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Mometasone Furoate Nasal Spray Relieves the Ocular Symptoms of Seasonal Allergic Rhinoconjunctivitis

Tsutomu Igarashi[1], Yuri Nakazato[1], Tomoyuki Kunishige[1], Miho Fujita[1], Yumi Yamada[1], Chiaki Fujimoto[1], Kimihiro Okubo[2] and Hiroshi Takahashi[1]

[1]Department of Ophthalmology, Graduate School of Medicine, Nippon Medical School
[2]Department of Head & Neck and Sensory Organ Science, Graduate School of Medicine, Nippon Medical School

Abstract

Background: Recent studies have examined the effects of intranasal corticosteroids (INSs) in relieving the ocular symptoms of seasonal allergic rhinoconjunctivitis (SAR) and perennial allergic rhinitis. However, because most of these studies were based on subjective assessments by patients, the associated factors and mechanism of action are unknown.

Methods: A single-center, randomized, double-blind, parallel-group study was carried out in which patients with SAR were randomly assigned to an INS mometasone furoate nasal spray (MFNS) group or to a placebo group and treated once daily for 4 weeks. Substance P concentrations in tears were measured, ocular and nasal symptoms were recorded by patients in an allergy diary, and findings were recorded by an ophthalmologist.

Results: There was no significant difference between treatment groups in the mean change from baseline of substance P concentration in tears after 4 weeks of treatment, but the mean change tended to increase in the placebo group and tended to decrease in the MFNS group ($P = 0.089$). All ocular and nasal symptom scores, except eye tearing, were significantly lower in the MFNS group than in the placebo group. Furthermore, substance P concentrations were strongly correlated with ocular and nasal symptom scores.

Conclusions: In patients with SAR, INSs tend to decrease the substance P concentration in tears, which is correlated with the severity of ocular and nasal symptoms.
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Key words: intranasal corticosteroids, seasonal allergic rhinoconjunctivitis, perennial allergic rhinitis, substance P, tear

Introduction

Seasonal allergic rhinoconjunctivitis (SAR) is a type I hypersensitivity reaction to allergens, such as pollen and house dust mites, in the nasal mucosa and conjunctivae. SAR is accompanied by the nasal symptoms of paroxysmal sneezing, profuse watery nasal discharge, and nasal mucosal swelling (nasal congestion), as well as ocular symptoms, such as intense itching of the eyes. The prevalence of SAR is increasing in Japan, with that of Japanese cedar

Correspondence to Tsutomu Igarashi, MD, PhD, Department of Ophthalmology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: tutomu@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

pollinosis in particular rising by more than 10% from 16.2% in 1998 to 26.5% in 2008[1]. Japanese cedar pollinosis is ranked among the top 3 forms of pollinosis in the world, alongside ragweed pollinosis in the United States and grass pollinosis in Europe, and research is being done on various ways to address and treat it.

One way to treat SAR is with drugs, specifically chemical mediator release inhibitors, chemical mediator receptor antagonists, T helper 2 (Th2) cytokine inhibitors, and corticosteroids[1]. Intranasal corticosteroids (INSs) are particularly effective in relieving the SAR nasal symptoms of sneezing, rhinorrhea, and congestion through their powerful anti-inflammatory action. Recent studies in the United States have also shown the efficacy of INSs in alleviating ocular symptoms, such as eye pruritus (itch), lacrimation (tearing), and ocular hyperemia (red eye)[2,3]. Mometasone furoate nasal spray (MFNS) is an INS containing the corticosteroid mometasone furoate hydrate. After being approved by the United States Food and Drug Administration in 1997, MFNS was approved in Japan in 2008. Numerous studies have addressed the effects of MFNS on ocular symptoms, and, in 2011, Bielory et al. reported the findings of their efficacy meta-analysis[4].

However, the mechanism responsible for relieving ocular symptoms remains unknown, and few studies of the subject have been performed by ophthalmologists[5,6]. The present study, therefore, investigated the mechanism of action by which MFNS relieves the ocular symptoms of SAR.

