

Recruitment factors which affect the outcome of a seasonal allergic rhinitis trial

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ABSTRACT

Although intranasal corticosteroids (INSs) are the first-line treatment for seasonal allergic rhinitis (SAR), some patients do not respond adequately, reflecting biological heterogeneity or confounding conditions. The objective of this study was to determine what recruitment factors identify SAR subjects who will be unresponsive to mometasone furoate (MF). We performed a 2-week, double-blind, placebo-controlled, parallel study on 40 subjects with SAR. Each subject underwent a decongestant test using oxymetazoline. Baseline nasal symptoms, nasal peak inspiratory flow (NPIF) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores were recorded. Next, subjects were randomized to either 200 µg of MF or placebo. Symptom diaries and NPIF measurements were completed twice daily. After 2 weeks, subjects repeated the RQLQ and the global assessment of symptoms. There was a significant reduction in symptoms in the MF group compared with placebo ($p \leq 0.05$) in patients with baseline total symptom scores of ≥ 6 . Multivariate analysis showed that treatment (MF versus placebo; $p = 0.049$) and amount of decongestion (percent change in NPIF after oxymetazoline; $p = 0.008$) predicted the improvement in total nasal symptoms. In clinical trials, SAR subjects must report multiple symptoms to be responsive to treatment with INSs. Our results also support the use of the decongestant test for choice of appropriate study volunteers, both to ensure participation of potentially responsive subjects and to eliminate those with confounding issues.

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Seasonal allergic rhinitis (SAR) is a common chronic disorder that is characterized by an IgE-mediated, hypersensitive, inflammatory response of the nasal mucosa to otherwise innocuous airborne allergens, such as tree, grass, and ragweed pollen.^{1–3} SAR is associated with enormous morbidities, affecting ~16% of the U.S. population and it constitutes a major socio-economic burden with more than \$6 billion spent for treating this condition in the year 2000.^{4–6} The common symptoms include nasal congestion, rhinorrhea, sneezing, and itchy nose and throat but additional symptoms such as headaches, difficulty sleeping, fatigue, and memory problems cause a significant toll on the patient's quality of life.^{2,3,7,8}

A number of pharmacologic interventions aiming at the alleviation of symptoms of allergic rhinitis exist.^{3,9}

For moderate-to-severe allergic rhinitis, guidelines recommend intranasal corticosteroids (INSs) as first-line treatment.^{10,11} However, not all patients respond equally to INSs. This variability could be explained by biological contribution from other medical conditions validated by history and nasal examination, such as nonallergic rhinitis, nasal polyps, deviated septum, and chronic rhinosinusitis, or by the inherent biases of subjective reporting of nasal symptoms used in clinical trials.²

Medications approved for the treatment of allergic rhinitis undergo testing in clinical trials. Interestingly, the number of participants needed for showing efficacy has increased dramatically in recent years. Other biological processes might contribute to patients' symptoms, despite their history of SAR and a positive skin test, which are the usual criteria for enrollment. Asthma clinical trials, in contrast to SAR trials, usually include an objective measure for entry such as forced expiratory volume in 1 second or the response to a bronchodilator.¹² Therefore, in addition to the usual entry criteria for allergic rhinitis clinical trials, developing an objective screening test might help to address the issue of concomitant biological conditions and increase the likelihood of enrolling patients with pure SAR.

Previous studies have shown that intranasally applied α -adrenoreceptor agonists relieve nasal congestion and improve airflow in patients with SAR as a result of vasoconstriction of the nasal sinusoids, which

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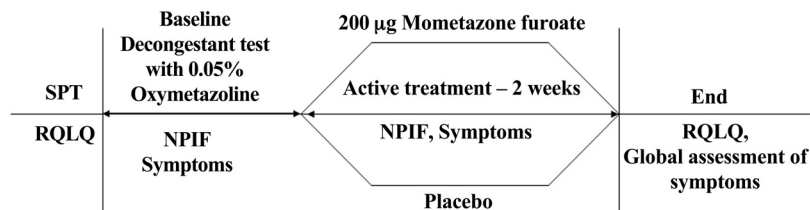


Figure 1. The schematic of study design and procedures performed during the study. The decongestant test was performed in all subjects before the start of the study. After randomization, patients were divided into a mometasone furoate and placebo groups and were advised to take the drug or the placebo for 2 weeks and record their symptoms. RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; NPIF, nasal peak inspiratory flow.

