
Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis

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Background: Intranasal corticosteroids and nonsedating antihistamines are the drug classes most often prescribed to treat allergic rhinitis (AR). Treatment guidelines recommend a combination of these agents for moderate-to-severe AR. However, clinical studies have found that combining an antihistamine with an intranasal corticosteroid provides few or no advantages over monotherapy with an intranasal corticosteroid.

Objective: To compare the efficacy of mometasone furoate nasal spray (NS) plus loratadine with that of monotherapy with the individual agents in patients 12 years and older with at least a 2-year history of seasonal AR.

Methods: In a multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study, 702 patients were randomized to receive mometasone furoate NS, 200 μ g, plus loratadine, 10 mg ($n = 169$); mometasone furoate NS, 200 μ g ($n = 176$); loratadine, 10 mg ($n = 181$); or placebo ($n = 176$) once daily for 15 days. Primary efficacy variables were total nasal symptom score (TNSS) and total symptom score (TSS) as recorded on diary cards.

Results: No statistically significant differences were observed between mometasone furoate NS plus loratadine and mometasone furoate NS monotherapy for the primary efficacy variables. For TNSS and TSS, all 3 active drug therapies were more effective than placebo ($P \leq .02$). Both mometasone furoate NS treatment regimens were more effective than loratadine or placebo for TNSS ($P < .01$ for both) and TSS ($P \leq .03$ for both), whereas loratadine was more effective than placebo for TNSS only ($P = .02$).

Conclusions: Combination therapy with mometasone furoate NS and loratadine provided benefits similar to monotherapy with mometasone furoate NS for the symptoms of seasonal AR. Therefore, mometasone furoate NS monotherapy was shown to be an effective treatment for seasonal AR.

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INTRODUCTION

Oral antihistamines and intranasal corticosteroids are the 2 drug classes recommended by treatment guidelines as first-line therapies for allergic rhinitis (AR), one of the most common and increasingly prevalent allergic disorders.^{1–3} Oral antihistamines effectively control the nasal symptoms of sneezing, itching, and rhinorrhea, but they are less effective than intranasal corticosteroids in relieving nasal congestion and in treating moderate-to-severe AR.^{1,4–7} Intranasal corticosteroids are effective for the treatment of all symptoms of AR, especially congestion, and are recommended as first-line treatment for moderate-to-severe or persistent AR.⁴ The greater therapeutic effect seen with intranasal corticosteroids may be related to their ability to suppress multiple stages of the allergic inflammatory reaction.⁸ Histamine plays a major

role in nasal symptoms associated with AR, but it is only 1 of many mediators involved in the allergic reaction.²

The European Academy of Allergy and Clinical Immunology has recommended use of an intranasal corticosteroid plus a nonsedating H₁-antihistamine for the treatment of AR based on the theory that combining agents that act on different components of the allergic reaction could have additive effects.^{4,8} However, this hypothesis has not been borne out by the results seen in some clinical studies,^{8–11} which concluded that the addition of an H₁-antihistamine to an intranasal corticosteroid was no more effective for improving symptoms of AR than was corticosteroid monotherapy. The intranasal corticosteroid mometasone furoate nasal spray (NS) has demonstrated efficacy and tolerability in the treatment of the nasal symptoms of seasonal AR (SAR) and perennial AR (PAR) in multiple randomized, double-blind, placebo-controlled studies.^{12–17} In addition, a 1-year, multicenter, open-label, nasal biopsy study in patients with PAR showed that treatment with mometasone furoate NS reduces the extent of inflammatory cell infiltration and restores inflamed nasal mucosa to a normal state, with a complete absence of nasal atrophy.¹⁸ The efficacy and safety of the nonsedating antihistamine loratadine in relieving the nasal

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symptoms of SAR has also been well established in randomized, double-blind, placebo-controlled trials.^{19–22} Prophylactic therapy with loratadine has been shown to suppress the symptoms of SAR and increase the number of symptom-free days.²³

The present study investigates the efficacy and safety of mometasone furoate NS combined with loratadine compared with monotherapy with either agent for the treatment of SAR. The principal objective of this study is to provide further evidence of similar efficacy with monotherapy and combination therapy with an intranasal corticosteroid.

METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 18 medical centers in every region of the United States except the Pacific Coast. This geographic diversity allowed for a representative sample of pollen counts during the study period (the spring allergy season, March to August 1995).

Participants were at least 12 years old and had at least a 2-year history of SAR. Study inclusion and exclusion criteria are listed in Table 1. The study was conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice, and appropriate institutional review boards approved the protocol and informed consent forms. Written informed consent was obtained from each participant or from the parent or guardian of each participant younger than 18 years.

The study consisted of 4 visits and 1 telephone contact. At screening (visit 1), participants received a thorough health evaluation, including physical examination, medical history taking, laboratory testing, and physician evaluation of rhinitis symptoms and overall condition. Participants were evaluated again at baseline (visit 2, study day 1) and at visits 3 and 4 (study days 8 and 15).

Patients who qualified for study entry had nasal congestion that was at least moderate (score ≥2), with a total nasal symptom score (TNSS) of at least 6 and a total symptom score (TSS), consisting of the total nonnasal symptom score and the TNSS, of at least 11 at the screening and baseline visits. Symptom severity was rated by patients and physicians

using a 4-point scale, with 0 indicating none (no sign or symptom present); 1, mild (sign or symptom clearly present but minimal awareness, easily tolerated); 2, moderate (definite awareness of sign or symptom, bothersome but tolerable); and 3, severe (sign or symptom hard to tolerate, interferes with activities of daily living or sleeping). Using the same scale, physicians and patients rated overall SAR condition at each office visit, including entire time since last visit and current observations. At the return visits (days 8 and 15) after treatment initiation, physicians and patients evaluated patient overall therapeutic response relative to baseline, including the current observation, using a scale from 1 to 5 (1, complete relief, and 5, treatment failure). Physicians and patients were blinded as to which patients received active drug or placebo during these assessments.

Between the screening and baseline visits, patients participated in a 3- to 7-day diary run-in phase during which they used daily diary cards to record the severity of 9 AR symptoms (nasal discharge, stuffiness, itching, and sneezing; ocular itching, tearing, and redness; and itching of the ears or palate), the occurrence of any adverse events (AEs), and the use of and dosing information for any concomitant medications. Patients were further instructed to bring their diary cards to the baseline visit to be reviewed by the study investigator. At this time, data on the use of concomitant medications were recorded in patients' case records.

At baseline, patients were randomly assigned to 1 of 4 treatment groups in a 1:1:1:1 ratio: mometasone furoate NS, 200 µg/d, plus loratadine, 10 mg/d; mometasone furoate NS, 200 µg/d, plus placebo tablet; placebo nasal spray plus loratadine, 10 mg/d; or placebo nasal spray plus placebo tablet. Separate randomization schedules were prepared for each center, and patients and investigators were masked to treatment identity.

Patients received their first dose of study medication (nasal spray and tablet) at baseline visit 2 (study day 1) under supervision in the physician's office to ensure proper use of the nasal spray and correct recording of data on diary cards. For the remaining 14 days of the study, patients self-administered 1 of the 4 treatments being studied. All doses were taken in the morning on awakening, on an empty stomach, and after recording symptom severity. Patients recorded their

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
2-y clinical history of SAR	Rhinitis medicamentosa
Symptoms of active disease	Nasal candidiasis
Positive skin prick test results in the past year	Nasal structural abnormalities
Good health	History of frequent rhinosinusitis or chronic purulent postnasal drip
No clinically significant disease (except SAR)	Asthma if long-term use of inhaled or systemic corticosteroids required
No clinically significant abnormalities on a screening electrocardiogram	Immunotherapy (unless taking a stable maintenance dose for ≥1 mo)

Abbreviation: SAR, seasonal allergic rhinitis.

symptoms again in the evening, approximately 12 hours later. At the 2 additional physician visits on study days 8 and 15, diary cards were reviewed for accuracy of recording and compliance with the dosing regimen, and physicians and patients evaluated response to therapy relative to baseline and the overall condition of SAR since the previous visit. Patients were contacted by telephone on day 4 to evaluate compliance, and they returned to the study center on days 8 and 15 for a nasal examination and a review of their diary cards to evaluate TNSS and TSS.

