



Mometasone furoate nasal spray increases the number of minimal-symptom days in patients with acute rhinosinusitis

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ARTICLE INFO

Article history:

Received for publication October 13, 2011.

Received in revised form January 17, 2012.

Accepted for publication January 20, 2012.

ABSTRACT

Background: Acute rhinosinusitis (ARS) is triggered by viral or, uncommonly, bacterial infection, causing inflammatory symptoms for ≤ 12 weeks.

Objective: To investigate effects of mometasone furoate nasal spray (MFNS) vs amoxicillin and placebo on minimal-symptom days.

Methods: A double-blind, parallel-group, placebo- and active-controlled 15-day study randomly assigned patients 12 years of age or older to MFNS 200 μ g twice daily, MFNS 200 μ g once daily, amoxicillin 500 mg 3 times daily, or placebo.

Patients had baseline rhinosinusitis major symptom score (MSS; combined rhinorrhea, postnasal drip, congestion, sinus headache, facial pain) of ≥ 5 and ≤ 12 (maximum: 15) for 7 to 28 days; scores were similar among groups. Minimal-symptom days and minimal-congestion days were defined post hoc by average AM/PM MSS ≤ 4 and average AM/PM congestion ≤ 1 .

Results: MFNS twice daily ($n = 234$) showed more minimal-symptom days vs placebo ($n = 246$) (62.69% vs 50.33%; $P < .0001$) or amoxicillin ($n = 248$) (54.35%; $P = .0040$). The MFNS QD was associated with numerically more minimal-symptom days than amoxicillin or placebo (54.72%; $P \leq .8982$). MFNS was associated with more minimal-congestion days than placebo (72.97%, 67.73%, and 56.67% for twice daily, once daily, and placebo; $P < .0001$, each vs placebo) and MFNS BID with more minimal-congestion days than amoxicillin (72.97% vs 64.15%; $P = .0007$). Median time to first minimal-symptom day sustained until study end was 8.5 days for MFNS BID vs. 11 for placebo ($P = .0085$).

Conclusion: MFNS 200 μ g twice daily significantly increased minimal-symptom days vs amoxicillin or placebo in patients with ARS. Results of this intranasal corticosteroids (INS) therapy indicate it can improve outcomes and potentially reduce inappropriate antibiotic use.

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Disclosures: Eli O. Meltzer: grant/research support: Alcon, Alexza, Amgen, Astellas, Boehringer Ingelheim, CRN, Forest, GlaxoSmithKline, Johnson & Johnson, MAP, Meda, MedImmune, Merck, Novartis, Sunovion, Teva; consultant/advisory board: Alcon, Amgen, Boehringer Ingelheim, Dey, Greer, ISTA, Johnson & Johnson, Kalypsys, Meda, Merck, ONO Pharma, Rady Children's Hospital San Diego, Sandoz, Schering-Plough, Sunovion, Stallergenes, Teva; speaker: Alcon, Dey, GlaxoSmithKline, Merck, National Jewish Health, Nycomed, Sanofi-Aventis, Schering-Plough, Sunovion. Davis Gates: employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ. Claus Bachert: grant/research support: Schering-Plough, Biotech, GSK, Bionorica; consultant: Uriach, Meda, Bionorica, Proctor&Gamble, GSK, Stallergenes, ALK, Allergopharma, FAES; speaker: Schering-Plough, Merck, Uriach, UCB, GSK, ALK, Stallergenes.

Funding Sources: Support for this study was provided by Schering-Plough, now Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. Medical writing and editorial assistance was provided by Rob Coover, MPH, of AdelphiEden Health Communications, New York, NY. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

Introduction

Acute rhinosinusitis (ARS) is an inflammation of the paranasal sinus mucosa and contiguous nasal mucosa, lasting up to 12 weeks.^{1,2} It affected approximately 26 million Americans in 2007, according to National Health Interview Survey data.³ Because most cases of ARS will eventually resolve on their own without treatment, European and American rhinosinusitis guidelines recommend therapy directed at the numerous symptoms, which may include nasal congestion, rhinorrhea, facial pain/pressure, postnasal drip, and headache.^{1,2,4}