Materials and Methods

(1) Study Design and Patients

This was a randomized, placebo-controlled, double-blind, parallel-group, comparative study conducted with the approval of the Institutional Review Board of Nippon Medical School. The subjects were patients with SAR who were being treated at the Departments of Ophthalmology and Otorhinolaryngology of Nippon Medical School Hospital from February through April in 2009 and 2010.

(2) Treatment Period, Dosage, and Administration

Patients were typically given 2 sprays of MFNS (200 μg/day mometasone furoate) or the placebo in each nasal cavity once daily for 4 weeks.

(3) Enrollment and Assignment of Subjects

The details of the study, including the possibility of the study drug being a placebo, were explained to prospective subjects using an informed consent form. Subjects who provided their consent were deemed eligible for enrollment and then randomly assigned to the MFNS group or the placebo group.

Male or female patient 15 years or older were eligible for inclusion if they had received a diagnosis of SAR from an ophthalmologist and an otorhinolaryngologist. The diagnosis was confirmed with an allergy test for cedar and cypress pollen and the presence of ocular symptoms (eye itching and tearing) and nasal symptoms (sneezing, rhinorrhea, and nasal congestion). The patients were also required to be able to fill in the diary cards accurately.

(4) Observations

1) Measurements of chemical mediators in tears

At baseline and after 2 and 4 weeks of treatment (or upon completion of treatment), the conjunctival sac was irrigated with 10 μL of physiological saline, and 5-μL tear samples were then collected, centrifuged, and subjected to measurement of substance P concentrations with an enzyme-linked immunosorbent assay kit (Cayman Chemical Co., Ann Arbor, MI, USA).

2) Ocular symptoms

Each patient was given a ocular/nasal allergy diary to record the details of ocular symptoms (eye itching, tearing) on a daily basis. These details were then confirmed when the patients visited the hospital. An ophthalmologist also performed clinical evaluations (ophthalmic evaluations) of the palpebral conjunctiva (redness, swelling, follicles, papillae) and the bulbar conjunctiva (redness, swelling) at each visit on the basis of the *Allergic Conjunctival Disease Diagnostic Criteria* (*2006 Guidelines for the Clinical Management of Allergic Conjunctival Diseases*)[7].

3) Nasal symptoms

Patients were instructed to record the details of nasal symptoms (sneezing, rhinorrhea, nasal congestion), the extent of impairment of daily activities, drug usage, other symptoms, and concomitant medications (drug name and dosage) each day in the allergy diary described above, and these details were then confirmed during their visits to the hospital.

4) Measurement of intraocular pressure

Intraocular pressures (IOPs) were measured before and after administration of the study drug using a noncontact tonometer (CT-80, Topcon Corp., Tokyo).

(5) Endpoints

1) Primary endpoint

The primary endpoint was substance P concentration in tears at 2 and 4 weeks compared to the baseline.

2) Secondary endpoints

The secondary endpoints were the following variables, wherein individual symptoms were scored according to guidelines at baseline, 2 weeks, and 4 weeks (or at the end of treatment): 1) individual ocular symptom and total ocular symptom scores (TOSS)[8]; 2) individual nasal symptom and total nasal symptom scores (TNSS)[1]; and 3) ophthalmic evaluation of the palpebral conjunctiva (redness, swelling, follicles, papillae) and the bulbar conjunctiva (redness, swelling)[7].

The TOSS and TNSS used a scale of 0 to 4 (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = most severe), whereas the ophthalmologist's evaluation of clinical findings was scored on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Shifts in IOP from baseline were compared in the same way. Correlations between the substance P concentration and ocular and nasal symptoms were also determined.

(6) Statistical Analysis

Intergroup comparisons of patient demographic characteristics were performed with Fisher's exact test or the Mann-Whitney U test. Intergroup comparisons of efficacy and safety endpoints were done with the Mann-Whitney U test based on changes in respective laboratory values and symptom scores. Correlations between substance P concentrations and respective symptom scores were determined with Spearman's rank correlation coefficient with a two-sided significance level of 5%. Statistical analysis of data was performed with Excel Statistics 2008 software program (Social Survey Research Information Co., Ltd., Tokyo).