Statistical Analysis

The primary efficacy variables were patient-rated average change in TNSS (nasal discharge plus stuffiness plus sneezing plus itching) and TSS (TNSS plus total nonnasal symptom score [eye tearing plus eye redness plus eye itching plus ear/palate itching]) during the 15-day study, from baseline to day 15 or study end point, that is, the last visit with nonmissing data. Results for the primary efficacy variables were based on diary card data, with morning and evening scores averaged. For the comparison of mometasone furoate NS plus loratadine vs mometasone furoate NS monotherapy, the primary efficacy variable was the average change in TSS. For the comparison of mometasone furoate NS plus loratadine vs loratadine monotherapy, the primary efficacy variable was the average change in TNSS. Secondary efficacy variables were patient- and physician-rated individual symptom scores plus physician and patient evaluations of therapeutic response and overall condition of SAR.

The primary efficacy analysis was based on the population of efficacy-evaluable patients, defined as randomized patients who met the eligibility criteria, remained compliant with the study protocol, and completed at least 1 valid postbaseline

visit (defined as a visit with no missing data). Confirmatory efficacy analyses and safety data were based on the intention-to-treat population, defined as all randomized patients who received at least 1 dose of study medication and had at least 1 postbaseline evaluation.

A 2-way analysis of variance was used for symptom scores, global evaluations, and secondary efficacy variables (total nonnasal symptom scores, individual symptom scores, physician and patient ratings of overall SAR condition at study visits, and evaluation of therapeutic response from baseline). All pairwise comparisons were based on the least squares means from the analysis of variance, using an individual .05 (2-sided) significance level with no adjustment for multiple comparisons.

With a patient population of at least 640, or 160 in each treatment group, the study was powered to detect treatment differences for TNSS and TSS at a level of 90%. For TNSS, $\alpha = .05$ (2-tailed) and an estimated pooled SD of 2.2 U enabled detection of treatment differences of at least 0.8 U for mean change from baseline with a power of 90%. For TSS, with the same α level and an SD of 4.4 U, treatment differences of at least 1.6 U for mean change from baseline could be detected with a power of 90%. Safety was evaluated based on physicians' clinical observations and patients' diary reports. At each visit, patients were questioned about AEs, and details of any reported event were recorded in case reports.

RESULTS

A total of 702 patients were enrolled and received at least 1 dose of study medication. At baseline, there were no statistically significant differences among treatment groups for demographic and clinical variables in the intention-to-treat

Table 2. Demographic and Clinical Characteristics of the Intention-to-Treat Population at Baseline

	MFNS + loratadine (n = 169)	MFNS alone (n = 176)	Loratadine alone (n = 181)	Placebo (n = 176)
Age, y				
Mean	26	26	25	26
Range	11–62	12–71	12–65	12–66
Sex, M/F, No.	84/85	87/89	90/91	91/85
Duration of AR, y				
Mean	14	13	14	13
Range	2–51	2–56	2–60	2–55
TNSS, mean $\pm$ SD ^a				
Physicians	8.7 $\pm$ 1.8	8.7 $\pm$ 1.7	8.5 $\pm$ 1.7	8.8 $\pm$ 1.8
Patients ^b	7.9 $\pm$ 2.0	7.8 $\pm$ 2.5	7.9 $\pm$ 2.2	8.0 $\pm$ 2.2
TSS, mean $\pm$ SD ^c				
Physicians	15.9 $\pm$ 3.1	16.1 $\pm$ 3.4	15.9 $\pm$ 3.2	16.2 $\pm$ 3.5
Patients ^b	14.3 $\pm$ 4.8	14.2 $\pm$ 4.7	14.4 $\pm$ 4.2	14.6 $\pm$ 4.2

Abbreviations: AR, allergic rhinitis; MFNS, mometasone furoate nasal spray; TNSS, total nasal symptom score; TSS, total symptom score.

