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Effect of mometasone furoate nasal spray on quality of life of patients with acute rhinosinusitis*

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SUMMARY

This study evaluated the effect of mometasone furoate nasal spray (MFNS) on health-related quality of life (HRQoL) in patients with acute, uncomplicated rhinosinusitis. In a randomized, double-blind, placebo-controlled trial, HRQoL was assessed in 340 patients using the Sino-Nasal Outcome Test (SNOT)-20 questionnaire at baseline and after 15 days of treatment with MFNS 200 g once-daily (q.d.) or twice-daily (b.i.d.), amoxicillin 500 mg three times daily (t.i.d.), or placebo. Baseline mean total scores for SNOT-20 were similar in the four groups (2.15–2.23). At endpoint, there was a statistically significant improvement in mean total score only with MFNS 200 g b.i.d. ($p = 0.047$ versus placebo). MFNS was associated with numerical improvements in all SNOT-20 items compared with placebo. Treatment with MFNS 200 g b.i.d. is associated with a significant improvement in HRQoL compared with placebo in patients with acute, uncomplicated rhinosinusitis.

Key words: acute rhinosinusitis, mometasone furoate, congestion, quality of life

INTRODUCTION

Acute rhinosinusitis (ARS) is a common upper respiratory tract disorder that involves inflammation of the nasal and paranasal sinus mucosa [1-3]. Symptoms associated with ARS generally last from several days to up to 4 weeks, although recent definitions of ARS state that symptoms can persist continuously or intermittently for up to 12 weeks [3]. Typical symptoms of ARS include congestion, purulent discharge, fever, headache, facial pain/pressure, dental pain, postnasal drip, cough, and tenderness around the sinus area [1,2].

ARS is thought to have a substantial impact on patients' health-related quality of life (HRQoL) and daily functioning, but this has not been well documented. It has been established, however, that patients with chronic rhinosinusitis (CRS) and nasal polyposis have functional and emotional impairments that substantially worsen their HRQoL [4,5]. HRQoL can be improved considerably in these patients by medical and surgical interventions [6,7], and guidelines now recommend that HRQoL measurements be included in clinical trials of interventions for ARS [2].

Current treatment for ARS commonly involves antibiotic therapy, although the use of antibiotics in the management of ARS is controversial [8]. A review of clinical studies found that treatment of ARS with antibiotics reduces the clinical failure rate by half and cures patients more quickly and more often than no treatment [8]. However, other reviews of clinical trial data have concluded that antibiotics afford little, if any, benefit over placebo [9,10]. Guidelines for the treatment of ARS recommend the initiation of antibiotic therapy if symptoms worsen after 5 to 7 days or persist after more than 10 days and are moderate or severe [11].

Studies have established, however, that intranasal corticosteroids are useful as adjunctive therapies to antibiotics in ARS [12–15]. For example, patients with ARS receiving mometasone furoate nasal spray (MFNS) 400 g twice daily (b.i.d.) plus amoxicillin/clavulanate potassium (ACP; 875 mg b.i.d.) for 21 days experienced a significantly greater reduction in total symptom score ($p < 0.01$) and individual symptom scores for nasal congestion, headache, and facial pain/pressure (all $p < 0.01$) than those patients who received ACP alone [13].

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In a recent multicenter, randomized, controlled study conducted to evaluate the efficacy and safety of MFNS monotherapy versus that of placebo or amoxicillin, MFNS was significantly superior to both placebo ($p < 0.001$) and amoxicillin ($p = 0.002$) for improvement of major symptoms of ARS [16]. At the time of the trial, no validated, disease-specific instruments for assessing HRQoL or the response to treatment in ARS were available [17]. The Sino-Nasal Outcome Test (SNOT)-20 questionnaire has, however, been validated in patients with CRS [18], and this instrument was used to assess the impact of ARS on HRQoL in a subset of patients from this study. This paper reports the effects of MFNS monotherapy on HRQoL compared with those of placebo or amoxicillin in patients with acute, uncomplicated rhinosinusitis.

METHODS

Protocol

The study was a randomized, double-blind, double-dummy, placebo-controlled trial conducted at 71 centers in 14 countries. The study was approved by local institutional review boards and conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice. All patients (and/or their guardian) provided written informed consent.

