



Early interventional treatment with intranasal corticosteroids compared with postonset treatment in pollinosis

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ABSTRACT

Background: The usefulness of early interventional treatment (EIT) with intranasal corticosteroids (INSs) compared with postonset treatment (POT) has not been clarified.

Objectives: To study the efficacy and safety of EIT with INSs compared with POT and placebo in Japanese cedar/cypress pollinosis.

Methods: We designed a 3-armed, double-blinded, randomized, placebo-controlled trial. Patients received mometasone furoate nasal spray (EIT group: $n = 25$), placebo ($n = 25$), or 4 weeks of placebo followed by 8 weeks of mometasone (POT group: $n = 25$) for a 12-week period starting on February 1, 2011. The primary end point was the comparison of the total nasal symptom score (TNSS) among the 3 groups. Total ocular symptom score (TOSS), total naso-ocular symptom score (TSS), Allergic Rhinitis and Its Impact (ARIA) on Asthma classification, and safety were the main secondary end points.

Results: The placebo and POT groups, but not the EIT group, had a significant exacerbation of TNSS and TOSS soon after the start of pollen counts being high on consecutive days. The 12-week mean TSS in the EIT group (score, 2.3) was significantly lower than in the placebo (5.0; $P < .01$) and POT (3.9; $P = .03$) groups. All patients in the placebo and POT groups were classified as having persistent rhinitis, whereas 80% of the EIT group met the ARIA classification criteria ($P = .03$). The quality-of-life score and nasal eosinophil cationic protein levels were lower in the EIT and POT groups compared with the placebo group. Daytime sleepiness, smell disturbance, and the mean dose of loratadine taken as the rescue medication were similar. Treatment with mometasone was well tolerated.

Conclusion: EIT with INSs is superior to POT in controlling pollinosis.

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Introduction

Allergic rhinitis (AR) is a global health care problem that greatly affects daily activity, work productivity, learning, sleep, and quality of life (QOL).¹ The most popular AR phenotype in Japan is the Japanese cedar/cypress pollinosis (JCCP), with a prevalence of 26.5%, followed by perennial rhinitis, with a prevalence of 23.4%.²

Initial dispersion of the pollen can cause a minimal persistent inflammation (MPI) characterized by an influx of inflammatory cells, such as eosinophils, into the nasal mucosa. These conditions lead to allergen-specific and nonspecific hypersensitivities, which contribute to the onset of AR symptoms.^{1,3} Thus, to decrease the

incidence of MPI, early interventional treatment (EIT), also known as starting preseasonal treatment, can be considered for pollinosis patients.^{1–3}

Intranasal corticosteroids (INSs) are the most potent drug for controlling AR-associated inflammation, and they are known to suppress both MPI and the priming effect.^{3–5} Studies support the efficacy and safety of INSs when used as EIT for pollinosis.^{6–8} For example, we performed a 2-armed, 12-week, double-blinded, randomized, placebo-controlled clinical trial (DB-RCT) whether EIT with mometasone furoate nasal spray is effective and safe as compared with placebo in JCCP.⁸ Mometasone furoate nasal spray was selected because it begins working within 48 hours.⁹ In this study, we demonstrated that, although the placebo group had a significant worsening of naso-ocular symptoms after the start of pollen counts being high on consecutive days, no worsening occurred in the mometasone furoate nasal spray group. Nasal eosinophil cationic protein (ECP) levels were significantly lower in the mometasone furoate nasal spray group. On the other hand, the

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plasma cortisol concentrations were similar between the mometasone furoate nasal spray and the placebo group, suggesting that EIT with mometasone furoate nasal spray for JCCP is both safe and effective.⁸ However, to date, there have been no DB-RCTs that have evaluated the efficacy and safety of EIT with INSS compared with postonset treatment (POT) in pollinosis. Thus, in 2011, we performed another DB-RCT with 3 groups (EIT, POT, and placebo).