Symptoms of ARS, particularly congestion, are associated with interference with daily activities⁵; thus, therapy achieving clinically relevant symptom reductions has important implications for patients' quality of life. The concept of a "minimal-symptom day" has been used to evaluate clinical efficacy of symptomatic therapies, including the intranasal corticosteroids (INSs) mometasone furoate nasal spray (MFNS) and beclomethasone dipropionate nasal spray and the monoclonal antibody omalizumab injection, in

preventing nasal allergic rhinitis symptoms such as congestion and rhinorrhea.^{6,7} The concept has also been applied to assess symptomatic relief associated with MFNS in patients with allergic rhinitis.^{8,9}

Randomized, placebo-controlled trials evaluating anti-inflammatory agents (such as INS in general and MFNS in particular) for ARS treatment have demonstrated significant clinical benefits, including effective symptom relief as well as good safety and tolerability.^{10–12} However, these trials have almost always evaluated INS only as adjunctive therapy with concomitant antibiotics, not as monotherapy vs placebo or antibiotic.^{10–14} In the first trial evaluating MFNS as monotherapy for ARS, MFNS 200 μ g twice daily produced significant symptom improvement vs both amoxicillin and placebo, without predisposing patients to disease recurrence or bacterial infection. Details of the study have been published: MFNS 200 μ g twice daily was statistically significantly superior to both amoxicillin and placebo in mean AM/PM major symptom score (MSS), mean AM/PM total symptom score (TSS), and 4 of 6 individual symptom scores (rhinorrhea, nasal congestion/stuffiness, sinus headache, and facial pain/pressure/tenderness). MFNS 200 μ g once daily showed superiority to placebo in mean MSS, mean TSS, and 2 individual symptom scores (rhinorrhea and nasal congestion/stuffiness), although it did not achieve statistical superiority to amoxicillin.¹⁵

Because ARS generally self-resolves, treatment is intended to provide symptomatic relief while the infection and inflammation run their course. Minimizing symptoms caused by the inflammatory changes triggered by infection can provide better quality of life, and analysis of days with minimal symptoms can illustrate a clinically important effect. In this post hoc analysis, we assessed the proportion of minimal-symptom days, proportion of minimal-congestion days, time (study day) to onset of action and to first minimal-symptom day sustained until study end, and treatment effect stratified by previous duration of symptoms for all treatment and placebo groups.

Methods

Study design

This post hoc analysis of minimal-symptom days was performed using data from a phase II, multicenter, randomized, double-blind, double-dummy study of MFNS 200 μ g twice daily or 200 μ g once daily vs amoxicillin and placebo in patients with ARS. The 71-center, 14-country study (NCT00750750; P02683) was conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice. Written informed consent was obtained from all patients; the protocol was approved by an independent ethics committee or independent review board before initiation at each center. Patients were treated for 15 days, with a subsequent 14-day follow-up. Patients were randomly assigned in a 1:1:1:1 ratio to MFNS 200 μ g twice daily, MFNS 200 μ g once daily, amoxicillin 500 mg three times daily, or placebo.

Randomization was performed according to a computer-generated code, stratified according to duration of rhinosinusitis symptoms before baseline (7–14 days and 15–28 days). Nine patients with qualifying baseline MSS and 6 days' duration of symptoms were assigned to the 7-to-14-days' duration stratum for analysis, because the centers at which these patients were randomized included the baseline day in duration of symptoms. Thus, subgroups will be identified as 6 to 14 days' duration and 15 to 28 days' duration.