Results

(1) Subjects

The safety analysis set consisted of 16 of the 18 patients with SAR enrolled in this study in 2009 and 2010, because 2 patients were excluded for failing to attend the initial and subsequent consultations.

The efficacy analysis set consisted of 11 patients, because 1 patient was excluded for administration outside of the heavy pollen dispersal period, 3 patients were excluded for using disallowed concomitant medications, and 1 patient was excluded for failing to complete the allergy diary. Patient demographic characteristics are shown in **Table 1**. There were no significant differences between the MFNS and placebo groups in terms of sex, age, duration of SAR, or observed baseline variables.

(2) Efficacy Evaluation

There was no significant intergroup difference in substance P concentration in tears after 4 weeks of treatment, but a declining trend in the mean change from baseline was seen in the MFNS group (N = 7), with a decrease of 44.3 pg/mL compared with an increase of 277.7 pg/mL in the placebo group (N = 4; P = 0.089) (**Fig. 1**). The change in substance P concentration in tears was positive for all patients in the placebo group but was nonexistent or negative in the MFNS group (data not shown). The amounts of change in TOSS and TNSS were significantly less in the MFNS group than in the placebo group, except for TOSS at 4 weeks (**Fig. 2**). The amounts of change in individual symptom scores were also significantly lower for all variables except tearing at 2 and 4 weeks in the MFNS group than in the

Table 1 Baseline subject demographics and characteristics (all randomized subjects)

	category	n			
All subject		MFNS 7	Placebo 4	P-value	
Gender	male	7	3	P=0.36	Fisher's test
	female	0	1		
Age	<29 y		0	P=0.67	Mann-Whitney U test
	<39 y	0	0		
	<49 y	1	4		
	50 y <=	4	0		
		2			
	Mean ± S.D. (Min-Max)	45.0 ± 7.9 (33–60)	44.0 ± 4.2 (40–49)	P=0.93	
Duration of SAR	<3 y	0	0	P=1.00	Fisher's test
	3 y <=	7	4		
Outcome measure	Substance P concentration in tears: mean ± SD	496.4 ± 205.4	365.6 ± 106.3	P=0.35	Mann-Whitney U-test
	TOSS: mean ± SD	3.00 ± 1.85	2.75 ± 0.43	P=0.69	
	TNSS: mean ± SD	4.86 ± 2.85	2.25 ± 2.27	P=0.25	
	IOP: mean ± SD	12.10 ± 2.13	12.67 ± 2.66	P=0.55	

Abbreviations: TNSS, total nasal symptom score; TOSS, total ocular symptom score; IOP, Intraocular pressure; MFNS, mometasone furoate nasal spray; SD, standard deviation.

