

Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis

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Abstract

Background: Intranasal corticosteroids (INSs) are a mainstay of treatment of allergic rhinitis (AR) nasal symptoms. The INS mometasone furoate nasal spray (MFNS) has well-documented efficacy and safety for the treatment and prophylaxis of nasal symptoms of seasonal AR (SAR) and for the treatment of nasal symptoms of perennial AR (PAR). Increasing interest has focused on whether INSs, including MFNS, may have beneficial effects on the ocular symptoms frequently associated with AR.

Methods: We performed a meta-analysis of 10 randomized, placebo-controlled trials of the efficacy of MFNS 200 mcg daily in relieving ocular allergy symptoms, including itching/burning, redness, and tearing/watering in both SAR and PAR. Four PAR studies and six SAR studies are included in the analysis. A fixed-effect inverse variance model was used to calculate weighted mean differences, 95% confidence intervals (CIs) for each comparison, and a combined overall treatment effect (Z) with P -value.

Results: In both analyses of SAR and PAR studies, including 3132 patients, all individual ocular symptoms were reduced in patients treated with MFNS. Overall treatment effect was significant for all three individual ocular symptoms in the SAR studies ($Z = 9.18$ for tearing, $Z = 10.15$ for itching, and $Z = 8.88$ for redness; $P < 0.00001$ for all) and in the PAR studies ($Z = 5.94$, $P < 0.00001$ for tearing; $Z = 2.43$, $P = 0.02$ for itching; and $Z = 2.42$, $P = 0.02$ for redness).

Conclusions: Our findings add to the growing body of literature supporting the positive class effect of INSs, including MFNS, on ocular symptoms associated with SAR and PAR.

Intranasal corticosteroids (INSs) are a mainstay of allergic rhinitis (AR) treatment based on their superior efficacy and safety in the treatment of AR nasal symptoms (1). Mometasone furoate nasal spray (MFNS) is an INS that is administered once daily; it has minimal systemic absorption and well-documented efficacy and safety for the treatment and prophylaxis of nasal symptoms of seasonal AR (SAR) and for the treatment of nasal symptoms of perennial AR (PAR) (2–6). More recently, a meta-analysis of 16 randomized, double-blind, placebo-controlled trials of MFNS for the treatment of AR provides level Ia evidence of its efficacy in treating nasal and non-nasal symptoms in SAR and PAR (7).

Increasing interest has focused on whether INSs, including MFNS, may have beneficial effects in reducing the ocular

symptoms frequently associated with AR (8). The eye is particularly susceptible to AR symptoms (itching [pruritis], redness [erythema], and tearing [epiphoria]) because it lacks a mechanical barrier to prevent the deposition of allergens, such as pollen, on the conjunctival surface (9). As such, AR is more appropriately termed allergic rhinoconjunctivitis because of these bothersome ocular symptoms that commonly coexist with nasal symptoms, particularly in patients with SAR (10). In fact, perhaps AR should be at times called conjunctivorhinitis. Current data indicate that ocular allergy symptoms have a substantial negative impact on patient quality of life and health care costs (11–13).

The effects of MFNS in alleviating ocular allergy symptoms have been assessed both prospectively (14) and

retrospectively (15–18) as part of several clinical trials of MFNS for the treatment of SAR. The data support the positive effect of MFNS on ocular allergy symptoms associated with SAR. The present meta-analysis was conducted to evaluate the efficacy of MFNS for treating ocular symptoms in patients with SAR and in patients with PAR.

Methods

Study selection

In the analysis of both the PAR and SAR data, clinical studies were selected and analyzed based on the following design considerations: randomized, double-blind, placebo-controlled studies with MFNS 200 mcg administered once daily in the morning in symptomatic patients ≥ 12 years of age with SAR or PAR.

