Efficacy and safety of mometasone furoate nasal spray in nasal polyposis

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Background: Studies have suggested that topical corticosteroids are effective in the treatment of nasal polyps; however, this has yet to be confirmed in a large, robust clinical trial.
Objective: To evaluate the efficacy and safety of mometasone furoate nasal spray (MFNS) for nasal polyposis.
Methods: A total of 354 subjects with bilateral nasal polyps and clinically significant congestion/obstruction participated in this multinational, randomized, double-blind, placebo-controlled study. Subjects received MFNS 200 μg once or twice daily or placebo for 4 months. Coprimary endpoints were (1) change from baseline to last assessment in physician-evaluated bilateral polyp grade score and (2) change from baseline averaged over month 1 in subject-assessed nasal congestion/obstruction. ANOVA was used for all efficacy endpoints, except for change in bilateral polyp grade score, for which baseline polyp grade was added as a covariate.
Results: Compared with placebo, MFNS 200 μg administered once or twice daily produced significantly greater reductions in bilateral polyp grade score ($P < .001$, $P = .010$, respectively) and congestion/obstruction ($P = .001$, $P < .001$), as well as improvement in loss of smell ($P < .001$, $P = .036$), anterior rhinorrhea ($P < .001$ for both), and postnasal drip ($P < .001$, $P = .001$) over month 1. MFNS 200 μg twice daily was superior to MFNS 200 μg once daily in reducing congestion/obstruction ($P = .039$), and there were more improvers in the MFNS 200 μg twice daily group ($P = .035$). MFNS was well tolerated in both groups.
Conclusion: MFNS 200 μg, once or twice daily, was safe and significantly superior to placebo in reducing polyp grade (size and extent) and improving congestion/obstruction and return of sense of smell. MFNS is an effective medical treatment for nasal polyposis and may reduce or delay the need for surgery. (J Allergy Clin Immunol 2005;116:1275-81.)

Key words: *Congestion, corticosteroid, clinical trial, intranasal, mometasone furoate, nasal polyps*

Rhinitis, sinusitis, and ocular diseases

Nasal polyposis is estimated to affect approximately 4% of the population.[1] Symptoms include nasal obstruction, congestion, nasal discharge, purulence, and postnasal drip.[2] More than 75% of patients have impaired sense of smell or loss of sense of smell.[3] Nasal polyposis is characterized by eosinophil-dominated inflammation of unknown cause and is often associated with asthma, aspirin sensitivity, or cystic fibrosis.[2] One possible mechanism for the development of nasal polyposis involves bacterial colonization of the nasal cavity, causing synthesis and release of enterotoxins that act as superantigens to stimulate the local immune system.[4] A hallmark of bilateral nasal polyposis, which is observed in approximately 90% of adults with the condition, is a mixed cellular infiltrate with predominant eosinophilia.[5] Increased levels of inflammatory mediators, such as IL-5,[6] eotaxin,[7] and eosinophilic cationic protein,[8] are also present.

Topical nasal corticosteroids reduce the eosinophil-associated inflammation associated with polyposis[9] and are therefore a rational choice for the management of this condition.[9,10] The literature contains several small studies showing the positive effects of topical nasal corticosteroids on nasal polyps;[11-17] however, these are limited by small patient numbers or short duration of treatment. Therefore, a large, appropriately powered trial was initiated to establish the benefits of the corticosteroid mometasone furoate on nasal polyp grade and the symptoms associated with nasal polyps.

This study evaluated the efficacy and safety of mometasone furoate nasal spray (MFNS) 200 μg administered once daily (QD) or twice daily (BID) as monotherapy, compared with placebo, in the treatment of patients with nasal polyposis.

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Abbreviations used
ANCOVA: Analysis of covariance
BID: Twice daily
LS: Least squares
MFNS: Mometasone furoate nasal spray
PNIF: Peak nasal inspiratory flow
QD: Once daily

METHODS

Study design

A randomized, double-blind, double-dummy, placebo-controlled study was carried out in 44 medical centers worldwide in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practices. The study protocol and statement of informed consent were reviewed and approved by an Institutional Review Board and Independent Ethics Committee.

Subjects who met eligibility criteria at the screening visit (day −14, visit 1) underwent a 14-day, single-blind, placebo run-in period to help exclude placebo responders and identify subjects with stable disease. Subjects who met eligibility criteria at the baseline visit (visit 2) were randomized in a 1:1:1 ratio to 3 treatment arms: MFNS 200 μg QD in the morning (AM) with matching placebo nasal spray in the evening; MFNS 200 μg BID in the morning and evening; or matching placebo nasal spray BID. MFNS was supplied as commercial Nasonex (Schering-Plough Corp, Kenilworth, NJ) in a metered-dose manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% wt/wt mometasone furoate calculated on the anhydrous basis. The aqueous medium contained glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, 0.25% wt/wt phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80.

