

Subjective and objective assessments in patients with seasonal allergic rhinitis: Effects of therapy with mometasone furoate nasal spray

Eli O. Meltzer, MD,^{a,b} Alfredo A. Jalowayski, PhD,^b H. Alice Orgel, MD, PhD,^{a,b} and Alan G. Harris, MD^c San Diego, Calif., and Kenilworth, N.J.

Background: Efficacy of topical nasal steroid therapy for allergic rhinitis is usually evaluated by patient and clinician assessments of subjective symptom changes in diaries and at clinical interviews.

Objective: We sought to complement the subjective measures with objective measures of nasal cytology, biochemistry, and function.

Methods: In this double-blind, randomized study patients with seasonal allergic rhinitis (SAR) 12 years of age or older received 200 µg mometasone furoate nasal spray ($n = 80$) or placebo spray ($n = 41$) once daily for 2 weeks. Subjective assessments by clinician and patient comprised symptom/sign scores and overall therapeutic response evaluations. Objective measures included nasal cytology, nasal biochemistry, nasal airway resistance (NAR), mucociliary clearance, and olfactory functions.

Results: Mometasone furoate produced a significantly greater decrease than placebo in subjective measures of SAR for total symptom score (-46% vs -30% , $p < 0.05$), total nasal score (-47% vs -30% , $p < 0.024$), individual nasal symptom scores, and overall therapeutic response. The objective measures of eosinophil, basophil, and neutrophil counts and mucociliary clearance were significantly better in mometasone furoate than in placebo-treated patients. Similarly, within-treatment statistically significant improvements were produced by mometasone furoate but not by placebo sprays for levels of eosinophilic cationic protein, tryptase and albumin, NAR, and odor identification. Significant positive correlations were found between NAR and nasal stuffiness and between eosinophils, basophils, and neutrophils and both eosinophilic cationic protein and albumin.

Conclusion: Subjective measures of SAR were significantly improved in the mometasone furoate group by comparison with placebo-treated patients. Objective assessments supported the subjective findings because within-treatment measures were frequently significantly improved after mometasone furoate treatment but not after placebo treatment. (*J Allergy Clin Immunol* 1998;102:39-49.)

Key words: Seasonal allergic rhinitis, intranasal glucocorticosteroid, mometasone furoate nasal spray, nasal cytology, mucociliary clearance, rhinomanometry, olfaction, inflammatory mediators, nasal lavage

Abbreviations used

CV:	Coefficient of variation
ECP:	Eosinophilic cationic protein
HPF:	High-power field
NAR:	Nasal airway resistance
NL:	Nasal lavage
SAR:	Seasonal allergic rhinitis
STT:	Saccharin transport time

Seasonal allergic rhinitis (SAR) is a major cause of morbidity in the United States.^{1,2} The disease is caused by an IgE-mediated reaction and is characterized by a constellation of nasal symptoms, namely congestion, rhinorrhea, itching and sneezing often accompanied by nonnasal symptoms, such as tearing, redness, and itching of the eyes, and itching of the ears, palate, or both. The effects of therapy on SAR have been evaluated mainly by subjective assessment of improvement in symptoms and signs, and numerous studies have demonstrated the efficacy of intranasal topical glucocorticoids in decreasing the subjective measures of allergic rhinitis.³⁻⁵ Objective measures have also shown that topical glucocorticoids are effective in normalizing the nasal cytogram^{6,7} and in decreasing mediator release and cytokine immunoreactivity.⁷⁻⁹

The complex mechanisms involved in the pathogenesis of allergic rhinitis,^{10,11} and the effects of therapeutic intervention, have been investigated primarily by laboratory challenges with either a nonspecific agent or with an allergen to which the person is sensitized.^{12,13} Challenge studies have been crucial in identifying and measuring many aspects of the allergic reaction. However, a laboratory challenge with a single agent does not replicate the continuing and varying exposure to multiple allergens that occurs when a person with allergies has symptoms under natural conditions. There is therefore a need for studies in the clinical setting that make use of multiple objective measures, as well as the customary subjective measures, in patients with SAR before and after treatment.

Mometasone furoate is a new glucocorticoid with high topical activity and low systemic absorption when administered intranasally.¹⁴ It has been shown to be effective for control and prophylaxis of SAR symptoms and for control of symptoms of perennial allergic rhini-

From ^aAllergy & Asthma Medical Group and Research Center, San Diego;

^bUniversity of California School of Medicine, San Diego; and ^cIntegrated Therapeutics Group, Schering-Plough Corporation, Kenilworth.

Received for publication Dec. 10, 1997; revised Apr. 6, 1998; accepted for publication Apr. 7, 1998.

Reprint requests: Eli O. Meltzer, MD, 9610 Granite Ridge Drive, Suite B, San Diego, CA 92123.

Copyright © 1998 by Mosby, Inc.

0091-6749/98 \$5.00 + 0 1/1/90842

tis.¹⁵⁻¹⁹ A dose-ranging study of mometasone nasal spray for SAR indicated that the optimum dose for symptom control was 200 µg once daily.²⁰ In some patients symptom relief within 12 hours of the first dose has been reported.¹⁵ We report here the results of treatment of patients with symptoms of SAR with topical mometasone furoate nasal spray evaluated by both subjective measures of symptom relief and objective measures of nasal cytology, nasal biochemistry, nasal airway resistance (NAR), mucociliary clearance, and olfactory functions.

METHODS

Patients aged 12 to 65 years or older with a history of SAR for 2 or more years were eligible for this single-center, double-blind, randomized, parallel-group, placebo-controlled study. The study was conducted April through August during the tree, grass, and weed pollen seasons in Southern California. Pollen counts showed average levels during this period, which were sufficiently high to cause symptoms in patients with SAR. Patients were required to be symptomatic at the time of the trial and to have had a positive skin test response to the relevant allergens within the previous 14 months. Patients had no significant medical condition or nasal abnormality that would interfere with the study. Medications known to affect allergy symptoms were discontinued as appropriate. This study was approved by an institutional review board.

At a screening visit, an informed consent, a medical and allergy history, a physical examination, and a mucosal sample for nasal cytology were obtained. A diary was given for patients to record nasal symptoms and signs (congestion, rhinorrhea, itching, and sneezing) and nonnasal symptoms and signs (itching or burning eyes, tearing, eye redness, and itching of ears/palate) twice a day. Symptoms/signs were scored on a scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe, with 0.5, 1.5 and 2.5 for symptoms of intermediate severity) for 7 days before entry to the study (baseline period). A total nasal symptom/sign score of 5 or greater (of the possible total of 12) on 8 or more of the 14 diary time points before the baseline visit and at least a 1+ nasal cytology score for eosinophils, basophils, or both were required as inclusion criteria.

At the baseline visit, the physician scored nasal and nonnasal symptoms and signs for the previous 24 hours; these scores constituted clinician-assessed baseline scores. Patient diary scores for morning and evening symptoms averaged over the previous 7 days constituted the patient-assessed baselines. Eligible patients were randomized to treatment with two sprays in each nostril each morning of either 50 µg/spray mometasone furoate aqueous nasal spray or placebo for 14 days. The study was designed so that twice as many patients were randomized to active treatment as to the placebo group. Before treatment was started, baseline objective tests of nasal function (other than nasal cytology samples obtained at the screening visit) were performed as described below.