Table 1 shows major inclusion and exclusion criteria. Prohibited medications included nasal cromolyn sodium; nasal atropine; nasal, oral, or ocular corticosteroids (except in patients using orally inhaled steroids for mild-to-moderate persistent asthma); short- and long-acting antihistamines; leukotriene pathway modifiers;

Table 1

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• ≥ 12 years old, either sex • Signs and symptoms of ARS for ≥ 7 days but ≤ 28 days • MSS^a ≥ 5 but ≤ 12 at screening and baseline, with ≤ 3 of 5 symptoms rated severe	• Signs or symptoms suggestive of fulminant bacterial rhinosinusitis^b • Chronic rhinosinusitis or sinus/nasal surgery ≤ 6 months prescreening • Atrophic rhinitis, otitis media, or nasal polyps^c • Symptomatic SAR • Allergy to corticosteroids • Asthma exacerbations ≤ 30 days prescreening and FEV1 $< 65\%$ of predicted value ≤ 3 months of screening

Abbreviations: ARS, acute rhinosinusitis; FEV1, forced expiratory volume in 1 second; MSS, major symptom score; SAR, seasonal allergic rhinitis.

^aRhinorrhea, postnasal drip, nasal congestion/stuffiness, sinus headache, facial pain/pressure/tenderness on palpation.

^bFever $\geq 101^\circ\text{F}/38.3^\circ\text{C}$, persistent severe unilateral facial pain/tooth pain, facial swelling, dental involvement, and/or worsening symptoms after initial improvement.

^cAssessed by signs and symptoms found in physical examination.

systemic or nasal antibiotics; nasal or long-acting decongestants; and nasal saline and douches. Aspirin up to 325 mg/d was permitted for cardiac prophylaxis. Nonsteroidal anti-inflammatory drugs (NSAIDs) were prohibited for ARS treatment. For conditions other than ARS, nonsteroidal anti-inflammatory drug use was limited to 3 days during the study period.

The primary efficacy variable was MSS (combined scores for rhinorrhea, postnasal drip, nasal congestion/stuffiness, sinus headache, and facial pain/pressure/tenderness on palpation over the paranasal sinuses) averaged over days 2 to 15. Patients evaluated and recorded their rhinosinusitis symptoms over the period of the previous 12 hours in the morning and evening each day as 0 (none), 1 (mild), 2 (moderate), or 3 (severe).

Time to onset of action was defined as the first day active treatment was statistically significantly different from placebo in MSS and sustained thereafter. The day on which MFNS 200 μ g BID first achieved statistical significance vs amoxicillin that was maintained until study end was also calculated.

A predefined subanalysis of the primary efficacy variable included descriptive statistics (population numbers, means, and standard deviations, by treatment) stratified according to patients' duration of prior symptoms (6–14 days or 15–28 days). Safety was assessed by adverse events (AEs), vital signs, clinical laboratory tests, and physical examination.

Post hoc statistical analysis

Minimal-symptom days were calculated by reviewing daily symptom diaries. The percentage of days with minimal symptoms (defined as average AM/PM MSS ≤ 4) was computed for each patient assigned to each treatment group. A score ≤ 4 was determined as the standard for minimal-symptom days, because this represents a less-than-mild severity evaluation for each of the 5 symptoms constituting the MSS; ≤ 4 also represents a greater than 50% reduction from baseline in mean symptom severity scores for all study groups (baseline MSS for MFNS 200 μ g twice daily, 8.28; MFNS 200 μ g once daily, 8.17; amoxicillin, 8.53; placebo, 8.36). The first day with minimal symptoms that were sustained for all subsequent study days within each group were determined using medians (50th percentile). *P*-values for between-group differences in first day with minimal symptoms were based on the log rank test.

Among major symptoms, congestion had the highest baseline severity rating; thus, an analysis of minimal-congestion days was also performed. A congestion score ≤ 1 was selected as the standard for minimal-congestion days, representing mild severity or less; this represents an approximately 50% reduction from baseline

