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ORIGINAL ARTICLE

Early Interventional Treatment with Intranasal Mometasone Furoate in Japanese Cedar/Cypress Pollinosis: A Randomized Placebo-Controlled Trial

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ABSTRACT

Background: Little is known about the safety and effectiveness of early interventional treatment (EIT) with intranasal corticosteroids for seasonal allergic rhinitis. We designed a double-blinded, randomized, placebo-controlled 12-week trial of EIT with mometasone furoate nasal spray (MFNS) for Japanese cedar/cypress pollinosis (JCCP).

Methods: A total of 50 JCCP patients received MFNS (200 μg once daily: $n = 25$) or placebo ($n = 25$) starting on February 1, 2010. Treatments continued until the end of April. The primary endpoint was the comparison of the total nasal symptom score (TNSS) between the MFNS and placebo groups. The secondary endpoints included comparisons of QOL, daytime sleepiness, nasal ECP levels, and safety.

Results: Continuous dispersion of Japanese cedar pollen began on February 22. Although the placebo group showed a significant worsening of symptoms after the start of the continuous dispersion, no worsening occurred in the MFNS group. A significant difference in the TNSS between the two groups was seen starting at 4 weeks after the treatment. Similar results were seen for QOL and sleepiness. Nasal ECP levels in March were significantly lower in the MFNS group. A total of 56% of the MFNS group progressed to a persistent allergic rhinitis state in accordance with the ARIA classification, as opposed to 84% of the placebo group. MFNS was well tolerated, and the plasma cortisol concentrations were similar between the two groups.

Conclusions: EIT with MFNS for JCCP is both safe and effective. This treatment can potentially lessen symptoms and help pollinosis patients remain in the intermittent state.

KEY WORDS

early interventional treatment, ECP, intranasal corticosteroids, Japanese cedar/cypress pollinosis, total nasal symptom score

INTRODUCTION

Allergic rhinitis (AR) is a global healthcare problem that greatly affects daily activity, work productivity, learning, sleep, and the quality of life (QOL).[1] The prevalence of AR has continued to rise over the past decade, with rates in Japan increasing from 29.8% in 1998 to 39.4% in 2008.[2]

The major AR phenotype in Japan is the Japanese cedar/cypress pollinosis (JCCP), which has a prevalence of 26.5%.[2] JCCP is mainly due to exposure to Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtuse*) pollen.[3] Dispersal of the cypress pollen in the spring occurs after that for

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cedar pollen. Since cedar pollen and cypress pollen contain several cross-reactive components, the pollinosis-related symptoms can therefore last for as long as 4 months, being present from February until early May in some subjects.[4,5] In addition, dispersion of Asian sand dust during the same season is also thought to exacerbate JCCP.[6]

Initial dispersion of the pollen can have a priming effect and cause a minimal persistent inflammation that is characterized by an influx into the nasal mucosa of inflammatory cells such as eosinophils. These conditions lead to allergen and non-specific irritant hypersensitivities, which contribute to the onset of AR.[1,7] Therefore, the Practical Guideline for the Management of Allergic Rhinitis in Japan (PG-MARJ) recommends that patients who annually experience substantial symptoms of pollinosis should receive early interventional treatment (EIT, or in other words prophylactic or initial treatment) starting immediately after pollen release or the onset of symptoms. The PG-MARJ recommends that physicians determine the drug regimen for individual patients based on the amount of expected pollen release during the season and the type and severity of symptoms that are usually experienced by each patient during the peak pollen season. Treatments need to be selected from among chromones, second-generation H_1-receptor antagonists (H1RA), leukotriene receptor antagonists, Th2 cytokine suppressor (suplatast) and the PGD_2/TXA_2 receptor antagonist (ramatroban) for EIT.[2] In contrast, the international guideline for AR, ARIA, recommends oral or topical H1RA, topical decongestants, topical chromones or nasal douching with saline for mild intermittent AR, which may be representative of early stage pollinosis.[1]

Intranasal glucocorticosteroids (INS) are the most effective drugs for controlling AR-caused inflammation, with the mechanism of action for these drugs using at least two pathways, the transactivation and the transrepression pathways.[8] As such, INS can control both the priming effect and the minimal persistent inflammation, and thus can potentially be used as EIT for pollinosis.[7] There has only been one significant report that has investigated the efficacy of INS when used as EIT for pollinosis.[9]