Patients returned to the research center on day 8 and day 15 of the double-blind treatment period after the morning dose for physician evaluation and diary review. Clinician scores were based on symptoms in the 24 hours before each visit and signs, which were evaluated at each visit. Patient scores were based on prespray morning and evening diary scores for the previous 7 days (week 1 and week 2). The overall therapeutic response was rated as complete or major control, moderate or mild control, or no response by physician and patient. Adverse events were recorded. On day 15, objective tests, including nasal cytology, were repeated.

Nasal cytology

A nasal mucosal sample was obtained from the patient's most patent nostril at the screening visit and on day 15 by using a disposable plastic curette (Rhino-probe; Arlington Scientific Inc., Arlington, Tex.), and the sample was processed as previously described.²¹

Nasal lavage and biochemistry

The nasal lavage (NL) technique previously described was used to collect nasal secretions.¹² In contrast to nasal challenge studies, only the first lavage specimen was collected at the baseline and day 15 visits for the biochemical analyses. All assays were performed in duplicate; baseline and day 15 samples from each patient were assayed concurrently. Eosinophilic cationic protein (ECP) levels in the NL fluid was determined by radioimmunoassay (Pharmacia Diagnostics AB, Uppsala, Sweden). If duplicate samples had a coefficient of variation (CV) of 15% or greater, the assay was repeated. Tryptase concentration in the NL was measured with the tryptase RIAC assay (Pharmacia Diagnostics AB, Uppsala, Sweden). If duplicate samples had a CV of 10% or greater, the assay was repeated. Histamine content of NL fluid samples was measured by radioimmunoassay (Immunotech, Marseille, France). The intraassay CV ranged from 4.1% to 8.9% depending on the concentration of histamine in the sample. Albumin concentration in NL fluid was measured by an ELISA procedure, (DAKO Corporation, Carpinteria, Calif.) similar to that previously described.¹³

Nasal airway resistance

Nasal patency was measured with a new computerized rhinomanometric system (RHINO; MultiSPIRO, San Clemente, Calif.). The method used an anterior, active, and uninasal technique through a mask and a pressure patch (RhinoPatch; Rhino Diagnostics, Inc., San Diego, Calif.) to measure intranasal pressure and flow simultaneously. The pressure and flow signals were digitized and analyzed to calculate airflow in liters per second for right and left nostrils, as well as total flow. Resistance was also calculated at -1.5 cm of water pressure for the individual nostrils and combined to give total NAR in centimeters of H₂O per liter per second. A RhinoPatch, with its tubing, was first attached to one of the nostrils, and the loose end of the tubing was inserted through a small hole on the face mask. The oxygen-type face mask, with its inflatable border, was placed over the nose and mouth and pressed to secure an airtight connection. A flow-sensing device (pneumotachometer) was attached to the mask, and a pressure transducer was connected to the pressure line. The patient was instructed to breathe normally three or four times while the pressure and flow measures were recorded and analyzed by the computer. This maneuver was repeated five consecutive times; the resistance values of the highest and lowest values were discarded, and the log-transformed mean of the remaining three values was used for analysis. Total nasal airway resistance (T_{NAR}) was calculated with the following formula:

$$T_{NAR} = (R_{NAR} \times L_{NAR}) / (R_{NAR} + L_{NAR})$$

Mucociliary clearance

The saccharin transport time (STT) is used to measure objectively the interaction between ciliary beating and removal of mucus secretion from the nose. The saccharin test previously described²² was modified to minimize any possible irritation to the mucosal tissue. We devised a 1-inch long, 20-gauge needle bent at 60° 3/8 of an inch from the tip and placed a 2-inch, 20-gauge flexible Teflon catheter over the barrel. By using a vacuum pump (Vacuum Pickup; Grobet File Co. of America, Inc., Carlstadt, N.J.) under visual

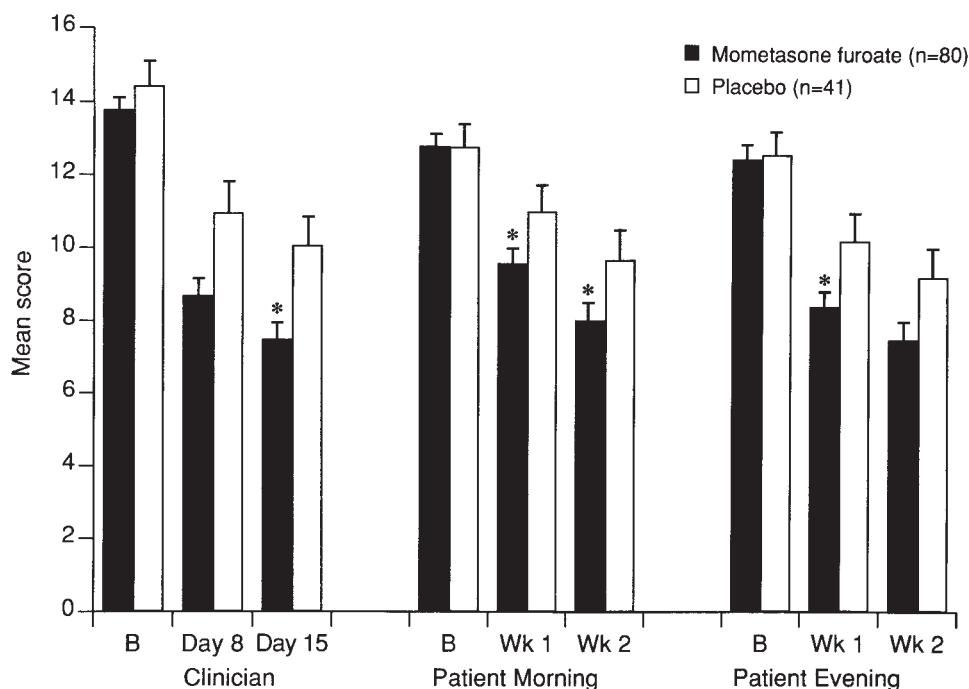


FIG. 1. Total SAR symptom/sign score (mean $\pm$ SEM). Sum of separate nasal and nonnasal scores, with clinician and patient assessments for morning and evening. * $p < 0.05$, mometasone furoate versus placebo.

inspection, a small particle of saccharin (1.0 to 1.5 mm) was applied to the superior surface of the inferior turbinate approximately 0.5 cm past its most anterior portion by release of the vacuum holding the particle in place at the catheter tip. The subject was instructed to swallow once every 30 seconds while sitting quietly and to refrain from sniffing, sneezing, or snorting. The time that it took for the subject to sense the bitter-sweet taste was recorded.

Olfaction

Olfactory evaluation followed the procedure of the Connecticut Chemosensory Clinical Research Center.²³ It entailed determination of both the odor threshold to 1-butanol and of the identification of everyday items by smell. Each of these two nasal functions was evaluated for one nostril at a time, with scores combined across nostrils.

