

# 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<sub>1</sub>-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.

Ann Allergy Asthma Immunol 1999;82:535-541.

## INTRODUCTION

Azelastine hydrochloride, a phthalazine derivative, is a high-affinity his-

tamine H<sub>1</sub>-receptor antagonist<sup>1</sup> administered as a nasal spray for the treatment of seasonal allergic rhinitis.

In addition to H<sub>1</sub>-receptor antagonism, azelastine also affects cells and chemical mediators of the inflammatory response as shown in in vitro studies<sup>2-7</sup> and in animal models of allergic inflammation.<sup>8-10</sup> In clinical trials in patients with seasonal allergic rhinitis, azelastine reduced levels of leukotrienes and kinins following nasal allergen challenge<sup>11</sup> 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.<sup>12</sup>

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In United States clinical trials,<sup>13-17</sup> 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, post-nasal 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<sup>13,14</sup> showed that azelastine nasal spray improved baseline symptom scores within 1 to 3 hours, while other studies<sup>18</sup> 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 non-gravid, 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, post-nasal 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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This research was funded by a grant from Wallace Laboratories, Division of Carter-Wallace, Inc., Half Acre Road, Cranbury, New Jersey.

Received for publication January 4, 1999.

Accepted for publication in revised form March 30, 1999.

scale: 0 = none, 1 = a little (1–3), 2 = moderate (4–6), 3 = quite a bit (7–10), 4 = severe (11–15), and 5 = very severe (greater than 15). Runny nose/sniffles, itchy nose, watery eyes, itchy eyes/ears, itchy throat/palate, cough, postnasal drip, and nasal congestion were scored according to the following scale: 0 = none, no symptoms; 1 = a little, very mild symptoms that are barely noticeable and do not interfere with any activity; 2 = moderate, mild symptoms that are noticeable and do not interfere with any activity; 3 = quite a bit, symptoms that are bothersome and interfere slightly with activity; 4 = severe, symptoms that are bothersome and interfere modestly with activity; and 5 = very severe, symptoms that are very bothersome and disabling.

Randomized patients received double-blind treatment for 7 days with either azelastine nasal spray (Astelin Nasal Spray, Wallace Laboratories) 2 sprays per nostril twice daily (1.1 mg/day) and a placebo capsule each morning or beclomethasone dipropionate monohydrate nasal spray (Beconase AQ, Glaxo Wellcome Inc.) 2 sprays per nostril twice daily bid (336 mcg/day) and a capsule containing one 10-mg loratadine tablet (Claritin, Schering Corporation) each morning. Dosages of study drugs were selected according to the manufacturers recommendations listed in the product labeling for each drug.

#### Blinding and Randomization

Study medications were provided in kits that were opened only by the patient, not in the presence of a study investigators or coordinator, to ensure that the double-blind was maintained. Commercially packaged azelastine nasal spray was provided in polyethylene bottles fitted with a metered-dose spray pump and over-labeled to mask the product identity. Commercially packaged beclomethasone nasal spray was provided in amber glass bottles fitted with metering atomizing pumps and nasal adapters and over-labeled to mask the product identity. Capsules containing one 10-mg loratadine tablet

were packaged in polyethylene bottles containing 10 capsules per bottle. Matching placebo capsules were packaged in identically appearing bottles and contained 10 capsules. Patients were assigned to double-blind treatment according to a computer-generated, random allocation scheme.

#### Efficacy and Safety Variables

The primary efficacy variable was the percentage of patients in each treatment group who did not require additional anti-rhinitis therapy, as evaluated by a physician assessment (either yes or no), at the end of the 7-day double-blind treatment period. The secondary efficacy variable was the percentage of patients in each treatment group who improved during the double-blind period based on a patient global evaluation of therapeutic effectiveness. The patient global evaluation recorded the degree of symptom improvement on the last day of treatment versus how they felt prior to receiving the first dose of study medication at the time of randomization using the following 5-point scale: +2 = much better, near complete or complete symptom relief; +1 = a little better, mild-to-moderate overall improvement in symptoms; 0 = no change, no symptom relief; -1 = a little worse, mild-to-moderate overall deterioration of symptoms; and -2 = much worse, marked deterioration of symptoms. Assessments of “a little better” or “much better” were considered improvements.

Safety was evaluated by the number of occurrences and percentage of patients reporting any adverse events that occurred during double-blind treatment.

#### Statistical Methods

To determine the sample size, the following assumptions were made: 45% of the patients treated with azelastine nasal spray would require additional anti-rhinitis therapy at the end of the study compared with 30% of the patients treated with loratadine tablets plus beclomethasone nasal spray. Approximately 170 patients in each of the treatment groups would provide 80% power at  $\alpha = 0.05$  (two-sided test) to detect a 15% difference between treatments.