Methods

Study design

The study was a single-center, 3-armed, parallel group DB-RCT that was performed from 2010 to 2011. The primary end point was the comparison of total nasal symptom scores (TNSS) that were obtained from diary cards filled out between February and April 2011.⁸ The patients filled in the cards once daily. The secondary end points were comparisons of the total ocular symptom score (TOSS), total symptom score (TSS; the sum of TNSS and TOSS), QOL determined by the Japanese Rhinoconjunctivitis Quality-of-Life Questionnaire (JRQLQ), daytime sleepiness determined by the Japanese edition of Epworth Sleepiness Scale (JESS), smell disturbance determined by the self-administered odor questionnaire (SOQ), frequency of use of rescue medication, ECP levels in nasal secretions, classification into intermittent or persistent rhinitis (based on the number of days with nasal symptoms during the study period), and safety.^{1,8,10–12} The JRQLQ, JESS, and SOQ were filled by patients every other week for a total of 7 times (February 1 and 15; March 1, 15, and 29; and April 12 and 26).

Screening visits were performed in December 2010 and continued until a total of 75 patients who lived near the Okayama University hospital fulfilled the inclusion and exclusion criteria. Inclusion criteria for the JCCP patients enrolled in the study were as follows: (1) male or female between the age of 16 and 65 years, (2) at least a 2-year history of JCCP, (3) sensitization to Japanese cedar pollen as assessed by a skin prick test, and (4) ability to accurately fill in diary cards. Patients were excluded from the study if they had any of the following: (1) concomitant sinonasal disease that could potentially affect the outcome of the trial (eg, nasal polyps, rhinosinusitis, or nasal septum deviation); (2) concomitant treatment for AR caused by allergens other than Japanese cedar/cypress pollen; (3) rhinitis medicamentosa and noninfectious, non-AR; (4) cedar pollen specific immunotherapy; (5) sinonasal surgery, including laser vaporization of inferior turbinates within 1 year; (6) medication with antiallergic drugs, including antihistamines, chromones, glucocorticoids, and decongestants, within 2 weeks of study initiation; (7) hypersensitivity to mometasone furoate nasal spray; (8) systemic infection, including mycosis; or (9) were pregnant and breastfeeding. Before study initiation, we estimated the sample size that would be required based on the mean and SD in the groups reported for our previous study.⁸ To yield an 80% study power for the mean (SD) values (0.48 [0.87] and 1.24 [1.20]) of the mometasone furoate nasal spray and placebo groups, a total of 20 patients were required for the primary end point of the symptom score ($\alpha=.05$). On the basis of these calculations, we determined that a sample size of 25 patients per each group would be necessary when assuming there would be a 20% dropout rate.

Allocation concealment was granted by the central registry and computer-generated block randomization. For a 12-week period (February 1 to April 25) patients received either mometasone furoate nasal spray (100 μ g per nostril once daily in the morning; EIT group) or the placebo. A third group of patients received placebo for the first 4 weeks (February 1 to February 28) followed by mometasone furoate nasal spray for 8 weeks (March 1 to April 25). We made placebo nasal spray with similar look, smell, and taste by ourselves. Placebo contains phenylethylalcohol (Wako Pure Chemical Industries, Osaka, Japan) in saline (Otsuka Pharmaceutical, Tokyo, Japan).

Placebo was packed in an opaque pump spray provided by Schering Plough Japan that is identical to mometasone furoate nasal spray. The nasal sprays were labeled with the patient's randomization code number. Patients were allowed to use loratadine, which was provided, and antihistamine eye drops (olopatadine hydrochloride; Kyowa Hakko Kirin Co, Tokyo, Japan) as rescue medications on demand. The study was approved by the institutional review board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (Rinri-996) and registered in the UMIN database (UMIN000005986). Before participation in the study, all patients provided written informed consent.

Nasal ECP levels

Nasal secretions were collected 4 times (in the middle of January, March, April, and May) by using filter papers placed on the surface of bilateral inferior turbinates for 5 minutes. After extraction, nasal ECP levels were determined by using Unicap ECP (Phadia, Uppsala, Sweden) as described previously.⁸

Measurement of pollen dispersion

Because use of Durham sampler is more popular than the Burkard sampler to monitor pollen dispersion in Japan, daily Japanese cedar and Japanese cypress pollen counts were performed with Durham samplers that were installed on the rooftops of the Okayama University Hospital buildings.¹³ Pollen grains were counted in a 2×2 -cm field (4 cm²) in a slide, and then mean pollen dispersal (grain/cm² daily) were determined. The first day of pollen counts being high on consecutive days was defined as the first of 2 consecutive days with pollen counts of 1 grain/cm² or more according to the criterion set by Palynological Society of Japan.^{8,14}

Statistical analysis

Values were expressed as the mean (SEM) for each study group. Efficacy was estimated by intention-to-treat analysis. Analysis of covariance (ANCOVA) or analysis of variance was used to compare the data between the groups, whereas the Wilcoxon signed-rank test was used for analysis within the groups. The proportion of patients using loratadine, the percentage of patients in the intermittent or persistent states, and the number of patients with adverse effects were compared with the χ^2 test. Statistical analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina). $P < .05$ was considered statistically significant.