Mometasone furoate nasal spray (MFNS) is one of the new generation INS that have a minimal bioavailability, thus, potentially making it fit for use as an EIT for pollinosis.[10] Recent meta-analysis has demonstrated level 1a evidence for the efficacy of MFNS in AR treatment versus placebo.[11] This previous review analyzed 16 articles that were published from 1966 to October 2007 and met the criteria for double-blinded, randomized, and placebo-controlled clinical trials (DB-RCT). Of these, 12 of the studies included pollinosis patients. However, the patients in most of the studies had already acquired substantial symptoms, and in addition, were only observed over a short period of time (from a single dose to 4 weeks). There was only one DB-RCT study conducted over an 8-week period that showed the efficacy and safety of MFNS as EIT for ragweed pollinosis.[9] However, since there have been no DB-RCT in Japan that have evaluated the efficacy and safety of INS as EIT for JCCP, we decided to perform a 12-week DB-RCT of EIT using MFNS for JCCP. The results presented here include information not only on the efficacy, including for the naso-ocular symptoms and QOL, but also provide safety profile information with regard to the MFNS plasma cortisol levels when used as EIT in pollinosis. These experimental results demonstrate for the first time that EIT with MFNS can potentially control the intermittent state and prevent worsening of pollinosis in patients that otherwise might lead to a persistent state.

METHODS

PATIENTS

Inclusion criteria for the JCCP subjects enrolled in the study were: (a) male or female between the age of 16 and 65 years; (b) at least a 2-year history of JCCP; (c) sensitization to Japanese cedar pollen as assessed by a skin prick test; and (d) ability to accurately fill in diary cards. Patients were excluded from the study if they had: (a) concomitant sinonasal disease that could potentially affect the outcome of the trial (e.g., nasal polyps, rhinosinusitis, nasal septum deviation); (b) concomitant treatment for AR caused by allergens other than Japanese cedar/cypress pollen; (c) rhinitis medicamentosa and non-infectious, non-allergic rhinitis; (d) cedar pollen-specific immunotherapy; (e) sinonasal surgery including laser vaporization of inferior turbinates within 1 year; (f) medication with anti-allergic drugs including H1RA, chromones, glucocorticoids and decongestants within 2 weeks of study initiation; (g) hypersensitivity to MFNS; (h) systemic infection including mycosis; or (i) were pregnant and breastfeeding.

STUDY DESIGN

The study was a single-center, double-blinded, randomized, placebo-controlled, two-parallel group trial that was carried out from 2009 to 2010. The primary endpoint was the comparison of MFNS and placebo total nasal symptom scores (TNSS) that were obtained from diary cards filled out between February and April 2010. The secondary endpoints were comparisons of the total ocular symptom scores (TOSS), total symptom score (the sum of TNSS and TOSS: T5SS), QOL, daytime sleepiness, smell disturbance, frequency of use of rescue medication, ECP levels in nasal secretions, and safety, which included plasma cortisol levels.

Screening visits were performed in December 2009 and continued until a total of 50 patients fulfilled the inclusion criteria. Prior to study initiation, we esti-

mated the sample size that would be required based on the mean and standard deviation in the groups reported for a previous study.[12] In order to yield an 80% study power for the mean and standard deviation values (1.1+/-1.1, 2.1+/-1.1) of the INS and placebo groups, a total of 20 subjects were required for the primary endpoint of the symptom score from the domestic clinical data (when using a 2-sided Student's *t*-test with $\alpha = 0.05$).[12] Based on these calculations, we determined that a sample size of 25 subjects per each group would be necessary when assuming there would be a 20% drop-out rate.

Patients were randomized and received either MFNS (100 μg per nostril once daily in the morning) or placebo during the 12-week double-blind phase. The inactive placebo contained benzalkonium chloride and phenylethyl alcohol, identically concentrated to active MFNS, in saline. Smell and appearance of device between MFNS and placebo were same. Allocation concealment was granted by the central registry and computer-generated block randomization. After the randomization, patients came in for a second visit in January 2010, so that the MFNS or placebo, diary cards with written instructions, the Japanese rhinoconjunctivitis quality-of-life questionnaires (JRQLQ), the Japanese edition of Epworth Sleepiness Scale (JESS) and the self-administered odor questionnaire (SOQ) could be distributed to each of the subjects.[13-15] During the patient visit, the investigator explained how to accurately fill in the diary card and questionnaires. The investigator also instructed each of the patients on how to correctly use the spray. After blood and nasal samples were collected at the second visits, the patients then started to fill in their diary cards.

Starting on February 1, patients began to receive either the MFNS or the placebo. Treatments continued for 12 weeks and finished at the end of April. Patients were allowed to use loratadine provided and eye drops as rescue medications on demand. JRQLQ, JESS and SOQ were filled every other week for a total of seven times (February 1 and 15, March 1, 15 and 29, and April 12 and 26). Patients returned for a visit every month in order to confirm the accuracy of their filling in the diary/questionnaires, to assess the occurrence of adverse events, and to collect blood and/or nasal samples. The study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Rinri-751), and registered in UMIN (UMIN000005985). Prior to participation in the study, all patients provided written informed consent.

