

Intranasal Mometasone Furoate Alleviates the Ocular Symptoms Associated with Seasonal Allergic Rhinitis: Results of a Post Hoc Analysis

Robert Anolik^a Robert A. Nathan^b Eric Schenkel^c Melvyn R. Danzig^d
Davis Gates^d Santosh Varghese^e

^aAllergy and Asthma Specialists, PC, Blue Bell, Pa., ^bAsthma and Allergy Associates, PC, Colorado Springs, Colo.,
^cValley Clinical Research Center, Easton, Pa., ^dSchering-Plough Research Institute, and ^eSchering-Plough Corporation,
Kenilworth, N.J., USA

Key Words

Mometasone furoate nasal spray · Seasonal allergic rhinitis ·
Ocular symptoms

Abstract

Background: Burdensome symptoms of allergic rhinitis (AR) include nasal and ocular symptoms such as itching, tearing and redness. Intranasal corticosteroids are efficacious in the treatment of nasal symptoms of AR. **Objective:** It was the aim of this study to determine the efficacy of the intranasal corticosteroid mometasone furoate nasal spray (MFNS) in relieving ocular symptoms associated with seasonal AR (SAR). **Methods:** Ocular symptom data were analyzed for subjects ≥ 12 years of age, randomized to MFNS 200 μg q.d. ($n = 176$) or placebo ($n = 177$) in a placebo-controlled, double-blind clinical trial. Post hoc efficacy analysis assessed the mean change from baseline in subject-reported total ocular symptom scores (TOSS) averaged over the treatment period. **Results:** Mean baseline TOSS was 4.91 for the MFNS group and comparable (5.05) for the placebo group – combined average for individual symptoms such as itching, tearing and redness ranged from 0 (no symptoms) to 9 (all symptoms, severe). Mean change from baseline in TOSS averaged over days 1–15 was -1.42 for the MFNS group and -0.94 for the placebo group ($p = 0.02$), for an observed treatment difference of 0.49 (statistical data rounded to 2 decimal positions).

Improvement in individual symptoms (eye itching, tearing and redness) contributed to this treatment effect; the greatest improvement occurred with tearing, which decreased -0.52 from the baseline score 1.59 in the MFNS group and -0.31 from 1.67 in those receiving placebo ($p < 0.01$), for an observed treatment difference of 0.21. Treatment with MFNS was safe and well tolerated. **Conclusion:** MFNS is effective in reducing ocular symptoms of SAR, in addition to its established efficacy in reducing nasal symptoms of SAR.

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Introduction

Ocular allergy associated with allergic rhinitis (AR) includes symptoms of tearing, itching and redness, which impair quality of life, daily activities and productivity [1]. The term ‘allergic conjunctivitis’ is often used to describe ocular symptoms that occur following allergen exposure [2]. International data indicate a high prevalence of coexistent nasal and ocular symptoms in patients with AR. In a large UK general practice trial in adults with seasonal AR (SAR), approximately 90% of subjects had experienced watery eyes during the previous hay fever season [3]. In a survey of 509 allergic patients who were symptomatic but not currently receiving treatment, 70% indicated AR-related conjunctivitis symptoms to be at least as

Table 1. Excluded medications

Systemic corticosteroids
High-potency topical corticosteroids
Inhaled corticosteroids
Topical nasal or ocular corticosteroids
Cromolyn sodium or nedocromil
Systemic antihistamines
Topical nasal or ocular antihistamines
Topical nonsteroidal anti-inflammatory drugs
Nasal atropine or ipratropium bromide
Nasal or oral decongestants

severe as nasal AR symptoms [4]. In the United States, an analysis of data from the National Health and Nutrition Examination Survey III concluded that more than 40% of adults experience ocular symptoms with AR [5]. A retrospective survey of Danish children, aged 5–15 years, found that 97% of those who had AR also had allergic conjunctivitis [6].

Ocular symptoms associated with AR have a substantial impact on both vision and overall quality of life. Two recent studies found that individuals 16–80 years old with SAR-related conjunctivitis experienced more ocular pain, a greater incidence of comorbidities (e.g., asthma, food allergies) and significant reductions in visual acuity and general quality of life compared with those without ocular symptoms [7, 8].