Results

Patient population

Of the 92 patients who were screened, 75 fulfilled the inclusion criteria. After enrollment in the study, patients were randomized into 1 of 3 groups, with 25 patients per group. The EIT group received mometasone furoate nasal spray for 12 weeks, the placebo group received placebo for 12 weeks, and the POT group received placebo for the first 4 weeks followed by mometasone furoate nasal spray for 8 weeks. Seventy-three patients (97.3%) completed the study. One patient in the placebo group dropped out because of de novo pregnancy. Another patient in the placebo group withdrew after 6 weeks because of treatment failure. Therefore, the intent-to-treat population consisted of 74 patients (25 patients each were treated with mometasone furoate nasal spray or placebo followed by mometasone furoate nasal spray, and 24 patients received placebo). The treatment groups were comparable with respect to demographic characteristics, which included age, sex, disease duration, and severity of JCCP (Table 1).

Table 1
Patient demographic and clinical characteristics

Characteristic	Mometasone furoate nasal spray (EIT: n = 25)	Placebo–mometasone furoate nasal spray (POT: n = 25)	Placebo (n = 24)
Sex			
Male	8	13	12
Female	17	12	12
Age, y			
Range	20–62	20–64	20–66
Mean (SD)	33.2 (12.2)	37.8 (17.5)	35.8 (13.0)
Disease duration, y			
Range	3–30	4–25	4–33
Mean (SD)	11.3 (6.3)	13.0 (6.3)	13.2 (7.3)
Severity of JCCP during past season			
Severe	22	17	18
Moderate	2	5	5
Mild	1	2	1
Unclear	0	1	0

Abbreviations: EIT, early interventional treatment; JCCP, Japanese cedar/cypress pollinosis; POT, postonset treatment.

Fluctuation of cedar and cypress pollen dispersion

During 2011, the first dispersion of Japanese cedar pollen occurred on January 28, and weak pollen dispersion (>1 grain/cm² daily) was seen on January 29, January 30, February 21, and February 22. Major continuous dispersion (≥ 1 grain/cm² daily) began on February 23. The highest cedar dispersion occurred on March 15, with 180 grains/cm² daily. The first dispersion of cypress pollen occurred on March 27, with major continuous dispersion beginning on March 28. The highest cedar dispersion occurred on April 26, with 80 grains/cm² daily. The total cedar and cypress pollen counts during the study period were 1,384 and 589 grains/cm², respectively (Fig 1). The amount of cedar/cypress pollen grains observed in 2011 was 60.6% of the mean amount of pollen grains observed from 2000 to 2010 (3,258.2 grains/cm²).⁸ Thus, the EIT and POT groups started mometasone furoate nasal spray treatment 3 weeks before and 1 week after the initiation of continuous pollen dispersion, respectively.

Primary end point efficacy

At week 4, when the continuous dispersion of Japanese cedar pollen began, both groups receiving placebo displayed a significant exacerbation of nasal symptoms in a similar manner, as shown by the changes in the TNSS from baseline (range in increase, 1.10 and 1.35; $P < .01$ by Wilcoxon signed-rank test). Thus, the group that received placebo for the first 4 weeks followed by mometasone furoate nasal spray for the next 8 weeks could be defined as the POT group. In the placebo group, the significant exacerbation lasted until the end of the study (week 12), which included the Japanese cypress pollen dispersion period (maximum range in increase, 3.89 at week 9; $P < .01$). Although the significant exacerbation lasted until week 10 in the POT group (maximum range in increase, 1.69 at week 6; $P < .05$), symptoms were not further exacerbated after the introduction of mometasone furoate nasal spray. Compared with the placebo group, the POT group reported significantly lower TNSSs in 5 weeks of the 9-week continuous pollen dispersion (maximum range in difference, 2.21 at week 7; $P < .05$ by ANCOVA).