DIARY CARDS

The patients' diary contained reports on the presence and intensity of three nasal symptoms (sneezing, rhinorrhea, and nasal congestion), and two ocular symptoms (watery and itchy eyes), along with information on any impairment of their daily life. Nasal and ocular symptoms were rated using a 5-point scale that ranged from 0 to 4 (0 = no symptoms, 1 = minimal, well tolerated symptoms, 2 = bothersome but tolerated symptoms, 3 = severe and hard to tolerate symptoms, and 4 = severest symptoms) according to PG-MARJ.[2] The TNSS, TOSS, and T5SS were calculated by adding the three nasal, two ocular, and five naso-ocular symptom scores, respectively. Mean weekly values of TNSS, TOSS, and T5SS were also calculated for the statistical analysis. Patients also recorded the use of loratadine and other drugs in their diary, and this was used to calculate the percentage of patients using loratadine and the dosage of loratadine for each week. In accordance with the ARIA classification, each subject group was further divided into intermittent or persistent state groups based on the presence of the nasal symptoms recorded in the diaries during the 12-week period.[1] Briefly, patients exhibiting nasal symptoms fewer than 4 days a week or for less than 4 weeks between February and April were placed in the intermittent state group. Patients exhibiting nasal symptoms more than 4 days a week and for more than 4 weeks during the study period were placed in the persistent state group.

NASAL ECP LEVELS

Nasal secretions were collected using filter paper. Two filter paper discs packed in a commercial nasal provocation kit (Torii Co., Tokyo, Japan) were placed on the surface of the inferior turbinates for 5 min. After the harvest, these discs were then placed into a 1.5 ml micro test tube (Eppendorf AG, Hamburg, Germany), and stored at -80℃ until assayed.

The discs were soaked with 0.8 ml of Dulbecco's phosphate buffered saline (Invitrogen, Grand Island, NY, USA) overnight at 4℃ with gentle rotation. ECP levels were determined by using Unicap ECP (Phadia, Uppsala, Sweden). The detection limit of the assay was 2 ng/ml. All results were normalized to the total protein content in the extracts as determined by the bicinchoninic acid assay (Pierce, Rockford, IL, USA).

PLASMA CORTISOL CONCENTRATION

Blood was sampled between 9 and 11 am at the second (January 2010) and at the final (May 2010) visit, with the plasma cortisol concentrations then determined. The reference range for the morning serum samples for healthy individuals is 8-25 μg/dl.

MEASUREMENT OF POLLEN DISPERSION

Daily Japanese cedar and Japanese cypress pollen counts were performed using Durham samplers that were installed on the rooftops of the Okayama University Hospital buildings. The first day of the major pollen period was defined as the first of 2 consecutive days where ≥1 grain/cm^2 were counted.[16]

Table 1 Patient demographics and clinical characteristics

Demographic		MFNS (n = 25)	Placebo (n = 25)	P-Value
sex	male	15	15	N.S.†
	female	10	10	
age (year)	range	19-39	19-47	N.S.‡
	mean +/- S.D.	26.6 ± 6.2	28.5 ± 8.5	
disease duration				N.S.‡
	1 year	0	0	
	1 year≤ <3 year	1	0	
	3 year≤	20	24	
	unclear	4	1	
severarity of JCCP during past season				N.S.‡
	severest	9	9	
	severe	11	11	
	moderate	4	4	
	mild	0	1	
	unclear	1	0	

N.S., not statistically significant. †Fisher's exact test. ‡Mann-Whitney's U-test.

STATISTICAL ANALYSIS

Values were expressed as the mean ± SEM for each subject group. Efficacy analyses were performed with the intent of population treatments in the future. A non-parametric Mann-Whitney's U-test was used to compare the data between groups, while the Wilcoxon signed-rank test was used for analysis within the groups. The percentage of patients using loratadine and the percentage in the intermittent or persistent states, along with the number of patients with adverse effects were compared using Fisher's exact probability test. Statistical analyses were performed using SAS (Statistical Analysis System) version 9.2, with $P < 0.0.5$ considered to be significant.

RESULTS

PATIENT POPULATION

Out of the 66 patients that were screened, a total of 50 patients fulfilled the inclusion criteria. After enrollment in the study, patients were randomized to one of two treatment medications, with 25 receiving MFNS, 200 μg once daily and 25 receiving placebo. All of the patients completed the study and there were no dropouts. The treatment groups were comparable with respect to demographic characteristics, which included age, sex, disease duration, and severity of JCCP (Table 1).

FLUCTUATION OF CEDAR AND CYPRESS POLLEN DISPERSION

During 2010, the first dispersion of the Japanese cedar pollen occurred on February 4, with major continuous dispersion beginning on February 22. The highest cedar dispersion was seen on March 12, with 18.5 grains/cm^2/day. The first dispersion of cypress pollen occurred on March 20, with major continuous dispersion beginning on April 4. The highest cedar dispersion was seen on April 20, with 67.0 grains/cm^2/day. The total cedar and cypress pollen count during the study period was 107.3 and 267.0 grains/cm^2, respectively (Fig. 1).