Oral antihistamines have generally been considered more effective than intranasal corticosteroids for the relief of allergic ocular symptoms. However, review of the literature indicates that intranasal corticosteroids may be as effective as, or even superior to, oral antihistamines in relieving ocular symptoms of AR [9–13]. According to a meta-analysis of randomized, controlled trials published between 1966 and 1997 comparing oral antihistamines and intranasal corticosteroids, only 2 of 11 studies in which ocular symptoms were evaluated found antihistamines to be superior to intranasal corticosteroids [10]. In both of those studies, the intranasal corticosteroid was beclomethasone [10, 14, 15].

Intranasal corticosteroids are recommended as first-line therapy for nasal symptoms of SAR [16, 17]. If individual agents of this class provide relief of both nasal and ocular symptoms, they may provide patients a more comprehensive treatment for their overall AR symptoms, beyond the demonstrated nasal benefits. The intranasal corticosteroid mometasone furoate nasal spray (MFNS) has been shown in controlled clinical trials to be effective

and well tolerated in the relief of nasal symptoms, particularly congestion, in subjects with seasonal and perennial AR [18–22].

In order to assess the effects of MFNS compared with placebo in relieving ocular symptoms in subjects with SAR, a post hoc analysis of a randomized, double-blind, placebo-controlled trial was conducted. Results of the source clinical trial were previously published [23].

Methods

Original Study Design

Subjects took part in a phase III, double-blind, randomized, placebo-controlled, multicenter clinical trial. All subjects were ≥ 12 years of age and had a 2-year clinical history of SAR. The diagnosis was confirmed by a positive skin prick test to a relevant allergen. Presence of ocular symptoms at study entry or baseline was not a requirement. Exclusion criteria included clinically significant nasal disease other than SAR, such as rhinitis medicamentosa or nasal candidiasis, or significant nasal structural abnormalities (e.g., large nasal polyps, marked septal deviation); a current or prior history of frequent rhinosinusitis or chronic purulent postnasal drip; or asthma requiring chronic use of inhaled or systemic corticosteroids (inhaled bronchodilators were permitted for asthma treatment). Subjects receiving immunotherapy were excluded unless they had been on a stable maintenance schedule for ≥ 1 month.

Concomitant medications permitted for asthma during the study included short-acting inhaled or oral β -agonists as needed, and theophylline if a subject was on a stable dose before and during therapy. Medications not permitted during the study are presented in table 1.

The study was conducted at 18 study centers in the United States in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Appropriate institutional review boards approved the protocol and informed consent forms. Written informed consent was obtained from each subject or from the parent or guardian of each subject < 18 years of age.

Study medication was administered once daily in the morning for 15 days. Subjects recorded the severity of ocular itching, redness and tearing on diary cards in the morning (AM) before the dose of assigned medication and again in the evening (PM), approximately 12 h after medication was administered. The severity of each ocular symptom was rated on a 4-point scale where 0 = none (no sign/symptom present), 1 = mild (sign/symptom clearly present but minimal awareness, easily tolerated), 2 = moderate (definite awareness of sign/symptom which is bothersome but tolerable), 3 = severe (sign/symptom is hard to tolerate, causes interference with activities of daily living and/or sleeping).

Post Hoc Evaluations

The main efficacy outcome in this formal post hoc analysis was the mean change from baseline in total ocular symptom score (TOSS) in the intent-to-treat population, defined as randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline evaluation. TOSS was defined as the sum of the ratings for each individual ocular symptom – itching, red-

ness and tearing – calculated using subject diary data; the maximal score was 9. The AM and PM scores were individually averaged for each subject. These scores were then averaged over the study period (days 1–15).

The mean changes in individual ocular symptoms over the study period were also analyzed. To be scientifically rigorous, the post hoc analysis included all randomized subjects, regardless of whether they presented with ocular symptoms or not. To evaluate only the subjects who were symptomatic at baseline, a subgroup analysis was performed in subjects with moderate-to-severe ocular symptoms (TOSS ≥ 4) at baseline. The mean changes from baseline in TOSS and each individual ocular symptom over the study period were analyzed.