In the EIT group, a significant exacerbation of nasal symptoms was not seen at week 4, and the exacerbation was delayed for 2 weeks compared with the controls. The TNSSs were significantly lower in the EIT group than in the placebo group for 8 of the 9 weeks of the continuous pollen dispersion period (maximum range in difference, 2.94 at week 11; $P < .01$). Furthermore, the EIT group exhibited significantly lower TNSSs compared with the POT at week

5 when the POT group also used active mometasone furoate nasal spray (range in difference, 1.64; $P < .05$) (Fig 2A).

Secondary end point efficacy

Ocular symptoms used to determine the TOSSs were significantly exacerbated in all groups during the continuous dispersion period. However, the EIT group displayed significantly lower TOSSs than the placebo group for 7 weeks of the 9-week continuous pollen-dispersion period (maximum range in difference, 1.59 at week 6; $P < .05$) and for 3 weeks compared with the POT group (maximum range in difference, 1.41 at week 5; $P < .05$). On the other hand, no significant alleviation of ocular symptoms occurred in the POT group compared with the placebo group (Fig 2B).

A similar and more evident result was seen in naso-ocular symptoms determined by TSSs. The EIT group displayed a lower TSS throughout the study period compared with the control group (Fig 2C). The mean TSS throughout the study period (week 1 to 12) in the EIT group was 2.3, which was significantly lower than in the placebo group (score, 5.0; $P < .01$) and the POT group (score, 3.9; $P = .03$). This difference was especially seen in March (week 5 to 8), when the POT groups received the active treatment (Fig 3). Weekly mean scores of individual naso-ocular symptoms are given in Table 2.

All groups exhibited an exacerbation of QOL after the continuous pollen dispersion. However, QOL from March to April was significantly better in both the EIT and POT groups compared with the placebo group. On the other hand, no significant difference was

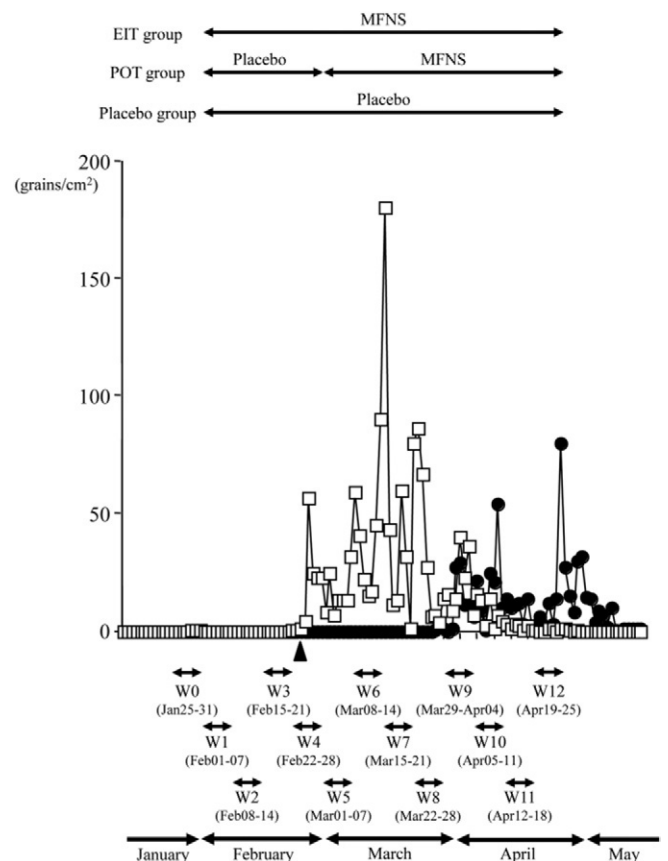


Fig 1. Fluctuation of cedar and cypress pollen dispersion in 2011 and the treatment schedule. The open squares and closed circles represent the cedar and cypress pollen counts, respectively. The arrowhead represents the beginning of continuous pollen dispersion. EIT, early interventional treatment; POT, postonset treatment; MFNS, mometasone furoate nasal spray; W, week.

