

Olfactory cleft inflammation is present in seasonal allergic rhinitis and is reduced with intranasal steroids

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ABSTRACT

Background: Allergic rhinitis (AR) is commonly associated with olfactory loss, although the mechanism is not well studied. This study was designed to determine the effect of mometasone furoate (MF) on olfactory loss in seasonal AR (SAR) and study its effect on inflammation in the olfactory region.

Methods: We performed a randomized, double-blind, placebo-controlled, parallel clinical trial in 17 patients with SAR who had symptoms of impaired olfaction. Subjects received MF or placebo for 2 weeks during their allergy season. Before and after treatment, we measured nasal peak inspiratory flow (NPIF), chemosensory quality of life, and objective olfactory function (the University of Pennsylvania Smell Identification Test). Additionally, nasal cytology samples were obtained from each visit, and a unilateral endoscopic biopsy specimen of the olfactory epithelium was obtained at the end of the study and scored for inflammation.

Results: Treatment with MF was associated with improved nasal symptoms ($p < 0.015$), NPIF ($p < 0.04$), reduced nasal inflammation ($p < 0.05$), and chemosensory-specific quality of life ($p < 0.03$). Histological analysis of the olfactory region reveals fewer eosinophils in the MF group when compared with placebo ($p < 0.012$). We found no improvement in objective olfactory function ($p > 0.05$).

Conclusion: The use of MF in SAR is associated with reduced eosinophilic inflammation in the olfactory region and improved symptoms of AR. The presence of eosinophils in the olfactory area in SAR may indicate a direct, deleterious effect of inflammation on olfactory epithelium in this disease. In this study we show that inflammation in SAR can affect the olfactory cleft, implicating a direct role for allergic inflammation in smell loss. Treatment with intranasal steroids is associated with decreased inflammation in the olfactory region in humans. This treatment is also associated with improved olfactory quality of life. (Am J Rhinol Allergy 24, 286–290, 2010; doi: 10.2500/ajra.2010.24.3478)

Key words: Eosinophil, human, inflammation, intranasal steroid, quality of life, randomized clinical trial, seasonal allergic rhinitis

Allergic rhinitis (AR) is a significant health problem with associated comorbidities, including olfactory dysfunction (OD).¹ Conversely, one of the most common etiologies of OD is AR. Up to 54% of patients with AR complain of a loss or diminution of the sense of smell.² When objective testing is performed, however, a smaller but still significant fraction of patients with AR show clinically significant smell loss.^{2–4} Differences in olfactory measures have been observed between subjects with perennial AR and seasonal AR (SAR), suggesting that different allergens may perturb the normal olfactory physiology in different ways.⁵ A mechanism for these effects is unknown.

Loss of olfaction in AR has generally been attributed to obstruction of airflow to the olfactory cleft secondary to nasal mucosal swelling from inflammation. However, the normal cyclic variations in nasal resistance (the nasal cycle) are not associated with olfactory loss.^{6,7} Additionally, treatment that improves symptoms of obstruction and reduces nasal edema can fail to improve hyposmia. These studies were confounded by concurrent diseases, surgical interventions, and other factors; however, they do show a disconnect between subjective and objective measures of nasal congestion and symptoms of OD,

suggesting that nasal obstruction is not the only mechanism responsible. An alternative explanation for smell problems in AR could be that damage from allergic inflammation to the olfactory epithelium itself causes the loss of smell directly. Indeed, in a study of inflammatory factors in chronic rhinosinusitis, Kern showed inflammatory infiltrates in biopsy specimens of human olfactory epithelium.⁸ These cells have an important role in AR as well.

Studies have suggested that intranasal corticosteroids may be effective in improving olfactory loss in AR.⁹ Meltzer examined olfaction as a secondary end point in a study of intranasal mometasone furoate (MF) in subjects with SAR.⁴ This double-blind, controlled, randomized study showed improvement in odor identification after 2 weeks of MF when compared with placebo. The mechanism of these effects is unclear, but could be a reduction of edema resulting in restored airflow/odorant access to the olfactory cleft or a resolution of inflammation in the olfactory mucosa itself. Interestingly, glucocorticoid receptor mRNA is expressed in mammalian olfactory epithelium, suggesting a potential direct role for steroids in this tissue.¹⁰

Whether the allergic inflammation extends to the olfactory epithelium in patients with SAR and whether the response to therapy is accompanied by a reduction in inflammation in the olfactory cleft remain unexplored.¹¹ The aim of this study was to determine if inflammation occurs in the olfactory area and whether treatment with an intranasal steroid affects that inflammation as response to therapy at the cellular level in the olfactory area itself. We hypothesized that SAR would lead to inflammation in the olfactory cleft, which would be reduced by MF.