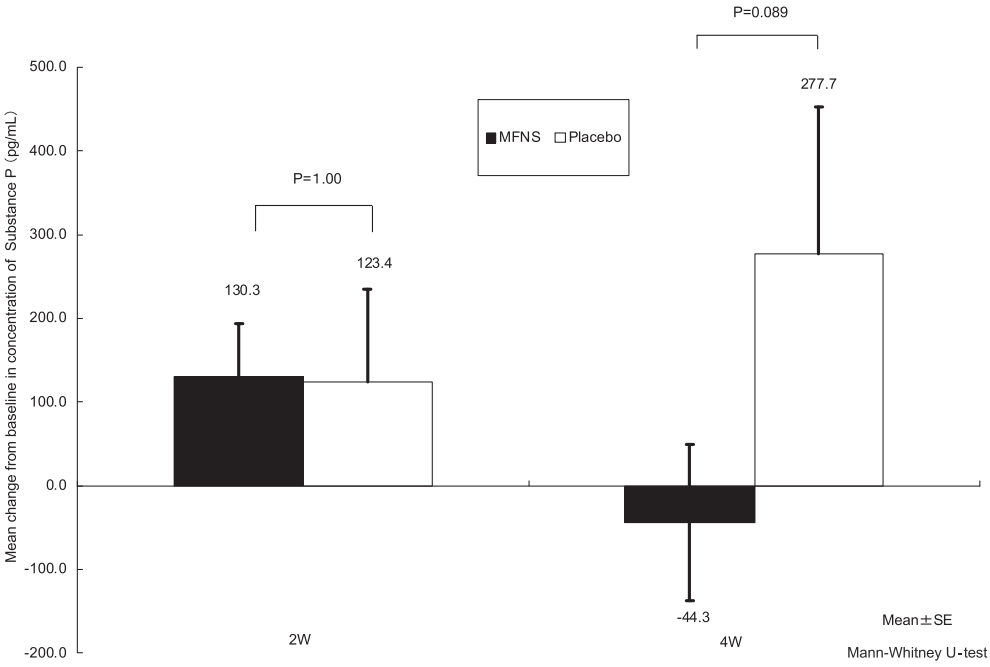

Fig. 1 No significant differences were seen in the mean change from baseline in the concentration of substance P between patients treated with MFNS and patients receiving placebo over the 2-week to 4-week treatment period. However, there was a declining trend in the MFNS group at week 4. Data are shown as mean ± SE, P-value versus placebo.

placebo group, thus demonstrating the efficacy of MFNS in relieving these symptoms **(Fig. 3)**.

There were almost no changes from baseline in any of the ophthalmic findings **(Fig. 4)**. Furthermore, there was a strong correlation between substance P concentration and both ocular itch and TNSS (r =

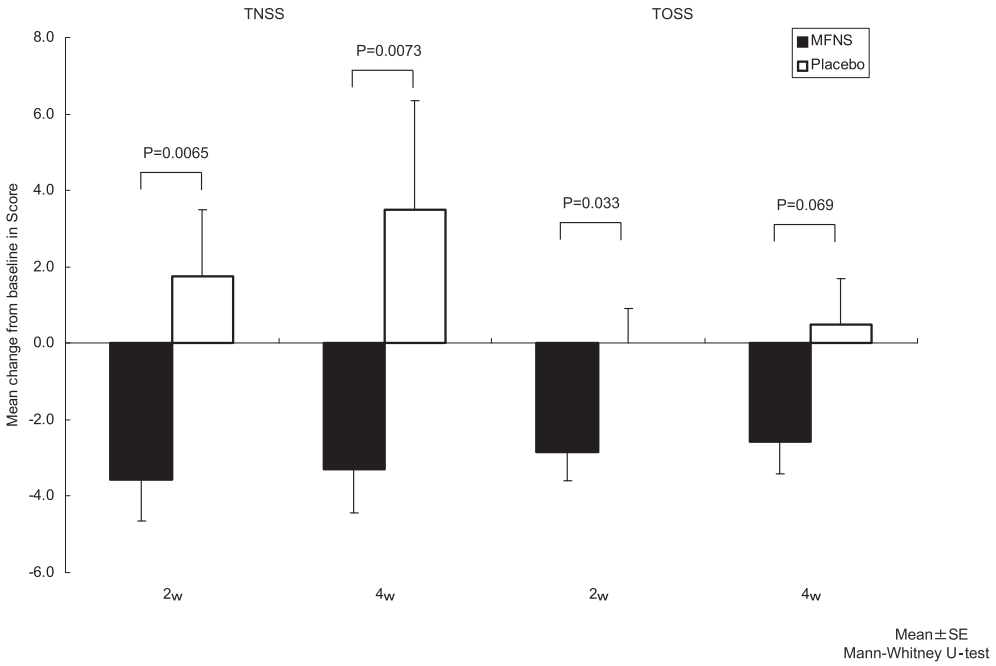

Fig. 2 Mean change from baseline in total ocular symptom score (TOSS) and total nasal symptom score (TNSS) reveals a significant improvement in the MFNS group versus the placebo group except for TOSS at 4 weeks. Data are shown as mean ± SE, P-value versus placebo.