Male and female patients at least 12 years of age were eligible for the study. Participants were required to have had symptoms of ARS for at least 7 days but not more than 28 days, with a major symptom score (MSS) of 5 to 12 at screening and baseline visits (see below for details of symptom scoring). In addition, no more than three of the five specified rhinosinusitis symptoms (rhinorrhea, postnasal drip, nasal congestion, headache, and facial pain/pressure) were to be rated as "severe." The main exclusion criteria for the study were: symptoms suggestive of fulminant bacterial rhinosinusitis (i.e. fever with a temperature of 101°F/38.3°C or above, persistent severe unilateral facial or tooth pain, facial swelling, dental involvement, or a worsening of symptoms after initial improvement); CRS or sinus or nasal surgery for CRS in the past 6 months; otitis or atrophic rhinitis; nasal polyps noted on anterior rhinoscopic examination; Kartagener's syndrome; or active symptomatic allergic rhinitis. Patients with asthma needed to be relatively stable, with no history of exacerbations within 30 days before screening and a forced expiratory volume in 1 second at least 65% of predicted within 3 months before screening. Concomitant medications that were not allowed during the study included nasal saline, nasal cromolyn sodium, ipratropium bromide, corticosteroids (excluding inhaled corticosteroids for mild-to-moderate persistent asthma), antihistamines, decongestants, and leukotriene pathway modifiers. Analgesics or non-steroidal anti-inflammatory drugs were not permitted for treatment of ARS.

Eligible patients were randomly assigned (1:1:1:1) to receive treatment with MFNS 200 µg q.d. (given in the morning) plus placebo spray in the evening, MFNS 200 µg b.i.d., amoxicillin 500 mg three times daily (t.i.d.), or placebo. Patients receiving MFNS were also given a matching placebo capsule t.i.d., whereas those receiving amoxicillin were given a matching placebo nasal spray b.i.d. Patients in the placebo group received placebo capsules t.i.d. and placebo nasal spray b.i.d. In all groups, nasal sprays were given for 15 days and capsules for the first 10 days. Treatment visits occurred at baseline and on days 8, 15 (end of treatment), and 29 (end of 14-day no-treatment follow-up period).

Health-related quality-of-life assessments

HRQoL was evaluated using the SNOT-20 questionnaire [18], which was administered at baseline and at day 15 or at the last treatment visit (endpoint). Because the SNOT-20 questionnaire has not been validated for CRS in languages other than English, it was administered only in the subgroup of patients in the study who were from English-speaking countries.

The SNOT-20 questionnaire consists of 20 items that assess the symptoms and emotional and social consequences of rhinosinusitis over the preceding 2 weeks, and takes approximately 10 minutes to complete. Each item is scored on a scale of 0 to 5 (0, no problem; 1, very mild problem; 2, mild/slight problem; 3, moderate problem; 4, severe problem; 5, problem as bad as it can get), with the mean total score calculated as the mean of the 20 individual item scores. A clinically meaningful change in HRQoL is indicated by a change in SNOT-20 score of 0.8 or more [18]. Patients were also asked to indicate the five items from the questionnaire that were most important to them.

HRQoL assessments also included interference by ARS with sleep and daily functioning. During the treatment period (not including baseline), patients rated interference with sleep and daily activities resulting from their rhinosinusitis symptoms on a daily basis, using a scale of 0 to 3 (0, no interference; 1, mild interference; 2, moderate interference; 3, severe interference).

Efficacy assessments

The severity of each symptom (rhinorrhea, postnasal drip, nasal congestion, headache, facial pain/pressure, and cough) was rated jointly by the investigator and the patient at each visit. Severity was also assessed twice daily by the patient and recorded in a diary. Symptom severity was scored using a scale from 0 to 3 (0, none; 1, mild; 2, moderate; 3, severe). MSS was defined as the sum of the score of the five rhinosinusitis symptoms excluding cough. Total symptom score was defined as the sum of the score of all six symptoms. The global response to treatment was assessed jointly by the investigator and the patient at the end of treatment, with response being rated on a scale of 0 to 4 (0, complete relief; 1, marked relief; 2, moderate relief; 3, slight relief; 4, no relief).