reduce blood flow and mucosal volume.^{13,14} Congestion induced by other etiologies not associated with cavernous sinus filling would be expected to show poorer responses to a decongestant. Thus, decreased responsiveness to a decongestant may suggest that another diagnosis is contributing to the patients' nasal symptoms and that this underlying condition might not be responsive to treatment. This needs to be further verified by a detailed history and nasal examination. This may, in turn, explain why only ~60% of patients entered in clinical trials report an excellent response to treatment with INSs.¹⁵

In the present study, we hypothesized that patients with pure SAR will decongest better with oxymetazoline (0.05%), a nasal decongestant, than those patients with another medical cause contributing to their symptoms of SAR. We further hypothesized that patients who decongest well would respond better to treatment with a topical INS versus a placebo in clinical trials.

METHODS

Study Design

We performed a 2-week, double-blind, placebo-controlled, parallel study on 40 healthy SAR adult subjects with a baseline congestion score of ≥ 2 (based on a nasal symptom questionnaire) and a history of tree or grass allergy during the 2008 spring allergy season. In the initial screening, the patients visited the Nasal Physiology Laboratory at the University of Chicago, where they completed a nasal symptom questionnaire and their allergy status was confirmed with a skin-puncture test for tree allergen mix (including white ash, American beech, river birch, black walnut, common cottonwood, American elm, shagbark hickory, maple, red oak, American sycamore, and black willow) and timothy grass. The qualified volunteers were asked to complete a nasal symptom questionnaire and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).¹⁶ After recording of the baseline nasal peak inspiratory flow (NPIF), a decongestant test was performed on all the subjects. Two sprays of 0.05% oxymetazoline were delivered to both nostrils and NPIF measurements were recorded. These measure-

ments were repeated after 10 minutes for determining any changes in the airflow, and percent decongestion was calculated using the equation,

$$\% \text{ Decongestion} = \frac{\left(\text{Average NPIF post-oxymetazoline} - \text{Average NPIF pre-oxymetazoline} \right)}{\text{Average NPIF pre-oxymetazoline}} \times 100$$

After the results from the decongestant test were obtained, the participants were randomized to receive either 200 µg of mometasone furoate (MF; Schering Corp., Kenilworth, NJ) or placebo once daily for 2 weeks (Fig. 1). All bottles of the study drug/placebo used for the study were obtained and labeled at the University of Chicago with subject code numbers. On entering the study, each subject was sequentially assigned study drug or placebo by a randomized code blocked in groups of four.

The participants recorded nasal symptoms and measured the NPIF twice daily throughout the 2-week study. They recorded the severity of sneezing, rhinorrhea, itchy nose, itchy eyes, and nasal congestion for the past 12 hours twice daily, assessing in the morning before taking the study medication and in the evening before going to bed. They also recorded in their diaries whether they took the study medicine each day or not. The subjects returned after 2 weeks for their final visit, during which their symptom diaries were collected, and they completed the end-of-study RQLQ and a global assessment of symptom improvement. No object measure of compliance was included in the study. Written informed consent was obtained from all participants.

Subjects

Subjects were between the ages of 18 and 60 years with a history of tree and/or grass SAR and the study period lasted between April 23 and July 2, 2008. All subjects had at least a 2-year history of allergy symptoms during the tree/grass season and reported symptomatic nasal congestion (score, ≥ 2) at entry. Subjects who had other medical conditions, were current smok-

ers, or had an upper respiratory tract infection at the time of screening were excluded. Women who were either pregnant, lactating, or of childbearing potential and not using contraception were also excluded. Subjects were excluded if they had used systemic glucocorticosteroids in the past 30 days, INs in the past 2 weeks, or oral antihistamines or decongestants in the past 7 days.

Pollen Counts

Pollen counts for Chicago were obtained from the National Allergy Bureau station in Melrose Park, IL.

RQLQ

The RQLQ is a disease-specific measure of a patient's quality of life, which has been validated.¹⁶ It includes domains that measure nasal and eye symptoms as well as those of activity, sleep, nonnose and noneye symptoms, and practical and emotional measures. A scale of 0–6 is used to record the patient responses, with lower scores reflecting a better quality of life. The average score of each domain was calculated as well as an overall domain score reflecting the average of all scores. Changes of ≥ 0.5 in the overall domain score have been considered clinically relevant in an earlier survey of patients with allergic rhinitis.