Table 2
Baseline demographic and clinical characteristics of randomized patients

Characteristic	MFNS 200 µg BID (n = 235)	MFNS 200 µg QD (n = 243)	Amoxicillin 500 mg TID (n = 251)	Placebo (n = 252)
Mean age, y	34.8	35.9	35.9	34.4
Age subgroup, n (%)				
12 to <18	15 (6)	17 (7)	11 (4)	14 (6)
18 to <65	219 (93)	219 (90)	234 (93)	236 (94)
≥65	1 (<1)	7 (3)	6 (2)	2 (1)
Female, n (%)	147 (63)	162 (67)	176 (70)	155 (62)
Race, n (%)				
White	97 (41)	99 (41)	105 (42)	108 (43)
Hispanic	104 (44)	107 (44)	107 (43)	110 (44)
Other	17 (7)	22 (9)	21 (8)	20 (8)
Black	14 (6)	11 (5)	12 (5)	8 (3)
Asian	3 (1)	4 (2)	6 (2)	6 (2)
SAR history, n (%)	50 (21)	40 (16)	40 (16)	44 (17)
PAR history, n (%)	66 (28)	65 (27)	58 (23)	67 (27)
Duration of prior rhinosinusitis symptoms, n (%)				
1–2 weeks	153 (65)	164 (67)	154 (61)	147 (58)
2–4 weeks	82 (35)	79 (33)	97 (39)	105 (42)

Abbreviations: MFNS, mometasone furoate nasal spray; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.

Numbers in this table refer to all randomized patients; not all patients could be included in each analysis because of missing data. Refer to Results for numbers used for each analysis.

in mean symptom severity scores for all study groups (baseline congestion for MFNS 200 µg twice daily, 2.02; MFNS 200 µg once daily, 2.06; amoxicillin, 1.98; placebo, 2.04).

Differences between treatment groups in percentages of minimal-symptom days and minimal-congestion days were assessed by analysis of covariance (ANCOVA), including effects of treatment, site, and duration of symptoms (6–14 days or 15–28 days) at baseline, with baseline symptom score as a covariate (MSS or congestion as appropriate), performed to determine least square means and *P*-values for each between-group difference. A similar ANCOVA model also was used to determine between-group differences within the subgroups classified by duration of symptoms (6–14 days or 15–28 days).

Results

Patients evaluated

Baseline characteristics among treatment groups showed no meaningful differences (Table 2). Restricting analyses to include only patients with data produced slightly different population numbers for each analysis.

Daily diary entries from 967 patients (MFNS 200 µg twice daily = 233, MFNS 200 µg once daily = 240, amoxicillin = 248, placebo = 246) were analyzed retrospectively in the minimal-symptom days post hoc analysis. Patients receiving MFNS 200 µg twice daily experienced a significantly greater percentage of minimal-symptom days vs those receiving MFNS 200 µg once daily (*P* = .0062), amoxicillin (*P* = .0040), or placebo (*P* < .0001) (Table 3). Patients receiving MFNS 200 µg once daily experienced a numerically but not significantly greater percentage of minimal-symptom days than those receiving placebo (*P* = .1286). No significant difference in the percentage of minimal-symptom days was found between MFNS 200 µg once daily and amoxicillin (*P* = .8982). Additionally, no significant dif-

ference in percentage of minimal-symptom days was found between amoxicillin and placebo treatment groups (*P* = .1585).

The number of minimal-symptom days across treatment groups, corrected for total number of treatment days per group, equaled 8.8 days, 7.7 days, 7.6 days, and 7.0 days for MFNS 200 µg twice daily, MFNS 200 µg once daily, amoxicillin, and placebo, respectively. The first day on which patients experienced mean AM/PM MSS < 4 was day 7 for MFNS 200 µg twice daily, day 8 for MFNS 200 µg once daily, day 9 for amoxicillin, and day 9 for placebo.

The MFNS 200 µg twice daily dose was associated with a significantly shorter time to first minimal-symptom day sustained until study end vs placebo. Median time to this end point was 8.5, 10, 11, and 11 days for MFNS 200 µg twice daily, MFNS 200 µg once daily, amoxicillin, and placebo, respectively (*P* = .0085 for BID vs placebo; other active treatments not significant vs placebo).

Population numbers for the post hoc analysis of minimal-congestion days were the same as in the analysis of minimal-symptom days. Patients receiving MFNS 200 µg twice daily experienced significantly more minimal-congestion days than those receiving MFNS 200 µg once daily (*P* = .0440), amoxicillin (*P* = .0007), or placebo (*P* < .0001) (Table 3). Patients receiving MFNS 200 µg once daily experienced significantly more minimal-congestion days than those receiving placebo (*P* < .0001), as did patients receiving amoxicillin (*P* = .0034). The difference between the MFNS 200 µg once daily and amoxicillin groups was not statistically significant.