Statistical methods

Statistical analyses were performed with SAS version 6.11 (SAS Institute, Cary, N.C.). The study design called for at least 99 evaluable patients, 66 in the active treatment group and 33 in the placebo group. The sample size was based on the total nasal symptom/sign score criterion for eligibility. Assuming a standard deviation of 2.5 and a significance level of 0.05 in a two-sided test, the planned sample size provided at least 80% power to detect a difference in score of 0.5 between treatment groups in the change from baseline of total nasal symptom/sign score. For continuous demographic and disease variables, comparability of treatment groups was assessed with a two-sample *t* test, and Fisher's exact test was used to assess comparability of treatment groups for categorical variables. For normally distributed data, a two-sample or paired *t* test was used. For distribution differences between treatment groups, the Mantel-Haenszel test was used. For nonnormally distributed data, the Wilcoxon rank sum test was used for

between-treatment analyses, and the one-sample Wilcoxon test was used for within-treatment analyses.

RESULTS

A total of 128 patients aged 12 to 65 years were enrolled at one study center and were randomized to receive 200 μ g mometasone furoate nasal spray ($n = 85$) or placebo ($n = 43$) once a day. Seven patients were not eligible for efficacy analyses, and 121 patients satisfactorily completed the 2-week treatment period (mometasone furoate, $n = 80$; placebo, $n = 41$). There were no statistically significant differences in demographic and disease characteristics (total symptom, total nasal symptom, and separate symptom scores) between the treatment groups at baseline.

The mean total SAR symptom/sign scores assessed by the clinician at baseline, day 8, and day 15 and by patients for baseline week, week 1, and week 2 for mometasone furoate and placebo groups are shown in Fig. 1. Reductions in mean total scores were noted for both treatment groups at both postrandomization visits by the clinician and by patients. The mometasone furoate group had a significantly greater decrease in scores by comparison with the placebo group on day 15 as assessed by the clinician (-47% vs -30% , $p = 0.049$), but the decrease was not significant on day 8. By comparison, patients' mean total morning score assessments were significantly reduced for both week 1 and week 2 in the mometasone furoate group by comparison with the placebo group (week 1: -26% vs -11% , $p = 0.02$; week

TABLE I. Clinician and patient assessment of total nasal symptoms and signs

	Mometasone furoate (n = 80)			Placebo (n = 41)			
Visit	Mean	(SEM)	Change	Mean	(SEM)	Change	P value*
Clinician assessment							
Baseline	8.18	(0.19)		8.60	(0.32)		
Day 8	5.32	(0.29)	−2.86 (−35%)	6.53	(0.42)	−2.07 (−24%)	0.299
Day 15	4.36	(0.29)	−3.82 (−47%)	5.99	(0.40)	−2.61 (−30%)	0.024
Patient assessment							
Morning							
Baseline	7.70	(0.18)		7.94	(0.30)		
Week 1	5.66	(0.23)	−2.04 (−26%)	6.67	(0.34)	−1.27 (−16%)	0.047
Week 2	4.78	(0.28)	−2.92 (−38%)	5.74	(0.40)	−2.20 (−28%)	0.134
Evening							
Baseline	7.32	(0.20)		7.68	(0.34)		
Week 1	4.93	(0.26)	−2.39 (−33%)	6.10	(0.34)	−1.58 (−21%)	0.073
Week 2	4.38	(0.28)	−2.94 (−40%)	5.49	(0.40)	−2.19 (−29%)	0.144

*Two-sample *t* test comparing treatment means of mometasone furoate versus placebo.

2: -39% vs -24%, $p = 0.029$). Evening scores showed improvements similar to the morning scores in both treatment groups (week 1: -32% vs -19%, $p = 0.038$; week 2: -40% vs -27%, $p = 0.076$). In both clinician and patient assessments of total nasal symptom scores, the mometasone furoate group had lower scores than the placebo-treated group after baseline. Actual scores, percent improvements, and p values are shown in Table I.

Clinician assessments of mean scores for the individual nasal symptoms, stuffiness/obstruction, rhinorrhea, nasal itch, and sneezing at baseline, day 8, and day 15, are presented in Fig. 2. There was a decrease in mean scores from baseline in both treatment groups; mean scores were consistently lower, and the percent improvement consistently greater, in the mometasone furoate group than in the placebo group on both day 8 and day 15. Although no statistically significant difference between treatment groups was seen for nasal itch (day 15: -50% vs -38%, $p = 0.211$), significant differences were demonstrated for stuffiness (day 15: -39% vs -22%, $p = 0.022$), rhinorrhea (day 8: -32% vs -22%, $p = 0.037$; day 15: -41% vs -26%, $p = 0.008$), and sneezing (day 8: -48% vs -26%, $p = 0.018$; day 15: -56% vs -39%, $p = 0.003$). Patient-assessed mean scores for the separate nasal symptoms for baseline, week 1, and week 2 were similar and were somewhat lower than clinician assessments (Fig. 2). For total and individual nonnasal mean symptom scores, there were no statistically significant differences between the mometasone furoate and placebo groups at any visit in either the clinicians' or patients' assessments.

Clinicians and patients also rated the overall therapeutic response to treatment by the amount of relief obtained. The percent of patients in each category of relief (patients' assessments) with each treatment on day 8 and day 15 are presented in Fig. 3. At both these treatment time points, the mometasone furoate group perceived their overall symptom relief to be of a sig-

nificantly greater magnitude ($p < 0.01$). On day 15, 44% of patients receiving mometasone furoate rated relief as total or marked by comparison with 8% of placebo patients ($p < 0.001$). Clinicians' assessments on day 15 were 41.3% versus 15.4% ($p = 0.015$).

Nasal cytology

All patients had eosinophils, basophils, or both present in the nasal mucosal sample obtained at the screening visit as required for enrollment in the study. More than 80% of patients also had neutrophils present. For each cell type, the mean (SEM) and median number of cells per 10 high-power fields (HPFs) at screening and the mean and median and change in mean and median number of cells on day 15 are presented in Table II. The p value for differences between treatment groups and the intragroup p values are also given. To summarize the nasal cytology data changes in individual patients, the percentage of patients with a decrease and the percentage with an increase in number of each cell type between screening and day 15 samples are depicted in Fig. 4.

Nasal mediators and albumin

NL recoveries were 7.4 ± 1 ml of the 10 ml of saline instilled. The results of quantitation of nasal mediators and albumin are summarized in Fig. 5. The quantity of albumin is an indicator of vascular permeability. There were no significant differences between the mometasone furoate and placebo groups in ECP, tryptase, histamine, or albumin at baseline or on day 15 (-67% vs -19%, -17% vs -3%, 88% vs -44%, and -52% vs -38%, respectively). However, within the mometasone furoate group the changes were significant for ECP ($p < 0.001$), tryptase ($p = 0.025$), and albumin ($p < 0.001$). No significant changes were seen in nasal mediator levels or albumin in the placebo group from baseline to day 15.

