials,[13–17] azelastine nasal spray, at a dosage of 2 sprays per nostril bid (1.1 mg/day), was effective in the management of a complex of symptoms associated with seasonal allergic rhinitis, including rhinorrhea, sneezing, nasal pruritus, postnasal drip, and itchy and watery eyes. Many patients with nasal congestion also experienced improvement in this symptom, an effect not typically associated with oral antihistamines. Onset and duration of action assessments[13,14] showed that azelastine nasal spray improved baseline symptom scores within 1 to 3 hours, while other studies[18] suggested that improvements may be evident in less than 30 minutes in some patients. Transient aftertaste, headache, somnolence, and nasal burning were the most commonly reported adverse experiences with azelastine nasal spray, and there have been no serious adverse experiences associated with its use.

An antihistamine alone or a nasal corticosteroid alone can be used as first-line therapy for the treatment of seasonal allergic rhinitis, and for those patients whose symptoms are not adequately controlled by either treatment often a combination of both an antihistamine with an intranasal corticosteroid is prescribed. Three multicenter, randomized, double-blind, parallel-group studies were conducted to compare the effectiveness of azelastine nasal spray monotherapy versus combination therapy with beclomethasone nasal spray plus loratadine tablets in patients with moderate-to-severe symptoms of seasonal allergic rhinitis who had not adequately responded to monotherapy with either a nasal steroid or an oral antihistamine and who would be considered candidates for combination therapy with a nasal steroid and an oral antihistamine. Efficacy was evaluated by (1) comparing the percentage of patients in each treatment group not requiring additional anti-rhinitis therapy based on a physician assessment at the end of the double-blind treatment period and (2) comparing the percentage of patients with symptomatic improvement in each treatment group based on a patient global rating of therapeutic effectiveness.

METHODS

Patients

All patients were 12 years of age or older with a documented history of seasonal allergic rhinitis. Each patient was currently being treated with a monotherapy regimen, either an oral antihistamine or a nasal steroid, and was considered by the investigator to be a candidate for combination therapy with an oral antihistamine plus a nasal steroid due to lack of adequate symptom control. Female patients were nongravid, non-nursing, of non-childbearing potential or, if of childbearing potential agreed not to become pregnant during the study. Sexually active females of childbearing potential were practicing an adequate method of birth control. Patients unable to use or tolerate nasal spray, patients with asthma, patients who were treated with any investigational drug within 30 days of enrollment into this study, and patients being treated with antidepressant drugs were excluded from participation. Patients were also excluded if they had an acute respiratory infection within 30 days of the study or any clinically significant acute or chronic illness. All patients signed a written informed consent document before entering the study, and written consent of a parent or legal guardian was required for patients under the legal age of consent.

Study Design

The three studies were carried out during the 1998 spring allergy season at 71 investigational sites distributed throughout the contiguous United States. These studies were randomized, double-blind, parallel-group trials consisting of 1- to 2-week baseline washout period (1 week for patients being treated with an oral antihistamine and 2 weeks for patients being treated with an intranasal steroid) followed by a 7-day double-blind treatment period. Chlorpheniramine maleate (Chlor-Trimeton Tablets 4 mg) was permitted on an "as needed" basis for the treatment of seasonal allergic rhinitis symptoms during the baseline washout period; however, it was not permitted for 48 hours before the patients were randomized to double-blind treatment.

After the baseline washout period and prior to randomization, a physician assessment was made of the severity of rhinitis symptoms, including nose blows, sneezes, runny nose/sniffles, itchy nose, watery eyes, itchy eyes/ears, itchy throat/palate, cough, postnasal drip, and nasal congestion. Patients who qualified for randomization to double-blind treatment had symptom rating scores of at least 18 (scale = 0 to 50) with at least three of the symptoms of moderate or greater than moderate intensity. For nose blows and sneezes, the actual number of each per day were counted and scored according to the following

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