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A patient preference study that evaluated fluticasone furoate and mometasone furoate nasal sprays for allergic rhinitis

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ABSTRACT

Background: Corticosteroid nasal sprays are the mainstay of treatment for allergic rhinitis. These sprays have sensory attributes such as scent and/or odor, taste and aftertaste, and run down the throat and/or the nose, which, when unpleasant, can affect patient preference for, and compliance with, treatment.

Objective: This study examined patient preference for fluticasone furoate nasal spray (FFNS) or mometasone furoate nasal spray (MFNS) based on their sensory attributes after administration in patients with allergic rhinitis.

Methods: This was a multicenter, randomized, double-blind, cross-over study. Patient preferences were determined by using three questionnaires (Overall Preference, Immediate Attributes, and Delayed Attributes).

Results: Overall, 56% of patients stated a preference for FFNS versus 32% for MFNS (p < 0.001); the remaining 12% stated no preference. More patients stated a preference for FFNS versus MFNS for the attributes of “less drip down the throat” (p < 0.001), “less run out of the nose” (p < 0.05), “more soothing” (p < 0.05), and “less irritating” (p < 0.001). More patients responded in favor of FFNS versus MFNS for the immediate attributes, “run down the throat” (p < 0.001), and “run out of the nose” (p < 0.001), and, in the delayed attributes, “run down the throat” (p < 0.001), “run out of the nose” (p < 0.01), “presence of aftertaste” (p < 0.01), and “no nasal irritation” (p < 0.001).

Conclusion: Patients with allergic rhinitis preferred FFNS versus MFNS overall and based on a number of individual attributes, including “less drip down the throat,” “less run out of the nose,” and “less irritating.” Greater preference may improve patient adherence and thereby improve symptom management of the patient’s allergic rhinitis.

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A llergic rhinitis is a global health problem that affects ~500 million people worldwide.1 The symptoms of allergic rhinitis include nasal congestion; cough; snoring; postnasal drip; reduced sense of smell; headache; and red, itching eyes, with symptoms being evident for >4 months of the year in approximately half of the patients. These symptoms can also affect patients’ quality of life by reducing sleep quality, increasing irritability and depression, and impacting social activities.2 Corticosteroid nasal sprays are the therapeutic mainstay for patients with allergic rhinitis.3,4 However, these nasal sprays have sensory attributes, such as scent and/or odor, taste, and aftertaste. Patients’ perceptions of these attributes may influence their preference for, and satisfaction with, treatment.5,6 Furthermore, perceptions of nasal spray attributes have been shown to influence treatment compliance.6 With unpleasant sensory attributes leading to a reduction in adherence, which, in turn, can lead to poor symptom management.7,8

Results from clinical trials of patients with allergic rhinitis show that clinical efficacy and tolerability are similar for different corticosteroid nasal sprays.9–11 However, previous studies of corticosteroid nasal sprays to determine the importance of different attributes in patient preference showed that patients can differentiate between the treatments based on attribute profiles.6,11–17 These findings highlight the potential role of treatment attributes in adherence and, consequently, in clinical outcomes. Fluticasone furoate (FF) and mometasone furoate (MF) are corticosteroids that are both delivered by using nasal sprays, but with different actuation systems. The FF nasal spray (FFNS) (Avamys GlaxoSmithKline, Ux-
bridge, UK [U.S. trade name, Veramyst\(^{18}\)] is side actuated, whereas the MF nasal spray (MFNS) (Nasonex Merck Sharp & Dohme Limited, Hoddesdon, UK\(^{19}\)) is top actuated. Furthermore, the FFNS delivery system has a shorter nozzle and lower volume per actuation than other nasal spray devices, which may result in less postnasal runoff.\(^{20}\) The FFNS and MFNS were optimized to reduce strong scent and/or odor and irritation because these are characteristics reported as being unfavorable to patients.\(^{13,20}\)

To date, there have been single-dose patient preference studies between FFNS and the fluticasone propionate nasal spray (FPNS) (Flixonase GlaxoSmithKline [U.S. trade name, Flonase]\(^{21}\))\(^{14}\) and between MFNS and FPNS.\(^{13}\) The only previous direct comparison of patient preferences for FF or MF involved administering each nasal spray for 2 weeks.\(^{22}\) In the current single-dose study (NCT02397915; GlaxoSmithKline (GSK) study no. 201474) of patients with allergic rhinitis, we examined patient preferences for the FF and MF aqueous corticosteroid nasal sprays, based on the sensory attributes of each. In addition, we evaluated whether the differences between the nasal sprays (e.g., actuation system, volume per actuation, fineness of spray, nozzle length) were reflected in the patient-assessed attribute ratings.