Treatment duration was 4 months, with study visits at day 8 (visit 3) and months 1, 2, 3, and 4 (visits 4, 5, 6, and 7, respectively). A nasal examination by endoscopy was performed by the investigator at each visit except visit 3, and polyps were graded by size and extent in both the left and right nasal fossa on a scale of 0 to 3 (0 = no polyps; 1 = polyp in middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyp reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; and 3 = large polyp reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate). The sum of the left and right nasal fossa polyp scores gave the total bilateral polyp grade. Investigators also evaluated subjects' therapeutic response at each visit on a qualitative scale ranging from complete relief of symptoms to no relief.

Subjects evaluated their symptoms (congestion/obstruction, loss of sense of smell, anterior rhinorrhea, and postnasal drip) each morning on a diary card immediately before dosing. Symptoms were scored on a scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe) to reflect the subject's condition at the time of scoring. After this symptom assessment, subjects also measured their peak nasal inspiratory flow (PNIF) each morning by using a PNIF meter (Clement Clarke International Ltd, Harlow, United Kingdom). Subjects were trained in using the meter at the baseline visit. Treatment compliance was evaluated at visits 3 through 7 by weighing study drug bottles without the subjects' knowledge. Compliance was defined as use of 59% to 138% of the reference study drug bottle weight. (Compliance is normally defined as the use of 70% to 120% of study drug bottle weight, but because the reference bottle weight could vary by 15%, the range was increased to account for this variability.)

Subjects

Subjects ≥18 years with a diagnosis of bilateral nasal polyps (graded ≥1 on each side) and clinically significant nasal congestion/obstruction (average morning score ≥2 for each of the last 7 days of the 14-day run-in period) were eligible for study entry. Subjects with asthma were included if they had a documented FEV_1 ≥80% of the predicted value within the 6 months before screening and no asthma exacerbations within 30 days before screening. Those treated with inhaled corticosteroids were required to be on a moderate, stable regimen of beclomethasone dipropionate ≤800 μg/d or equivalent for ≥1 month before screening and to remain on a stable regimen throughout the study period.

Subjects were not included in the study if they had a history of seasonal allergic rhinitis within the past 2 years, sinus or nasal surgery within the previous 6 months or ≥3 nasal surgeries (or any surgical procedure preventing an accurate grading of polyps), presumed fibrotic nasal polyposis, or complete or near complete nasal obstruction. Subjects with the following diagnoses were also excluded: nasal septal deviation requiring corrective surgery; nasal septal perforation; acute sinusitis, nasal infection, or upper respiratory tract infection at screening or in the 2 weeks before screening; ongoing rhinitis medicamentosa; Churg-Strauss syndrome; dyskinetic ciliary syndromes; cystic fibrosis; glaucoma or a history of posterior subcapsular cataracts; allergies to corticosteroids or aspirin; or any other clinically significant disease that would interfere with the evaluation of therapy.

Concomitant medications that would interfere with study evaluations were not permitted, including nasal sodium cromolyn; nasal atropine or ipratropium bromide; corticosteroids (except oral inhaled corticosteroids for asthma or mild-strength or mid-strength topical corticosteroids for dermatologic purposes); antihistamines; decongestants; topical, oral, or ocular anti-inflammatory drugs; or topical nasal or oral antifungal agents. Acetaminophen (paracetamol) was encouraged for analgesic purposes, with the use of nonsteroidal anti-inflammatory drugs limited to 5 consecutive days if alternative analgesia was required. Antibiotics were administered for any bacterial infections that occurred during the study, at the discretion of the principal investigator.

Efficacy endpoints

The study had 2 primary efficacy endpoints: (1) change from baseline to endpoint (at 4 months or last study visit) in bilateral polyp grade score, and (2) change from baseline in congestion/obstruction score averaged over the first month of treatment.

Secondary endpoints included change from baseline in loss of smell, anterior rhinorrhea, and postnasal drip score averaged over each month of treatment. Other assessments were change from baseline in PNIF at months 1, 2, 3, and 4, the proportion of subjects demonstrating an improvement (defined as a reduction in bilateral polyp grade score of ≥1.0 from baseline and a reduction in congestion/obstruction score of ≥0.5 from baseline) at the endpoint, and the investigators' evaluation of symptomatic therapeutic response at day 8 and months 1, 2, 3, and 4.

Safety assessments

Safety assessments included adverse event reporting, laboratory tests, vital signs, and physical examination. Details of all reported adverse events were recorded throughout the study, with severity graded as mild, moderate, severe, or life-threatening, and a relationship to treatment assigned. At all visits, vital signs were measured. Clinical laboratory tests and a physical examination were performed at the screening visit (visit 1) and the last treatment visit (visit 7). Change from baseline to the endpoint in 24-hour urinary cortisol levels (corrected for creatinine) was measured in a subset of subjects at 28 centers.