The first dose of study medication was to be taken by each subject between the AM and PM diary recordings on the day of the baseline visit. The baseline AM diary score was defined as the average of the baseline visit score and the AM scores from the 3 consecutive days prior to the baseline visit; the baseline PM score was defined as the average of the PM scores from the 3 prior consecutive days. The baseline average was defined as the average of the 4 baseline AM scores and the 3 baseline PM scores.

Safety was evaluated based on the physician’s clinical observations and subject reports. Subjects were questioned about adverse events at each physician visit, and details of any reported event were recorded.

Statistical Analysis

For the post hoc analysis, treatment differences were assessed using a 2-way analysis of variance corrected for treatment and center effects. All pairwise comparisons were based on the least squares means from the analysis of variance, using an individual 5% (2-sided) significance level to assess treatment comparisons.

Results

Daily diary entries from 353 subjects were retrospectively analyzed. A total of 176 subjects received MFNS 200 μg q.d. and 177 received placebo. The demographic characteristics of the 2 treatment groups were comparable at baseline (table 1). Mean changes in ocular symptoms over the study period were analyzed in subjects with both baseline and post-baseline data (176 subjects in the MFNS group and 173 in the placebo group). The mean TOSS at baseline was 4.91 in the MFNS group and 5.05 in the placebo group (± 1.84 pooled standard deviation). These scores indicate that most subjects presented with moderate-to-severe ocular symptoms at baseline; however, the magnitude of the standard deviation, close to 2 points, indicates that there were subjects who entered the study with symptoms of lesser severity (TOSS < 4).

Mean Change from Baseline for TOSS

In the intent-to-treat population, subjects receiving treatment with MFNS experienced a significantly ($p =$

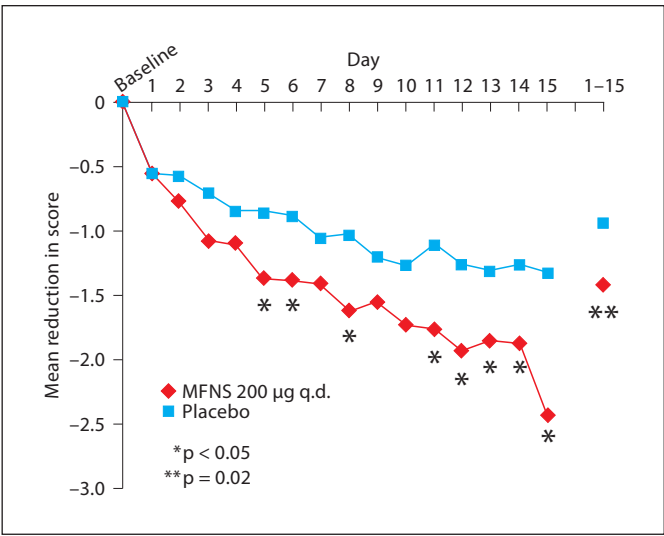


Fig. 1. Mean change from baseline in total ocular symptoms over the 15-day treatment period in the intent-to-treat population.

Table 2. Baseline demographic and clinical characteristics of the intent-to-treat population

	Treatment group	
	MFNS 200 μg (n = 176)	placebo (n = 177)
Age, years		
Mean	26	26
Range	12–71	12–66
Males/females	87/89	91/85
Duration of AR, years		
Mean	13	13
Range	2–56	2–55
Mean TOSS ¹	4.91	5.05
Ocular symptoms ≥ 4 on TOSS, n	126	127
Mean TOSS	5.84	5.91

¹ Combined average of AM and PM scores for 3 ocular symptoms (itching eyes, tearing eyes, redness of eyes): score range 0 (no symptoms) to 9 (all symptoms severe).

0.02) greater reduction from baseline in TOSS averaged over days 1–15 compared with those receiving placebo (table 2; fig. 1). The TOSS decreased by -1.42 (-20.9%) from 4.91 at baseline in the MFNS group; the decrease in the placebo group was -0.94 (-2.6%) from 5.05 at baseline, with a treatment difference of 0.49. For the individual ocular symptoms, the mean reduction in tearing was