^a The total of 4 individual nasal symptom scores (rhinorrhea, nasal stuffiness, nasal itching, and sneezing) combined. Individual scores: 0 indicates no symptoms; 1, mild; 2, moderate; and 3, severe.

^b For the efficacy population: MFNS + loratadine, n = 166; MFNS alone, n = 166; loratadine, n = 175; and placebo, n = 165.

^c The total of individual symptom scores for 4 nasal symptoms plus nonnasal symptom scores (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate) combined. Individual scores: 0 indicates no symptoms; 1, mild; 2, moderate; and 3, severe.

and efficacy populations. Physician- and patient-evaluated baseline TNSSs and TSSs in these populations were also similar among treatment groups (Table 2). Thirty-nine patients discontinued therapy (Table 3), and 30 patients were excluded from the efficacy analysis because of noncompliance with the dosing regimen, not meeting the entry criteria, not receiving sufficient medication, insufficient efficacy data, or unacceptable baseline examination. Therefore, 672 patients were evaluated for efficacy: mometasone furoate NS plus loratadine ($n = 166$), mometasone furoate NS monotherapy ($n = 166$), loratadine monotherapy ($n = 175$), and placebo ($n = 165$).

Patients were enrolled for 15-day study periods at various points throughout the allergy seasons, and daily pollen counts were recorded at each study center. Pollen counts varied among the study centers, with some but not a complete correlation between pollen count and geography. Low pollen counts were recorded at study centers in the western states of Colorado and Utah but also in the northeastern state of Connecticut (rarely >100 – 200 grains/ M^3). High values were seen in southern states, such as Georgia and Texas (frequently $>1,000$ – $2,000$ grains/ M^3), and midrange to elevated levels in the neighboring northern states of Pennsylvania and Ohio (approximately 200 – 500 grains/ M^3).

Improvement From Baseline in TNSSs

Patients' morning and evening diary records of TNSSs during the 15 days of therapy showed that all 3 active treatments were more effective than placebo ($P \leq .02$). Mometasone furoate NS plus loratadine and mometasone furoate NS monotherapy were not significantly different from each other, and both were more effective than loratadine monotherapy in reducing TNSSs ($P < .01$ for both) (Fig 1). For individual nasal symptoms, no statistically significant differences were observed between mometasone furoate NS combination therapy and mometasone furoate NS monotherapy (Table 4). Diaries showed that the greatest improvement occurred with sneezing, with all 3 active treatments more effective than placebo ($P \leq .02$). Mometasone furoate NS combination therapy led to greater improvement than loratadine monotherapy ($P \leq .05$) and placebo ($P < .01$) for all 4 nasal symptoms. Mometasone furoate NS monotherapy was also significantly more effective than loratadine monotherapy for

all symptoms ($P \leq .02$) except nasal itching and was superior to placebo for the 4 nasal symptoms ($P \leq .01$). Loratadine monotherapy was associated with greater improvement than placebo for all symptoms ($P \leq .04$) except nasal discharge.

Improvement From Baseline in TSSs

No significant differences were observed between mometasone furoate NS combination therapy and mometasone furoate NS monotherapy in reducing the average TSS from days 1 to 15, and both were more effective than loratadine monotherapy ($P \leq .03$) (Fig 2). Diaries rated all 3 active treatments as significantly more effective than placebo.

Improvement From Baseline in Nonnasal Symptoms

Patients rated mometasone furoate NS plus loratadine ($P = .01$), mometasone furoate NS monotherapy ($P = .01$), and loratadine monotherapy ($P \leq .02$) as more effective than placebo in reducing mean total nonnasal symptom scores. The differences between the 2 mometasone furoate NS treatment groups were not significant. The reductions in total nonnasal symptom scores from baseline to the end point were -3.7 (-51%) with combination therapy, -3.9 (-52%) with mometasone furoate NS monotherapy, -3.1 (-43%) with loratadine monotherapy, and -2.4 (-33%) with placebo.