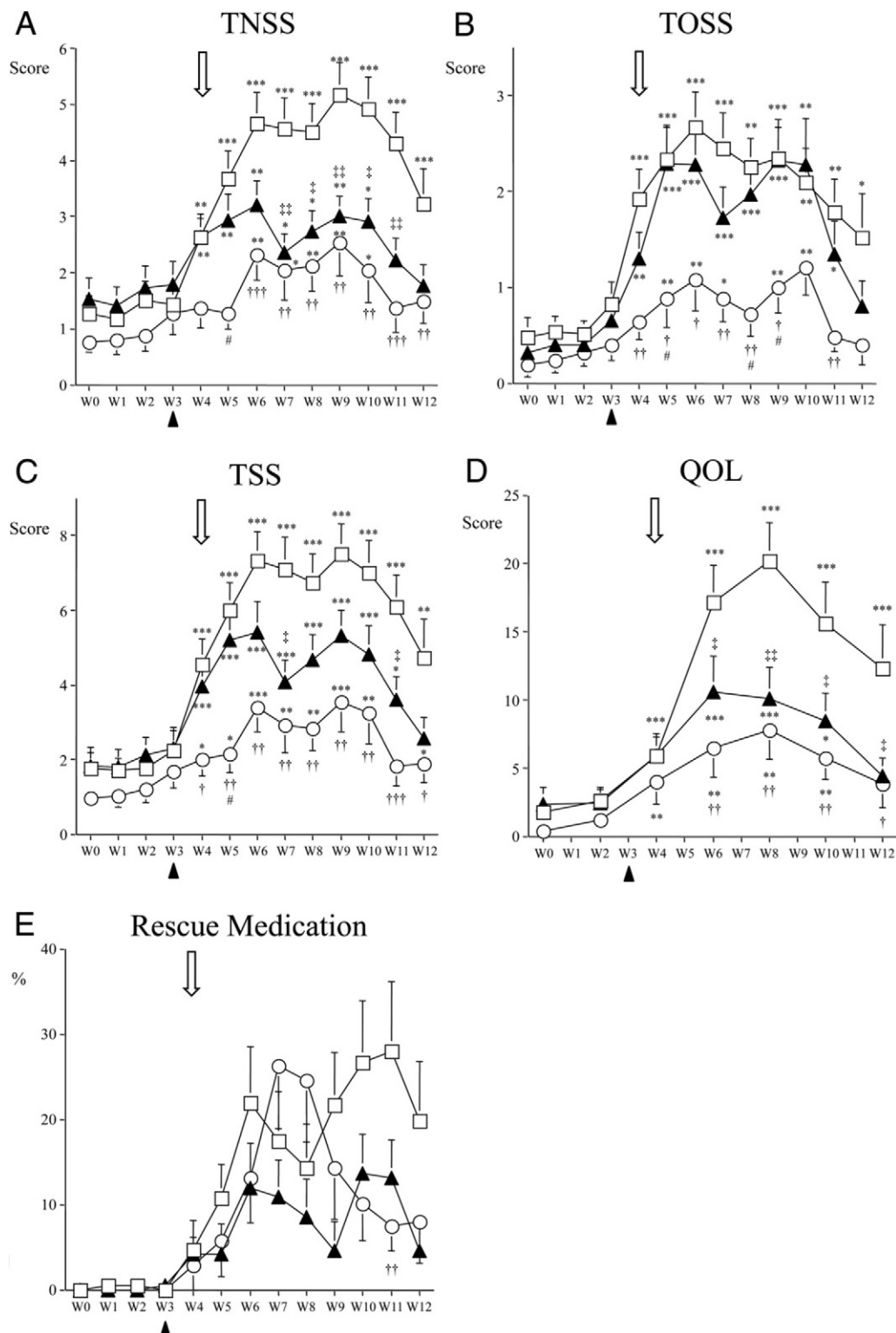


Fig. 2. Weekly reflective total nasal symptom score (TNSS; A), weekly total ocular symptom score (TOSS; B), weekly total naso-ocular symptom score (TSS; C), biweekly quality of life (QOL) as determined by Japanese Rhinoconjunctivitis Quality-of-Life Questionnaire (D), and weekly use of loratadine as a rescue medication (E) from the baseline in early interventional treatment (EIT) (circle), postonset treatment (POT) (triangle), or placebo treatment (square) groups. Results are expressed as mean (SEM). Analysis of covariance (A–C) was used to compare data among the groups ($^{\dagger}P < .05$, $^{\dagger\dagger}P < .01$, $^{\dagger\dagger\dagger}P < .001$ in EIT vs placebo groups; $^{\ddagger}P < .05$, $^{\ddagger\ddagger}P < .01$ in POT vs placebo, $^{\#}P < .05$ in EIT vs POT). The Wilcoxon signed-rank test was used for analysis within the groups ($^{*}P < .05$, $^{**}P < 0.01$, $^{***}P < .001$). The arrowhead indicates the beginning of continuous pollen dispersion. The arrow indicates the day when the POT group switched from placebo to mometasone furoate nasal spray. W indicates week.

seen between the EIT and the POT group throughout the study period (Fig 2E). Daytime sleepiness and smell disturbance monitored by using the JESS and SOQ, respectively, were similar among the 3 groups (data not shown).