METHODS

Overview

We performed a 2-week, parallel, randomized, double-blind study in subjects with SAR (ragweed or grass) who were experiencing both AR symptoms and olfactory impairment at the time of entry into the

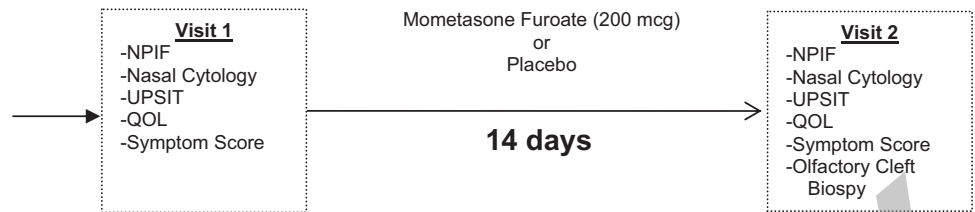
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Figure 1. Study design. Both treatments were daily nasal sprays given in the morning. NPIF, nasal peak inspiratory flow; QOL, quality of life; UPSIT, University of Pennsylvania Smell Identification Test.



study. Subjects were enrolled during relevant allergy seasons in Chicago, IL, from 2006 to 2008.

Subjects

We recruited healthy individuals 18–59 years old with a history of allergic sensitivity to ragweed or grass pollen in the last 2 years in Chicago and a positive skin-puncture test. We excluded women of childbearing potential not using contraceptive methods and those who were pregnant or breastfeeding. We also excluded smokers, subjects with upper respiratory tract infections, and those with chronic rhinosinusitis or nasal anatomic deformities such as severe septal deviations or nasal polyps. Subjects were also excluded if they had used systemic corticosteroids in the past 30 days, intranasal steroids in the past 2 weeks, oral antihistamines or decongestants in the past 7 days, or topical antihistamines or decongestants in the past 24 hours. Our Institutional Review Board approved the study, and written informed consent was obtained. The trial was registered online at clinicaltrials.gov, as required by the NIH.

Study Design

At entry, subjects underwent endoscopy to rule out anatomic obstruction of the olfactory cleft. They were asked to report on subjective outcome measures including nasal symptom scores and chemosensory quality of life. Objective measures were also obtained including nasal peak inspiratory flow (NPIF), the University of Pennsylvania Smell Identification Test (UPSIT), and nasal cytology. Participants were then randomized to either MF (standard dosing, 200 µg/day) or placebo. The outcome measures were repeated after 2 weeks. Additionally, during that visit, a unilateral endoscopic biopsy of the olfactory region was performed (Fig. 1).¹²

Drug Coding, Dosing, and Pollen Counts

All study medications were provided, coded by the manufacturer (Schering-Plough). The treatment was assigned by a randomized code and blocked in groups of two. As each subject entered the study, the nurse coordinator assigned that subject to the next sequential study number available. Study investigators and subjects were blinded to the treatment throughout the study. Pollen counts for the Chicago area were obtained from the National Allergy Bureau Pollen and Mold Report Certified Counting Station in Melrose Park, IL.

Nasal Symptom Score

Nasal symptom scores were recorded using standard methods.¹³ At each visit, subjects were asked to evaluate symptoms of runny nose, stuffy nose, itchy/watery eyes, postnasal drip, and sneezing symptoms on a scale from 0 to 3 (0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe). All scores were summed to give a total nasal symptom score. A decrease in scores between visits signifies an improvement in nasal symptoms.

Quality of Life Questionnaire

Goldberg designed and validated a chemosensory questionnaire in patients with cancer of the head and neck.¹⁴ Because the items concern smell and taste issues, they are applicable for this study. Patient responses were recorded on a scale of 1 (never) to 5 (always). The total

quality of life scores are reported and an increase in scores indicates improved quality of life.¹⁴

Nasal Peak Inspiratory Flow

Nasal airflow was objectively measured using the In-Check Peak Inspiratory Flow Meter (Ferrais Medical, Louisville, CO). Measurements were performed in triplicate; the average value was analyzed. An increase in NPIF signifies improved nasal airflow.