**METHODS**

**Patients**

The patients were men and women, 18–65 years of age, with either seasonal or perennial allergic rhinitis confirmed by a positive allergen skin test result within 12 months of study treatment. Women who were pregnant or breast-feeding were excluded, as were patients with an infection or structural abnormality of the respiratory system. In addition, patients who used an intranasal corticosteroid within 4 weeks of study participation, other intranasal medications within 1 week of study participation, medications that could disturb taste or smell, significant inhibitors of the cytochrome P450 subfamily CYP3A4 within 4 weeks of study participation, or who had a history of sensitivity to the study procedures or drugs were excluded. Use of perfume or strong-smelling cosmetic products, oral rinse or similar products, tobacco, or inhaled or oral nicotine-containing products (within 12 hours before the start of dosing) were also causes for exclusion from enrollment.

**Study Drugs**

FFNS suspension delivered 27.5 \(\mu\)g FF per actuation with excipients: glucose anhydrous, dispersible cellulose, polysorbate 80, benzalkonium chloride, disodium edetate, and purified water. MFNS suspension delivered 50 \(\mu\)g per actuation with excipients: benzalkonium chloride, dispersible cellulose (microcrystalline cellulose and carmellose sodium), glycerol, sodium citrate, citric acid monohydrate, polysorbate 80, and purified water.

**Study Design and Objectives**

This was a multicenter, randomized, double-blind, single-dose, crossover patient preference study (Fig. 1). The study was carried out at 12 sites across four countries: Argentina (4 sites), Australia (3), Russia (2), and South Korea (3). Patients with allergic rhinitis were randomized 1:1 (by using a computer-generated code) to one of two treatment sequences: either a single dose each of MFNS followed by FFNS, or a single dose each of FFNS followed by MFNS. The FFNS (110 \(\mu\)g) was administered as two sprays of 27.5 \(\mu\)g FF per spray in each nostril, and the MFNS (200 \(\mu\)g) was administered as two sprays of 50 \(\mu\)g MF per spray in each nostril. The primary objective was to determine overall patient preference for FFNS or MFNS by using the Overall Preference Questionnaire (OPQ). Secondary objectives were to determine the patient preference for individual attributes of FFNS or MFNS by using the OPQ and to compare the patient ratings for individual attributes of FFNS and MFNS by using the Immediate Attributes Questionnaire (IAQ) and the Delayed Attributes Questionnaire (DAQ).

| SCREENING | PERIOD 1 | FOLLOW-UP |
|-----------|----------|-----------|
| Washout   | Immediate Attributes Questionnaire | Preference Questionnaire |
| Immediate Attributes Questionnaire | 30 min | 24h and 96h |
| Perfusion FF or MF | Immediate Attributes Questionnaire | Immediate Attributes Questionnaire |
| Delayed Attributes Questionnaire | Period 2 | Delayed Attributes Questionnaire |

**Figure 1.** Study schema. TNSS = Total Nasal Symptom Severity; FF = fluticasone furoate; MF = mometasone furoate.
Study Procedures

The patients were screened for eligibility, randomized, and administered all treatments in one day. During screening, a linguistically validated instantaneous Total Nasal Symptom Severity (TNSS) questionnaire was completed by the patient to assess the potential impact of the degree of rhinitis symptomatology at baseline on the patient’s assessment of nasal spray attributes. The TNSS assessed the symptoms: nasal congestion, rhinorrhea, sneezing, and pruritus. Each of the four symptoms was scored individually on a four-point scale (0, none; 1, mild; 2, moderate; 3, severe), and the scores were added to obtain the TNSS score (see Supplemental Appendix 1 for full details). The patients were blindfolded, and treatment with FFNS or MFNS was administered by an independent person who was not involved with any protocol-related assessments. The second study treatment was administered 30 minutes after the first treatment. Washout procedures were performed to cleanse the mouth and nasal passage 10 minutes before the first and second nasal spray treatments by using a method established in previous studies.15,14,17

Study Questionnaires and Assessments

Two sets of attribute questionnaires were completed after each medication (FFNS or MFNS); immediate (immediately after dosing) and delayed (2 minutes after dosing). The OPQ was completed immediately after the DAQ for the second treatment. All questionnaires were linguistically validated and provided in the primary language of the country where the patient was enrolled. The IAQ, DAQ, and OPQ have been used previously.13,14 The OPQ required the patient to state his or her overall preference for treatment with FFNS or MFNS and for each attribute (Supplemental Table 1); a “no preference” response was available and was included in the statistical analyses. The IAQ and DAQ each used a seven-point Likert scale, which ranged from 0 to 6, to rate individual attributes (Supplemental Tables 2 and 3; Supplemental Appendix 1). Safety information was collected by recording adverse events (AE) while at the study site and during follow-up telephone contact with the patients. Follow-up safety assessments took place 24–4 hours and 96–4 hours after treatments.