Tolerability assessments

Safety assessments included adverse events, vital signs, a limit-

ed physical examination, a nasal examination, and clinical laboratory tests.

Statistical methods

Analyses and summaries were based on the group that included all randomized patients (intent-to-treat analysis). The primary efficacy endpoint in the study was the mean morning/evening MSS over the 15-day treatment period, which was analyzed using an analysis of variance (ANOVA) model that included sources of variability resulting from treatment, center, and duration of previous sinusitis episode. The primary and secondary treatment comparisons were MFNS 200 g b.i.d. versus placebo and versus amoxicillin, respectively. Pairwise treatment comparisons were based on the least-squares (LS) means from the ANOVA model and were tested at a two-sided α level of 0.05.

The study was powered (90% at a two-sided α level of 0.049) to detect a difference of at least 0.7 points in mean morning/evening MSS over days 1 to 15 between treatment groups. This provided a target sample size of approximately 940 patients (235 patients per treatment group).

The analysis of quality of life was exploratory. The primary HRQoL variable of interest was the change from baseline in the SNOT-20 mean total score. Pairwise comparisons between treatments were based on contrasts of the LS means from the ANOVA model. For the individual SNOT-20 items, no statistical analyses were performed and only descriptive statistics are presented.

RESULTS

A total of 981 patients were randomly assigned to treatment, with 243 receiving MFNS 200 µg q.d., 235 receiving MFNS 200 µg b.i.d., 251 receiving amoxicillin, and 252 receiving placebo. The majority of patients in each treatment group completed the study (Figure 1).

There were no clinically relevant differences between the treatment groups with regard to the baseline characteristics of patients (Table 1). Baseline symptom data were also similar. The mean MSS range at baseline was 8.17 to 8.53, indicating that most patients had mild-to-moderate disease.

Quality of life

The SNOT-20 questionnaire was administered to 340 patients enrolled in the study. The 331 patients who completed the questionnaire at baseline and endpoint included 81 patients receiving MFNS 200 µg q.d., 84 receiving MFNS 200 µg b.i.d., 84 receiving amoxicillin 500 µg t.i.d., and 82 receiving placebo (Figure 1). The baseline LS mean total scores for SNOT-20 were similar in the four treatment groups, ranging from 2.15 in both MFNS treatment groups to 2.23 in the amoxicillin group and 2.22 in the placebo group.

There was a clinically meaningful (≥ 0.8) improvement (reduction) in LS mean total scores on the SNOT-20 questionnaire in all four treatment groups at endpoint (Figure 2), but the only significantly greater improvement was with MFNS 200 µg b.i.d. (1.36) versus placebo (1.08; $p = 0.047$). No other pairwise treatment comparisons demonstrated significant between-treatment differences.