Four studies are included in the PAR analysis and six studies in the SAR analysis. In all four of the PAR studies and four of the six SAR studies, the primary endpoint of the individual studies was analysis of nasal symptoms, although data on non-nasal symptoms (i.e. ocular symptoms and ear and palate itching) were collected. Data on the efficacy and tolerability of MFNS in treating the nasal symptoms (3, 5, 6, 19, 20) and efficacy in treating the ocular symptoms (17, 18) of AR in these studies have been reported elsewhere. Raw data on ocular symptoms for this analysis were provided by the study sponsor. The other two SAR studies included in this analysis prospectively evaluated MFNS for the treatment of ocular symptoms (20, 21).

In the SAR studies, patients had a minimum 2-year history of SAR documented by a positive skin-prick test reaction (wheal diameter ≥ 3 mm greater than diluent control) to a seasonal allergen within the last year and were clinically symptomatic at screening and baseline visits. Among the four SAR studies in which the primary endpoint had been analysis of nasal symptoms, minimum screening and baseline symptom scores were total nasal symptom score (TNSS) ≥ 6 , nasal congestion score ≥ 2 , and non-nasal symptom score ≥ 5 . No minimum ocular symptom score was required at baseline. Treatment duration was 15 days in three of the studies and 29 days in the fourth, but only data from the first 15 treatment days of the latter study were included in this meta-analysis.

In the two SAR studies that prospectively evaluated ocular symptom outcomes, minimum symptom scores at screening were rhinorrhea ≥ 2 ; nasal congestion ≥ 2 ; TNSS (sum of individual symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing) ≥ 6 (moderate to severe); total ocular symptom score (TOSS, sum of individual symptom scores for ocular itching, tearing/watering, and ocular redness) ≥ 4 ; and overall evaluation of SAR ≥ 2 (moderate). Treatment duration was 15 days.

In the PAR studies, patients had a confirmed ≥ 2 -year history of PAR with skin test positivity to a perennial extract including dust mites, molds, or animal dander. Patients had to be clinically symptomatic at screening and baseline (nasal rhinorrhea and/or congestion score ≥ 2 , TNSS ≥ 5), but no

minimum ocular symptom score was required at baseline. Study duration was 12 weeks, but only data from the first 30 days were analyzed.

Efficacy assessments

During the run-in (3 days) and treatment periods, patients rated the severity of their ocular symptoms (itching/burning, redness, and tearing/watering) on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Symptom scores assessing severity over the previous 12 h (prior) were recorded in a diary each morning (AM) on arising prior to administration of MFNS and approximately 12 h later in the evening (PM). Therefore, the evening entries reflected daytime symptoms and morning entries reflected nighttime symptoms. The daily prior score for each symptom was obtained from the average of the reflective AM and PM individual symptom scores.

Statistical analysis

Two meta-analyses were performed: one evaluated the treatment effect of MFNS 200 mcg daily on ocular symptoms in SAR; the other evaluated the treatment effect of MFNS 200 mcg daily on ocular symptoms in PAR. Data from treatment days 1 to 15 were analyzed in the six SAR studies, and data from treatment days 1 to 29 were analyzed in the four PAR studies. Each of the daily observations for each study was entered into analysis; thus, there were 90 measures of treatment effect from the 15 daily observations in the six SAR studies and 116 measures of treatment effect from the 29 daily observations in the four PAR studies. Overall treatment effect was analyzed using RevMan™ (version 5; Cochrane collaboration, Oxford, UK). We used a fixed-effect inverse variance model to calculate weighted mean differences, 95% confidence intervals (CIs) for each comparison, and a combined overall treatment effect (Z) with P -value. Study heterogeneity (i.e. between-study variability) was evaluated with the Cochran's Q statistic test (distributed as a chi-squared [χ^2] statistic with k [number of studies] – 1 degrees of freedom) and the calculation of the I-squared (I^2) statistic. The I^2 statistic describes the percentage of variation across studies that is because of heterogeneity rather than chance and ranges from 0 (no heterogeneity) to 100 (maximum heterogeneity) (22).