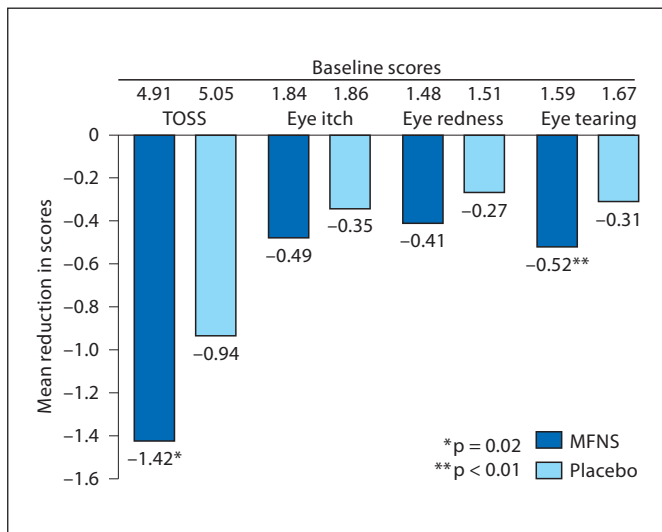


Fig. 2. Mean change from baseline in total ocular symptoms and individual symptom scores averaged over the study period in the intent-to-treat population.

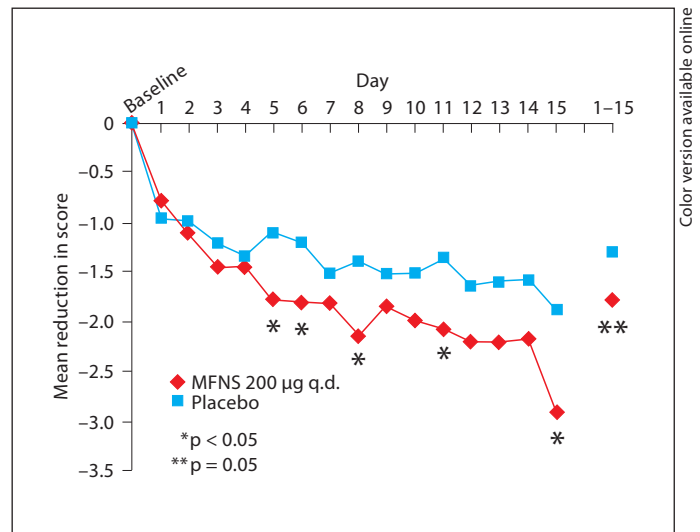


Fig. 3. Mean change from baseline in total ocular symptoms over the 15-day treatment period in subjects with baseline TOSS ≥ 4 .

Table 3. Mean change from baseline over the 15-day treatment period in total ocular and individual symptom scores in the intent-to-treat population

Mean score	Treatment group		P value
	MFNS 200 µg (n = 176)	placebo (n = 177)	
Total ocular symptoms			
Baseline	4.91	5.05	
Days 1–15	–1.42	–0.94 ¹	0.02
Change from baseline, %	–20.9	–2.6	
Ocular itching			
Baseline	1.84	1.86	
Days 1–15	–0.49	–0.35 ¹	NS
Change from baseline, %	–22.9	–10.4	
Ocular redness			
Baseline	1.48	1.51	
Days 1–15	–0.41	–0.27 ¹	NS
Change from baseline, %	–18.3	–0.9	
Ocular tearing			
Baseline	1.59	1.67	
Days 1–15	–0.52	–0.31 ¹	<0.01
Change from baseline, %	–24.5	–5.8	

¹ n = 173 for placebo; subjects with both baseline and post-baseline data were included in the analysis.

NS = Not significant.

significantly greater with MFNS than with placebo: -0.52 (-24.5%) versus -0.31 (-5.8% ; $p < 0.01$). The mean reductions in symptom scores for itching and redness were numerically but not statistically significantly greater with MFNS than with placebo (fig. 2).

Subgroup Analysis in Subjects with Moderate-to-Severe Ocular Symptoms (TOSS ≥ 4) at Baseline

At baseline, 253 (72%) of the 353 randomized subjects had moderate-to-severe ocular symptoms (TOSS ≥ 4): 126 subjects in the MFNS group and 127 in the placebo group (table 3; fig. 3). Mean changes in ocular symptoms over the study period were analyzed in subjects with both baseline and post-baseline data (126 subjects in the MFNS group and 124 in the placebo group). The mean change from baseline for TOSS averaged over days 1–15 was greater in subjects receiving MFNS than in those receiving placebo, -1.78 (-29%) versus -1.29 (-22%). The treatment difference of 0.49 attained a p value of 0.05 due to the reduced sample size (table 3). Consistent with the findings in the intent-to-treat population, the mean reduction in tearing in the subgroup was significantly greater with MFNS than with placebo: -0.66 (-33.9%) versus -0.45 (-21.0% ; $p = 0.02$), with a treatment difference of 0.21. The mean reductions in scores for eye itching and redness were numerically but not statistically superior in the MFNS group (fig. 4).