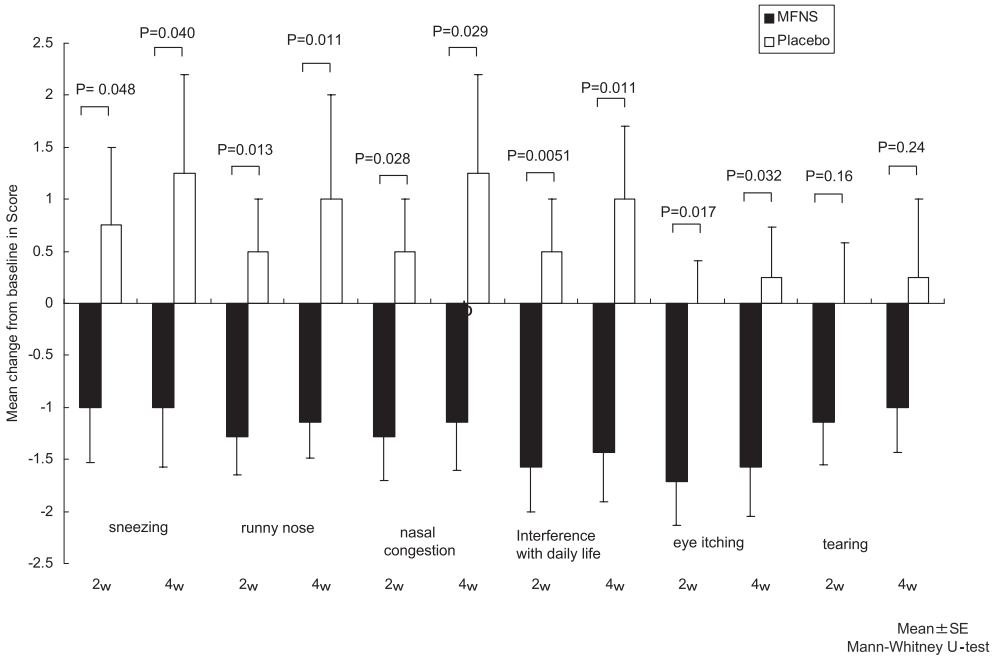

Fig. 3 The mean change from baseline in individual ocular and nasal symptom score, except for tearing, was significantly greater in the MFNS group than in the placebo group over the 2-week to 4-week treatment period. Data are shown as mean ± SE, P-value versus placebo.

0.0647 and r = 0.603, respectively; P<0.05) **(Fig. 5a, 5b)**.

(3) Safety Evaluation

The IOP was within the normal range for all patients in both treatment groups, and there was

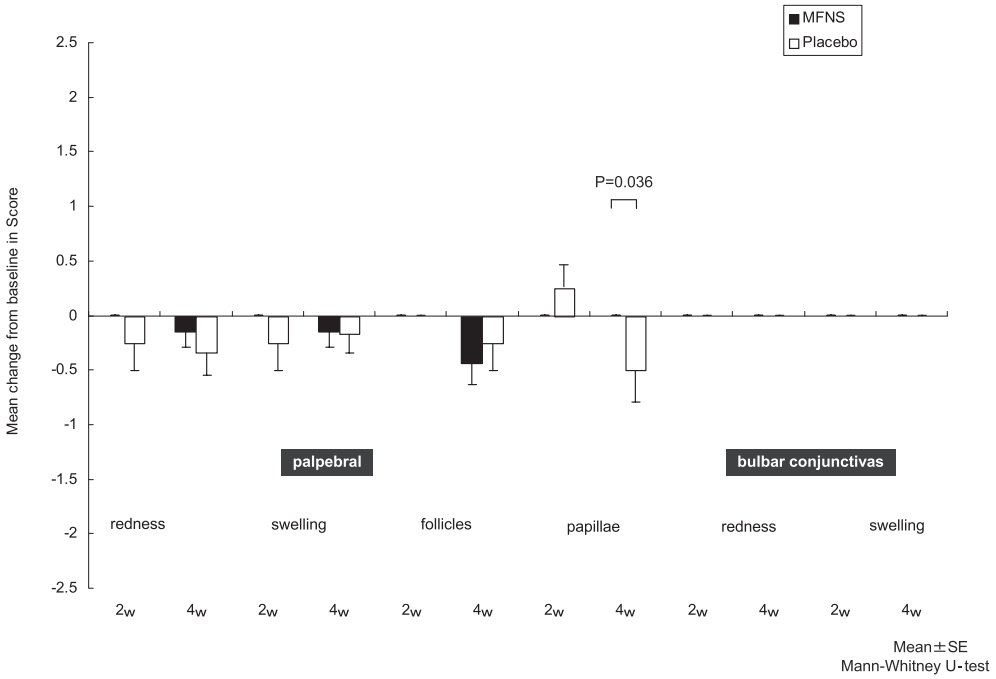

Fig. 4 Mean change from baseline in clinical ocular observation by ophthalmologists in patients receiving MFNS or placebo, over the 2-week to 4-week treatment period. Clinical ophthalmic findings showed no significant change in any of the variables because of the moderate extent of baseline findings. Data are shown as mean ± SE, P-value versus placebo.