Results

The characteristics of the four PAR and six SAR randomized, controlled trials included in this meta-analysis are summarized in Table 1 (5, 6, 14, 17, 19, 21). Among the 1833 patients with SAR included in the efficacy analysis, 920 were randomized to receive MFNS and 913 were randomized to receive placebo. Among the 1299 patients in the PAR studies' efficacy evaluable population, 651 patients received MFNS and 648 patients received placebo. Mean baseline demographic characteristics were comparable between treatment and placebo groups among the four retrospectively analyzed

Table 1 Characteristics of clinical trials in this meta-analysis of efficacy of MFNS vs placebo for ocular symptoms in SAR and in PAR

Trial*	Data	Duration†	Treatment group (n)	Placebo group (n)
PAR studies				
PAR C92280	Retrospective	12 weeks	164	164
PAR I92293 (5)	Retrospective	12 weeks	143	141
PAR I94078	Retrospective	12 weeks	171	173
PAR I94079 (6)	Retrospective	12 weeks	182	184
SAR Studies				
P05067 (21)	Prospective	15 days	211	215
P05106 (14)	Prospective	15 days	220	209
SAR 94145 (17)	Retrospective	15 days	176	176
SAR C93013	Retrospective	28 days	113	116
SAR C93184 (19)	Retrospective	15 days	101	100
SAR I94001	Retrospective	15 days	104	103

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

*All studies were randomized, double blind, placebo controlled.

†For PAR studies, data from first 29 days of treatment included in analysis; for SAR studies, data from 15-day study period included in analysis.

SAR studies, among the two prospectively analyzed SAR studies, and among the PAR studies (Table 2). Mean baseline ocular symptom scores were also comparable between MFNS- and placebo-treated patients in each of these three groups. These baseline scores were lower in the PAR studies and in the retrospectively analyzed SAR studies compared with the prospectively analyzed SAR data because no minimum baseline ocular symptom score was required except in the prospectively analyzed SAR studies.

MFNS-treated patients experienced significantly greater reductions vs placebo in each of the three ocular symptoms evaluated in both the PAR studies and the SAR studies. In the SAR analysis, the mean differences [95% CI] in symptom scores between MFNS-treated and placebo-treated patients were ocular tearing (-0.09 [-0.10 , -0.07]), itching (-0.10 [-0.12 , -0.08]), and redness (-0.08 [-0.10 , -0.06]) over 15 days of treatment (Fig. 1). Overall effect was significant for all three individual symptoms ($Z = 9.18$ for tearing, $Z = 10.15$ for itching, and $Z = 8.88$ for redness; $P < 0.00001$ for all). Heterogeneity was low-to-moderate (22) among studies for ocular tearing ($\chi^2 = 116.99$, $P = 0.03$; $I^2 = 24\%$), itching ($\chi^2 = 257.73$, $P = 0.00001$; $I^2 = 65\%$), and redness ($\chi^2 = 144.46$, $P = 0.0002$; $I^2 = 38\%$).

In the PAR analysis, the mean differences [95% CI] in symptom scores were ocular tearing (-0.04 [-0.05 , -0.03]), itching (-0.02 [-0.03 , -0.00]), and redness (-0.02 [-0.03 , -0.00]) over 29 days of treatment (Fig. 2). Significant overall effect was seen for the three symptoms ($Z = 5.94$, $P < 0.00001$ for ocular tearing; $Z = 2.43$, $P = 0.02$ for itching; and $Z = 2.42$, $P = 0.02$ for redness). Interstudy heterogeneity was not significant for the symptom of ocular tearing ($\chi^2 = 72.71$, $P = 1.00$; $I^2 = 0\%$), itching ($\chi^2 = 75.05$, $P = 1.00$; $I^2 = 0\%$), and redness ($\chi^2 = 42.50$, $P = 1.00$; $I^2 = 0\%$).