Symptom Diaries

Each participant recorded his/her symptoms twice daily. Participants assessed sneezing, rhinorrhea, nasal congestion, and itchy nose on a scale from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms). Daily total symptom scores were calculated for each symptom by adding the two scores of each day. Overall total daily symptom scores were calculated by adding all of the scores of all symptoms per day.

Nasal Peak Inspiratory Flow

NPIF (L/min) was measured using In-Check Peak Inspiratory Flow Meter (Ferraris Medical, Inc., Orchard Park, NY). The laboratory personnel instructed each subject on using the flow meter at their first visit. Three NPIF readings were taken before the decongestant test and three readings were taken 10 minutes after application of the decongestant. The decongestant test results were evaluated by calculating the percentage change between the highest score from both the sets. On the symptom diaries, subjects recorded the best of the three NPIF measurements at the two time points. Daily NPIF values were evaluated by adding the two daily measurements of each day.

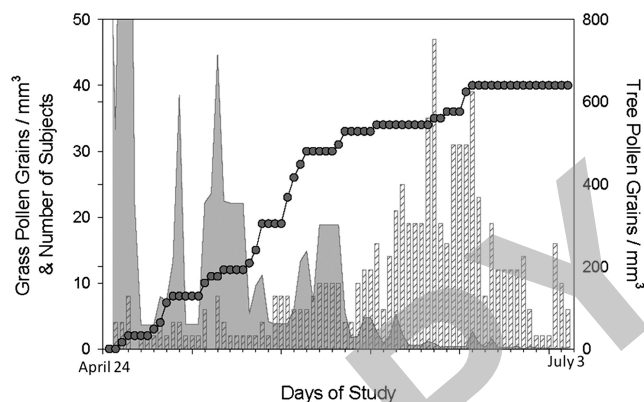


Figure 2. Tree and grass pollen counts for the 2008 spring allergy season and the number of patients enrolled for the study.

Global Assessment

At the last visit, the patients were asked to assess the effectiveness of the double-blind study drug in relieving their SAR symptoms by using a 7-point categorical scale (3 = significantly improved, 2 = moderately improved, 1 = mildly improved, 0 = no change, -1 = mildly worse, -2 = moderately worse, and -3 = significantly worse).

Statistical Analysis

RQLQ data are normally distributed (represented as mean $\pm$ SEM) and were analyzed using the Student's *t*-test. The symptom score and NPIF data were not normally distributed and were analyzed with nonparametric statistics, with data represented as medians and range. These comparisons were performed with use of the Mann-Whitney *U* test. All analyses were performed by use of Systat (Systat Software, Inc., Chicago, IL). Multivariate analysis was performed using SPSS (SPSS, Inc., Chicago, IL). The value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

The Chicago tree/grass pollen counts during the period of April 24 and July 3, 2008 were typical of our spring allergy season (Fig. 2). A total of 60 subjects were screened, and of these, 40 qualified for the study based on their symptoms (total baseline symptom score of ≥ 2) and allergy status (tree/grass/both). There were no dropouts, and 20 subjects in each treatment group (MF or placebo) completed the study. We chose to include 40 subjects in our study based on our prior experience with placebo-controlled intranasal steroid and other drug studies,^{17,18} and it represented a number of subjects that we could recruit at one center. The demographic characteristics of the study population in terms of age, sex, and race as well as their skin-prick test reactivity have been tabulated in Table 1 and show no significant differences in the two groups.

Table 1 Demographics of patients in the mometasone furoate and the placebo groups

Characteristic	Mometasone Furoate	Placebo
Race		
White	8	7
Black	10	9
Hispanic	1	2
Asian	1	1
Other	0	1
Gender (M/F)	14/6	10/10
Age (yr; mean $\pm$ SD)	32.6 $\pm$ 9.36	35 $\pm$ 12
Grass wheel (mm; mean $\pm$ SD)	8.5 $\pm$ 2.9	7.7 $\pm$ 3.5
Tree wheel (mm; mean $\pm$ SD), mm	8.4 $\pm$ 3.6	9.9 $\pm$ 4.3

No adverse events were reported or observed during the study.