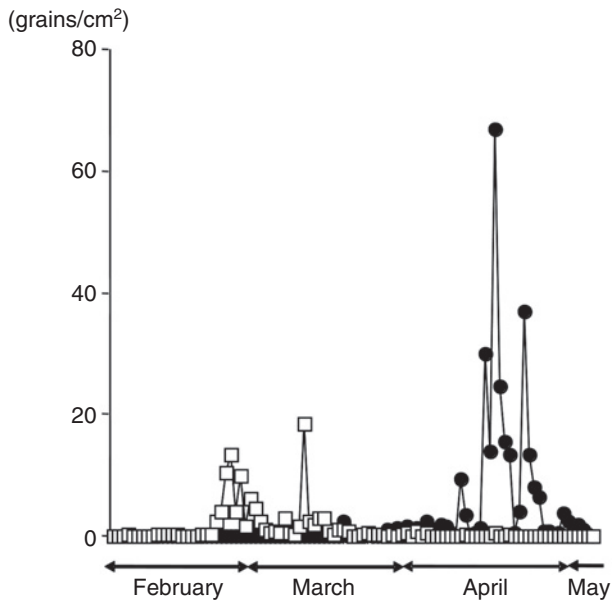


Fig. 1 Fluctuation of cedar and cypress pollen dispersion in 2010. The open squares and closed circles represent the cedar and cypress pollen counts, respectively.

PRIMARY ENDPOINT EFFICACY

Once there was continuous dispersion of Japanese cedar pollen, the placebo group began to display a sig-

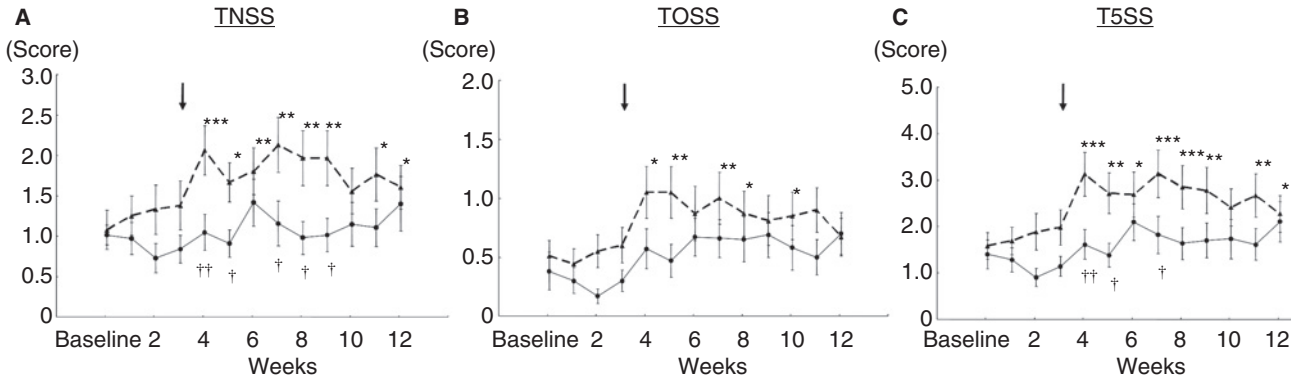


Fig. 2 Weekly reflective total nasal symptom score (TNSS: **A**), total ocular symptom score (TOSS: **B**), and total naso-ocular symptom score (T5SS: **C**) from the baseline through 12 weeks after the start of either MFNS treatment (circle) or placebo (triangle). Results are expressed as mean ± SEM. Mann-Whitney's U-test was used to compare data between the groups ($^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$). The Wilcoxon signed-rank test was used for analysis within the groups ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$). Arrow shows the beginning of continuous pollen dispersion.