Discussion

The present meta-analysis included 10 randomized, placebo-controlled trials demonstrating that MFNS 200 mcg daily is effective in relieving ocular allergy symptoms in both SAR and PAR. In both the SAR and PAR analyses, which included a total of 3132 patients, all individual ocular symptoms were reduced in patients treated with MFNS. This is particularly noteworthy in light of the fact that entry criteria

Table 2 Baseline demographic and clinical characteristics in patients with SAR and PAR

Characteristic	PAR studies		Two prospectively analyzed SAR studies		Four retrospectively analyzed SAR studies	
	MFNS (n = 660)	Placebo (n = 662)	MFNS (n = 431)	Placebo (n = 424)	MFNS (n = 494)	Placebo (n = 495)
Age						
Mean years (range)	34.0 (12–74)	32.3 (12–73)	36.1 (12–73)	36.2 (11–79)	30.1 (12–71)	30.2 (13–71)
Sex*						
Male, n (%)	321 (48.7)	312 (47.3)	159 (37.0)	169 (40.0)	244 (49.4)	248 (50.1)
Female, n (%)	338 (51.3)	347 (52.7)	272 (63.1)	255 (60.0)	250 (50.6)	247 (50.0)
Race*						
Caucasian, n (%)	513 (77.8)	487 (74.0)	334 (77.5)	318 (75.0)	428 (86.8)	436 (88.3)
Non-Caucasian, n (%)	146 (22.2)	171 (26.0)	97 (22.5)	106 (25.0)	65 (13.2)	58 (11.7)
Mean baseline ocular symptom scores†						
Eye itching	0.89	0.93	2.48	2.47	1.68	1.72
Eye redness	0.68	0.70	2.23	2.26	1.35	1.40
Eye tearing	0.70	0.74	2.33	2.33	1.39	1.45

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

*Demographic numbers may not add up to entire population numbers because of the participants who dropped out immediately and for whom demographic information was not reported.

†Baseline summarized for patients with baseline and postbaseline efficacy observation.

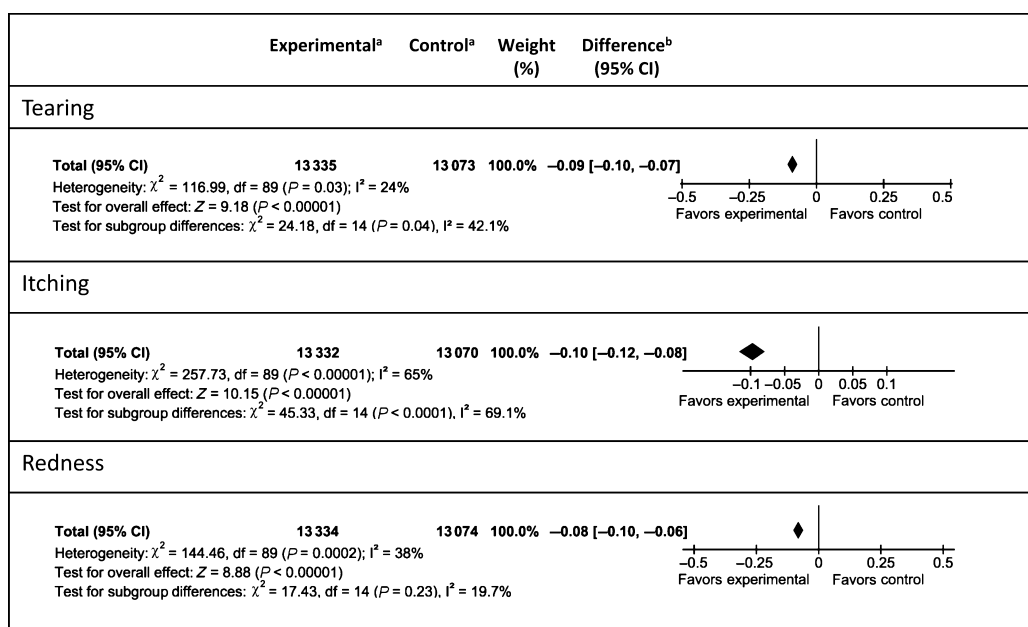


Figure 1 Improvement in tearing, itching, and redness in patients with SAR treated with MFNS for 2 weeks. ^aIndicates the total number of daily observations from all studies combined.