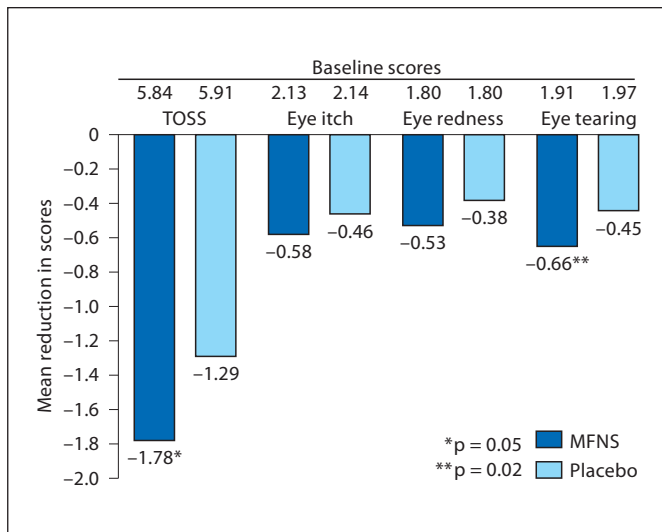


Fig. 4. Mean change from baseline in total ocular symptoms and individual symptom scores averaged over the study period in subjects with baseline TOSS ≥ 4 .

Safety

Mometasone furoate was safe and well tolerated. Mild-to-moderate adverse events were reported by 36 and 41% of subjects who received MFNS and placebo, respectively. No serious adverse events were reported. The most common treatment-related adverse events reported by subjects in the MFNS and placebo groups, respectively, were headache (6 and 7%), epistaxis (1 and 3%), pharyngitis (1 and 2%) and somnolence (1 and 1%; table 4).

Discussion

In this analysis, subjects in the MFNS 200 μg q.d. group reported greater reductions in TOSS and the individual ocular symptoms of itching, tearing and redness compared with the placebo group.

Although the presence of ocular symptoms was not an inclusion criterion for the clinical study, all randomized subjects were included in this post hoc analysis. As a result, some subjects with a baseline TOSS as low as zero were included in the analysis, decreasing the overall mean scores for TOSS and for individual ocular symptoms in the analysis population. Despite this, the reductions in TOSS and ocular tearing were significantly greater after treatment with MFNS compared with placebo; the treatment differences were 0.49 ($p = 0.02$) and 0.21 ($p \leq 0.01$), respectively. The mean reductions in ocular itching and

Table 4. Mean change from baseline in total ocular and individual symptom scores over the 15-day treatment period in subjects with a TOSS ≥ 4 at baseline

Mean score	Treatment group		p value
	MFNS 200 μg (n = 126)	placebo (n = 127)	
Total ocular symptoms			
Baseline	5.84	5.91	
Days 1–15	–1.78	–1.29 ¹	0.05
Change from baseline, %	–29.0	22.0	
Ocular itching			
Baseline	2.13	2.14	
Days 1–15	–0.58	–0.46 ¹	NS
Change from baseline, %	–26.1	–20.9	
Ocular redness			
Baseline	1.8	1.8	
Days 1–15	–0.53	–0.38 ¹	NS
Change from baseline, %	–23.2	–13.6	
Ocular tearing			
Baseline	1.91	1.97	
Days 1–15	–0.66	–0.45 ¹	0.02
Change from baseline, %	–33.9	–21.0	

¹ n = 124 for the placebo group; subjects with both baseline and post-baseline data were included in the analysis.

NS = Not significant.

Table 5. Common treatment-related adverse events reported in the MFNS and placebo groups

Adverse event, %	Treatment group	
	MFNS 200 μg (n = 176)	placebo (n = 176) ¹
Headache	6	7
Epistaxis	1	3
Pharyngitis	1	2
Somnolence	1	1

¹ One placebo subject with baseline efficacy data did not receive the first treatment dose, and therefore, was excluded from the adverse event summaries.

redness were numerically greater in the MFNS group than in the placebo group, but the differences were not statistically significant, presumably due to the low levels of symptoms at baseline.