Demographic characteristics in the two treatment groups were compared using analysis of variance for continuous variables and chi-square tests for categorical variables. The number and percentages of patients considered not to require additional anti-rhinitis treatment were compared by Fisher's Exact test. The percentages of patients who improved based on global evaluation were compared by the chi-square test. The number of occurrences and the percentage of patients reporting each adverse experience were summarized descriptively.

## RESULTS

#### Patient Disposition

The three studies were conducted at 71 investigational sites and included a total of 1,070 patients who were randomized to double-blind treatment. The number of sites for each of the three studies and the number of patients randomized by treatment group at each site are shown in Table 1. More than 98% of the patients enrolled in each of the three studies completed the double-blind treatment period (Table 2). Three patients treated with azelastine nasal

Table 1. Number of Sites and Patients Randomized by Treatment Group

Study No.	No. of Sites	Az NS	Beclo NS + L	Total
1	23	173	169	342
2	24	182	180	362
3	24	183	183	366
<b>Total</b>	<b>71</b>	<b>538</b>	<b>532</b>	<b>1070</b>

Az NS = azelastine nasal spray and Beclo NS + L = beclomethasone nasal spray plus loratadine tablets.

Table 2. Patient Disposition

Status	Study 1 (N = 342)		Study 2 (N = 362)		Study 3 (N = 366)	
	Az NS	Beclo NS + L	Az NS	Beclo NS + L	Az NS	Beclo NS + L
Randomized	173	169	182	180	183	183
Total discontinued and reasons:	3	1	4	1	3	3
Intercurrent illness	0	1	0	0	1	1
Protocol violation	2	0	1	0	1	1
Withdrew consent	1	0	0	0	0	0
Treatment failure	0	0	1	0	0	0
Adverse experience	0	0	2	1	1	1
Completed study	170	168	178	179	180	180

Az NS = azelastine nasal spray and Beclo NS + L = beclomethasone nasal spray plus loratadine tablets.

spray discontinued the study because of an adverse experience (one due to sinusitis, one due to excessive sneezing, and one due to an upper respiratory infection). Two patients treated with loratadine tablets plus beclomethasone nasal spray discontinued the study because of an adverse experience (one due to a combination of vertigo, nausea, and chest discomfort and the other due to nasal burning).

#### Demographic and Clinical Characteristics

Patients in the three studies were comparable with regard to demographic (Table 3) and clinical (Table 4) characteristics at baseline. In all three studies, the percentage of females (57% to 63%) was higher than males (37% to 43%) and the majority of the patients were white (81% to 90%). The mean age of the patients was approximately

35 years with a range of 12 to 80 years. On average, patients had a 14- to 16-year history of seasonal allergic rhinitis and had moderate-to-severe symptoms, as determined by baseline symptom scores that ranged from 18 to 47 among patients treated with azelastine nasal spray and from 18 to 48 among patients treated with loratadine tablets plus beclomethasone nasal spray. More than 80% of the patients in each treatment group in each of the studies had a previous inadequate response to therapy with an oral antihistamine and 13% to 17% had a previous inadequate response to therapy with an intranasal corticosteroid.

#### Efficacy

The primary efficacy variable was the percentage of patients in each treatment group who did not require additional anti-rhinitis therapy as deter-

mined by physician assessment at the end of the 7-day double-blind treatment period. In each of the three studies, the physician assessment demonstrated that monotherapy with azelastine nasal spray was comparable in effectiveness to combination therapy with loratadine tablets plus beclomethasone nasal spray in managing the symptoms of seasonal allergic rhinitis. In each of the three studies (Table 5), there were no statistically significant differences in the percentage of patients treated with azelastine nasal spray (range: 32% to 45%) versus patients treated with loratadine tablets and beclomethasone nasal spray in combination (range: 39% to 46%) who did not require additional anti-rhinitis medication. A subset analysis based on prior medication use indicated that there were no significant differences

Table 3. Demographic Characteristics

Characteristic	Study 1		Study 2		Study 3	
	Az NS N = 173	Beclo NS + L N = 169	Az NS N = 182	Beclo NS + L N = 180	Az NS N = 183	Beclo NS + L N = 183
Gender						
Male	38%	41%	37%	43%	43%	38%
Female	62%	59%	63%	57%	57%	62%
Race						
White	81%	87%	88%	90%	83%	86%
Black	11%	4%	7%	4%	5%	6%
Other	8%	9%	5%	6%	12%	8%
Age (yr)						
Mean	35.0	36.0	34.6	36.2	34.9	34.8
Median	36.0	34.0	35.5	37.0	37.0	35.0
Range	12–67	12–80	12–64	12–74	12–72	12–75

Az NS = azelastine nasal spray and Beclo NS + L = beclomethasone nasal spray plus loratadine tablets.