In the onset of action protocol-specified analysis, MFNS 200 µg twice daily (*n* = 234) showed statistical superiority to placebo (*n* = 252) in MSS at day 2 that was maintained through study end (*P* ≤ .043). The statistical superiority of MFNS 200 µg twice daily to amoxicillin (*n* = 251) first occurred on day 2, was not significant on day 3, returned to significance on day 4, and was then sustained

Table 3
Minimal-symptom days and minimal-congestion days

	MFNS 200 µg BID	MFNS 200 µg QD	Amoxicillin	Placebo
% Minimal-symptom days (SE)	62.69% (2.2217) ^{a,b}	54.72% (2.1951)	54.35% (2.1325)	50.33% (2.1146)
% Minimal-congestion days (SE)	72.97% (1.9867) ^{a,b}	67.73% (1.9623) ^a	64.15% (1.9029) ^a	56.67% (1.8919)

Abbreviation: MFNS, mometasone furoate nasal spray.

^a*P* < .05 vs placebo.^b*P* < .05 vs amoxicillin.

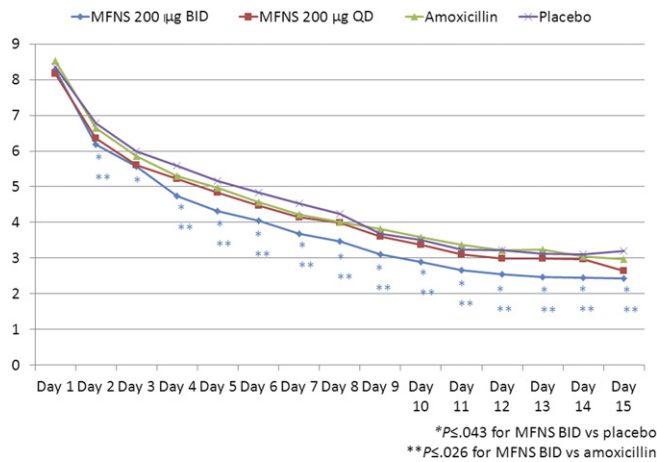


Fig. 1. Onset of action vs placebo and change in major symptom score vs amoxicillin and placebo.

through study end ($P \leq .026$). MFNS 200 μg once daily ($n = 243$) was significantly superior to placebo only on days 2 and 15 ($P \leq .030$). MFNS 200 μg once daily did not show significant differences vs amoxicillin at any time point. Differences in MSS between amoxicillin and placebo were not statistically significant at any time point (Fig 1).

In the subgroup analysis of response by duration of prior rhinosinusitis symptoms (Table 4), predefined descriptive statistics show that MFNS 200 μg twice daily achieved numerically superior MSS reductions vs amoxicillin and placebo in both subgroups: those with baseline duration of symptoms from 6 to 14 days and those with duration from 15 to 28 days. MFNS 200 μg once daily achieved numerically superior MSS reductions vs amoxicillin and placebo in the 15 to 28 days' duration subgroup. Treatment group differences among the 2 subgroups in reduction of symptoms to a minimal level generally corresponded to between-group differences in the total study population and indicated a dose-related efficacy of MFNS. In the post hoc ANCOVA among patients with symptoms of 6 to 14 days' duration, patients receiving MFNS 200 μg twice daily experienced a greater percentage of minimal-symptom days vs those in the MFNS 200 μg once daily, amoxicillin, and placebo groups ($P \leq .0153$). Among patients with symptoms of 15 to 28 days' duration, MFNS 200 μg BID was associated with a significantly greater percentage of minimal-symptom days vs amoxicillin ($P = .0285$) or placebo ($P = .0014$).