Estimates of percentage change from baseline presented a challenge due to a number of subjects who reported

baseline scores near zero. A small change from baseline score resulted in a large percentage change from baseline. To address this issue, a subgroup analysis that includes data from subjects with moderate-to-severe ocular symptoms at baseline (TOSS ≥ 4) was performed. This analysis produced treatment differences between the MFNS and placebo groups of 0.49 ($p = 0.05$) for TOSS and 0.21 for ocular tearing ($p = 0.02$), as in the analysis of all randomized subjects, but the estimates of the percentage decreases were more reliable (29 vs. 22% for TOSS and 33.9 vs. 21% for ocular tearing). In the subgroup analysis, the increased p value of 0.05 was likely due to a 28% reduction in sample size, as opposed to a reduction in treatment benefit.

Data from other studies examining MFNS versus placebo for relief of allergic eye symptoms are consistent with these findings [24–26]. MFNS 200 μg q.d. significantly reduced the ocular symptoms (itching, redness and tearing) of SAR in an analysis of 207 subjects with SAR who received MFNS ($n = 104$) or placebo ($n = 103$) as part of a phase III, randomized, double-blind, placebo-controlled study [24]. The mean reduction in TOSS of -21.9% with MFNS was significantly greater than that of -11.6% in the placebo group ($p < 0.05$).

A pooled analysis of data from 4 randomized, double-blind, placebo-controlled clinical trials ($n = 991$) demonstrated that over a 2-week period, MFNS 200 μg q.d. produced significantly greater reductions from baseline in TOSS as well as in scores for the 3 individual ocular symptoms (itching, redness and tearing) [25]. A subgroup analysis of subjects in the pooled group whose baseline TOSS was ≥ 4 showed statistically significant improvements in total and individual ocular symptoms among those treated with MFNS compared with placebo. Subjects in the MFNS group experienced an improvement in 2-week average TOSS of -1.97 (32.3%) compared with placebo, -1.51 (25.0% improved; $p < 0.05$). Scores for individual symptoms of eye itching (-0.69 vs. -0.56), eye redness (-0.6 vs. -0.45) and eye tearing (-0.69 vs. -0.5) also improved significantly ($p < 0.05$) compared with placebo [25].

In another retrospective pooled analysis of the same study population, MFNS significantly decreased the overall symptoms of SAR and the individual symptoms of ocular itching, redness and tearing within 2–4 days of the initiation of therapy [26]. When AM and PM TOSS in these patients were analyzed separately, overall reductions in both scores were similar in the MFNS group and significantly greater than with placebo ($p \leq 0.001$) [27]. The small difference in the magnitude of effect (0.21) be-

tween MFNS and placebo for PM (approximately 12 h after the dose) and AM (approximately 24 h after the dose) TOSS indicated that the duration of the therapeutic effect of MFNS was 24 h.

Results of double-blind, randomized, controlled trials lasting from 2 to 4 weeks have shown that fluticasone propionate nasal spray and fluticasone furoate nasal spray are more effective than placebo in relieving the ocular symptoms of SAR [12, 28, 29].

A retrospective analysis of pooled data from 7 double-blind, randomized, placebo-controlled trials of fluticasone propionate nasal spray in subjects with SAR showed that this agent significantly decreased TOSS [30]. A clinically relevant difference (defined as a difference of 25 points in mean change from baseline) favoring fluticasone propionate over vehicle placebo was seen in physician ratings of TOSS after 7 (difference 25.1, $p < 0.001$) and 14 days (difference 31.6, $p < 0.001$) of treatment. Results of subject ratings were consistent with the physician ratings. A subsequent 28-day, multicenter, double-blind, double-dummy, randomized trial in 471 subjects with SAR found that fluticasone propionate produced significantly greater reductions in TOSS than either placebo vehicle ($p < 0.001$) or oral loratadine ($p = 0.028$) and in individual ocular symptoms of itching, tearing and redness ($p < 0.001$ vs. vehicle and $p \leq 0.045$ vs. loratadine) [12].