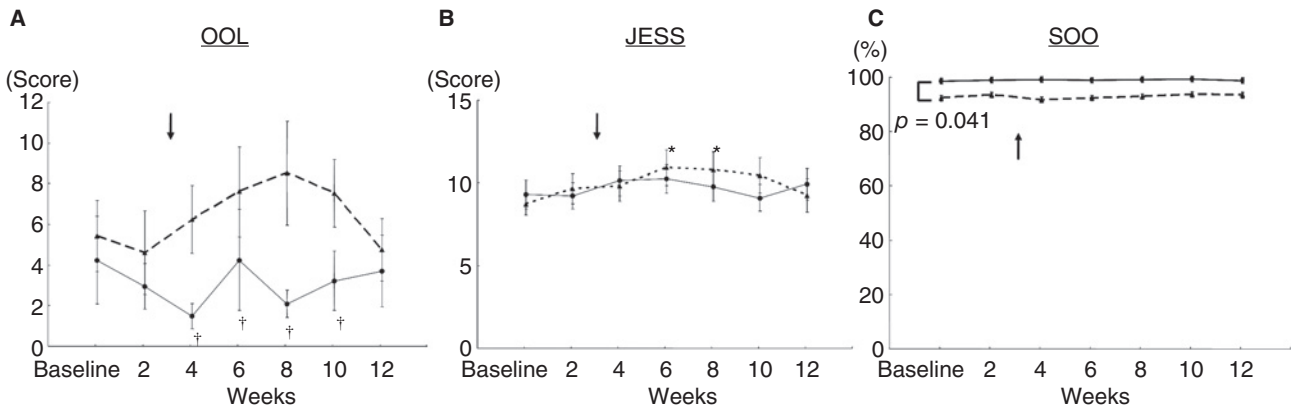


Fig. 3 Plots of biweekly reflective QOL, as determined by JRQLQ (**A**), sleepiness, as determined by JESS (**B**), and smell disturbance, as determined by SOQ (**C**). Data were collected and analyzed from baseline until 12 weeks after initiation of treatment with MFNS (circle) or placebo (triangle). Results are expressed as mean ± SEM. Mann-Whitney's U-test was used to compare data between the groups ($^{\dagger}p < 0.05$). The Wilcoxon signed-rank test was used for analysis within the groups ($^{*}p < 0.05$). Arrow shows the beginning of continuous pollen dispersion.

nificant exacerbation of the nasal symptoms, as shown by the changes in the TNSS from baseline. With the exception of 1 week (from April 5 to 11) this significant exacerbation lasted until the end of the study, which included the Japanese cypress pollen dispersion period. However, no significant exacerbation was noted in the group receiving MFNS until the very end of the study. As compared with the placebo group, there were significantly lower TNSS seen after the continuous pollen dispersion in the MFNS group (Fig. 2A).

SECONDARY ENDPOINT EFFICACY

Similar to the TNSS, ocular symptoms used to determine the TOSS were significantly exacerbated in the placebo group but not in the MFNS group after the continuous dispersion. However, there was no significant difference between the two groups for the TOSS (Fig. 2B). Naso-ocular symptoms determined by T5SS were also significantly exacerbated in the placebo group, although this was not observed in the MFNS group. As compared to the placebo group, there was a significantly lower T5SS seen in the MFNS group once there was continuous pollen dispersion (Fig. 2C).

From February 1 through April 26, patients filled out the JRQLQ every other week (a total of seven times) in order to monitor their QOL. As compared to the placebo group, there was a significant reduction in the total QOL score at 4 weeks after starting the treatment in the MFNS group, which indicates a good QOL in these patients (Fig. 3A). Similarly, daytime sleepiness and smell disturbance were monitored by using the JESS and SOQ, respectively. A sig-

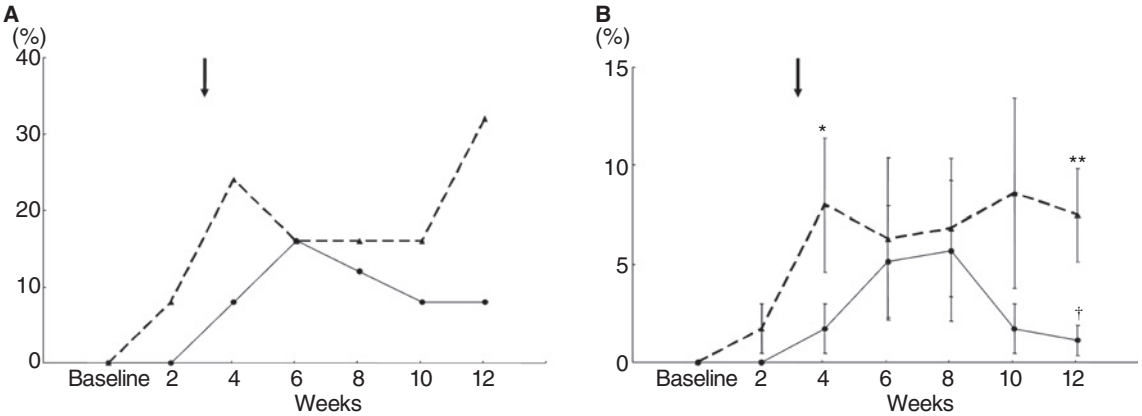


Fig. 4 Comparison of biweekly usage of loratadine as a rescue medication between EIT treatment with MFNS (circle) and placebo (triangle). Percentage of patients taking loratadine (**A**) and dosage of loratadine (**B**) were calculated from the diary cards collected from baseline until 12 weeks after initiation of treatment. Results are expressed as mean ± SEM. Mann-Whitney's U-test was used to compare the data between the groups ($^{\dagger}p < 0.05$). The Wilcoxon signed-rank test was used for analysis within the groups ($^{*}p < 0.05$, $^{**}p < 0.01$). Arrow shows the beginning of continuous pollen dispersion.