The total symptom scores at baseline were similar between the two groups. The results for the decongestant test (median percent change in NPIF) were 40% (10–114%) and 19% (–22–142%) in the MF and the placebo group, respectively; they tended to show a greater responsiveness in the MF group ($p = 0.066$). The RQLQ data analysis showed that the two groups were similar at baseline for the overall and the individual domains. Also, the baseline total symptom score (MF median = 7 [3–12] and placebo median = 7 [3–10]) and NPIF values (MF median = 115 L/min [60–160] and placebo median = 105 L/min [60–190]) were similar in the two groups, with no significant differences ($p > 0.05$).

When the median change in total symptom scores from the baseline values were compared in the two groups for each treatment day (Fig. 3), a significant reduction was observed for the MF group when compared with placebo for days 2, 3, 4, 12, and 13 ($p \leq 0.05$). However, the median individual total symptom scores for days 1–14 showed no differences between MF and placebo (Table 2).

Both the MF and the placebo groups showed improvements in RQLQ between visits (Fig. 4). However, when the change in scores from visit 2 to visit 1 were compared between the two groups, there were no significant differences except in the sleep domain, where subjects taking MF had lower mean $\pm$ SEM scores (better quality of life; -1.53 ± 0.24) than those on placebo (-0.85 ± 0.24 ; $p = 0.02$). No significant differences with the median NPIF values were observed between patients treated with MF (median = 16.7 [9.4–150]) and placebo (median = 22.6 [–27.8–112.5]; Fig. 5).

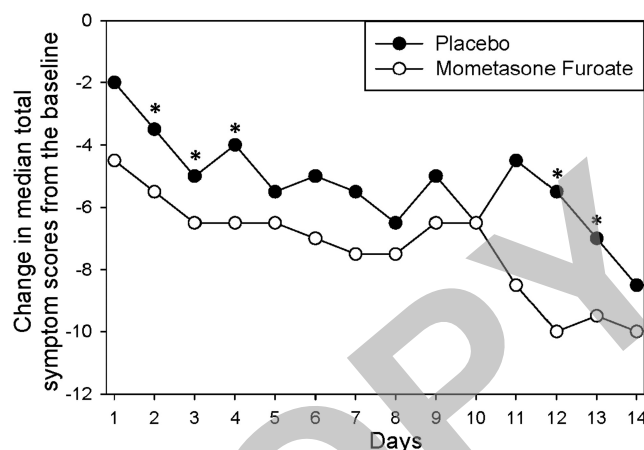


Figure 3. Change in median total symptom scores from the baseline during the study ($n = 20$ in mometasone furoate [MF] and placebo, respectively). There was a significant reduction in symptom scores compared with baseline (asterisk indicates $p \leq 0.05$) between the two groups for days 2, 3, 4, 12, and 13.

Table 2 Median (range) individual nasal symptoms during days 1–14 ($p > 0.05$)

Symptom	Mometasone Furoate ($n = 20$)	Placebo ($n = 20$)
Total symptoms	5.5 (0–20)	6.75 (0–22)
Sneezing	0 (0–6)	1.5 (0–6)
Rhinorrhea	0 (0–6)	1.75 (0–6)
Nasal congestion	3 (0–6)	3 (0–6)
Itchy eyes	1.3 (0–6)	2.0 (0–6)

The global assessment data were available for 19 and 18 patients in the MF and placebo groups, respectively. Both groups reported improvement with no significant difference in between them ($p = 0.37$).

Subgroup Analysis

Because of the less-than-expected positive results in the initial analysis done with patients who qualified based solely on a self-reported baseline congestion score of ≥ 2 and the fact that most SAR trials require an entry baseline total symptom score of ≥ 6 (including congestion, sneezing, runny nose, stuffy nose, itchy eyes, and nose), we reanalyzed our results using this criterion. This yielded 13 subjects in each group. The median percent change in NPIF on administration of oxymetazoline in this subgroup was 38% (10–114%) in the MF group and 12% (–22–142%) in the placebo group, respectively; these values were significantly different from each other ($p = 0.03$) despite randomization. Thus, subjects in the MF group seemed to respond better to the decongestant.