^bDifference = weighted mean difference by fixed-effect inverse variance model. MFNS, mometasone furoate nasal spray; SAR, seasonal allergic rhinitis.

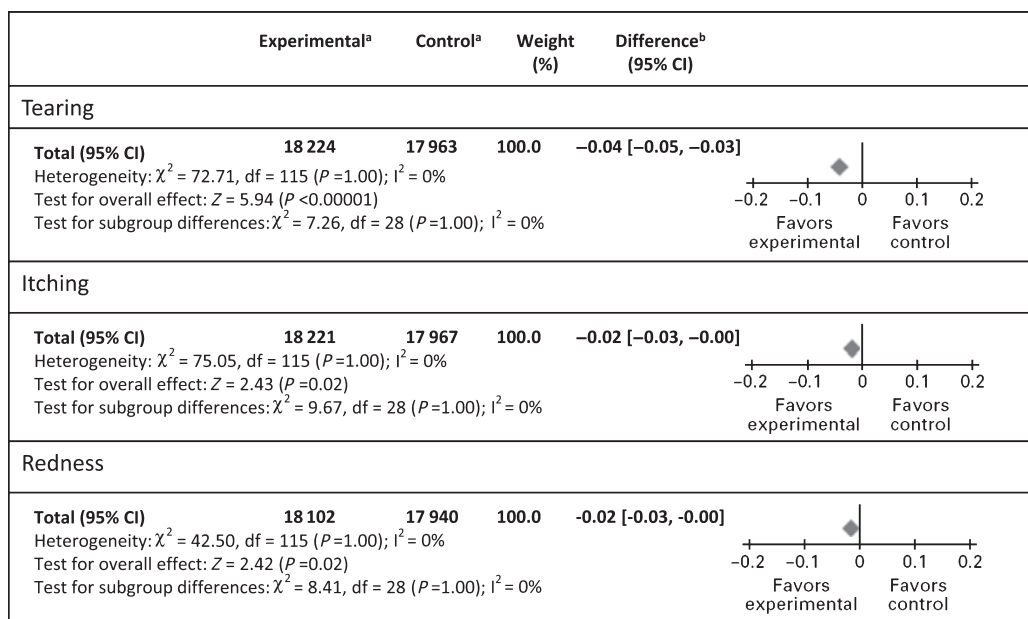


Figure 2 Improvement in tearing, itching, and redness in patients with PAR treated with MFNS for 30 days. ^aIndicates the total number of daily observations from all studies combined. ^bDiffer-

ence = weighted mean difference by fixed-effect inverse variance model. MFNS, mometasone furoate nasal spray; PAR, perennial allergic rhinitis.

for all but two of the SAR trials did not include a minimum ocular symptom score. Furthermore, the overall beneficial effect of MFNS was consistent across ocular symptoms even though there was a variable degree of heterogeneity among the SAR studies.

Our findings add to the growing body of literature supporting the positive class effect of INSs, including MFNS, on ocular symptoms associated with SAR (15, 17, 18, 23–31). Our results are consistent with findings from individual studies and pooled analyses examining MFNS for relief of aller-

gic eye symptoms (15, 16). For example, an analysis of pooled data from four randomized, placebo-controlled, double-blind, clinical studies of adults and adolescents ($n = 991$) with SAR indicated that patients receiving MFNS had significantly greater reductions in TOSS (-1.33 [-19.8%] *vs* -0.94 [-5.6%]; $P < 0.05$) and in the individual component symptoms of itching, tearing, and redness, compared with those receiving placebo during the entire 2-week study (16). A subgroup analysis among patients with moderate-to-severe ocular symptoms showed an even greater improvement in symptom scores with MFNS *vs* placebo (-1.97 [-32.0%] *vs* -1.51 [-25.0%]; $P = 0.002$) (15).