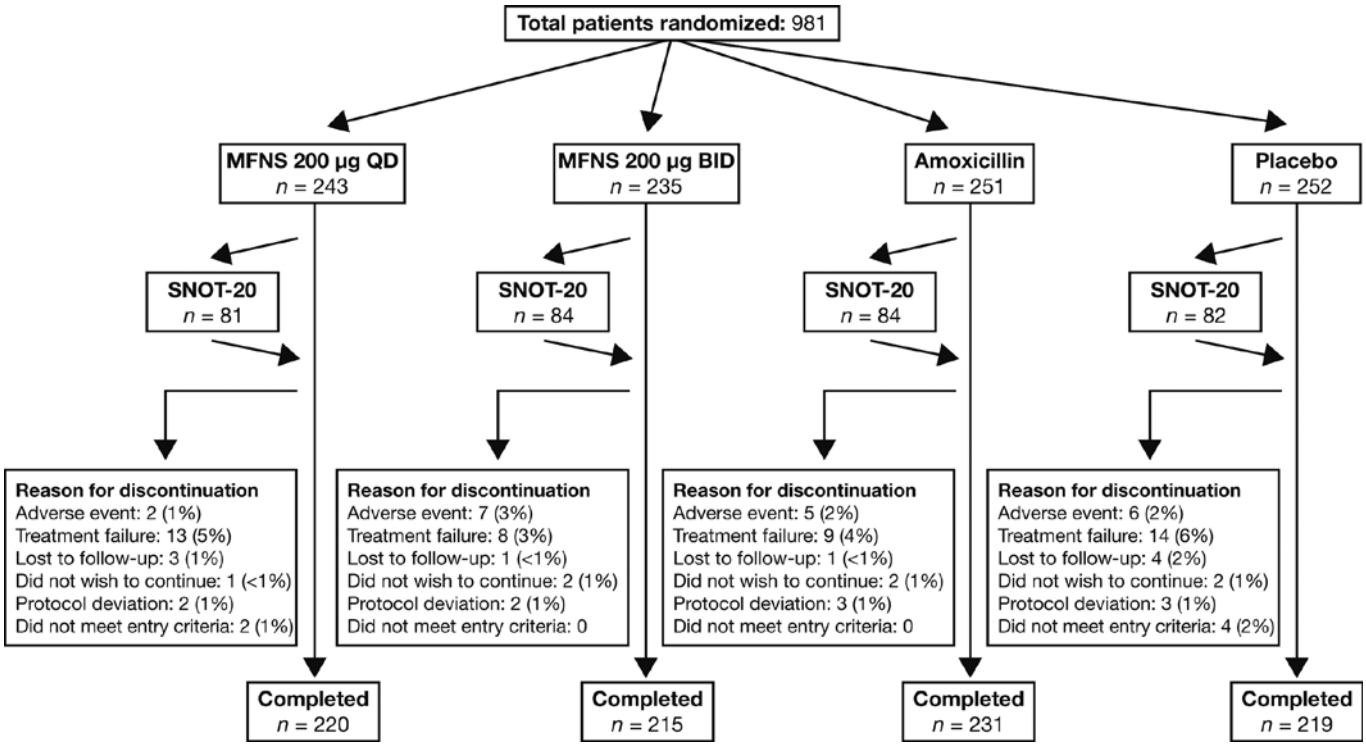

Figure 1. Study disposition by treatment group.

Table 1. Patient demographic data.

	MFNS 200 µg q.d. a.m. (n = 243)	MFNS 200 µg b.i.d. (n = 235)	Amoxicillin 500 mg t.i.d. (n = 251)	Placebo (n = 252)
Mean age, years (range)	35.9 (12–76)	34.8 (12–66)	35.9 (12–69)	34.4 (12–68)
Male, %	33	37	30	38
Mean weight, kg	72.61	71.48	69.05	71.05
History of SAR, %	16	21	16	17
History of PAR, %	27	28	23	27
Duration of prior rhinitis symptoms, %				
1-2 weeks	67	65	61	58
>2-4 weeks	33	35	39	42
Mean morning/ evening MSS	8.17	8.28	8.53	8.36

Table 2. Mean improvement (reduction) in individual SNOT-20 items from baseline to endpoint in patients treated with MFNS 200 µg b.i.d. versus placebo.

	MFNS 200 µg b.i.d. (n = 84)		Placebo (n = 82)		
	Mean baseline score	Mean improvement from baseline	Mean baseline score	Mean improvement from baseline	Treatment difference
Night waking	2.44	1.7	2.63	1.1	0.6
Thick nasal discharge	2.52	1.7	2.66	1.2	0.5
Reduced concentration	2.06	1.4	2.02	1.0	0.4
Fatigue	2.61	1.6	2.65	1.2	0.4
Postnasal discharge	3.11	1.4	3.01	1.0	0.4
Reduced productivity	2.07	1.3	1.98	0.94	0.36
Sneezing	2.04	1.3	2.05	0.99	0.31
Frustrated	2.26	1.6	2.43	1.3	0.3
Need to blow nose	2.89	1.4	3.01	1.1	0.3
Runny nose	2.69	1.4	2.76	1.1	0.3
Cough	2.07	1.3	2.02	1.0	0.3
Sad	0.95	0.71	0.93	0.44	0.27
Embarrassed	0.76	0.56	0.67	0.34	0.22
Lack of sleep	2.51	1.6	2.85	1.4	0.2
Wake up tired	2.69	1.5	2.96	1.3	0.2
Difficulty falling asleep	2.07	1.4	2.40	1.2	0.2
Facial pain/pressure	2.43	1.4	2.54	1.2	0.2
Ear fullness	2.10	1.2	2.07	1.0	0.2
Dizziness	1.06	0.84	1.26	0.76	0.08
Ear pain	1.23	0.74	1.21	0.67	0.07

Table 3. Interference with daily activities and with sleep during 2 weeks' treatment with MFNS, amoxicillin, or placebo.