No statistically significant differences between combination therapy and mometasone furoate NS monotherapy were noted in diaries for individual nonnasal symptoms. However, both treatments were more effective than placebo ($P \leq .04$) for reducing ocular itching, tearing, and redness and ear/palate itching. According to patient ratings, combination therapy was significantly more effective than loratadine ($P \leq .03$) for all nonnasal symptoms except ear/palate itching, whereas the only nonnasal symptom for which mometasone furoate NS monotherapy provided significantly greater improvement than loratadine was ocular tearing ($P = .04$). Patients rated loratadine monotherapy as more effective than placebo ($P \leq .05$) for all individual nonnasal symptoms except eye redness.

Physician Evaluations

Physician evaluations of TNSSs, TSSs, individual symptom scores, and nonnasal symptom scores at the 4 study visits generally supported the results recorded in patient diaries. In

Table 3. Patients Who Withdrew From Treatment and Reasons for Withdrawal

Reason for withdrawal	Patients, No. (%)			
	MFNS + loratadine ($n = 169$)	MFNS alone ($n = 176$)	Loratadine alone ($n = 181$)	Placebo ($n = 176$)
Adverse event	2 (1)	4 (2)	4 (2)	8 (5)
Treatment failure	1 (<1)	2 (1)	1 (<1)	8 (5)
Lost to follow-up	0	0	0	1 (<1)
Noncompliance with protocol	0	1 (<1)	2 (1)	1 (<1)
Did not meet entry requirements	0	2 (1)	1 (<1)	1 (<1)
Total	3 (2)	9 (5)	8 (4)	19 (11)

Abbreviation: MFNS, mometasone furoate nasal spray.

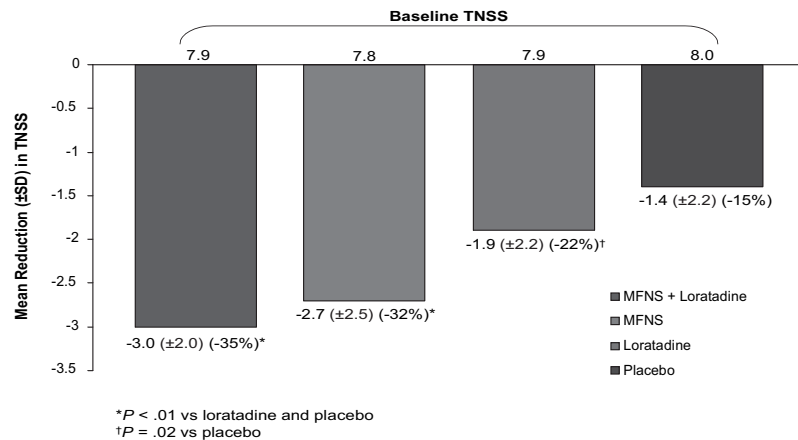


Figure 1. Total nasal symptom score (TNSS) mean $\pm$ SD reductions from baseline during the 15-day treatment period: pooled data from patient diaries. MFNS indicates mometasone furoate nasal spray.

Table 4. Decrease From Baseline in Individual Nasal Symptoms, Days 1–15, Patient Diaries