Patients were allowed on-demand use of loratadine and the eye drops (olopatadine hydrochloride) during the study period. Fourteen (56.0%), 15 (60.0%), and 19 (79.2%) patients in the EIT, POT, and placebo group, respectively, used loratadine at least once, and the

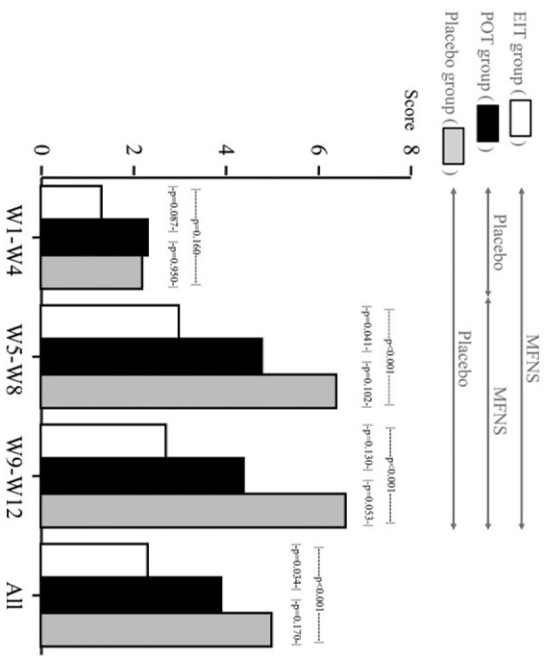


Fig. 3. Comparison of mean total symptom scores (TSS) among early interventional treatment (EIT) (open bar), postonset treatment (POT) (closed bar), and placebo (grayish bar). Mean TSSs from week (W) 1 to W4, from W5 to W8, from W9 to W12, and for 12 weeks throughout the treatment period were calculated. Analysis of variance was used to compare data among the groups. MFNS indicates mometasone furoate nasal spray.

difference did not reach statistical significance ($P = .15$ by χ^2 test). The mean dose of loratadine was also similar among the 3 groups, with the exception of week 11, when the placebo group took significantly more loratadine than the EIT group ($P < .05$, Fig 2F).

Efficacy of mometasone furoate nasal spray based on the ARIA classification

In accordance with the Allergic Rhinitis and Its Impact on Asthma (ARIA) classification scheme, patients were classified as having intermittent or persistent rhinitis based on the number of days with nasal symptoms. All patients were classified as having intermittent rhinitis at the moment of their inclusion (December 2010). During the 12-week period from February to April, all patients in the placebo and POT groups were classified as having persistent rhinitis, whereas 80% of the EIT group met the ARIA classification criteria ($P = .03$; Fisher exact probability test).

Effect of mometasone furoate nasal spray on nasal ECP levels

The ECP levels in the nasal secretions in April were significantly lower in the EIT group ($5.3 [3.1]$ ng/mL/mg protein, $P < .01$) and the POT group ($34.1 [16.0]$ ng/mL/mg protein, $P < .01$) compared with the placebo group ($298.5 [91.6]$ ng/mL/mg protein). Although the ECP level in nasal secretions was lower in the EIT group compared with the POT group, the difference was not statistically significant ($P = .08$). No significant differences were seen in ECP levels at other time points.

Safety

We collected the safety data from diary cards and interviews when patients came to hospital to collect nasal secretions. All treatments were well tolerated and had a similar safety profile. There were 10, 15, and 13 adverse events reported in the patient diaries in the EIT group, the POT group, and the placebo group, respectively. However, 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.