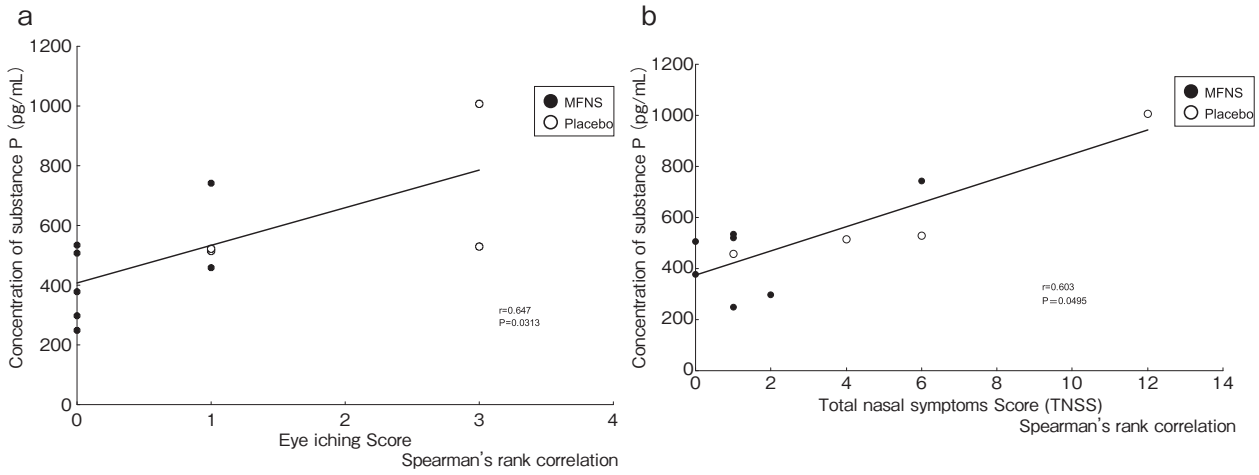

Fig. 5 There was a strong correlation between eye itching (a)/total nasal symptom score (TNSS: b) and substance P concentration after 4 weeks of treatment with MFNS (closed circle) or placebo (open circle), respectively. Correlation coefficient (r) with P-value.

little change from baseline: −0.38 ± 0.75 in the MFNS group and −0.33 ± 0.80 in the placebo group (mean ± SE). There was also no significant intergroup difference in the change from baseline in IOP (data not shown).

Discussion

Japanese cedar pollen-induced SAR (Japanese cedar pollinosis) is accompanied by both intense nasal symptoms (sneezing, rhinorrhea, and nasal congestion) and ocular symptoms (eye itching and tearing). A national survey conducted after Japanese

cedar pollen dispersion in 2007 identified the main causes of discomfort as "runny nose" and "itchy eyes"[9], indicating that ocular symptoms are key factors in decreasing quality of life. Current guidelines on the treatment of ocular symptoms recommend the administration of eye drops and oral antihistamines with antiallergic activity. However, a recent meta-analysis has shown that INSs are almost as effective as oral antihistamines for treating the ocular symptoms of SAR[3].