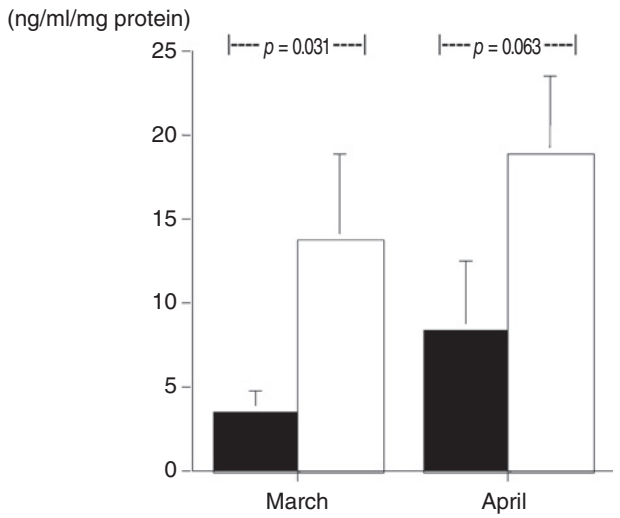


Fig. 5 Comparison of nasal ECP levels between EIT treatment with MFNS (closed bar) and placebo (open bar). Nasal secretions were collected by filter paper in mid March and mid April. Results are expressed as mean ± SEM. *P* values were determined by using Mann-Whitney's U-test.

nificant exacerbation of sleepiness from baseline was noted in the placebo group between March 15 and 29. This deterioration was not seen in the MFNS group, although no significant difference was seen between the two groups throughout the study period (Fig. 3 B). In contrast, there was no change from the baseline for the smell disturbance for either the MFNS or placebo group, although the difference between the two groups was significant at baseline ($p = 0.041$, Fig. 3C).

Patients were allowed on-demand use of loratadine during the study period. With the exception of during March, the percentage of patients taking loratadine in the MFNS groups after the pollen dispersion was lower than that in the placebo group, although the difference was not statistically significant (Fig. 4A). In addition, the dosage of loratadine was also lower in the MFNS group, with the difference becoming statistically significant during the last 2 weeks of April (Fig. 4B).

EFFICACY OF MFNS BASED ON THE ARIA CLASSIFICATION

In accordance with the ARIA classification scheme, patients were classified as having intermittent or persistent rhinitis based on the number of days with nasal symptoms present during the 12-week period between February and April. While 84% of the placebo group were classified as having persistent rhinitis, only 56% of the MFNS group met the ARIA classification criteria ($p = 0.062$; Fisher's exact probability test).

EFFECT OF MFNS ON NASAL ECP LEVELS

ECP levels in the nasal secretions in mid March were significantly lower in the MFNS group as compared to the placebo group ($p = 0.031$). While there was also a reduction of the ECP levels in the MFNS group in mid April, this difference was not statistically significant ($p = 0.063$) (Fig. 5).

SAFETY

Both the treatments were well-tolerated, and had a similar safety profile (Table 2). While there were nine and eight adverse events reported in the patient dia-

Table 2 Adverse events that were reported during the study regardless of the relationship to the treatment

Adverse events	MFNS (n = 25) 7 subjects (9 events)	Placebo (n = 25) 8 subjects (8 events)
common cold	5	5
cough	1	1
poor physical condition	1	1
epistaxis	2	0
headache	0	1