Symptom	Decrease, mean (%)				P value		
	MFNS + loratadine (A)	MFNS alone ^a (B)	Loratadine alone ^b (C)	Placebo (D)	A vs B	A vs C	A vs D
Nasal discharge							
Baseline	2.1	2.1	2.1	2.1			
Days 1–15	-0.7 (-27)	-0.7 (-29)	-0.4 (-16)	-0.3 (-9)	NS	<.05	<.01
Nasal stuffiness or congestion							
Baseline	2.3	2.2	2.3	2.2			
Days 1–15	-0.7 (-29)	-0.7 (-27)	-0.4 (-16)	-0.3 (-8)	NS	<.05	<.01
Sneezing							
Baseline	1.8	1.7	1.7	1.7			
Days 1–15	-0.8 (-42)	-0.7 (-39)	-0.6 (-28)	-0.4 (-14)	NS	<.05	<.01
Nasal itching							
Baseline	1.8	1.7	1.9	1.9			
Days 1–15	-0.7 (-33)	-0.6 (-23)	-0.6 (-25)	-0.4 (-17)	NS	<.05	<.01

Abbreviation: MFNS, mometasone furoate nasal spray; NS, not significant.

^a MFNS vs loratadine: $P \leq .02$ for nasal discharge, nasal stuffiness, and sneezing; $P = NS$ for nasal itching. MFNS vs placebo: $P \leq .01$ for all 4 symptoms.

^b Loratadine vs placebo: $P \leq .04$ for nasal stuffiness, sneezing, and nasal itching; $P = .13$ for nasal discharge.

examining patients and reviewing their diary cards for overall condition and symptom relief, physicians found that the 2 mometasone furoate NS treatment regimens were not significantly different from each other but were more effective than loratadine monotherapy and placebo ($P < .01$ for both at all time points). Loratadine was not significantly more effective than placebo on physician evaluations, except on day 15 and at the study end point ($P \leq .02$).

At baseline, physicians classified 2% or fewer patients in each group as having mild symptoms of SAR. On day 15, symptoms of SAR were absent or mild in 63% of patients in the combination treatment group, 61% in the mometasone furoate NS monotherapy group ($P < .01$ vs loratadine and placebo for both comparisons with the mometasone furoate NS treatment groups), 42% in the loratadine monotherapy group, and 41% in the placebo group. On days 8 and 15, the

percentages of patients with complete or marked relief of symptoms of SAR were 35% and 47%, respectively, with combination therapy ($P < .01$ vs loratadine and placebo); 28% and 38% with mometasone furoate NS monotherapy ($P < .01$ vs loratadine and placebo); 16% and 27% with loratadine monotherapy; and 13% and 23% with placebo.

Safety

The 3 active treatment regimens were safe and well tolerated. The incidence of AEs was relatively, but not significantly, higher with loratadine monotherapy (47%) and placebo (41%) than with mometasone furoate NS plus loratadine and mometasone furoate NS monotherapy (37% and 36%, respectively). Headache was the most frequently reported AE, occurring in 4%, 6%, 8%, and 7% of patients receiving combination therapy, mometasone furoate NS monotherapy,

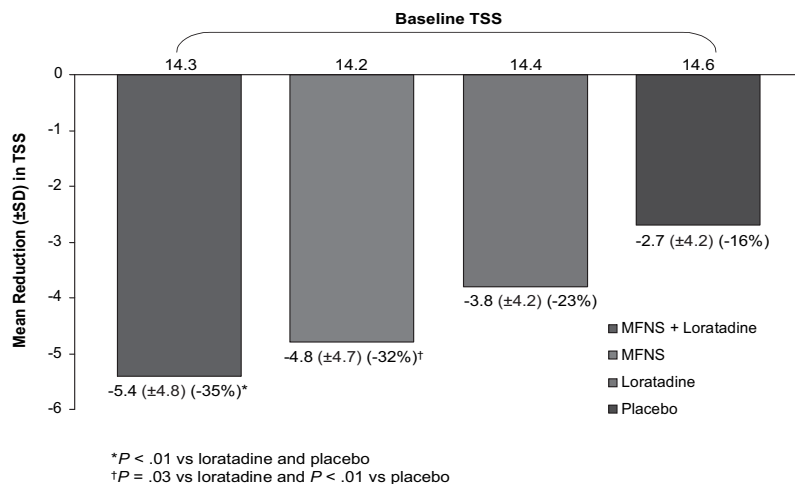


Figure 2. Total symptom score (TSS) mean $\pm$ SD reductions from baseline during the 15-day treatment period: pooled data from patient diaries. MFNS indicates mometasone furoate nasal spray.

loratadine monotherapy, and placebo, respectively. Other common AEs observed in 4% or fewer patients in each group were epistaxis (defined to include a broad range of bleeding episodes from frank bleeding to bloody nasal discharge to flecks of blood in the mucus), pharyngitis, nasal burning, and somnolence (Table 5). Most AEs were mild to moderate in severity and of short duration.