Statistical Analysis

Sample size was based on an overall preference for FFNS instead of MFNS in 60% of the patients (as observed as the preference for FFNS instead of FPNS in the study by Meltzer et al.14) and a significance level of 0.05. By using a two-sided, one-sample test, a sample size of 263 patients provided 90% power to show the expected difference in proportions. Approximately 300 patients were randomized to ensure availability of data from at least 263 evaluable patients. The per-protocol population included all patients who were randomized and who received FFNS and MFNS, did not have a significant deviation from the protocol, and completed both treatment periods and the associated questionnaires. The safety population included all patients who were randomized. Overall and individual preference questions were analyzed by using a Cochran-Mantel-Haenszel test stratified by country and rhinitis symptomatology. Immediate and delayed attribute ratings were assessed separately in terms of the difference between treatments in mean rating scores. This assessment used analysis of variance mixed models with attribute rating as the re-
response variable; subject as the random effect; and coun-
try, treatment, period, baseline rhinitis symptomatology
subgroup, and treatment sequence as main effects. The
set of attribute preferences and each of the two sets of
individual attributes ratings (immediate and delayed)
were adjusted for multiple comparisons by using the
Hochberg method.23

Ethics and Good Clinical Practice

The study was conducted in accordance with the
International Conference on Harmonisation Good
Clinical Practice requirements and the ethical prin-
ciples outlined in the Declaration of Helsinki. Ethical
approvals were obtained from an institutional review
board for each participating site. All patients provided
written informed consent.

RESULTS

Patient Baseline Demographics and Rhinitis
Assessments

Overall, 300 patients were recruited; a total of 276 pa-
tients completed the study and were included in the
per-protocol population. Two patients withdrew from
the study prematurely, which resulted in 298 patients
available for the safety population analyses. In the safety
population, 185 patients (62%) were women and the ma-
jority (73%) were white (Table 1). The duration of rhinitis
was ≥10 years in 230 patients (77%), with 193 patients
(64%) reporting seasonal allergic rhinitis and 161 patients
(54%) reporting perennial allergic rhinitis. The mean
(standard deviation) TNSS score was 3.6 ± 2.9; 162 pa-
tients (54%) were asymptomatic (TNSS score, ≤3), and
138 patients (46%) were symptomatic (TNSS score, ≥4).

Patient Preferences, Overall and By Attribute

There was a significant (p < 0.001) difference in
patients’ stated preference for FFNS or MFNS. The
majority of patients (56% [n = 155]) stated a preference
for FFNS (110 μg), 32% (n = 87) preferred MFNS (200
μg), and 12% (n = 34) stated no preference (Fig. 2).
When preference for specific attributes was exam-
ined, significantly more patients preferred FFNS
than MFNS for “less drip down the throat” (p <
0.001), “less run out of the nose” (p < 0.05), “more
soothing” (p < 0.05), and “less irritating” (p < 0.001)
(Fig. 2). Both the symptomatic (TNSS score, ≥4) and
asymptomatic (TNSS score, ≤3) subgroups preferred
FFNS to MFNS, with a trend for a larger proportion
of patients who preferred FFNS in the asymptomatic
group (not tested due to a lack of statistical power in
the subgroups).

Patient Ratings for Individual Attributes

When immediate attributes were assessed (Figs. 3 and
4) (Likert scale), there was a significant difference be-
tween treatments in the mean rating scores of immediate
“run down the throat” (p < 0.001) and immediate “run
out of the nose” (p < 0.001) (Fig. 4). Other mean attribute
rating scores did not differ significantly between the
groups. Examination of the ratings of delayed attributes
(Figs. 5 and 6) (Likert scale) showed statistically signifi-
cant differences in the rating scores between the FFNS
and MFNS treatments to the questions: “Did medicine
run down the throat?” (p < 0.001), “Did medicine run out
of the nose?” (p < 0.01), “Did product have an after-
taste?” (p < 0.01), “Did product cause nasal irritation?”
(p < 0.001), and “How bothersome was nasal irritation?”
Other mean attribute rating scores for the questions: “How satisfied with the product?” and “How likely to comply if prescribed?” did not differ significantly between the treatment groups (data not shown).