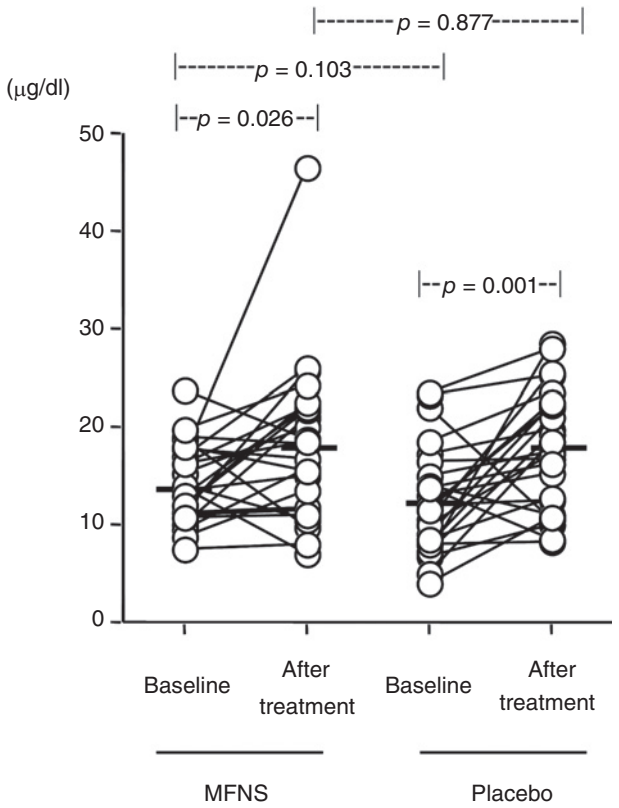


Fig. 6 Comparison of plasma cortisol levels between EIT treatment with MFNS and placebo. Blood samples were collected during the morning in January (baseline) and in May (after treatment). Bar represents the mean value. *P* values were determined by using Mann-Whitney's U-test (between groups) and the Wilcoxon signed-rank test (within groups).

ries in the MFNS and placebo group, respectively, none of the events caused any of the patients to drop out of the study. In most cases, these adverse events were related to a common cold and considered to be unrelated to the treatment.

Plasma cortisol concentrations were similar between the two groups before and after the study. Interestingly, the cortisol levels did not decrease but instead, there was a significant increase after the 12th week of the trial for both the placebo and the MFNS groups (Fig. 6).

DISCUSSION

Glucocorticoids anti-inflammatory effect is due to the down-regulation of the pro-inflammatory genes via several mechanisms, including the protein-protein interactions that sequester protein kinase A and CREB-binding protein from NF-κB.[17,18] The interaction between NF-κB, CREB, and the CREB-binding protein leads to the acetylation of chromatin and the subsequent transcription of proinflammatory genes, such as the genes encoding cytokines, inflammatory enzymes, adhesion molecules, and inflammatory receptors.[19] Thus, as compared to post-onset treatments, EIT with INS may be more effective in controlling pollinosis due to lower activity of NF-κB in the nose during the early exposure to pollens. In addition, when there is exposure to a low pollen count, EIT with INS may have clinically beneficial effects on the minimal persistent inflammation, a time when nasal inflammation is present prior to the initial onset of allergic symptoms.[7,20]

To the best of our knowledge, there have only been two other randomized studies that have investigated the efficacy of using INS for EIT.[9,21] Graft *et al.* performed an 8-week DB-RCT for ragweed pollinosis, and showed that the proportion of minimal symptom days was significantly higher in both the MFNS and in the beclomethasone dipropionate groups when compared with a placebo group.[9] Pitsios *et al.* investigated an open-labeled trial, and reported that when patients with pollinosis due to grass, parietaria and/or olive trees received MFNS starting 2 to 4 weeks prior to the pollen season, these patients had more days without symptoms, a lower TNSS, and were more satisfied with the treatment as compared to those patients who were treated with nedocromil sodium.[21] The reason why we selected MFNS in the present study was safety such as the extremely low bioavailability because patients were planned to receive MFNS for 12 weeks.[10]

Results of the present study demonstrated that as compared to placebo, EIT with MFNS significantly alleviated nasal and naso-ocular symptoms, improved the QOL, decreased the dosage of loratadine that had to be taken as a rescue medication, and decreased the ECP nasal secretion levels in JCCP. Similar

trends were seen for the ocular symptoms and sleepiness, although the differences between the two groups did not reach a level of significance. In particular, both nasal and ocular symptoms remained around baseline levels throughout the pollen dispersal period in the MFNS group, whereas the symptoms were significantly exacerbated in the placebo group. When taken together with the other findings, such as the similarity of the frequency of adverse events between the two groups, and the fact that there were no dropouts or any decreased plasma cortisol levels in both of the groups, the present findings may provide additional evidence that EIT with MFNS can be effectively and safely used to treat JCCP.

Although AR is not a life-threatening disease, it substantially impairs the QOL.[1] Several DB-RCTs have shown that INS can effectively reduce the QOL impairments that are associated with AR.[22,23] Meltzer *et al*. reported that a 4-week treatment with MFNS in perennial AR patients significantly improved the QOL, as monitored by the Rhinoconjunctivitis Quality of Life Questionnaire-Standard (RQLQ-S).[22] Bairadini *et al*. also showed that a 4-week treatment with MFNS in patients with persistent AR concomitant with intermittent asthma improved the QOL, as monitored by the Rhinasthma questionnaire.[23] In a recent systematic review, it was clearly demonstrated that fluticasone furoate nasal spray not only improved the nasal symptoms but also the ocular symptoms and QOL.[24] In contrast, Craig *et al*. demonstrated that an 8-week treatment with topical nasal fluticasone in the perennial AR patients did not lead to any significant improvement of the QOL, as monitored by the RQLQ.[25] Our current findings are consistent with the former reports, and suggest that EIT with MFNS following the exposure to pollen can prevent exacerbations of the QOL in JCCP patients.

