Onset of symptomatic effect of mometasone furoate nasal spray in the treatment of nasal polyposis

Catherine Butkus Small, MD,[a] Paul Stryszak, PhD,[c] Melvyn Danzig, PhD,[c] and Angela Damiano, MD[b]
Valhalla, NY, and Kenilworth, NJ

Background: The efficacy of the intranasal corticosteroid mometasone furoate nasal spray (MFNS) for treatment of nasal polyposis was demonstrated in 2 large clinical trials.
Objective: To evaluate the onset of MFNS symptomatic effect, data from the 2 trials were pooled and analyzed to determine the first day subjects experienced significant symptom relief.
Methods: Subjects with nasal polyposis randomized to MFNS 200 μg twice daily or placebo scored symptoms on a 3-point scale (0 = none; 3 = severe) and measured peak nasal inspiratory flow immediately before the morning dose. Onset of symptomatic effect was defined as the first day a statistically significant ($P < .05$) lasting response was observed for MFNS compared with placebo.
Results: A total of 447 subjects with bilateral nasal polyps and clinically significant nasal congestion/obstruction were analyzed. Compared with placebo, MFNS 200 μg twice daily demonstrated statistically significant ($P < .05$) relief of anterior rhinorrhea by day 2 (–10.9% vs +5.7%), nasal congestion by day 3 (–15.1% vs –7.6%), postnasal drip by day 5 (+1.1% vs +4.6%), and sense of smell by day 13 (–9.6% vs –5.6%). Significant improvement in peak nasal inspiratory flow was seen by day 2 (increase of 6.22 L/min vs 1.48 L/min for placebo; $P = .03$).
Conclusion: Mometasone furoate nasal spray 200 μg twice daily rapidly improves the symptoms of nasal polyposis, leading to lasting relief of most major symptoms within 2 (24 hours after the first dose) to 5 days of initiating therapy. (J Allergy Clin Immunol 2008;121:928-32.)

Key words: *Nasal polyposis, mometasone furoate, efficacy onset, intranasal corticosteroids, clinical trial*

Abbreviations used
LS: Least squares
MFNS: Mometasone furoate nasal spray
PNIF: Peak nasal inspiratory flow

Approximately 4% of the population has nasal polyps.[1] Symptoms include nasal obstruction, nasal congestion, nasal discharge, rhinorrhea, purulence, and postnasal drip.[2] More than 75% of patients with nasal polyps also experience impairment or loss of sense of smell.[3]

The cause of nasal polyps is not completely understood, although they are often associated with asthma, aspirin sensitivity, or cystic fibrosis. Enterotoxins released in the nasal cavity by colonizing bacteria such as *Staphylococcus aureus* may act as superantigens that influence the activity of both immunomodulatory and proinflammatory effector cells.[4] Nasal polyposis is characterized primarily by eosinophilic inflammation, which initiates an autocrine inflammatory mechanism causing persistent eosinophilia, as well as by increased levels of other inflammatory mediators, such as IL-5, eotaxin, and eosinophilic cationic protein.[5-7] In bilateral nasal polyposis, the typical form of the disease in adults, a mixed cellular infiltrate consisting primarily of eosinophils occurs.[6]

Topical intranasal corticosteroids, which inhibit the eosinophil-associated inflammation found with polyposis without affecting the immune response, have been shown in numerous studies to reduce polyp grade (size and extent), improve symptoms, and delay or reduce the need for surgery.[2,8-17] Intranasal corticosteroids are currently considered the medical treatment of choice for nasal polyposis.[18] In 2 recent, large, multicenter, placebo-controlled studies, mometasone furoate nasal spray (MFNS) demonstrated significant, lasting symptom relief compared with placebo in nasal congestion/obstruction, anterior rhinorrhea, and postnasal drip scores, and significantly improved sense of smell. Peak nasal inspiratory flow rates and quality of life assessment scores also significantly increased with MFNS.[17,19] In these studies, 200 μg MFNS taken twice daily was superior to a 200-μg/d dose in reducing nasal congestion/obstruction. In addition, a greater percentage of these subjects demonstrated an overall improvement in their symptoms after 4 months.[17] As a result, data on the 200-μg twice-daily dose of MFNS from these trials were pooled and further analyzed to evaluate the onset of the symptomatic effect of MFNS on nasal polyposis.