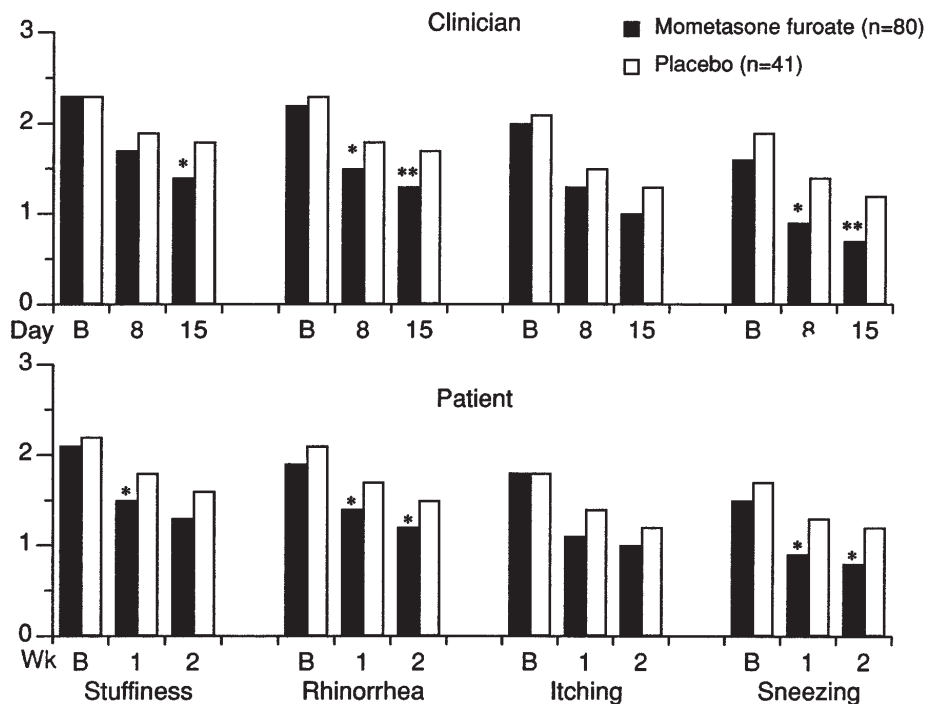


FIG. 2. Nasal symptom/sign score (mean) for each symptom on each visit, with clinician and patient evening assessments. * $p < 0.05$; ** $p < 0.01$, mometasone furoate versus placebo. B, Baseline.

Nasal airway resistance

Nasal airway resistance (NAR) measures were found to have a nonnormal distribution; there were no statistically significant differences between treatment groups at baseline or on day 15. Within treatment groups, median NAR was improved for mometasone furoate-treated patients between baseline and day 15 for total NAR (-16% , $p < 0.001$) and for the worst nostril (-36% , $p < 0.001$), with no significant change in the placebo group.

Mucociliary clearance

Mean STT increased in the mometasone furoate group compared with no change in the placebo group (11.89 to 13.29 minutes vs. 9.85 to 9.21 minutes, $p = 0.002$). This longer transit time is more normal and is consistent with the greater decrease in the rhinorrhea symptom scores in the mometasone group.

Olfactory functions

Of the seven odors tested, 80% to 85% of patients correctly identified 12 to 14 odors at baseline (sum of both nostrils). On day 15, 91.3% of patients receiving mometasone correctly identified 12 to 14 odors ($p = 0.002$) by comparison with an increase to 87.2% of placebo patients (not significant). Measurement of the threshold concentration at which the odor of 1-butanol was detected was normal in 90% of patients at baseline and showed no significant change on day 15 in either treatment group.

Safety evaluations

Both treatment groups had a similar safety profile, including local and systemic adverse events.

Correlations between parameters

Correlation coefficients were calculated between the subjective measures of total nasal symptom score and the separate nasal symptom scores for nasal stuffiness, rhinorrhea, nasal itching and sneezing, and objective measures on day 15. A positive correlation was found only between total NAR and nasal stuffiness in the mometasone furoate-treated patients ($p = 0.034$). A comparison of nasal cytology cell counts and nasal mediator levels on day 15 showed a positive correlation between ECP and eosinophils and basophils ($p < 0.001$) and neutrophils ($p = 0.05$) ($\rho = 0.45, 0.30$, and 0.19 , respectively) and between albumin and eosinophils and basophils ($p = 0.001$) and neutrophils ($p < 0.05$) ($\rho = 0.40, 0.30$, and 0.22 , respectively.)

DISCUSSION

In previous studies topical nasal steroids have been shown to decrease the nasal, and sometimes the ocular, symptoms and signs of SAR. Symptoms and signs have improved with all the topical steroids evaluated to date whether the medication was delivered by means of an aerosol propellant, as an aqueous nasal spray, or in a powder formulation. To improve compliance, it has been possible to institute once daily dosing without loss of

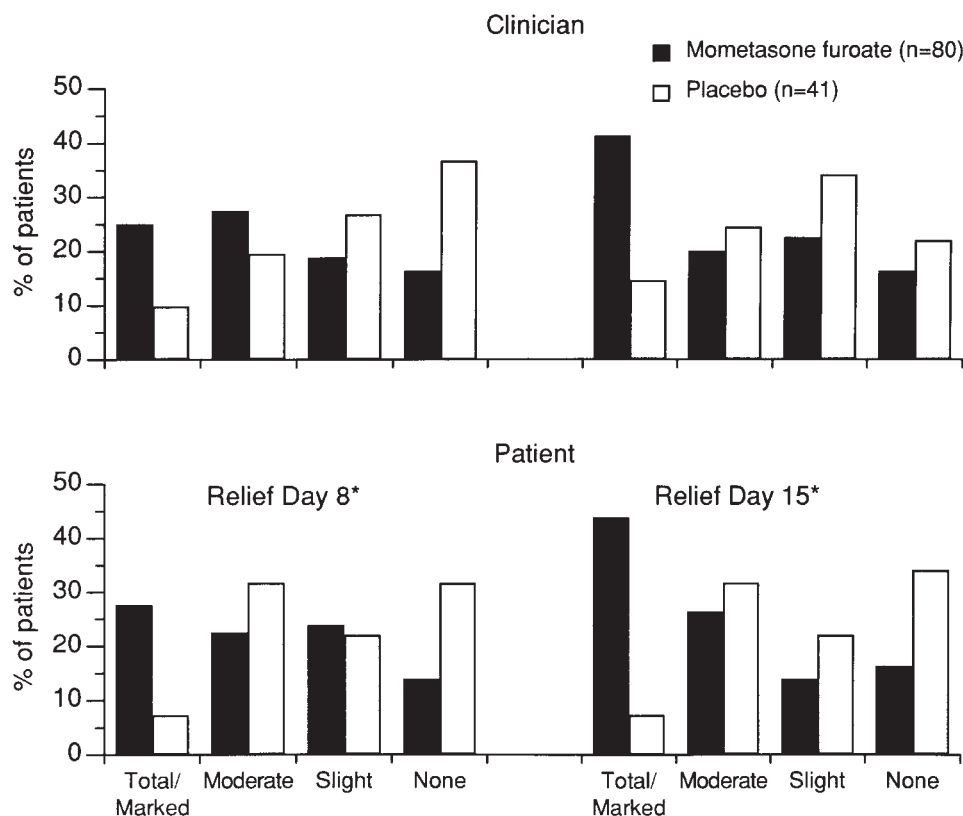


FIG. 3. Clinician and patient assessment of therapeutic response. Percent of patients in mometasone furoate and placebo treatment groups with each rating of improvement on day 8 and day 15. * $p < 0.05$ mometasone furoate versus placebo.

efficacy.^{3-7,24-31} In this double-blind, placebo-controlled study a new topical glucocorticosteroid, mometasone furoate aqueous nasal spray (200 μ g once daily) was also shown to significantly decrease the symptoms and signs of SAR by comparison with placebo. Because the customary assessments of therapeutic efficacy are very subjective, we have scrutinized different aspects of the subjective efficacy analyses and have also evaluated a number of objective measures in an attempt to determine which are the most valuable.