University of Pennsylvania Smell Identification Test

Olfaction was assessed using the UPSIT, a reliable, validated measure of the ability to identify common odors.¹⁵ This test has 40 forced-preference “scratch ‘n sniff” questions. Raw scores are reported and an increase in UPSIT score denotes an improvement, specifically in olfactory identification.¹⁵

Nasal Cytology

Nasal cytology specimens were obtained with a Rhinoprobe (Arlington Scientific, Springville, UT) from the inferior turbinate. Specimens were prepared and stained with Diff Quick Stain Set (Dade Behring, Deerfield, IL). Specimens were analyzed under light microscopy (oil immersion, 1000×). Two hundred leukocytes were counted and identified as neutrophils, eosinophils, or mononuclear cells. Percentage of eosinophils was then calculated.¹⁶ When 200 cells could not be counted, as many cells as possible were examined. If the total number of cells was <50, the slide was considered technically inadequate for interpretation and not used for analysis.¹²

Olfactory Region Biopsy

The nose was decongested and anesthetized with phenylephrine and lidocaine, topically first (by spray), followed by applying a cotton-tipped applicator medial to the middle turbinate. A rigid endoscope (Karl Storz, El Segundo, CA) was used to view the more accessible olfactory area and a small portion of mucosa was obtained using cup forceps (~2 × 2 mm). This area was anterior and high in the nose, along the septum, and medial to the middle turbinate near its anterior origin, as described by Leopold.¹⁷ All samples were immediately placed in 10% neutral buffered formalin. After fixation, the samples were processed through a series of alcohol, xylene, and paraffin solutions. The tissue was then embedded in paraffin, sectioned at 4 µm, and stained with hematoxylin and eosin. The number of eosinophils was then counted in three high-powered fields (HPE; oil immersion, 1000×).

Statistical Analysis

The data for NPIF and UPSIT were normally distributed and were analyzed using parametric statistics. Changes between pre- and post-treatment were analyzed using paired *t*-test and a comparison between groups was made using unpaired *t*-test. Nasal cytology, olfactory histology, and symptom scores were not normally distributed and were therefore analyzed by nonparametric tests. Paired analysis was performed using the Wilcoxon signed-ranks test and nonpaired analysis was performed using the Mann-Whitney *U* test. All analyses were performed with Systat 12 (Systat Software, San Jose, CA). A value of $p \leq 0.05$ was considered significant.

Table 1 Characteristics of the study population

Demographics	Mometasone Furoate (<i>n</i> = 8)	Placebo (<i>n</i> = 9)	<i>p</i> Value
Age, yr (mean, range)	40 (24–49)	38 (23–52)	0.752
Male (<i>n</i> ; %)	2 (25)	5 (56)	0.201
Allergen sensitivity			
Ragweed (<i>n</i> ; %)	5 (63)	6 (66)	
Grass (<i>n</i> ; %)	3 (37)	3 (33)	
Baseline values			
Chemosensory QOL (mean ± SEM)	24.3 ± 0.808	28.7 ± 1.92	0.078
UPSIT raw score (median, range)	32 (27–37)	31 (17–37)	0.459
NPIF (median, range)	103 (90–147)	118 (67–191)	0.224
TNSS (median, range)	16.5 (13–26)	12 (6–26)	0.440
Eosinophils (median, range)	1.55 (0.5–4)	0.5 (0–1.5)	0.028

NPIF = nasal peak inspiratory flow; QOL = quality of life; TNSS = total nasal symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