METHODS

Pooled data from 2 randomized, multinational, double-blind, placebo-controlled, parallel-group 4-month clinical trials conducted between June

From [a]the Division of Infectious Diseases and [b]the Division of Otolaryngology, New York Medical College, Westchester Medical Center, Valhalla; and [c]the Schering-Plough Research Institute, Kenilworth.
Supported by a grant from the Schering-Plough Research Institute.
Disclosure of potential conflict of interest: P. Stryszak is employed by Schering-Plough. M. Danzig has consulting arrangements with, owns stock in, and was formerly employed by Schering-Plough. The rest of the authors have declared that they have no conflict of interest.
Received for publication May 23, 2007; revised October 18, 2007; accepted for publication November 12, 2007.
Available online January 31, 2008.
Reprint requests: Catherine Butkus Small, MD, Division of Infectious Diseases, Munger Pavilion Rm 245, Valhalla, NY 10595. E-mail: Catherine_Small@nymc.edu.
0091-6749/$34.00

doi:10.1016/j.jaci.2007.11.018

2001 and March 2003 were further analyzed.[17,19] Subjects were at least 18 years of age, had endoscopically confirmed bilateral nasal polyps, and were required to have clinically significant nasal congestion on each of the last 7 days of a 14-day placebo run-in period. Further inclusion/exclusion criteria have been previously reported.[17,19] Subjects evaluated their symptoms, including nasal congestion/obstruction, loss of sense of smell, anterior rhinorrhea, and postnasal drip every morning immediately before dosing, using a diary card with a 0 to 3 scale (0 = none; 3 = severe). A lower percentage score correlated with greater symptom improvement. Peak nasal inspiratory flow (PNIF) was measured with a meter, with a higher score indicating greater symptom improvement.

Polyps were graded by size and extent monthly in both nostrils on the following scale: 0 = no polyps; 1 = polyps in middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; and 3 = large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate.[17]

The onset of symptomatic effect of MFNS 200 μg twice daily was the efficacy endpoint, defined as the first day when a statistically significant response ($P < .05$) was observed for MFNS versus placebo over month 1 of the study. If statistical significance for a symptom was not achieved by day 7, the study period was extended until statistical significance was reached. Symptoms were evaluated for as long as 45 days. Differences between treatment groups in changes from baseline (day 1) for each day of the study were assessed by a 2-way ANOVA. Least square (LS) means, pooled SDs, *P* values, and pairwise comparison *P* values were obtained from ANOVA with treatment, baseline asthma status, and side effects. Because this was a *post hoc* analysis of data, there were no prospectively defined primary and secondary endpoints.

RESULTS

Data from 447 subjects were analyzed. Of these, 224 received MFNS 200 μg twice daily and 223 received placebo. There were no significant differences in demographic characteristics. Bilateral polyp scores were 4.20 in both groups (Table I). Baseline symptom scores and PNIF scores also did not differ between the groups. A statistically significant improvement was observed for all symptoms except sense of smell at day 7 compared with placebo. This improvement in symptoms continued until day 45, except for sense of smell, which improved significantly until day 44 (Table II).