In the subgroup of patients with 6 to 14 days of symptoms, MFNS 200 μg BID was associated with significantly more minimal-congestion days than MFNS 200 μg once daily ($P = .0150$), amoxicillin ($P = .0014$), and placebo ($P < .0001$). In this subgroup, MFNS 200 μg once daily was also superior to placebo ($P = .0020$), as was amoxicillin ($P = .0237$). In the subgroup with 15 to 28 days of symptoms, MFNS 200 μg twice daily ($P = .0010$) and MFNS 200 μg once daily ($P = .0086$) were both associated with significantly more minimal-congestion days versus placebo. No other between-group differences were seen in subgroup analyses of minimal-symptom days or minimal-congestion days.

Table 4
MSS at baseline and for days 2–15 by duration of symptoms

	MFNS 200 μg BID	MFNS 200 μg QD	Amoxicillin	Placebo
6–14 days MSS at baseline (n)	8.18 (153)	8.04 (164)	8.40 (154)	8.39 (147)
6–14 days MSS for days 2–15 (n)	3.57 (152)	3.97 (162)	4.09 (154)	4.30 (143)
15–28 days MSS at baseline (n)	8.42 (81)	8.41 (79)	8.62 (97)	8.33 (105)
15–28 days MSS for days 2–15 (n)	3.98 (82)	4.13 (78)	4.57 (95)	4.79 (104)

Abbreviations: MFNS, mometasone furoate nasal spray; MSS, major symptom score.

Treatment-emergent AE rates were similar among the treatment groups: 36.2%, 35.4%, 33.5%, and 38.1% with MFNS 200 μg twice daily, MFNS 200 μg once daily, amoxicillin, and placebo, respectively. Most AEs were of mild or moderate severity and considered unlikely to be related to treatment. No clinically meaningful changes in laboratory parameters, vital signs, or physical examinations were noted.

Discussion

This analysis shows that 2 weeks of MFNS 200 μg twice daily is associated with a significantly greater proportion of minimal-symptom and minimal-congestion days vs antibiotic or placebo in patients with ARS. Advantages were seen for the twice-daily dosing regimen over once-daily dosing, which showed a numerically but not significantly greater percentage of minimal-symptom days than antibiotic or placebo, although MFNS 200 μg once daily was associated with a significantly greater percentage of minimal-congestion days vs placebo.

Prescription of antibiotics continues to be a common default response to an ARS diagnosis, despite most cases being viral in origin and clinical trial data suggesting that antibiotics provide no benefit to most patients even when clinical diagnosis or duration of symptoms suggests bacterial complication.^{1,16–20} Risks of adverse events and the likelihood of contributing to increased microbial resistance make the advisability of antibiotic use questionable in many cases.^{1,2} Given that patients with likely bacterial causes were excluded from the current study, and the widespread resistance seen across numerous bacterial species, the lack of efficacy seen with amoxicillin was not unanticipated and serves to further confirm its inappropriateness as a standard of care for ARS.

Acute rhinosinusitis is primarily an inflammatory condition. Because corticosteroids have broad anti-inflammatory activity, INSs are a reasonable choice for symptomatic relief.^{1,2} Previously, most trials have evaluated INS as adjunctive therapy in the treatment of ARS, together with antibiotics; in this setting, INSs have demonstrated significant clinical benefit by providing effective additional symptom relief, good safety, and tolerability in pediatric and adult patients.^{10–12}

Although INSs have repeatedly been demonstrated to improve ARS outcomes in combination with antibiotics, previous evaluations of INS monotherapy in acute respiratory inflammatory conditions have not conclusively shown benefit.^{21,22} Puhakka et al²¹ treated patients with the “common cold” (nasal drainage and 1 of the following: cough, headache, hoarseness, myalgia, nasal congestion, oral temperature over 37°C, or sore throat; patients with only sore throat were excluded). Subjects ($N = 199$) received fluticasone propionate 200 μg or placebo 4 times daily for 6 days, with a 14-day follow-up. Fluticasone propionate was associated with no significant differences vs placebo in frequency of symptoms over the course of treatment or follow-up.²¹ Another trial randomly assigned 240 adults with acute nonrecurrent sinusitis to receive 500 mg amoxicillin 3 times daily for 7 days, 200 μg budesonide per nostril once daily for 10 days, both active treatments, or placebo. Neither budesonide nor amoxicillin was associated with significantly lower TSS (combined scores for nasal blockage, nasal discharge, unpleasant taste/smell, facial pain, pain in head/jaws/teeth

on bending, restriction of daily activity, level of wellness, and headache) at 10 or 14 days. Additionally, neither active treatment showed significant advantage in time to cure (defined as resolution of symptoms).²²