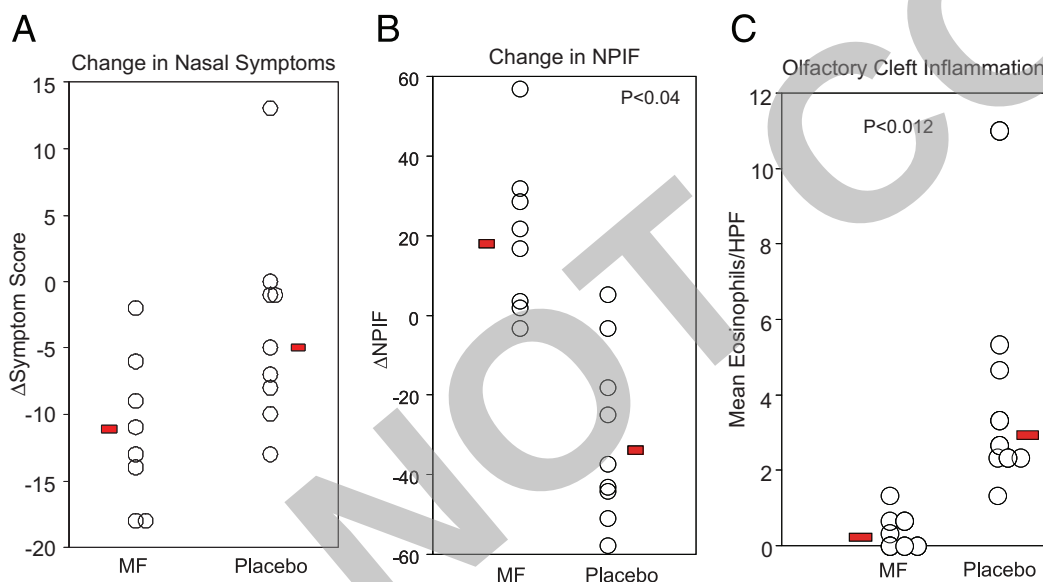


Figure 2. (A) Change in total nasal symptom score from initial visit to 2-week treatment with mometasone or placebo. Individual data points are depicted with the horizontal bars representing medians. Mometasone led to greater reduction of symptoms than placebo. (B) Nasal peak inspiratory flow (NPIF). Regarding changes from initial visit for all measurements of NPIF, a negative number represents worsening, and a positive number represents improvement. Horizontal bars depict medians. (C) Biopsy specimens were scored for inflammation by counting the number of eosinophils in three high-power fields, with the average reported. Subjects receiving MF showed significantly reduced numbers of eosinophils in the olfactory region compared with placebo.

RESULTS

Subjects

Seventeen subjects were enrolled and completed the trial and there were no dropouts. There were six female and two male subjects in the MF group (*n* = 8) and four female and five male subjects in the placebo group (*n* = 9). Analysis of demographic characteristics showed that the study groups were comparable (Table 1). There were more eosinophils at baseline in the nasal cytology compared with the placebo group, but remaining parameters showed no differences. Pollen counts were comparable across the ragweed seasons (*p* > 0.05) and the percentage of subjects experiencing low/moderate allergen counts (either allergen) also showed no differences across seasons or between groups (*p* > 0.05).

Symptom Scores

Within the MF group, there was a significant decrease in the total nasal symptom score over the 2-week study period (median, V1, 16.5, V2, 5; *p* < 0.012) but not in the placebo group (median, V1, 12, V2, 11; *p* ≥ 0.05; Fig. 2 A). The net change in symptom score across the trial was calculated and showed a significant difference between MF and placebo in favor of MF (MF, −12; placebo, −5; *p* < 0.023).

Nasal Peak Inspiratory Flow

Nasal airflow was significantly improved for the MF group (median, V1, 103 L/minute, V2, 133 L/minute; *p* < 0.036) but not in the group on placebo (median, V1, 118 L/minute, V2, 110 L/minute; *p* ≥ 0.05). When the net change across the treatment period was compared between treatments, there was a significant improvement in airflow with MF when compared with placebo (median MF change, 19.2 L/minute, versus median placebo change, −37.5 L/minute; *p* < 0.002) as shown in Fig. 2 B.

Quality of Life Questionnaire

After 2 weeks of MF, subjects showed a significant improvement in their chemosensory quality of life (mean, V1, 24, V2, 30.5; *p* < 0.027), whereas there was no change in the placebo group (mean, V1, 28.7, V2, 32.4; *p* ≥ 0.05; Fig. 3). Across the trial, the net difference between the groups was similar (mean MF change, 6.29, versus mean placebo change, 3.78; *p* < 0.21).

Nasal Cytology

The MF group had more eosinophils at baseline compared with placebo (median MF V1, 1.55%, placebo 0.5%; *p* < 0.028). Despite this, subjects treated with MF showed a reduction of eosinophils in nasal

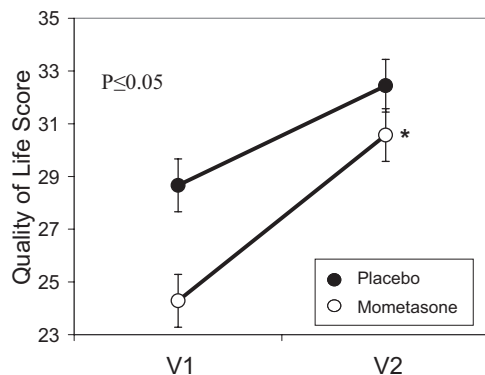


Figure 3. Change in chemosensory quality of life (QOL). The overall quality of life score calculated from the Coping Style Questionnaire (CSQ) is shown. Mean $\pm$ SEM for the two groups at enrollment (V1) and after 2 weeks of treatment (V2). Increases on the y-axis indicate better quality of life.

cytology samples between visits (median, V1, 1.55%, V2, 0%; $p < 0.0496$). Subjects treated with placebo showed no reduction (median, V1, 0.5%, V2, 0.7%; $p \geq 0.05$). The net improvement in inflammation was significantly higher with MF (median MF change of -1.35% versus median placebo change of -0.1% ; $p < 0.010$).