Much of the data available to date on INS efficacy for ocular symptoms has been in the form of secondary endpoints in studies focusing primarily on nasal symptoms of AR (32). Of particular note is the inclusion in our analyses of two randomized, double-blind, placebo-controlled trials that prospectively evaluated the efficacy of MFNS in reducing ocular allergy symptoms as a primary endpoint (14, 21). One of these, conducted by Prenner et al. (14), is the first prospective study to be published demonstrating the efficacy of once-daily MFNS in reducing ocular symptoms in patients with moderate-to-severe SAR.

MFNS is among the newer INSs with systemic bioavailability of $<1\%$ (33), which also includes fluticasone furoate (34) and fluticasone propionate (33). The newer INSs exhibit negligible or no evidence of associated systemic adverse events (namely hypothalamic–pituitary–adrenal axis suppression in adults and children) (35–43). Results of double-blind, randomized, controlled trials from 2 to 4 weeks in duration also have demonstrated the efficacy of other newer INSs. In a double-blind, 28-day study in 471 patients with SAR randomized to receive fluticasone propionate, oral loratadine, or placebo, the use of fluticasone propionate yielded statistically significantly greater decreases in TOSS, the primary endpoint, compared with placebo ($P < 0.001$) and with loratadine ($P = 0.028$) (44). Furthermore, a retrospective analysis of pooled data from the fluticasone propionate and placebo arms of seven studies demonstrated significantly greater reductions in TOSS with fluticasone propionate after 7 and 14 days of treatment ($P < 0.001$) in patients with SAR (23).

Two prospective studies by Kaiser et al. and Fokkens et al. (25, 27) in patients with SAR, designed to assess TOSS as a secondary endpoint, reported statistically significant mean changes in TOSS with fluticasone furoate compared with placebo (-2.23 *vs* -1.63 , $P = 0.004$; -3.00 *vs* -2.26 , $P < 0.001$, respectively). Similarly, Martin et al. (26) reported significantly greater mean changes from baseline in TOSS with fluticasone furoate *vs* placebo.

In addition to these data, several studies have demonstrated that older INSs with higher systemic bioavailability have a positive effect on ocular symptoms associated with SAR: budesonide (bioavailability 31%) (45), beclomethasone (44%) (46), and triamcinolone acetonide (46%) (47), as evaluated second to nasal symptoms (27–30, 48).

Most research to date evaluating the efficacy of INSs for ocular symptoms associated with AR has been conducted on patients with SAR, resulting in few data in the literature

regarding the efficacy of INSs for the ocular symptoms that may coexist with PAR (49).

Our analysis of 1299 patients with PAR (651 of whom received MFNS) in four randomized, placebo-controlled studies demonstrates that MFNS is associated with significant improvements *vs* placebo in ocular tearing, itching, and redness in this group of patients. In both the SAR and PAR studies, MFNS achieved a significant overall effect *vs* placebo for all ocular allergy symptoms. Patients with PAR had lower baseline symptomatology because of the perennial nature of the disease, which may account for the somewhat smaller treatment effect in the PAR analysis *vs* the SAR analysis.

The mechanism of action of INSs in relieving ocular symptoms of AR is not yet fully understood, but several theories have been postulated. Some authors suggest that improved drainage of the nasolacrimal duct related to the anti-inflammatory action of INSs reduces exposure of the conjunctiva to allergens and inflammatory mediators (24). However, the finding that duct patency is maintained in patients with symptomatic allergic response after ocular challenge argues against this theory (50).