Table 4. Baseline Clinical Characteristics

Characteristic	Study 1		Study 2		Study 3	
	Az NS N = 173	Beclo NS + L N = 169	Az NS N = 182	Beclo NS + L N = 180	Az NS N = 183	Beclo NS + L N = 183
Rhinitis duration (yr)						
Mean	16.2	16.2	15.0	16.9	14.4	14.8
Median	12.0	11.0	11.0	15.0	10.0	11.0
Symptom score						
Mean	27.5	26.6	26.2	27.0	27.4	26.9
Median	27.0	26.0	25.0	27.0	27.0	27.0
Range	18–47	18–48	18–47	18–47	18–46	18–42
Previous inadequate response to:						
Antihistamine	84%	87%	86%	82%	85%	85%
Nasal steroid	16%	13%	14%	17%	13%	13%
Other	—	—	—	1%	2%	2%

Az NS = azelastine nasal spray and Beclo NS + L = beclomethasone nasal spray plus loratadine tablets.

Table 5. Primary Efficacy Variable: Percentage of Patients Not Requiring Additional Therapy by Physician Evaluation

Treatment	Study 1*	Study 2*	Study 3*
Az NS	36%	45%	32%
Beclo NS + L	46%	46%	39%

Az NS = azelastine nasal spray and Beclo NS + L = beclomethasone nasal spray plus loratadine tablets.

\* No statistically significant differences between treatment groups.

between treatment groups regarding the percentage of patients who did not require additional therapy regardless of whether the patient had a previous inadequate response to an antihistamine or a previous inadequate response to an intranasal steroid. Patients with a prior inadequate response to loratadine (N = 367) made up the largest subgroup in the studies.

The secondary efficacy variable was the percentage of patients in each treatment group who improved during the double-blind treatment period based on a patient global evaluation. The results of the patient global evaluation were consistent with those of the physician assessment. Between 77% and 84% of the patients treated with azelastine nasal spray monotherapy had symptomatic improvement versus 85% to 90% of the patients treated with combination therapy (Table 6).

Table 6. Secondary Efficacy Variable: Percentage of Patients with Overall Improvement in Symptoms Relative to Baseline by Patient Evaluation

Treatment	Study 1¶	Study 2*	Study 3*
Az NS	80%	77%	84%
Beclo NS + L	90%	86%	85%

Az NS = azelastine nasal spray and Beclo NS + L = beclomethasone nasal spray plus loratadine tablets.

¶ Statistically significant difference between treatment groups,  $P = .04$ .

\* No statistically significant difference between treatment groups.

### Safety

Adverse experiences occurring with an incidence of 2% or greater in either treatment group are shown in Table 7 for the three studies combined. Overall, the treatments were well tolerated. The most commonly reported adverse experience with azelastine nasal spray was transient aftertaste (8%), while the most commonly reported adverse experience with loratadine tablets and beclomethasone nasal spray in combination was headache (6%). Somnolence was reported by 2% of the patients treated with azelastine nasal spray and by 1% of the patients treated with loratadine tablets plus beclomethasone nasal spray.

### DISCUSSION

The ability of azelastine to affect inflammatory cells and inflammatory

mediators in addition to histamine suggested that azelastine nasal spray could be effective treatment for both the histamine-related early-phase symptoms as well as the late-phase effects of seasonal allergic rhinitis. Clinically, antihistamines have not treated rhinorrhea and congestion as effectively as they have nasal pruritus and sneezing because chemical mediators other than histamine contribute to the etiology of the former two symptoms.<sup>19</sup> In vitro studies, animal studies, and clinical studies in patients with seasonal allergic rhinitis have shown that, in addition to its H<sub>1</sub>-receptor antagonist activity, azelastine also has anti-inflammatory properties, as demonstrated by its effects on inflammatory cells and inflammatory mediators, including leukotrienes, kinins, and superoxide free radicals in both the early- and late-phase of the allergic reaction.

Studies in animal models of allergy demonstrated that azelastine significantly inhibited leukotriene-mediated lung anaphylaxis.<sup>8</sup> In vitro studies showed that azelastine inhibited phospholipase A<sub>2</sub>, leukotriene C<sub>4</sub> synthase,<sup>2</sup> and 5-lipoxygenase<sup>20</sup> all of which are enzymes required for the synthesis of leukotrienes from arachidonic acid. Additionally, azelastine has been identified as a 5-lipoxygenase activating protein (FLAP) inhibitor.<sup>21</sup> 5-Lipoxygenase activating protein couples with 5-lipoxygenase to initiate the oxidation of arachidonic acid that

Table 7. Incidence of Adverse Experiences

Adverse Experience*	Azelastine N = 538	Loratadine + Beclomethasone N = 532
Transient aftertaste	8%	1%
Headache	5%	6%
Rhinitis	3%	1%
Somnolence	2%	1%