In assessing efficacy of drugs in the clinical setting, great importance is attached to the statistical significance of differences between the response to active medications versus response to placebo. The response to placebo is present in all studies and is affected somewhat by the study design. This is a well-recognized issue,³²⁻³⁴ but it has not been fully characterized in relation to allergic rhinitis. In this study all subjective assessments of nasal and nonnasal symptoms and signs showed greater improvement in mometasone furoate—than in placebo-treated patients. For example, the mean total nasal symptoms score of mometasone-treated patients decreased by approximately 47% from baseline to day 15 by comparison with a decrease of 30% for the same period in placebo patients. Estimates of medication and placebo response calculated from reports of previous studies of

intranasal steroids show comparable responses.^{19,28-30} The differences in improvement between active medication and placebo may appear to be small, but in this study many more patients reported total or marked relief on day 15 with mometasone furoate than with placebo, especially in the patient assessments (44% vs 8%, $p < 0.001$).

Several studies have shown that the greater number of inflammatory cells present in nasal secretions and mucosa during natural exposure to allergen³⁵⁻³⁸ are usually decreased by treatment with topical nasal glucocorticoids.^{3-7,24,31} In this study, after intranasal mometasone furoate, the median number of eosinophils in mucosal samples decreased to zero cells per 10 HPFs, significantly fewer than found in placebo patients. Absence of eosinophils is such a consistent finding after topical steroid treatment that compliance may be questioned in patients purportedly using one of these agents if more than rare eosinophils are found. In this study there was also a smaller but statistically significant decrease in eosinophils in the placebo patients. This latter finding is unusual.

Basophilic cells are present in smaller numbers than eosinophils in the nasal mucosal cytograms of allergic patients and are detected in a smaller proportion of patients.⁶ A decrease in basophilic cells is also usually seen in patients receiving topical steroids, but the differ-

TABLE II. Summary of nasal cytology data (cells per 10 HPFs)

Visit	Cell type	Mometasone furoate (n = 78)			Placebo (n = 39)			p Value*
		Mean	SEM	Median	Mean	SEM	Median	
Screening	Eosinophils	7.09	(1.87)	1.65	9.19	(2.35)	3.90	<0.001
Day 15	Actual	1.06	(0.31)	0	7.83	(3.47)	1.20	
	Change	-6.17		-1.40	-0.47		-0.30	
	Intragroup p value†			<0.001			0.034	
Screening	Basophils	4.39	(0.59)	2.15	3.29	(0.60)	1.80	0.008
Day 15	Actual	4.99	(0.71)	3.05	8.90	(1.26)	6.60	
	Change	+0.64		0	+5.57		+3.20	
	Intragroup p value†			0.458 (NS)			<0.001	
Screening	Neutrophils	14.76	(2.90)	2.95	20.65	(4.93)	4.70	0.024
Day 15	Actual	6.70	(2.28)	0.35	13.77	(4.38)	1.20	
	Change	-7.15		-1.40	-5.33		-1.20	
	Intragroup p value†			<0.001			0.117	

NS, Not significant.

*Wilcoxon rank sum test comparing median counts of mometasone furoate versus Placebo.

†One-sample Wilcoxon test comparing median changes from screening.

ence between active and placebo groups was not statistically significant in some studies. In this study there was a small increase in basophilic cells in the patients receiving mometasone furoate (not significant), and a large increase was observed in placebo patients ($p < 0.001$). The difference between treatments was significant ($p = 0.008$), which is consistent with the antiinflammatory effect of topical corticosteroids in reducing the allergen-triggered influx of both basophils and mast cells into the airway.³⁹

Neutrophils have been reported in 60% to 80% of patients with SAR; approximately 50% to 70% of patients have neutrophils present at the end of 2 to 4 weeks of treatment with a topical steroid.⁶ The difference between active treatment and placebo and between the percentages of patients with increases or decreases in neutrophils has not generally been significant. In this study there was a highly significant decrease in neutrophils within the mometasone furoate group ($p < 0.001$), and this decrease was significant by comparison with placebo ($p < 0.024$).

The decrease in inflammatory cells after treatment with topical corticosteroids has been shown in several studies to be associated with a reduction in mediators, such as ECP, tryptase, and histamine.⁴⁰⁻⁴⁴ Albumin, a marker for increased plasma exudation during the inflammatory process, has also been shown to decrease as the rhinitis improves.⁴⁵ In this study the levels of ECP, tryptase, and albumin decreased significantly after 2 weeks of treatment with mometasone furoate, corroborating the findings of other studies of topical intranasal steroids for the treatment of SAR. Histamine levels increased in the mometasone furoate group, but the increase was not statistically significant. In contrast, no significant changes in these mediators or albumin levels took place in the placebo group.

A good correlation was found between ECP levels in lavage fluid and eosinophils in nasal scrapings. The levels of ECP, however, did not correlate with symptom scores in this study. Other investigators have also found a

lack of this correlation,^{46,47} indicating the complex interaction between mediators and the host. Individual differences in how the patients experience varying degrees of severity confound the subjective measures.

Strong correlations have been reported between the levels of histamine and the presence of basophilic cells. However, this has been observed when the assays of histamine levels have been made in the tissue sample in which the cell count was performed.^{44,48} Comparing levels of mediators in secretions with the presence of cells in the superficial mucosa (as was the methodology in this study) or in the submucosa, as with biopsy samples, may not yield a strong relationship. The three compartments (the submucosa, epithelial mucosal layer, and secretions), although interconnected and related, may have different events happening concurrently. In this study the mean number of basophilic cells in the nasal mucosal scrapings did not correlate significantly with the levels of histamine in the NL fluid. Although there was an increase in the median number of basophilic cells in both treatment groups, which was statistically significant in the placebo group, there was no statistically significant change in histamine levels in either group.

Histamine levels in NL fluid have been found to decrease after treatment with topical steroids.⁴⁹ However, most studies have used a challenge model, in which several lavages are performed to establish a low, stable baseline of mediators, including histamine. The antigen challenge then produces only an attenuated histamine release.¹² Several other studies have reported wide variations of histamine levels, primarily in the quantity in the first NL fluid.⁵⁰ Our study measured the level of histamine in the first and only wash at baseline and on day 15 and represented the amount of histamine accumulated in the secretions over a period of time. For this, and perhaps other reasons, we did not detect a significant decrease in histamine levels after 2 weeks of treatment with mometasone furoate, although a challenge model may have been able to show a significant decrease in the rate in which histamine is released.⁵¹ It appears from the results of