	Interference with daily activities*			Interference with sleep*		
	Mean score, Days 2–15	p value		Mean score, Days 2–15	p value	
		Versus placebo	Versus amoxicillin		Versus placebo	Versus amoxicillin
MFNS 200 µg q.d. (n = 240)	0.82	0.026	0.736	0.73	0.071	0.755
MFNS 200 µg b.i.d. (n = 234)	0.76	< 0.001	0.135	0.66	0.002	0.286
Amoxicillin 500 mg t.i.d. (n = 249)	0.83†	0.056	–	0.71	0.032	–
Placebo (n = 247)	0.93†	–`–	0.82	–	–	

* Interference with daily activities and sleep were scored on a seale from 0 (none) to 3 (severe). Higher score indicates worse interference with daily activities or sleep.

† Values for two subjects missing.

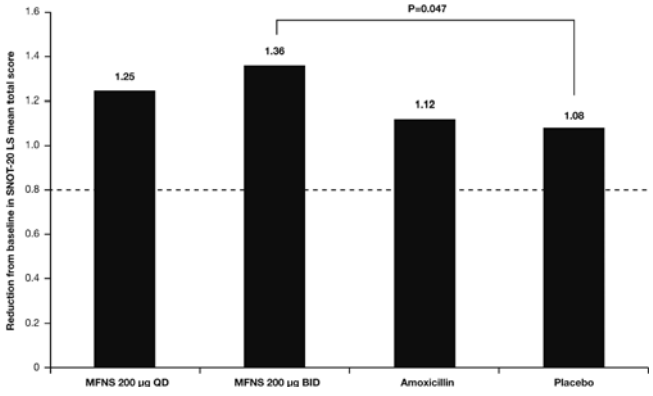

Figure 2. Improvement (reduction) in Sino-Nasal Outcome Test-20 least-squares (LS) mean total score from baseline to endpoint. Dotted line indicates level of a clinically meaningful change. LS means were obtained from the ANOVA model with effects for treatment and site.

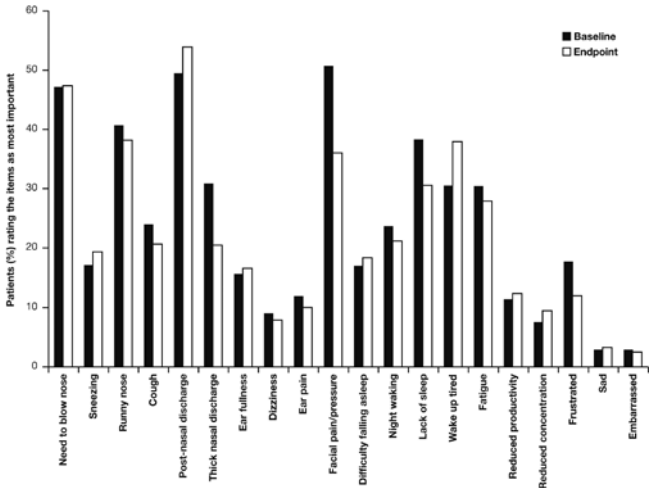

Figure 3. Individual Sino-Nasal Outcome Test-20 items rated to be most important by patients at baseline and endpoint (patients could select up to five items).

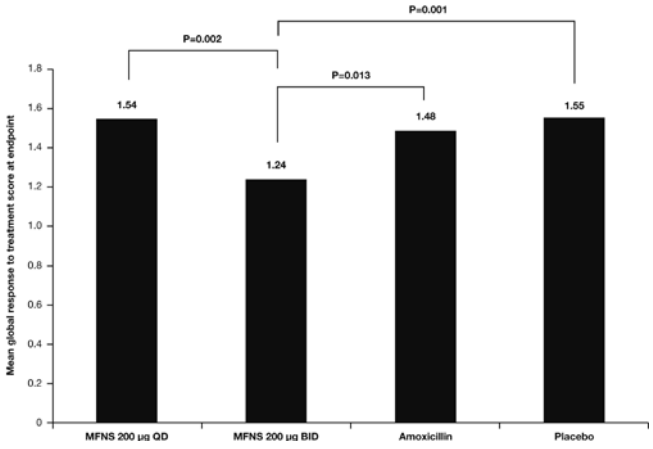

Figure 4. Global response to treatment at the end of treatment with mometasone furoate nasal spray, amoxicillin, or placebo. Least-square means were obtained from the ANOVA model with effects for treatment, site, and duration of symptoms. A lower score indicates greater relief of symptoms.