In contrast, the primary analysis of the current study showed superiority for monotherapy with MFNS 200 μ g BID vs amoxicillin and placebo in MSS over 2 weeks of treatment in patients with ARS.¹⁵ Furthermore, MFNS 200 μ g twice daily was associated with significant benefits in health-related quality of life, as measured by the Sino-Nasal Outcome Test-20.²³ This dosage of MFNS was associated with statistically significant improvement from baseline in mean total Sino-Nasal Outcome Test-20 questionnaire score vs placebo ($P = .047$). MFNS 200 μ g QD was associated with numerically but not significantly greater improvement vs placebo. Patients with ARS have reported congestion to be the most irritating of their symptoms⁵; the significant increases in minimal-congestion days seen with both MFNS dosages in the current analysis thus have considerable implications for patients' quality of life during ARS episodes.

Results of this current post hoc analysis confirm that MFNS 200 μ g twice daily can provide clinically relevant symptomatic relief, indicating that INS can be used to ease patients' symptoms while their ARS resolves without antibiotics. A full 2.5 days' advantage in median time to minimal symptoms offers the potential for earlier return to work and normal functioning. This adds to the literature indicating the benefits of INS monotherapy in ARS, as also shown in a recent retrospective analysis including 12,864 patients with ARS who received MFNS or antibiotics or both; the analysis found that patients who received MFNS without antibiotics or combination therapy had fewer subsequent doctor visits related to their ARS than did those who received antibiotics alone ($P \leq .001$).²⁴ However, because the strength of evidence from a retrospective analysis or the present post hoc analysis is limited, further confirmation from prospectively designed trials would be welcome.

In this post hoc analysis of data from a multicenter, randomized, placebo-controlled trial, MFNS 200 μ g twice daily provided a significantly greater percentage of minimal-symptom days vs amoxicillin 500 mg 3 times daily or placebo, whereas MFNS 200 μ g once daily provided a numerically greater percentage of minimal-symptom days vs amoxicillin 500 mg 3 times daily or placebo. Efficacy of MFNS in relieving congestion, the most severe symptom at baseline, was noteworthy, because patients receiving MFNS 200 μ g twice daily experienced significantly more minimal-congestion days vs those taking amoxicillin or placebo, and patients receiving MFNS 200 μ g once daily experienced significantly more minimal-congestion days vs those receiving placebo. MFNS onset of action was rapid; patients receiving MFNS 200 μ g twice daily saw significant reductions in MSS vs placebo as early as day 2, whereas MFNS 200 μ g once daily achieved superiority to placebo at day 2, although this was not maintained. MFNS 200 μ g twice daily was associated with a significantly shorter time to first minimal-symptom day sustained until study end vs placebo; this may allow patients to return to work and normal life earlier. Quick induction of relief and significantly more minimal-symptom days with MFNS 200 μ g twice daily vs amoxicillin or placebo suggest that for most patients with uncomplicated ARS, symptomatic relief can be achieved rapidly and without concomitant antibiotic therapy with MFNS 200 μ g twice daily.