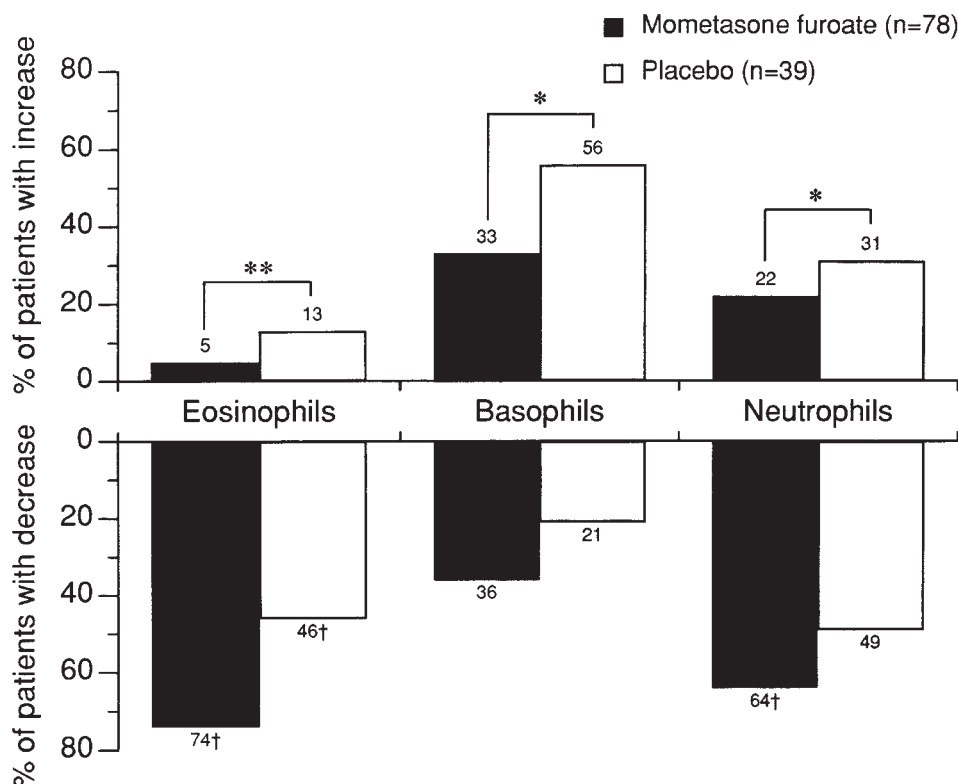


FIG. 4. Percent of patients with increase or decrease in eosinophils, basophils, and neutrophils among those with evaluable paired pre- and posttreatment specimens. * $p \leq 0.05$; ** $p \leq 0.001$, mometasone furoate versus placebo. † $p \leq 0.05$ baseline to day 15 within treatment.

challenge and in vitro studies that topical steroids inhibit, but do not completely stop, the release of histamine by metachromatic cells,⁵² wherever they may be located, into the nasal secretions. The presence of histamine in secretions may explain why some symptoms, such as itching and sneezing, sometimes persist. A study comparing the effectiveness of an intranasal steroid and an antihistamine found the latter more effective in controlling these symptoms, although the steroid was superior in relieving the symptoms and signs of obstruction.⁵³ Despite these findings, long-term treatment with topical steroids usually has produced significant decreases in histamine levels, although the effects reported after a shorter time (e.g., 2 weeks of treatment) has varied.^{44,49} The measurement of histamine levels in nonchallenge studies appears to be therefore less desirable as an objective measure.

Albumin levels in NL fluid from naturally exposed patients with SAR are reported to be a useful marker for changes in mucosal inflammation. In this study albumin levels were found to be strongly correlated with the numbers of eosinophils, basophils, and neutrophils. Topical steroids reduce the number of inflammatory cells, mediators, and cytokines and restore the normal permeability of the mucosal membrane, preventing further albumin-containing exudate from reaching the nasal secretions. The measurement of albumin in NL fluid is therefore a

good indicator of changes in the inflammatory process.

NAR decreased significantly in patients treated with mometasone furoate for 2 weeks, with no significant changes observed in the placebo group. Additionally, a positive correlation between NAR and nasal stuffiness score in patients ($p < 0.05$) was found. This corroborates a previous report that the complaint of nasal obstruction, but not other symptoms, correlated well with nasal resistance measurements in patients with SAR during the pollen season.³¹

The rate of mucus transport can be altered by changes in ciliary beating frequency or by changes in the volume and/or rheological properties of the mucus and serous fluid surrounding the cilia, or by both. A modified saccharin test has been used as an objective measure of mucociliary clearance.^{22,54} Although the mean transit times vary considerably among investigators, it appears that the transport rates in patients with symptoms of allergic rhinitis uncomplicated by infection or sinusitis are faster than rates in healthy control subjects. The mean STT for healthy control subjects previously reported was 13.5 ± 1.32 (SEM) minutes.⁵⁵ In this study at baseline, mometasone-treated patients with active symptoms of allergic rhinitis had a mean STT of 11.89 ± 0.81 (SEM), whereas the placebo group had a mean STT of 9.85 ± 1.05 (not statistically significant). An improvement in symptoms, particularly rhinorrhea, would be expected to

increase STT toward the normal time. On day 15, the mometasone-treated group had a mean STT of 13.29 ± 0.73 , and the placebo group had a mean STT of 9.21 ± 1.09 ($p = 0.002$). Thus mucociliary clearance, as measured by STT, improved significantly in the group of patients treated with mometasone furoate for 2 weeks, whereas the placebo-treated group remained essentially unchanged.

Previous investigators have concluded that allergic rhinitis is a major etiologic factor contributing to smell disorders on the basis of finding a significantly higher olfactory threshold in allergic patients compared with control subjects.^{56,57} In this study a determination of the odor threshold for butanol and an odor identification test were used to measure changes in olfaction in this allergic rhinitis population. The great majority of patients were found to have normal olfaction at baseline according to these tests. Therefore it was difficult to detect any further improvement in smell function by the odor threshold test, and no significant changes were detected in either treatment group. However, the odor identification test, the more sensitive of the two tests, showed a small but statistically significant improvement in the mometasone furoate group comparing baseline values to those at day 15. The placebo group experienced no significant changes.

The difference in the olfactory test results in this study from those of previous studies could be accounted for by differences in the population studied. Many patients in other studies had a diagnosis of sinusitis on the basis of physical findings, imaging results, or both.⁵⁷ Many also had nasal polyps. In one study a significant improvement in olfactory function was found in seven of 17 patients treated with intranasal budesonide, and changes in nasal patency were positively correlated with olfactory function.⁵³ Olfactory function in allergic patients seems to be impaired only when the degree of obstruction is severe enough to prevent airflow from reaching the olfactory cells. Otherwise, a moist vascular and swollen mucosa appears to have beneficial effects on olfaction.⁵⁸ Another study demonstrated that a pronounced allergic reaction is necessary to impair olfactory threshold. In that challenge model, changes in olfactory threshold correlated with increased secretion rather than with decreased objective nasal patency measurements.⁵⁹ More recently, decreased olfactory function was reported in patients with SAR in season; a better correlation was found with levels of ECP in nasal secretion than with nasal volume flow changes as measured by acoustic rhinometry.⁶⁰ This study demonstrated that the majority of patients with SAR and without other nasal problems had a normal sense of smell. It also demonstrated that those patients with hyposmia could derive benefit from the use of an intranasal steroid for 2 weeks. Patients with severe hyposmia or anosmia may require longer duration of treatment to detect significant improvement in the sense of smell. The test is simple