DISCUSSION

The results of this study provide further evidence that adding an H_1 -antihistamine to an intranasal corticosteroid does not provide a significantly greater benefit for the treatment of SAR over that seen with intranasal corticosteroid monotherapy. Monotherapy with mometasone furoate NS was as effective in improving TNSSs and TSSs as combination therapy with loratadine. Although patient diaries noted some additive effects with loratadine in further improving TNSSs and TSSs, the difference did not reach statistical significance. Furthermore, mometasone furoate NS alone and with loratadine were more effective than loratadine monotherapy and placebo in improving most nasal and nonnasal symptoms.

Table 5. Most Frequently ($\geq 2\%$) Reported Treatment-Related Adverse Events

Adverse event	Patients, No. (%)			
	MFNS + loratadine	MFNS alone	Loratadine alone	Placebo
Headache	6 (4)	10 (6)	14 (8)	13 (7)
Epistaxis	6 (4)	2 (1)	2 (1)	6 (3)
Pharyngitis	3 (2)	1 (1)	4 (2)	3 (2)
Nasal burning	3 (2)	0	0	0
Somnolence	3 (2)	1 (1)	4 (2)	2 (1)

Abbreviation: MFNS, mometasone furoate nasal spray.

A smaller ($N = 24$) study²⁴ comparing mometasone furoate NS monotherapy with mometasone furoate NS plus loratadine reached similar results. In this single-center prospective study, adolescents (mean age, 12.17 years; range, 9–18 years) with moderate-to-severe SAR sensitive to grass pollen were randomized into 2 treatment groups receiving mometasone furoate NS plus loratadine ($n = 12$) or mometasone furoate NS monotherapy ($n = 12$). Subjective (diary card data of nasal and ocular symptoms) and objective (nasal smear, peak nasal inspiratory flow [PNIF], and nasal biopsy) criteria were used to evaluate treatment response. Improvements vs baseline were noted in both groups for TSSs, increases in PNIF, and decreases in eosinophil levels. Except for a greater improvement in nighttime symptoms with combination therapy than with monotherapy, no difference in treatment effect was noted between the 2 groups.

Results of the studies with mometasone furoate NS are similar to those seen in other clinical studies of combination treatment with other intranasal corticosteroids and antihistamines.^{8–11,25–28} For example, in a double-blind, placebo-controlled, crossover study of SAR, the addition of levocetirizine to fluticasone propionate nasal spray did not lead to any clinically significant incremental benefits. No statistically significant differences were seen between the 2 groups in quality-of-life assessments, TNSS, PNIF, or nasal nitric oxide levels.⁸ Both treatment regimens showed significantly greater improvement for change from baseline for all of these efficacy variables except nasal nitric oxide levels. Three other AR studies^{11,25–27} with a combined population of nearly 800 reviewed treatment with the intranasal corticosteroids fluticasone propionate, beclomethasone dipropionate, and budesonide as monotherapy or in combination with antihistamines and reached similar conclusions. Monotherapy with intranasal corticosteroids was found to be as effective as the combination regimen, and both intranasal corticosteroid regimens

provided significantly greater symptom relief than monotherapy with an antihistamine or placebo.