\* Minimum incidence = 2% in either group, three studies combined.

is liberated from membrane phospholipid by phospholipase A2. In addition, azelastine caused dose-dependent inhibition of superoxide free radical production in human neutrophils and eosinophils.<sup>7</sup>

These in vitro and in vivo effects on chemical mediators of inflammation have been substantiated in controlled clinical trials. Pretreatment with single doses of orally administered azelastine significantly reduced leukotriene and kinin concentrations in nasal lavage fluids following nasal allergen challenge in seasonal allergic rhinitis patients.<sup>11</sup> In a single-dose study, azelastine nasal spray positively affected both early- and late-phase allergic responses, including reductions in inflammatory cell (eosinophils and neutrophils) migration, and downregulation of intercellular adhesion molecule-1 (ICAM-1) expression following allergen challenge.<sup>12</sup> In another controlled clinical trial, azelastine nasal spray decreased nasal airway resistance as determined by passive anterior rhinomanometry.<sup>22</sup>

As a result of these findings, it was considered that, besides antihistaminic activity, azelastine nasal spray might also be expected to have clinically relevant anti-inflammatory activity as well. An open-label pilot study was therefore conducted that included patients with seasonal allergic rhinitis whose symptoms were not adequately controlled by either an oral antihistamine or a nasal steroid and who were candidates for combination therapy with both an antihistamine and a nasal steroid. The clinicians were asked to use azelastine nasal spray instead of the combination therapy. The results of this open-label study indicated that approximately 80% of the patients re-

sponded positively to azelastine nasal spray monotherapy and did not require combination therapy.

In addition to the open-label pilot study, the three studies reported in this publication were undertaken. It was prospectively determined to assess whether or not patients with moderate-to-severe symptoms of seasonal allergic rhinitis, who were determined by their physicians to need combination therapy with both an oral antihistamine plus an intranasal corticosteroid after failing to have their symptoms adequately controlled by one or the other as monotherapy, could be effectively treated with azelastine nasal spray monotherapy. The primary efficacy variable of these three studies was the clinical assessment by the investigator at the end of the double-blind treatment period as to whether or not the patients required additional anti-rhinitis medication added to their treatment regimens.

The results of the studies clearly demonstrated that azelastine nasal spray monotherapy was as effective as combination therapy in improving moderate-to-severe symptoms of seasonal allergic rhinitis. The physician global assessment of the need for additional anti-rhinitis therapy and the patient global assessment of efficacy indicated that the patients treated with azelastine nasal spray monotherapy had symptomatic improvement comparable to patients treated with the combination of loratadine tablets plus beclomethasone nasal spray. There were no significant differences between treatment groups in the percentage of patients who did not require additional anti-rhinitis therapy as determined by the physician, regardless of whether the patient had a previous inadequate

response to an antihistamine or a previous inadequate response to an intranasal corticosteroid. A substantial percentage of patients with seasonal allergic rhinitis who are candidates for combination therapy with both an oral antihistamine and a nasal steroid were therefore adequately controlled with azelastine nasal spray monotherapy.

Multiple therapeutic options exist for the treatment of allergic rhinitis and the risks and benefits of each therapeutic option must be considered in light of the individual patient's symptom complex. Once prescribed, therapy must then be evaluated based on the patient's clinical response and tolerance of the treatment. Azelastine nasal spray represents a useful addition to the available therapies for the treatment of seasonal allergic rhinitis. Azelastine nasal spray can be used either in place of oral antihistamines or in combination with intranasal corticosteroids or, as demonstrated in these studies, as an alternative to combination therapy with both an oral antihistamine and intranasal corticosteroid. These clinical results were consistent with the findings of the previously conducted in vitro studies, animal studies, and clinical studies, indicating that the pharmacologic profile of azelastine includes not only antihistaminic activity but also anti-inflammatory activity as well.

Antihistamines effectively relieve the acute H<sub>1</sub>-receptor-mediated symptoms of an allergic reaction such as rhinorrhea, nasal itching, and sneezing but are not as effective as intranasal corticosteroids for treating the late-phase symptom of congestion that results from the release of inflammatory chemical mediators other than histamine. The pharmacologic effects of azelastine include not only H<sub>1</sub>-receptor antagonism but also inhibitory effects on inflammatory mediators such as leukotrienes and kinins. Since the three studies presented in this paper all demonstrated that azelastine nasal spray was as effective as combination therapy with an oral antihistamine and an intranasal corticosteroid, a reasonable clinical interpretation of the findings

could be that azelastine nasal spray provided more than a simple antihistaminic effect and indeed provided relief in patients with a symptom (congestion) usually linked with the late-phase inflammatory response. This effect can be distinguished from a vasoactive response based on the pharmacology of azelastine and further supports the clinical significance of the anti-inflammatory action of azelastine nasal spray.

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