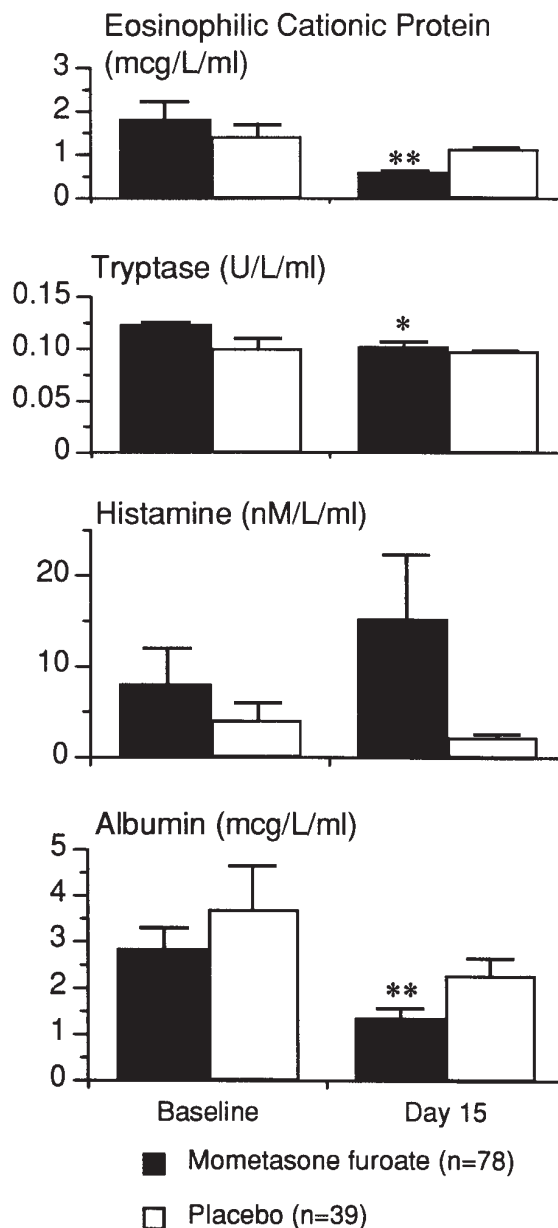


FIG. 5. Concentration (mean $\pm$ SEM) of ECP, tryptase, histamine, and albumin in NL fluid at baseline and day 15. * $p \leq 0.05$, ** $p \leq 0.001$ within treatment, baseline to day 15.

to perform and noninvasive, with the only drawback that it is time consuming to administer.

The goals of this study were to evaluate various subjective and objective assessments of nasal disease and to see if they changed with topical mometasone furoate treatment. The study demonstrated that each of these parameters contributed valuable additional information because no single parameter or specific limited panel of measures fully characterized an individual or group of patients with allergic rhinitis or the effect of therapy on them. Overall, this study clearly showed that mometasone furoate nasal spray (200 μ g/day) is an effective treatment for SAR.

We thank Susan Dion, RMA, CCRC, Corrine Bivins, MA, Jennifer Rosa, LVN, Ana Partida and Kristen Konar for technical assistance. We also thank Rongdean Chen, PhD, of Integrated Therapeutics Group, Schering-Plough Corporation, for statistical analyses.

REFERENCES

- Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99:S808-14.
- Meltzer EO, Nathan RA, Selner JC, Storms W. Quality of life and rhinitic symptoms: results of a nationwide survey with the SF-36 and RQLQ questionnaires. *J Allergy Clin Immunol* 1997;99:S815-9.
- Naclerio RM, Mygind N. Intranasal steroids. In: Mygind N, Naclerio RM, editors. *Allergic and non-allergic rhinitis: clinical aspects*. Copenhagen: Munksgaard; 1993. p. 114-22.
- Mygind D, Dahl R. The rationale for use of topical corticosteroids in allergic rhinitis. *Clin Exp Allergy* 1996;26(suppl 3):2-10.
- Fokkens WJ, Godthelp T, Holm AF, Blom H, Klein-Jan A. Allergic rhinitis and inflammation: the effect of nasal corticosteroid therapy. *Allergy* 1997;52(suppl 36):29-32.
- Meltzer EO, Orgel HA, Rogenes PR, Field EA. Nasal cytology in patients with allergic rhinitis: effects of intranasal fluticasone propionate. *J Allergy Clin Immunol* 1994;94:708-15.
- Alvarado-Valdes CA, Blomgren J, Weiler D, Gleich GJ, Reed CE, Field EA, et al. The effect of fluticasone propionate aqueous nasal spray on eosinophils and cytokines in nasal secretions of patients with ragweed allergic rhinitis. *Clin Ther* 1997;19:273-81.
- Bradding P, Feather IH, Wilson S, Holgate ST, Howarth PH. Cytokine immunoreactivity in seasonal rhinitis: regulation by a topical corticosteroid. *Am J Respir Crit Care Med* 1995;151:1900-6.
- Levenson T, Greenberger PA. Immunologic effects of intranasal corticosteroids. *Allergy Asthma Proc* 1996;17:157-9.
- Baraniuk JN. Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 1997;99:S763-72.
- Naclerio RM. Pathophysiology of perennial allergic rhinitis. *Allergy* 1997;52(suppl 36):7-13.
- Naclerio RM, Meier HL, Kagey-Sobotka A, Adkinson NF Jr, Meyer DA, Norman PS, et al. Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis* 1983;128:597-602.
- Proud D, Bailey GS, Naclerio RM, Reynolds CJ, Cruz AA, Eggleson PA, et al. Tryptase and histamine as markers to evaluate mast cell activation during the responses to nasal challenge with allergen, cold, dry air and hyperosmolar solutions. *J Allergy Clin Immunol* 1992;89:1098-110.
- Brannan MD, Seilberling M, Cutler DL, Cuss FM, Afrime MB. Lack of systemic activity with intranasal mometasone furoate [abstract]. *J Allergy Clin Immunol* 1996;97:198.
- Davies RJ, Nelson HS. Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis. *Clin Ther* 1997;19:27-38.
- Graft D, Aaronson GD, Chervinsky P, Kaiser H, Melamed H, Pedinoff A, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. *J Allergy Clin Immunol* 1996;98:724-31.
- Herbert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (NasonexTM) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 1996;51:569-76.
- Drouin M, Yang WH, Bertrand B, Van Cauwenberge P, Clement P, Dalby K, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. *Ann Allergy Asthma Immunol* 1996;77:153-60.
- Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. *Ann Allergy Asthma Immunol* 1997;79:370-8.
- Bronsky EA, Aaronson DW, Berkowitz RB, Chervinsky P, Graft D, Kaiser H, et al. Dose ranging study of mometasone furoate (Nasonex) in seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;79:51-6.
- Meltzer EO, Jalowayski AA. Nasal cytology in clinical practice. *Am J Rhinol* 1988;2:47-54.
- Andersen I, Camner P, Jensen PL, Philipson K, Proctor DF. Nasal clearance in monozygotic twins. *Am Rev Respir Dis* 1974;110:301-5.
- Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. *Laryngoscope* 1988;98:83-8.
- Bronsky EA, Dockhorn RJ, Meltzer EO, Shapiro G, Boltansky H, LaForce C, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;97:915-21.
- Munch E, Gomez G, Harris C, Lack RP, Edwards VA, O'Connor P, et al. An open comparison of dosage frequencies of beclomethasone dipropionate in seasonal allergic rhinitis. *Clin Allergy* 1981;11:303-9.
- Prenner BM, Chervinsky P, Hampel FC Jr, Howland WC, Lawrence M, Meltzer EO, et al. Double-strength beclomethasone dipropionate (84 µg/spray) aqueous nasal spray in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;98:302-8.
- Pedersen B, Larsen BB, Dahl R, Hedbys L, Mygind N. Budesonide powder administration for the treatment of grass-pollen-induced allergic rhinitis. *Allergy* 1994;49:855-60.
- Siegel SC, Katz RM, Rachelefsky GS, Geller BD, Montag LL, Brandon ML, et al. Multicentric study of beclomethasone dipropionate nasal aerosol in adults with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1982;69:345-53.
- Nathan RA, Bronsky EA, Fireman P, Grossman J, LaForce CF, Lemanske RF Jr, et al. Once daily fluticasone propionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis. *Ann Allergy* 1991;67:332-8.
- Munk ZM, Pearlman D, Graft D, Green A, Hampel F, Pleskow W, et al. Intranasal fluticasone propionate is effective and well-tolerated in adolescents with seasonal allergic rhinitis. *Pediatr Asthma Allergy Immunol* 1994;8:39-46.
- Orgel HA, Meltzer EO, Kemp JP, Welch MJ. Clinical, rhinomanometric, and cytologic evaluation of seasonal allergic rhinitis treated with beclomethasone dipropionate as aqueous nasal spray or pressurized aerosol. *J Allergy Clin Immunol* 1986;77:858-64.
- Beecham HK. The powerful placebo. *JAMA* 1995;159:1602-6.
- Ernst E, Resch KL. Concept of true and perceived placebo effects. *Br Med J* 1995;311:551-3.
- Kleijnen J, de Craen AJ, van Everdingen J, Krol L. Placebo effect in double-blind clinical trials: a review of interactions with medications. *Lancet* 1994;344:1347-9.
- Hansel FK. Cytologic diagnosis in respiratory allergy and infection. *Ann Allergy* 1966;24:564-9.
- Murray AB, Andersen DO. The epidemiologic relationship of clinical nasal allergy to eosinophils and to goblet cells in the nasal smear. *J Allergy* 1969;43:1-8.
- Malmberg H. Symptoms of chronic and allergic rhinitis and occurrence of nasal secretion granulocytes in university students, school children and infants. *Allergy* 1979;34:389-94.
- Pipkorn U, Karlsson G, Enerback L. The cellular response of the human allergic mucosa to natural allergen exposure. *J Allergy Clin Immunol* 1988;82:1046-54.
- Bascom R, Waschs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol* 1988;81:580-9.
- Meltzer EO, Jalowayski AA, Field EA, Rogenes PR, Kral KM. Intranasal fluticasone propionate reduces histamine and tryptase in the mucosa of allergic rhinitis [abstract]. *J Allergy Clin Immunol* 1993;91:298.
- Garrelts IM, Veld TDG, Nahori M, Vargaftig BB, van Wijk RG, Zijlstra FJ. Interleukin-5 and eosinophil cationic protein in nasal lavages of rhinitis patients. *Eur J Pharmacol* 1995;275:295-300.
- Lozewsics S, Wang J, Duddle J, Thomas K, Chalmers S, Reilly G, et al. Topical glucocorticosteroids inhibit activation by allergen in the upper respiratory tract. *J Allergy Clin Immunol* 1992;89:951-7.
- Scadding GK, Darby YC, Austin CE. Effect of short-term treatment with fluticasone propionate nasal spray on the response to nasal allergen challenge. *Br J Clin Pharmacol* 1994;38:447-51.
- Juliussøn S, Holmberg K, Karlsson G, Enerback L, Pipkorn U. Mast cells and mediators in the nasal mucosa after allergen challenge. Effects of four weeks' treatment with topical glucocorticoid. *Clin Exp Allergy* 1993;23:591-9.