One possible reason for the absence of added efficacy from combination therapy may be that intranasal corticosteroids affect more inflammatory cells involved in the allergic response than do antihistamines. In brief, intranasal corticosteroids suppress or inhibit the activity or migration of inflammatory agents such as interleukin 3 (IL-3), IL-4, IL-5, and IL-13; eotaxin; intercellular adhesion molecule-1; mast cells and basophils (both of which migrate to the nasal epithelium); and eosinophils and eosinophil products. They also reduce the release of histamine, among other actions.^{4,25,28–32}

In contrast, H₁-antihistamines exert an antiallergic effect primarily through antagonizing the effects of histamine by selectively binding to the H₁-histamine receptor. The binding of an antihistamine to this receptor does not result in receptor activation and does not elicit a tissue response.⁴ As noted previously herein, many other mediators are released during the allergic reaction. The additional anti-inflammatory effects of antihistamines have not been fully clarified,²⁵ although studies^{24,33–35} have found that antihistamines also prevent release of mediators from basophils and mast cells and inhibit cytokine production and inflammatory cell influx.

Given the multiple anti-inflammatory effects of intranasal corticosteroids in AR, further anti-inflammatory activity provided by the inclusion of an antihistamine may be redundant. In addition, intranasal corticosteroids administered as monotherapy have been shown to be more effective than antihistamine monotherapy for the nasal symptoms of AR and equally beneficial in treating ocular symptoms.^{24,25,28} In this study, mometasone furoate NS monotherapy was significantly superior to loratadine monotherapy for most efficacy variables studied. The only variables in which the therapeutic effects of mometasone furoate NS and loratadine monotherapy were similar were nasal itching and some nonnasal symptoms, the primary components of which were ocular symptoms. The latter result supports other studies^{5,25} showing that these 2 classes of drugs are equally effective for treating ocular symptoms.

This study also had the largest participant population (N = 702) in a clinical trial of intranasal corticosteroid combination therapy and monotherapy. More patients participated in this study, to our knowledge, than in any other published clinical trial comparing combination therapy with monotherapy. Most studies had 100 or fewer participants,^{8,10,24,26–28} and only 2 studies^{9,11} could be identified with several hundred (N = 454 and 600). Size alone does not necessarily ensure the validity of results seen in a study. However, combined with adequacy of study design and a robust statistical analysis, a large sampling of a patient population can add substance to a study's findings.

Combining an antihistamine with an intranasal corticosteroid has not been associated with an increase in either the number or the severity of AEs compared with monotherapy with either agent in this or other studies.^{5,8–11,24} Headache was the most frequently reported AE in each treatment group in

this study, and its occurrence was lowest in patients receiving combination treatment. Other AEs were similar in each treatment group. Mometasone furoate NS and loratadine are well tolerated when administered individually.^{12–21} The safety and tolerability of the combination regimen in the present trial were also similar to those reported in other trials^{4,9,10,28,36} with intranasal corticosteroid-antihistamine combinations.

An interesting observation in this study was physician evaluations of a lack of significant effect for loratadine vs placebo for overall disease condition and therapeutic response. The reason for this result was thought to be the high response rates in the placebo group. This high response rate was not considered in patient evaluations, in which significance for loratadine vs placebo was more often achieved. This study included patients with at least moderate-to-severe symptoms of SAR, a population for whom intranasal corticosteroids are specifically recommended⁴ and one that is used in most studies with intranasal corticosteroids and antihistamines.^{4,10–22}

The results of this study suggest that for people with moderate-to-severe SAR, the addition of loratadine to mometasone furoate NS provides no additional clinical benefit over mometasone furoate NS monotherapy. No statistically significant differences were observed between mometasone furoate NS monotherapy and mometasone furoate NS plus loratadine on patient and physician ratings of symptomatic relief and overall clinical response. With the exceptions noted (ie, patient-rated nasal itching and some ocular symptoms), in which the therapeutic effects of mometasone furoate NS and loratadine monotherapy were similar, the mometasone furoate combination and monotherapy regimens were generally more effective than loratadine monotherapy and placebo for the primary efficacy outcomes of TNSS and TSS, and both were safe and well tolerated. The study provides additional and, given the large size of the study population, important evidence of the similar efficacy of intranasal corticosteroid-antihistamine combination therapy and intranasal corticosteroid monotherapy.

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