Olfactory Area Biopsy

Subjects receiving MF showed significantly lower numbers of eosinophils in the olfactory specimens (median, 0.167/HPF; range, 0–1.33) compared with placebo (median, 2.67/HPF; range, 1.33–11; $p \leq 0.02$) as shown in Figure 2 C.

Olfactory Function Testing

At baseline, the majority of subjects (12/17) were categorized as mild to moderate OD by norms (2 were categorized as severe or anosmic and 3 were normal). After treatment, the raw UPSIT score of two subjects improved, and the remainder stayed the same. Overall, there was no significant difference across the trial in the MF group. Three subjects on placebo improved in olfactory function, five remained the same, and one subject decreased. Hence, there were no significant changes in this group either (median MF change of 0.6 versus median placebo change of 1; $p \geq 0.05$). There was no difference in the net change between the groups ($p \geq 0.05$). When scored by percentile according to age/sex norms, there was no significant improvement for either treatment or for the net difference between groups (data not shown, $p \geq 0.05$). There was also no association between pollen count and response (data not shown).

DISCUSSION

One of the most frustrating but common symptoms of SAR is olfactory loss. Indeed, the placebo group developed classic symptoms of SAR in response to seasonal pollen exposure and showed decreased olfaction by testing. The present data suggest that the use of intranasal steroids improved allergic inflammation within the olfactory area as evidenced by decreased eosinophilia in this location. In parallel, treatment with MF provided relief in SAR symptoms, consistent with prior work,^{1,18,19} as well as improved nasal inflammation as a positive control.²⁰ Notably, 85% of MF-treated patients indicated an improvement in their olfactory quality of life, despite a lack of improvement in olfactory testing.

Our novel finding of more eosinophilic inflammation in the olfactory area in placebo compared with MF suggests that allergic inflammation may affect the olfactory area and is responsive to therapy. Our data support the concept that the decline of olfaction in SAR may be related to a direct inflammatory effect on olfactory neurons them-

selves (a sensorineural loss), although our data do not exclude a contribution of reduced airflow. Further demonstration of direct interaction between inflammatory cells and their mediators and olfactory neurons remains to be shown.

The mechanism for the reduction in eosinophils in the olfactory area could be from direct delivery of the medication or *via* reduction in neural reflexes that promote inflammation, potentially including this region.^{21–23} Delivery of intranasal steroids in the head down forward position has been found to improve olfaction in smell clinic patients, perhaps related to deposition of the drug more superiorly in the nose.²⁴ Our study used traditional delivery and was not designed to distinguish these possibilities, and it could not answer the related one of whether allergens themselves are able to access the mucosa of the olfactory cleft directly. It does prove that inflammation occurs in the olfactory area, a novel finding.

Our goal was to determine whether inflammation affects the area where olfaction occurs rather than to directly prove interaction of inflammatory cells/mediators with olfactory neurons. Leopold showed that the high anterior septum and medial middle turbinate contains olfactory neurons and we used these accessible landmarks for our biopsies. Further study of the interaction of inflammatory cells and olfactory neuron function is warranted but was not feasible in this clinical investigation.

We were unable to match the reduction in olfactory inflammation with a clinical improvement in objective olfactory function. A longer duration of treatment with MF may be needed to show significant objective changes. The effects of mediators on olfactory neurons may be durable and may require time or differences in regulation to reverse. Additionally, restoration of normal olfactory physiology may lag behind the reduction in inflammation. Other measures may be more sensitive to subtle changes and more useful,²⁵ although we used the standard clinical olfactory test. For example, neurophysiological testing using an olfactometer to determine chemosensory event-related potentials in response to specific stimuli may be a more sensitive indicator of changes in olfaction.²⁶ Klimek *et al.* have explained that olfactory discrimination testing does not normally indicate differences because it seems to be dependent on problems of the central nervous olfactory system rather than by a problem with the nose and olfactory epithelium.^{27,28} Finally, a small sample may have precluded the ability to see an effect. Our data may be useful in power calculations for future studies.

In conclusion, we showed that subjects with SAR experiencing OD show a significantly reduced number of eosinophils in the olfactory cleft with the use of MF. Our data also hint at an improvement in chemosensory quality of life with MF. Additional study of the effects of allergic inflammation on olfaction in humans may provide insights into olfactory physiology and a mechanism for these effects.

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