Two 2-week trials of fluticasone furoate nasal spray in subjects with SAR showed that this intranasal corticosteroid was significantly more effective than vehicle placebo in reducing TOSS as well as total nasal symptom score over the treatment period [28, 29]. In these trials, fluticasone furoate was also more effective than vehicle placebo in reducing individual ocular symptoms of itching/burning, tearing/watering and redness ($p < 0.05$). Of interest, only the reflective scores were reported, but the instantaneous ones (indicative of 24-hour effects) were not.

Overall, the results of these clinical studies with MFNS and other intranasal corticosteroids indicate that this class of agents has a positive impact on reducing ocular symptoms of SAR. Several hypotheses have been put forth to explain the mechanism by which intranasal corticosteroids, which have proven efficacy in reducing nasal symptoms of SAR, also reduce SAR-related ocular symptoms.

One hypothesis suggests that the anti-inflammatory properties of intranasal corticosteroids may reduce ocular irritation by modulating or normalizing increases in reflex neuronal activity induced by allergens [12, 31–34]. A second hypothesis suggests the improvement in eye symptoms is achieved by decreasing nasal congestion,

thereby improving drainage through the nasolacrimal duct [12, 30]. The improved drainage may reduce retention of allergen in the conjunctiva, thereby decreasing edema and inflammation at the nasolacrimal duct [12].

Although the safety of intranasal corticosteroids is well established [35], notably in newer compounds dosed once daily in the AM, concerns persist regarding potential systemic side effects [36]. Ocular side effects such as evidence of cataracts, glaucoma or increased ocular pressure have not been shown in clinical trials to be associated with intranasal corticosteroid therapy [37–40] with the exception of 1 study with budesonide [41] and 1 study of fluticasone furoate [42].

A large-scale retrospective observational study in the UK demonstrated that cataracts were not associated with the use of intranasal corticosteroids in a study population limited to those <70 years of age ($n = 88,301$) [40]. There was no diagnosis of cataracts or glaucoma in 61 patients 18–40 years old after 1 year of treatment with fluticasone propionate 200 μg q.d. [38]. Bross-Soriano and colleagues [39] assessed the effects of fluticasone propionate, mometasone furoate (both 200 μg q.d.), beclomethasone dipropionate (400 μg b.i.d.) and placebo on intraocular pressure in 360 patients for 1 year, concluding that recorded variations remained within normal limits (10–21 mm Hg).

In an open trial of intranasal budesonide (200 μg b.i.d.) in 78 children with perennial AR, lenticular changes were found in 6 children [41]. Small lenticular opacities were present in 2 children at the start of the study and persisted through 12 months of treatment. Transient lenticular opacities developed in 2 other children after 6 and 12 months of treatment; these disappeared during continued budesonide therapy. The ophthalmologist did not consider findings in the remaining 2 children (1 transient lenticular vesicle and 1 central unilateral opacity) to be related to budesonide therapy. Intraocular pressures were normal in all patients at study entry and after 12 months of budesonide therapy.

In a placebo-controlled trial in which 605 adults and adolescents (aged ≥ 12 years) received 1 year of treatment with fluticasone furoate (110 μg q.d.), 12 subjects had an increase in intraocular pressure to ≥ 21 mm Hg at 1 on-therapy assessment only: week 12 (21 mm Hg, $n = 2$) and week 52 (21 mm Hg, $n = 5$; 22 mm Hg, $n = 4$; 24 mm Hg, $n = 1$) [42]. There was no evidence of glaucoma in these 12 patients; corresponding changes in funduscopy cup-to-disc percentages or reports of visual field disturbances were absent. Four subjects who had intraocular pressure ≥ 21 mm Hg at baseline showed reductions after week 6.

Posterior subcapsular cataracts not present at baseline were reported in 2 subjects, 1 receiving fluticasone furoate and 1 receiving placebo [42].

Conclusions

Treatment with MFNS reduced the scores for both total and individual ocular symptoms of SAR in this post hoc analysis of a subgroup of subjects from a larger trial, including those with moderate-to-severe symptoms. The results of this analysis show that MFNS is effective for both nasal and ocular symptoms of SAR and may, therefore, be an appropriate therapy for all symptoms of this allergic disease.

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