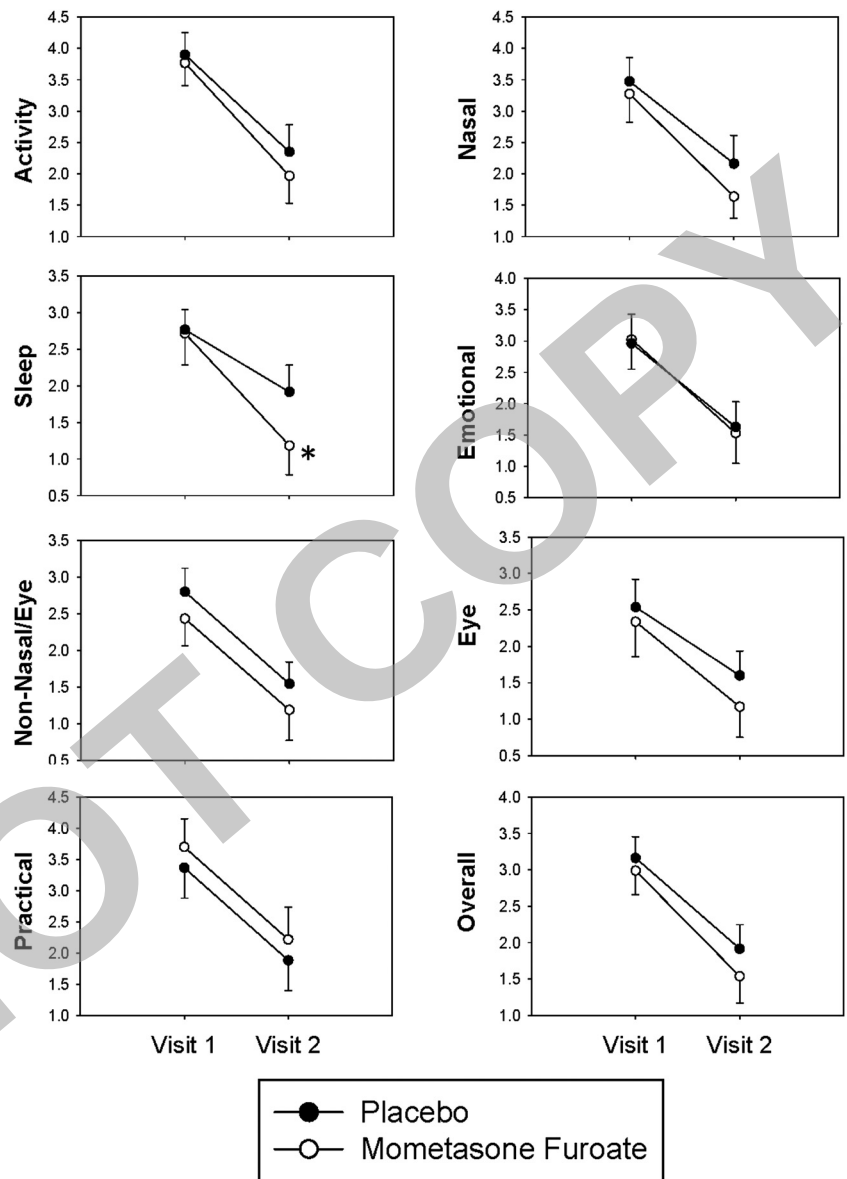


Figure 4. Mean $\pm$ SEM values for the individual domains of the Rhinoconjunctivitis Quality of Life (RQLQ) questionnaire ($n = 20$ in mometasone furoate [MF] and placebo, respectively). The asterisk indicates $p = 0.02$ for the difference in the sleep domain between the two groups at visit 2.

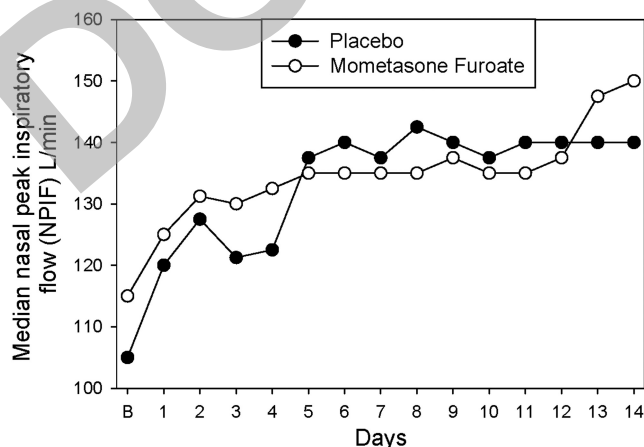


Figure 5. Median nasal peak inspiratory flow (NPIF). B indicates the baseline measurements ($n = 20$ in mometasone furoate [MF] and placebo, respectively).