Sleep disturbance is commonly observed in congested subjects, and can lead to daytime sleepiness.[26,27] In the present study, TNSS and JESS was correlated significantly ($p = 0.019$) and positively ($\rho = 0.332$, by Spearman's correlation coefficient by rank test) in mid March. Leukotriene receptor antagonists and INS have both been reported to improve sleep disturbance and daytime sleepiness.[28-30] For example, Meltzer *et al*. demonstrated that a 4-week treatment with MFNS improved the ESS from 12.5 to 10.6, whereas there was no significant improvement seen with the placebo treatment (13.3 to 13.7).[30] When we used the JRQLQ and JESS for estimations in the present study, significantly impaired sleep disturbance and daytime sleepiness was noted in the placebo group following the pollen dispersion, whereas there was no deterioration noted throughout the study period for the MFNS group. These results are consistent with previous reports, and suggest that control of minimal persistent inflammation by EIT with MFNS can prevent sleep-related disturbances that follow pollen exposure.

Nasal ECP levels have been shown to increase following allergen exposure, and are considered to be one of the biomarkers that reflect allergic inflammation in the nose.[31,32] Several reports have also demonstrated that INS can reduce nasal ECP levels.[33,34] In addition, Wand *et al*. recently reported that nasal ECP levels were one of the biomarkers noted during INS treatment in AR patients.[35] The present findings were consistent with these previous reports, and suggest that the reason why EIT with MFNS is so effective for JCCP might be related to its ability to control eosinophilic inflammation in the nose. Collection of nasal lavage fluid is a popular method to determine nasal ECP levels.[31,36] In the present study, we chosen paper disc method since this method seems to be simple and painless as compared to the lavage method. It is important to investigate a correlation of nasal ECP levels between the two methods in the future.

EIT with MFNS alleviated ocular symptoms as compared to placebo. It is known that INS is effective for not only nasal but also ocular symptoms of seasonal allergic rhinitis.[37] A reduction of excess stimulation of naso-ocular reflex and an improvement of nasolacrimal ducts drainage by controlling nasal inflammation may contribute to the efficacy of INS on ocular symptoms.[37,38]

Since JCCP can last from February until May, we performed a 12-week DB-RCT that covered almost the entire pollen season. Using this time period enabled us to investigate whether EIT with MFNS could modify the state of pollinosis in accordance with the ARIA guidelines.[1] Despite the fact that the 2010 total pollen count was much lower (374.3 grains/cm^2) than the average counts observed from 2000 to 2009 (3,546.6 grains/cm^2), 84% of our placebo group progressed to the persistent state. On the other hand, only 56% of the MFNS group progressed to the persistent state, with the remainder of the subjects continuing to be classified as intermittent state. This is first time that experimental data has been able to show that EIT with INS can prevent the progression of patients with pollinosis to the persistent state along with being able to help control patient conditions so that they remain within the intermittent state. However, even though our study was able to document this, the differences observed between the groups did not reach statistically significant levels. This was most likely due to the sample size in the current study and/or the lower than average pollen counts. Future studies with larger sample sizes and/or with elevated pollen counts will need to be undertaken in order to confirm this clinically critical effect.

Morning plasma cortisol concentrations were similar between the MFNS and placebo groups for both the pre-seasonal and post-seasonal samples. This result reflects the finding that the systemic bioavailabilities seen after the intranasal administrations with

mometasone were less than 1%, which suggests that continuous usage of MFNS at a standard dose for 12 weeks in non-pediatric, non-elderly Japanese does not affect the hypothalamic-pituitary-adrenal axis.[10] When taken together with the findings that there were no differences for the incidence of the adverse events between the two groups, the present study confirms the previously reported meta-analysis, and suggests that EIT with MFNS is both well-tolerated and safe to administer in humans.[11]

Interestingly, plasma cortisol levels increased after administration of not only MFNS but also placebo. Seasonal variation in plasma cortisol levels is known, and the present result consists with the report by Hoekstra *et al*. showing that higher level of the cortisol levels was seen in March-May in allergic asthmatics.[39] In addition, it is known that exposure to daylight can affect plasma cortisol levels.[40] Thus, irrespective of MFNS administration, a significant higher concentration of plasma cortisol in May as compared with January may reflect a seasonal variation due to an increased exposure to daylight.

In conclusion, EIT that uses 200 μg of MFNS once daily is both effective and safe for treating JCCP. In particular, EIT with MFNS maintained the levels of both the symptoms and the QOL at baseline values throughout almost the entire pollen season. As such, this ultimately prevented the progression to the persistent state and made it possible to control and maintain these pollinosis patients at the intermittent state. However, since the cedar and cypress pollen dispersal in 2010 was lower than average, further investigations at higher pollen dispersion levels will be required in order to confirm the margin of efficacy for this treatment. These studies are currently being undertaken.

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