Several studies have investigated the mechanisms of INSs in relieving the ocular symptoms of SAR[4,5] Because the direct effects of INSs on the eye, such as IOP elevation, have been ruled out by numerous case studies[10], Prenner et al. have instead argued that their main action is indirect[5]. One possible indirect mechanism of action of INSs is that they alleviate nasolacrimal duct edema and reduce the release of inflammatory mediators from the conjunctival sac, resulting in relief of ocular symptoms. In patients with allergic rhinitis, the opening of the nasolacrimal duct below the inferior nasal concha may be obstructed owing to mucosal hypertrophy, which is relieved by INSs. In fact, the use of INSs to treat the rhinitis of patients with epiphora has been found to reduce lacrimation[11]. The most important mechanism of INSs is thought to be reductions in the concentrations of histamines and other nasal inflammatory mediators[12], thus suppressing the naso-ocular reflex and relieving ocular symptoms. O'Meara et al. have reported that the use of nasal filters in patients with SAR significantly relieves not only nasal symptoms but also the ocular symptoms of itching and tearing[13]. Furthermore, a recent study by Callebaut et al. has found that ocular symptoms are induced following nasal antigen exposure and that these symptoms are correlated with histamine concentration in tears[14]. These results suggest that pruritus and other ocular symptoms of SAR may be indirectly caused by a naso-ocular reflex triggered by an allergic reaction in the nasal mucosa.

The INS MFNS features much lower systemic absorption and higher glucocorticoid receptor affinity than those of its counterparts[15], and in 1997 it was approved in the USA as a once-daily treatment for allergic rhinitis. It is the only INS indicated for administration before pollen season and for the treatment of nasal polyps and is the most used INS in the world. MFNS was approved for use in Japan in 2008[16,17]. The findings of a recent meta-analysis have also shown that the efficacy of MFNS against ocular symptoms is equivalent or superior to those of other INSs[6]. However, most previous studies evaluating the efficacy of MFNS against ocular symptoms have been based on the subjective scoring by patients of symptoms, such as ocular itching and tearing, whereas analyses of clinical findings by ophthalmologists are few.

Changes in the levels of chemical mediators in the tears of patients with SAR were measured following administration of an INS, and the factors that contributed to the relief of ocular symptoms were clarified. Previous studies have described elevated levels of chemical mediators, such as eosinophil cationic protein (ECP), immunoglobulin E (IgE), histamine, eotaxin-2, and substance P, in patients with allergic conjunctival diseases, including SAR and vernal conjunctivitis[18–24]. In present study, levels of 5 mediators—ECP, eotaxin-2, IgE, substance P, and histamine—were measured in a pilot study to select a chemical mediator present in tears for assessment, and eventually substance P was chosen due to its good repeatability. Substance P is released in a retrograde fashion from sensory nerve endings via an axonal reflex and acts on mast cells, vascular endothelial cells, keratinocytes, Langerhans cells, and other cells as a proinflammatory agent. Substance P has been discovered in significantly higher levels in patients with allergic conjunctivitis than in healthy persons[24].

The present study did not find any significant difference in change from baseline in substance P concentration in tears between the MFNS group and the placebo group, but MFNS treatment had an inhibitory effect on substance P levels. MFNS was also found to relieve oculonasal symptoms, whereas substance P concentrations were strongly correlated with ocular itching and TNSS. These findings suggest that a relief of ocular symptoms accompanies an improvement in nasal symptoms and that the substance P concentration in tears is

involved in this improvement.

The objective findings related to ocular symptoms were also investigated in terms of the efficacy of MFNS in relieving palpebral conjunctivitis (redness, swelling, follicles, papillae) and bulbar conjunctivitis (redness, swelling), but there was no change in scores indicative of improvement or exacerbation. We attribute this finding to most patients having only mild symptoms at baseline and to the low amounts of airborne pollen in Japan in 2009 and 2010.

In terms of safety, the systemic response to INSs is considered to be weak because of their lack of effect on IOP and their low bioavailability[10]. Similarly, in the present study, treatment with MFNS did not affect IOP, and no other adverse effects were seen, thus suggesting that MFNS is well tolerated.

In conclusion, the present findings indicate that INSs are effective in relieving ocular symptoms in SAR and that the mechanism of action involves a reduction of substance P concentrations in tears via an indirect pathway. Because the present study was a pilot study of a small population, the results remained statistically insignificant. Future studies targeting an even greater number of subjects are necessary. We would also like to address the question of which are more important for ocular symptoms: simple allergic reactions at a localized area of the eye or indirect reactions caused by the naso-ocular reflex.

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