It is important to note here that similar to the entire group, the RQLQ data analysis showed similar baseline overall and individual domain RQLQ scores for the MF and placebo subgroups with baseline total symptom score of ≥ 6 . Also, the median baseline total symptom score (MF, 8 [6–12]; placebo, 7 [6–10]) and NPIF values (MF, 120 L/min [60–160]; placebo, 105 L/min [60–190]) were similar in the two groups, with no significant differences between them ($p > 0.05$).

Interestingly, we observed a significant reduction in the total symptom score compared with the baseline value on all treatment days in the MF subgroup ($n = 13$) except on days 1 and 10, when compared with the placebo subgroup ($n = 13$; $p \leq 0.05$; Fig. 6).

Also, improvements in the RQLQ were observed in the sleep, nonnose/eye, practical, nasal, emotional, and activity domains as well as the overall score on

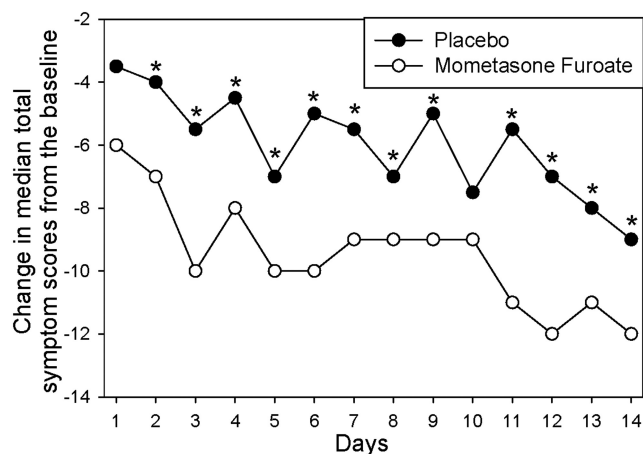


Figure 6. Change in median total symptom scores from the baseline during the study in subjects with baseline symptom scores of ≥ 6 ($n = 13$ in mometasone furoate [MF] and placebo, respectively). There was a significant reduction in the symptom scores compared with baseline (asterisk indicates $p \leq 0.05$) between the two groups for all the days except days 1 and 10.

comparison of the first visit to the second in both treatment groups (Fig. 7). However, there were no significant differences between the groups except in the sleep domain, which approached marginal significance when the difference in scores from visit 2 to visit 1 were compared in the two groups ($p = 0.08$).

There was no significant difference when the two groups were compared with respect to the total change in NPIF values from the baseline on days 1–14 (MF median = 16.7 [–9.4–150] and placebo median = 22.6 [–27.8–66.7]). There was also no significant difference in the global assessment between the two groups ($p = 0.35$).

Furthermore, we wanted to determine which variables actually contributed to the change in the total nasal symptom score. For this, we performed a multivariate analysis and found that the treatment groups (MF and placebo; $p = 0.049$) and the percent change in NPIF on administration of oxymetazoline ($p = 0.008$) interacted to affect the difference in the total nasal symptom score from the baseline in the subgroup with baseline symptom score of ≥ 6 (Table 3).

DISCUSSION

Nasal congestion in SAR is the symptom that is the most bothersome to patients and occurs primarily as a result of inflammatory mediator-induced vascular congestion.^{2,19,20} The degree of nasal congestion may be evaluated subjectively by measuring symptom scores and airflow can be objectively measured using NPIF. Topical INSs, including MF, have been shown to be highly effective and safe in the treatment of SAR, including the symptom of nasal congestion.^{3,11,15,21,22}

They have also been shown to improve the patient's quality of life.¹¹

INSs relieve nasal congestion predominantly by reducing the number and activation of inflammatory cells during the late phase and by reducing the number of mast cells in the nasal mucosa during the allergy season.¹¹ However, not all SAR patients respond equally well to treatment with INSs²; therefore, the need for the development of an objective test that predicts response to INS therapy becomes important. The decongestion test, which measures the reversibility of nasal airflow after the administration of a vasoconstrictor drug, may thus serve as a useful tool, not only clinically but also as an inclusion criterion for enrolling patients in clinical trials.^{13,14,23} Severe inflammation is generally characterized by a poor response to the test.¹⁴