Treatment-Order Effects

The proportion of patients who preferred FFNS to MFNS overall was greater in the group that was administered FFNS first (70% FFNS versus 22% MFNS).
compared with the total per-protocol population (56% FFNS versus 32% MFNS). When MFNS was administered first, the overall proportions of patients who preferred FFNS or MFNS were 43 and 41%, respectively.

**AEs**

Overall, five patients (2% of the safety population) reported AEs related to receiving FFNS treatment and 13 patients (4%) reported AEs related to receiving MFNS (Table 2). The AE profile was generally similar between the treatment arms. No new safety signals were observed in this study. There were no serious AEs.

**DISCUSSION**

We presented a patient preference study of single treatments of the nasal corticosteroid sprays FFNS and MFNS for allergic rhinitis. The treatments were compared based on sensory attributes and assessed by using patient questionnaires. Results from the OPQ showed that patients reported an overall preference for FFNS (110 μg) instead of MFNS (200 μg). Both patients who were symptomatic and patients who were asymptomatic preferred FFNS to MFNS, with a trend for a greater difference in preference in the asymptomatic group. However, this trend could not be tested statistically because there was insufficient statistical power in the individual subgroups. Patients preferred FFNS instead of MFNS based on the individual attributes of “less run down the throat,” “less run out of the nose,” “more soothing,” and “less irritating.” These preferences may relate to the lower spray volume of aqueous solution used in FFNS (total volume, 200 μL), compared with MFNS (total volume, 400 μL) as well as differences in nozzle lengths and the fineness and dispersal of the spray. There was little difference in preference for the treatments based on taste- or odor-related attributes, which may be because both FFNS and MFNS were developed to minimize odor, although...
there was a preference for FFNS based on aftertaste. It should be noted that, although only 12% of the patients indicated that they had no overall preference for FFNS instead of MFNS, between 26 and 72% of the patients expressed no preference for either FFNS or MFNS based on individual attributes.

Compared with the total per-protocol population, a greater proportion of patients preferred FFNS when it
was given first (although it was not possible to test this statistically in this study). However, patients were randomly assigned to one of two treatment sequences (FFNS then MFNS or MFNS then FFNS), and the statistical analysis of variance models did take account of the treatment order. The difference in spray volume may also contribute to the possible association between treatment order and preference. Because the MFNS has a larger volume, it may linger longer despite the washout and may lead to blunting of the perception of the

Figure 6. DAQ ratings for running down the throat, soothing feeling, and nasal irritation (per-protocol population*). *(A–D) Show the per-protocol population; (E) is a subset of the per-protocol population. (E) Contains responses only from patients who responded other than “None” in (D). DAQ = Delayed Attributes Questionnaire; FFNS = fluticasone furoate nasal spray; MFNS = mometasone furoate nasal spray.
second spray (FFNS). This finding was consistent with the study by Shah et al., which showed that patients randomized to receive budesonide aqueous nasal spray before FPNS had a stronger preference for budesonide aqueous nasal spray than those who received budesonide aqueous nasal spray second.

Results of the current study complement previous findings. A study that used a similar methodology to that described here reported that patients preferred MFNS (53%) instead of FPNS (34%). In a further single-dose study by the same group, patients preferred FFNS (60%) instead of FPNS (33%). A study in Japan also investigated patient preference for FFNS or MFNS by using a crossover design, although over a longer 2-week treatment period per spray. The results showed that FFNS was overall significantly preferred to MFNS.

Relationships between nasal spray attributes and treatment compliance and adherence were previously reported. Results from one study showed that “aftertaste” was the attribute patients indicated would be most likely to affect adherence to treatment; however, “taste,” “run down the throat,” “run out of the nose,” “smell,” and “feel of the spray” were also proposed as likely to affect adherence. Results from a survey carried out in 2006 showed that the majority of patients (61%) who stopped taking a nasal allergy medication did so because of a characteristic of the medication and not because of a change in their condition.

A strength of the current study was that it was conducted at different sites, in different parts of the world, with a view to representing the global use of these treatments. Ethnic differences in nasal physiology have been suggested to impact nasal spray deposition. However, we did not stratify patients for this potential difference in this study. A potential study limitation was that this was a 1-day study, so it is possible that preferences may change over time. In addition, the treatment in this study was administered by a trained health care professional with the patient blindfolded to maintain the blind study. However, regular clinical practice would be for the patient to self-administer the spray.

CONCLUSION
In this study we showed that, overall and based on the individual attributes, patients with allergic rhinitis preferred FFNS to MFNS. Greater preference may improve patient adherence and thereby improve symptom management of patient’s allergic rhinitis.

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