Another postulated mechanism is the application of the steroid to the eye through either systemic absorption or nasolacrimal reflux (8). However, the low systemic bioavailability ($<1.0\%$) and minimal systemic absorption of the INSs, particularly the newer agents (MFNS, fluticasone propionate, and fluticasone furoate), make it unlikely that INSs act systemically to relieve ocular symptoms (33, 34, 51). Additionally, the minimal effects of INSs on intraocular pressure suggest that direct effects upon the eye are unlikely, except perhaps in selected populations with a predilection to increased intraocular pressure (44, 52, 53).

A third proposed mechanism for the efficacy of INSs in ocular symptoms of AR is that reduced nasal inflammation moderates the allergen-caused increase in reflex neuronal activity (8). Naclerio et al. (54) performed a study in 20 patients pretreated with either placebo or the antihistamine azelastine before unilateral nasal antigen challenge; increased symptoms and secretion weights suggested a nasal-ocular reflex, which was reduced by antihistamine pretreatment. Agents such as INSs may thus reduce ocular symptoms by modulating this pathway. It has also been suggested that the systemic immune effects of INSs, as manifested by the decreased immune profile in the lung and improvement in asthma symptoms in patients with AR and asthma treated with INSs, may be responsible for their positive effects on ocular symptoms of AR (15). This improvement in asthma symptoms with INSs further supports the validity of the 'one airway, one disease' concept (15, 55).

One potential limitation of our analysis is that not all the studies included have been published, thus limiting the ability to replicate the analyses. In addition, although the degree of heterogeneity of the scores used to evaluate outcomes was low among analyzed PAR studies by both the traditional chi-squared test and the modern I^2 measurement, heterogeneity was variable and significant among the SAR studies. It should be noted that heterogeneity is not uncommon among

meta-analyses, and the magnitude of heterogeneity in this analysis compares favorably with that found in other meta-analyses (7). In an analysis of 509 meta-analyses in the Cochrane database, Higgins et al. (22) found that roughly a quarter had I^2 values over 50%; the present meta-analysis found an I^2 over 50% in only one outcome (itching) in the SAR studies. Study design may account for some of the heterogeneity. The retrospectively analyzed SAR studies included some patients with no or minimal ocular symptoms at baseline, resulting in lower mean baseline ocular symptoms than in the prospective studies. Inclusion of these patients may have lowered the treatment effect seen in the retrospective studies and is a possible contributor to the observed heterogeneity when retrospective and prospective studies were analyzed together. In published retrospective analyses of the treatment effect of MFNS on ocular symptoms of SAR, greater treatment effect has been seen in subgroups of patients with moderate-to-severe ocular symptoms at baseline (17, 18). Additionally, although all studies analyzed in this article prohibited ocular corticosteroids during the study period, the prospective SAR studies included a more comprehensive range of restricted medications with possible ocular activity than did the other trials. This, along with the fact that specific lists of restricted medications varied among all studies, is a possible source of heterogeneity.

The results of these analyses support a growing body of evidence, suggesting that INSs as a class, including MFNS, have a positive clinical impact on ocular allergy symptoms. While the ocular component of allergies is often considered among the most bothersome symptoms by patients with AR, its incidence and severity are often underestimated by physicians (11, 56, 57). This highlights the need for more effective communication between patients and physicians regarding the nature, severity, and impact of symptoms and how to obtain maximum benefit from available treatment options (57).

Given the well-established safety and efficacy of MFNS in managing the nasal symptoms of AR, current data suggest that MFNS may represent an effective first-line therapy for

comprehensive nasal and ocular allergy symptom relief, with minimal risk for systemic side effects. Overall, the results of our meta-analysis, along with those of other clinical trials and pooled analyses of MFNS and other INSs, demonstrate a positive impact of this class of agents on reducing ocular symptoms of AR.

Author contribution

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All authors have read and approved this submission.

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