In this study, we recruited SAR patients with moderate congestion (score, ≥ 2) to check the usefulness of the decongestant test in predicting the response to treatment with intranasal steroids. Also, because earlier reports show that subjects allergic to pollens show more severe inflammation than do subjects with allergy to perennial allergens,^{14,24,25} we chose seasonal allergic subjects who tested positive to tree and/or grass pollens using a skin-prick test. Our results show that MF was better able to relieve nasal symptoms associated with SAR when compared with placebo in the subjects with baseline symptom scores of ≥ 6 , and a positive decongestant test, despite the smaller number of subjects included. Thus, selecting patients for entry into an SAR clinical trial based on these parameters including the decongestant response and better-characterized baseline symptom scores should decrease the number of subjects who need to be studied.

This observation was confirmed in the multivariate analysis performed on this subgroup (Table 3). We found that the treatment groups (MF and placebo) and the percent change in NPIF on administration of oxymetazoline were key variables that affect the difference in the total nasal symptom score from the baseline in the subgroup with a baseline symptom score of ≥ 6 . The patients in the MF group reported 2.51 points lower nasal symptoms than those receiving placebo. In contrast, the same analysis, when performed in all the patients recruited for the study, failed to show any statistically significant differences, pointing toward a flaw in our recruitment strategy ($p > 0.05$; data not shown). Because we were primarily interested in the effectiveness of the decongestant test, we recruited patients with a positive skin test for the relevant antigens and a positive congestion score, ignoring the other symptoms of allergic rhinitis, *i.e.*, patients with total symptom scores of ≥ 6 . These subjects probably have a higher incidence of false positive skin tests and a higher incidence of other causes for nasal congestion. Additionally, the moderate pollen counts toward the