Acknowledgment

Medical writing and editorial assistance was provided by Rob Coover, MPH, of AdelphiEden Health Communications, New York,

NY. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

References

- [1] Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg*. 2007;137(Suppl 3):S1–S31.
- [2] Fokkens W, Lund V, Mullol J, European Position Paper on Rhinosinusitis and Nasal Polyps group. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology*. 2007;20(Suppl):1–136.
- [3] Pleis JR, Lucas JW. Summary health statistics for U.S. adults: National Health Interview Survey, 2007. National Center for Health Statistics. *Vital Health Stat* 10. 2007;235:1–153.
- [4] Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg*. 2004;131(6 Suppl):S1–S62.
- [5] Klossek JM, Mesbah K. Presentation and treatment of acute maxillary sinusitis in general practice: a French observational study. *Rhinology*. 2011;49:84–89.
- [6] Graft D, Aaronson D, Chervinsky P, 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;98:724–731.
- [7] Casale TB, Condemni J, LaForce C, et al. Omalizumab Seasonal Allergic Rhinitis Trial Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA*. 2001;286:2956–2967.
- [8] Nelson H, Graft D, Gates D, Gopalan G. Mometasone furoate nasal spray (MFNS) increases the number of days with minimal symptoms in patients with PAR. Poster presented at: American College of Allergy, Asthma and Immunology 2010 Annual Scientific Meeting, November 11–16, Phoenix, AZ.
- [9] Clement P, Gates D, Gopalan G. Mometasone furoate nasal spray significantly increases time-to-symptom recurrence in subjects with perennial allergic rhinitis. *Allergy*. 2009;64(Suppl. 90):S94.
- [10] Nayak AS, Settipane GA, Pedinoff A, et al. Nasonex Sinusitis Group. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann Allergy Asthma Immunol*. 2002;89:271–278.
- [11] Zalmanovici A, Yappe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev*. 2007;18:CD005149.
- [12] Meltzer EO, Charous BL, Busse WW, Zinreich SJ, Lorber RR, Danzig MR, the Nasonex Sinusitis Group. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. *J Allergy Clin Immunol*. 2000;106:630–637.
- [13] Barlan IB, Erkan E, Bakir M, Berrak S, Basaran MM. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol*. 1997;78:598–601.
- [14] Dolor RJ, Witsell DL, Hellkamp AS, Williams JW Jr, Califf RM, Sime DL, Ceftin and Flonase for Sinusitis (CAFFS) Investigators. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. *JAMA*. 2001;286:3097–3105.
- [15] Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol*. 2005;116:1289–1295.
- [16] Gill JM, Fleischut P, Haas S, Pellini B, Crawford A, Nash DB. Use of antibiotics for adult upper respiratory infections in outpatient settings: a national ambulatory network study. *Fam Med*. 2006;38:349–354.
- [17] Zucker D, Engels EA, Balk E, et al. Agency for Health Care Policy and Research. Publication # 99-E-016. Evidence Report/Technology Assessment Number 9. Diagnosis and treatment of acute bacterial rhinosinusitis.
- [18] Bucher HC, Tschudi P, Young J, et al. Effect of amoxicillin-clavulante in clinically diagnosed acute rhinosinusitis: a placebo-controlled, double-blind, randomized trial in general practice. *Arch Intern Med*. 2003;163:1793–1798.
- [19] Van Buchem FL, Knottnerus JA, Schrijnemaekers VJJ, Peeters MF. Primary care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. *Lancet*. 1997;349:683–687.
- [20] Stalman W, van Essen GA, van der Graaf Y, De Melker RA. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? A placebo-controlled double-blind randomized doxycycline trial. *Br J Gen Pract*. 1997;47:794–799.
- [21] Puhakka T, Mäkelä MJ, Malmström K, et al. The common cold: effects of intranasal fluticasone propionate treatment. *J Allergy Clin Immunol*. 1998;101:726–731.
- [22] Williamson IG, Rumsby K, Bengt S, et al. Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. *JAMA*. 2007;298:2487–2496.
- [23] Bachert C, Meltzer EO. Effect of mometasone furoate nasal spray on quality of life of patients with acute rhinosinusitis. *Rhinology*. 2007;45:190–196.
- [24] Maiese EM, de Moor C, Reardon G, McLaughlin J, Navaratnam P. Effectiveness of mometasone furoate nasal spray with or without antibiotics vs antibiotic monotherapy in patients with acute rhinosinusitis in the United Kingdom. *J Allergy Clin Immunol*. 2011;127(2 suppl 1):AB120.