There was a greater numerical improvement (reduction) in all 20 individual items of the SNOT-20 with MFNS 200 µg b.i.d. than with placebo. Treatment differences ranged from 0.07 to 0.6 points (Table 2). The greatest improvement from baseline with MFNS 200 µg b.i.d. (1.7) and the greatest difference from placebo (0.6) were for the individual item night waking (Table 2). The percentages of patients who considered each SNOT-20 item as one of the five most important in affecting their health at baseline and endpoint are shown in Figure 3. The five SNOT items that were considered to be most important by patients at baseline (in descending order of frequency) were facial pain/pressure, postnasal discharge, need to blow nose, runny nose, and lack of a good night's sleep (highlighted rows in Table 2). These five items were similar among the four treatment groups at baseline, and all showed greater numerical improvement with MFNS 200 µg b.i.d. than with placebo.

Treatment with MFNS µg b.i.d. also was associated with a statistically significant reduction in ARS-related interference with sleep and daily activities. Patients receiving MFNS 200 µg b.i.d. reported significantly less interference with daily activities than those receiving placebo ($p < 0.001$) over the 15-day treatment period (Table 3). Similarly, there was significantly less interference with sleep in the MFNS 200 µg b.i.d. group than in the placebo group ($p = 0.002$) (Table 3). In addition, MFNS 200 µg q.d. was significantly better than placebo with regard to interference with daily activities ($p = 0.026$), and amoxicillin was significantly better than placebo with regard to interference with sleep ($p = 0.032$).

Efficacy

Efficacy results from the study have been reported in full previously [14] and will be summarized here. For the primary efficacy variable of mean MSS over the 15-day treatment period, MFNS 200 µg b.i.d. was significantly superior to placebo ($p < 0.001$) and amoxicillin ($p = 0.002$) (Table 4). In addition, MFNS 200 µg q.d., but not amoxicillin, was significantly superior to placebo ($p = 0.018$). At the end of treatment, MFNS 200 µg b.i.d. demonstrated a significant improvement over MFNS 200 µg q.d. ($p = 0.002$), placebo ($p = 0.001$), and amoxicillin ($p = 0.013$) in terms of the global response to treatment (Figure 4).

Tolerability

All treatments were well tolerated and there were no unexpected adverse events. The incidence of treatment-emergent adverse events was similar among the four treatment groups, with 35.4%, 36.2%, 33.5%, and 38.1% of patients experiencing adverse events in the MFNS 200 µg q.d., MFNS 200 µg b.i.d., amoxicillin, and placebo groups, respectively. Overall, the most frequently reported treatment-related adverse events were epistaxis (which included a wide range of bleeding episodes, from frank bleeding to bloody nasal discharge to flecks of blood in the mucus) (3.8%) and headache (2.3%). Treatment-related epistaxis was reported by more patients in the MFNS 200 µg b.i.d. group (5.1%) than in the MFNS 200 µg q.d. (3.3%), amoxi-

Table 4. Effect of treatment on mean MSS during 2 weeks' treatment.

	Mean MSS		Treatment difference over days 2–15			
	Baseline	Days 2–15	Versus placebo	p value	Versus amoxicillin	p value
MFNS 200 μg q.d.	8.17	4.16	0.45	0.018	0.24	0.192
MFNS 200 μg b.i.d.	8.28	3.80	0.81	<0.001	0.60	0.002
Amoxicillin 500 mg t.i.d.	8.53	4.40	0.21	0.275	–	–
Placebo	8.36	4.61	–	–	–	–

cillin (3.2%), and placebo (3.6%) groups. No clinically meaningful changes in laboratory parameters, vital signs, or limited physical examination were noted in any treatment group.