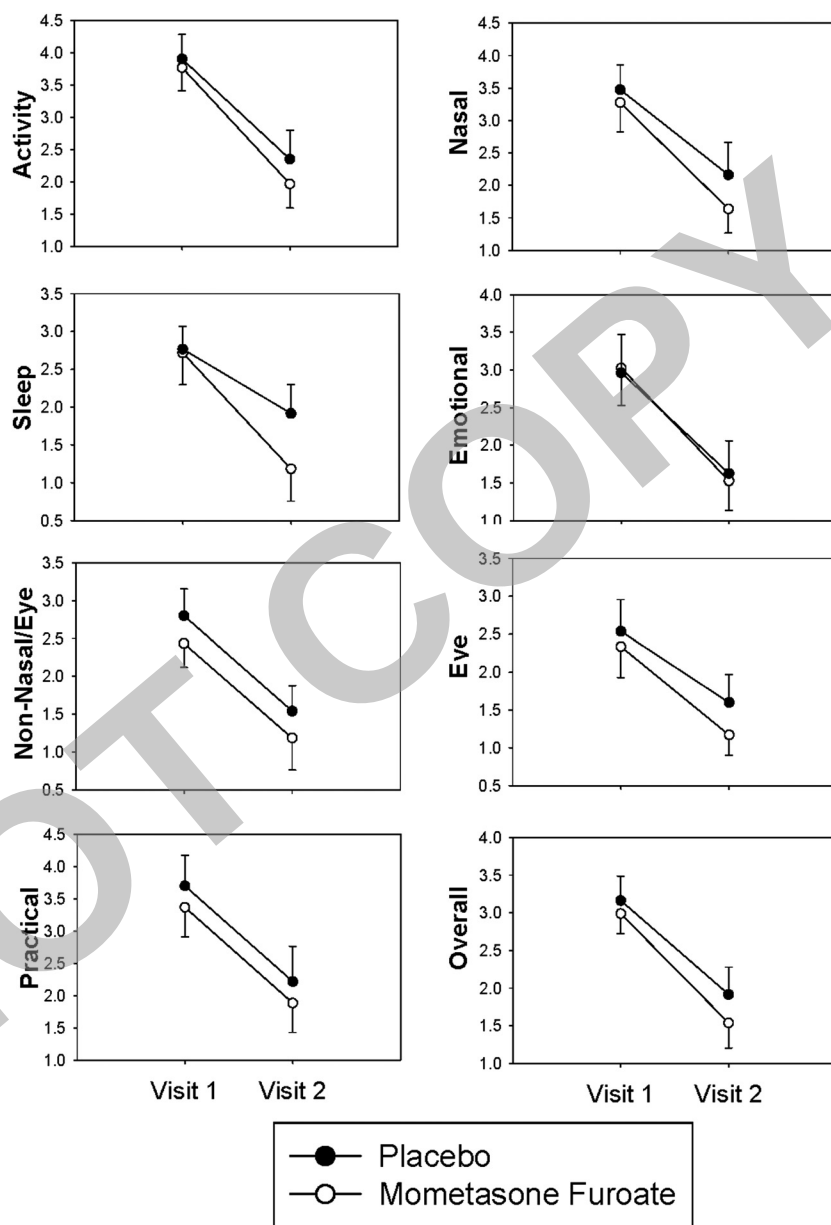


Figure 7. Mean $\pm$ SEM values for the individual domains of the Rhinoconjunctivitis Quality of Life (RQLQ) for the subgroup with baseline symptom scores of ≥ 6 ($N = 13$ in mometasone furoate [MF] and placebo, respectively). For the difference in the sleep domain between the groups at visit 2, $p = 0.08$ was observed.

end of our study (Fig. 2) could have affected the outcome of our results. Repeating this study with a larger number of patients having baseline symptom scores of ≥ 6 would strengthen our conclusion about the effectiveness of the decongestant test.

It is also important to note that although our patients were randomized for entry into the study, the patients who received MF decongested more on administration of oxymetazoline when compared with the patients in the placebo group, and this difference was significant in the subgroup with baseline symptom scores of ≥ 6 ($p = 0.03$). One subject from the placebo group showed a marked decrease in the NPIF postadministration of the decongestant. This reflects a paradoxical response to the decongestant, which has been observed earlier in the literature.^{26,27} In the multivariate analysis

done in the subgroup of individuals with baseline total symptom score of ≥ 6 , the percent change in NPIF during the decongestant test was a significant contributor to the determination of the total nasal symptom score and predicted nonlinearly the difference in the total nasal symptom score from the baseline (Table 3). We also found that the difference in the total nasal symptom score from the baseline was the lowest when the percent change in NPIF during the decongestant test was $\leq 40\%$. Marked differences in these scores were observed in the treatment groups when these values exceeded 40%, thereby adding to the value of this test for the assessment of patients for clinical trials for SAR.

In the RQLQ scores, it was observed that both the MF and the placebo groups showed improvements.

Table 3 Multivariate analysis in individuals with baseline symptom scores of ≥ 6 to predict variables that affect the difference in total nasal symptom score from the baseline symptom score

Parameter	Estimate	p Value
Drug mometasone furoate	-2.51	0.049
Placebo	0	—
Percent change in NPIF on administration of oxymetazoline	-0.12	0.008

NPIF = nasal peak inspiratory flow.

However, statistically significant improvements were observed only in the sleep domain of the RQLQ in the main group and marginally significant improvements were observed in the subgroups with total symptom scores of ≥ 6 . This is not surprising because SAR and, in particular, the symptom of congestion has been known to affect sleep at night, cause daytime sleepiness in these patients, and reduce patients' daytime performance.²⁸⁻³⁰ In this regard, INs have been the most effective, in contrast to both first- and second-generation antihistamines, in improving the performances in these patients by reducing nasal congestion, nocturnal sleep disturbances, and daytime sleepiness.^{30,31}

The results for the NPIF measured during the season were not significantly different in the NPIF values in any of the MF versus the placebo groups in all of the analyses performed. The smaller number of subjects with total symptom scores of ≥ 6 and the variability of the NPIF values probably explain the lack of a significant result for this parameter.

In summary, our study identified factors that influence the response of patients involved in an SAR clinical trial. The medical history and skin test positivity are essential enrollment criteria; however, there is a need for an additional measure to identify pure SAR subjects. This observation is supported by the ever-increasing need to enroll more and more patients in SAR trials. We first identified that despite a predominant symptom, true SAR patients need to report multiple symptoms to be considered responsive to treatment. Second, using the decongestant test as an additional objective measure helps in the selection of volunteers who are more responsive to treatment. In essence, the decongestant test focuses the differential diagnosis on SAR, eliminating other contributors to the subject's symptoms.^{13,14,23} Potentially, the decongestant test could predict which patients in clinical practice would benefit most from treatment.

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