Anterior rhinorrhea

A statistically significant improvement in LS mean anterior rhinorrhea score was first experienced on day 2 (24 hours after the first dose; –0.18 [–10.9%] MFNS vs +0.03 [5.7%] placebo; Fig 1). The placebo-adjusted treatment effect was –0.21 (95% CI, –0.33 to –0.10; $P < .001$). Improvement in anterior rhinorrhea remained significantly greater at day 7 with a decrease of –0.27 (–19.5%) for MFNS versus an increase of 0.03 (8.5%) for placebo, a treatment effect of –0.30 (95% CI, –0.43 to –0.19; $P < .001$). The maximum treatment effect, defined as the largest decrease in symptom score from baseline, was seen on day 24, with a 37.8% decrease. MFNS-treated subjects continued to improve significantly compared with placebo every day until day 45 ($P < .001$; Fig 1; Table II).

Nasal congestion/obstruction

Least square mean nasal congestion scores improved significantly from baseline in MFNS-treated subjects, with a statistically significant improvement first experienced on day 3 (–0.34 [–15.1%] MFNS vs –0.20 [–7.6%] placebo). The placebo-adjusted treatment effect was –0.14 (95% CI, –0.25 to –0.04; $P < .01$). Statistically significant improvement continued to day 7 (–0.52 [–21.9%] MFNS vs –0.21 [–6.6%] placebo), for a treatment effect of –0.31 (95% CI, –0.44 to –0.19; $P < .01$). The maximum treatment effect occurred on day 43, with a 37.7% decrease. Significant improvement in the MFNS-treated group compared with placebo continued until day 45 ($P < .001$; Fig 2; Table II).

TABLE I. Demographics of 447 subjects with bilateral nasal polyposis

	MFNS 200 μg twice daily (n = 224)	Placebo (n = 223)
Mean age, y (range)	47.8 (18.0-77.0)	49.2 (18.0-81.0)
Age subgroup, n (%)		
18 to <65 y	196 (87.5)	192 (86.1)
>65 y	28 (12.5)	31 (13.9)
Male (%)	63	63
Asthma history, n (%)	45 (20.1)	42 (18.8)
Perennial allergic rhinitis history, n (%)	48 (21.4)	42 (18.8)
Initial bilateral polyp grade scores	4.20	4.20

Postnasal drip

Mometasone furoate–treated subjects first experienced a statistically significant reduction in postnasal drip compared with placebo on day 5 (–0.18 [+1.1%] MFNS vs 0.0 [+4.6%] placebo), a treatment effect of –0.18 (95% CI, –0.30 to –0.05; $P < .05$; Fig 3). Symptoms continued to improve significantly through day 7 (–0.18 [–7.3%] MFNS vs 0.02 [+10.1%] placebo), a treatment effect of –0.20 (95% CI, –0.32 to –0.08; $P < .05$). The maximum treatment effect occurred on day 42, with a 22.6% decrease. MFNS-treated subjects continued to improve compared with placebo every day until day 45 ($P < .003$; Fig 3; Table II).

Sense of smell

Sense of smell in MFNS-treated subjects improved significantly and remained significantly greater than placebo for the first time on day 13 (–0.22 [–9.6%] MFNS vs –0.10 [–5.6%] placebo), a treatment effect of –0.12 (95% CI, –0.24 to –0.00; $P < .05$). MFNS-treated subjects had a statistically significant improvement in sense of smell compared with placebo on most, but not all, treatment days, until but not including day 45 ($P < .05$). Improvement in symptom scores was significant on days 13 to 31, day 34, and days 38 to 44 (Fig 4; Table II). The maximum treatment effect was reached on day 39, with a 20.9% decrease.

PNIF

A statistically significant increase in PNIF rates in MFNS-treated subjects compared with placebo occurred on day 2, with an increase of 6.22 L/min (9.2%) vs 1.48 L/min (2.1%), a treatment effect of 4.74 L/min (95% CI, 0.43-9.05; $P = .031$). The difference between MFNS and placebo was not significant on day 3, but returned to significance on day 4, with an increase of 11.98 L/min (18.4%) for MFNS compared with 2.50 L/min (2.1%) for placebo. This treatment effect was 9.38 L/min (95% CI, 4.71-14.26; $P < .001$), and continued through day 7 (18.19 L/min [30.1%]