DISCUSSION

The patients in this study had acute, uncomplicated rhinosinusitis and were chosen to represent the general population of patients presenting with symptoms of ARS in general practice. Patients were enrolled based solely on clinical diagnostic criteria, and those with a high probability of having a bacterial infection were excluded. Thus, patients in the current study were likely to be suffering from inflammation as the result of a viral infection or a mild-to-moderate bacterial infection.

The results of the study demonstrate that patients with acute, uncomplicated rhinosinusitis have an impaired HRQoL and that monotherapy with MFNS 200 μg b.i.d. is effective in improving HRQoL in such patients. Notably, MFNS 200 μg b.i.d. was effective in improving those problems that were considered to be most important by patients. The reduction in SNOT-20 scores also showed that patients receiving MFNS 200 μg b.i.d. had greater improvements in their nasal symptoms and sleep problems than placebo recipients. This, in turn, was associated with an improvement in patient functioning and emotional well-being. The effects of MFNS on HRQoL are in addition to its beneficial effects on the symptoms of ARS, as reported previously [16]: treatment with MFNS 200 μg b.i.d. for 15 days resulted in significantly greater improvements in overall symptoms (mean MSS) and in individual symptoms of sinus headache, facial pain/pressure, rhinorrhea, and nasal congestion than those seen with placebo treatment ($p < 0.001$).

MFNS 200 μg b.i.d. produced a significantly greater improvement in the SNOT-20 mean total score than that seen with placebo ($p = 0.047$). There was, however, no significant difference between the lower dose of MFNS (200 μg q.d.) and placebo in the improvement in SNOT-20 mean total score. These findings are consistent with the superiority of MFNS 200 μg b.i.d. over placebo with regard to symptom relief and suggest that the higher dose of MFNS is required for effective treatment of ARS. Indeed, a previous study of MFNS as adjunctive therapy to antibiotics in the treatment of rhinosinusitis supports the use of MFNS 200 μg b.i.d. in this condition [15].

There was a clinically meaningful improvement in HRQoL after 2 weeks' treatment in all four treatment groups. This could be explained as a consequence of the improvement or resolution of the disease process and is reflected both in the symptomatic improvement and in the global response to treatment.

The lack of a good night's sleep was one of the five SNOT-20 items that was rated as being most important by patients, with night waking as the individual SNOT-20 item that showed the greatest numerical improvement with MFNS 200 μg b.i.d. The daily ratings of interference with sleep during treatment also showed that patients with ARS experienced mild sleep disturbance and that those who were treated with MFNS 200 μg b.i.d. experienced significantly less interference with sleep and interference with daily activities than placebo recipients. Sleep disturbance as a result of ARS has not been well studied, but studies in patients with allergic rhinitis, in which nasal congestion is also a predominating symptom, indicate that nasal congestion is indeed associated with sleep disturbance [19]. Moreover, treatment with topical corticosteroids in patients with allergic rhinitis can alleviate nasal congestion and improve sleep quality and patients' quality of life [19,20]. As mentioned previously, in the current study, MFNS 200 μg b.i.d. provided effective relief from nasal congestion in patients with ARS [16]. Taken together, these findings indicate that improvement of nasal congestion and reducing sleep disturbance are two ways that MFNS 200 μg b.i.d. may improve HRQoL in patients with ARS.

Few previous studies have examined the effects of treatments for ARS on HRQoL. Moreover, the few studies that have been performed have examined the effects of antibiotics and used different instruments for measuring HRQoL [21,22]. The SNOT-20 questionnaire, although not validated for use in patients with ARS at the time of this study, was selected for use as the most appropriate health-status/quality-of-life tool available. It should be noted, however, that the HRQoL analysis reported here was exploratory only. In addition, the SNOT-20 questionnaire was used only at two time points-baseline and end of treatment.

In conclusion, the results of this multicenter, randomized, placebo-controlled study demonstrate that MFNS monotherapy is a safe and effective treatment for adult patients with acute, uncomplicated rhinosinusitis. Overall, MFNS 200 μg b.i.d. provided a significantly greater improvement in HRQoL in the MFNS 200 μg b.i.d. group than in the placebo group, as reflected in the SNOT-20 mean total score. Further controlled studies are warranted to assess HRQoL as a primary outcome in patients with ARS treated with intranasal corticosteroids.

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