45. Svensson C, Gronneber R, Anderson M, Alkner U, Anderson O, Billing B, et al. Allergen challenge-induced entry of α 2-macroglobulin and tryptase into human nasal and bronchial airways. *J Allergy Clin Immunol* 1995;96:239-45.
46. Wang D, Clement P, Smitz J, de Waele M, Derde M-P. Monitoring nasal allergic inflammation by measuring the concentration of eosinophil cationic protein and eosinophils in nasal secretions. *Allergy* 1995;50:147-51.
47. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of systemic steroid pretreatment. *Am Rev Respir Dis* 1988;138:406-12.
48. Meltzer EO, Orgel HA, Jalowayski AA. Histamine levels and nasal cytology in children with chronic otitis media and rhinitis. *Ann Allergy Asthma Immunol* 1995;74:406-10.
49. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med* 1987;316:1506-10.
50. Lebet B, Bousquet J, Moret A, Chanal I, Godard P, Michel F. Correlation between symptoms and the threshold for release of mediators in nasal secretions during nasal challenge with grass-pollen grains. *J Allergy Clin Immunol* 1988;82:869-77.
51. Therattil J, Chavarria V, Cosachov J, Kumar N, Wang SK, Sansone G, et al. The effect of mometasone furoate on early and late phase inflammation in patients with seasonal allergic rhinitis (SAR) [abstract]. *Ann Allergy Asthma Immunol* 1997;78:129.
52. Schleimer RP, Schulman ES, MacGlashan DW, Peters SP, Adams GK III, Adkinson NF Jr. Effects of dexamethasone on mediator release from human lung fragments and purified human lung mast cells. *J Clin Invest* 1983;71:1830-5.
53. Hilberg O. Effect of terfenadine and budesonide on nasal symptoms, olfaction, and nasal patency following allergen challenge. *Allergy* 1995;50:683-8.
54. Rutland J, Cole PJ. Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. *Thorax* 1981;36:654-8.
55. Mackay I, Greenstone SP, Holmes P, Cole P. A nose clinic: initial results. *J Laryngol Otol* 1983;97:497-502.
56. Cowart BJ, Flynn-Rodden K, McGeady SJ, Lowry LD. Hyposmia in allergic rhinitis. *J Allergy Clin Immunol* 1993;91:747-51.
57. Apter AJ, Mott AE, Frank ME, Clive JM. Allergic rhinitis and olfactory loss. *Ann Allergy Asthma Immunol* 1995;75:311-6.
58. Schneider RA, Wolf S. Relation of olfactory acuity to nasal membrane function. *J Appl Physiol* 1960;12:914-20.
59. Bende M, Hinriksdottir I, Murphy C. Olfactory threshold after nasal allergen challenge. ISOT and AChemS XIX meeting [abstract]. 1997. p. 182.
60. Klimek L, Eggers G. Olfactory dysfunction in allergic rhinitis is related to nasal eosinophilic inflammation. *J Allergy Clin Immunol* 1997;100:158-64.

Bound volumes available to subscribers

Bound volumes of The Journal of Allergy and Clinical Immunology are available to subscribers (only) for the 1998 issues from the Publisher, at a cost of \$97.00 for domestic, \$125.19 for Canadian, and \$117.00 for international subscribers for Vol. 101 (January-June) and Vol. 102 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone 1 (800) 453-4351 or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.