Table 2
Weekly mean scores of individual naso-ocular symptoms^a

Week	Sneezing			Rhinorrhea			Nasal congestion			Itchy eyes			Watery eyes		
	EIT	POT	Placebo	EIT	POT	Placebo	EIT	POT	Placebo	EIT	POT	Placebo	EIT	POT	Placebo
0	0.24 (0.09)	0.40 (0.12)	0.44 (0.13)	0.28 (0.09)	0.68 (0.15)	0.52 (0.15)	0.24 (0.09)	0.44 (0.15)	0.32 (0.10)	0.16 (0.12)	0.24 (0.12)	0.32 (0.14)	0.04 (0.07)	0.08 (0.08)	0.16 (0.09)
1	0.16 (0.17)	0.40 (0.12)	0.38 (0.10)	0.36 (0.16)	0.64 (0.14)	0.46 (0.10)	0.28 (0.11)	0.36 (0.15)	0.33 (0.16)	0.20 (0.13)	0.24 (0.12)	0.42 (0.12)	0.04 (0.04)	0.16 (0.11)	0.13 (0.07)
2	0.20 (0.08)	0.40 (0.13)	0.58 (0.12)	0.36 (0.17)	0.72 (0.15)	0.58 (0.15)	0.32 (0.10)	0.60 (0.17)	0.33 (0.14)	0.20 (0.10)	0.20 (0.08)	0.38 (0.10)	0.12 (0.09)	0.20 (0.12)	0.13 (0.07)
3	0.44 (0.14)	0.63 (0.17)	0.42 (0.10)	0.44 (0.16)	0.79 (0.18)	0.50 (0.15)	0.40 (0.13)	0.38 (0.13)	0.50 (0.17)	0.28 (0.14)	0.43 (0.15)	0.54 (0.16)	0.12 (0.09)	0.21 (0.10)	0.29 (0.11)
4	0.44 (0.13)	1.04 (0.16)	1.00 (0.16)	0.56 (0.16)	0.92 (0.16)	0.92 (0.18)	0.36 (0.13)	0.67 (0.13)	0.71 (0.21)	0.52 (0.14) ^b	0.88 (0.16)	1.38 (0.19)	0.12 (0.09)	0.48 (0.15)	0.54 (0.16)
5	0.36 (0.13) ^{c,d}	1.13 (0.20)	1.33 (0.19)	0.64 (0.17)	1.13 (0.21)	1.38 (0.22)	0.28 (0.09) ^b	0.67 (0.17)	0.96 (0.18)	0.64 (0.22) ^{c,d}	1.50 (0.22)	1.58 (0.20)	0.24 (0.12)	0.79 (0.22)	0.75 (0.17)
6	0.80 (0.16) ^{b,d}	1.36 (0.22)	1.71 (0.19)	0.80 (0.19) ^c	1.29 (0.19)	1.67 (0.24)	0.72 (0.16)	0.60 (0.13)	1.29 (0.22)	0.84 (0.22) ^c	1.52 (0.26)	1.71 (0.19)	0.24 (0.13) ^c	0.76 (0.19)	0.96 (0.19)
7	0.72 (0.18) ^b	0.92 (0.16) ^e	1.61 (0.19)	0.68 (0.21) ^b	1.04 (0.16) ^e	1.70 (0.22)	0.64 (0.20)	0.40 (0.10) ^e	1.26 (0.24)	0.64 (0.17) ^b	1.24 (0.23)	1.78 (0.25)	0.24 (0.10)	0.48 (0.15)	0.73 (0.15)
8	0.52 (0.12) ^f	1.04 (0.17)	1.50 (0.19)	0.88 (0.21)	1.08 (0.16)	1.67 (0.22)	0.72 (0.18)	0.60 (0.17) ^g	1.33 (0.18)	0.44 (0.13) ^{f,i}	1.36 (0.22)	1.46 (0.19)	0.28 (0.12)	0.60 (0.17)	0.79 (0.15)
9	0.84 (0.17) ^b	1.28 (0.18)	1.70 (0.19)	0.92 (0.25) ^c	1.12 (0.16) ^e	1.91 (0.23)	0.80 (0.19)	0.60 (0.15) ^g	1.57 (0.25)	0.76 (0.16) ^{c,d}	1.56 (0.24)	1.57 (0.21)	0.24 (0.13)	0.76 (0.23)	0.78 (0.17)
10	0.67 (0.20) ^b	1.25 (0.22)	1.61 (0.20)	0.71 (0.24) ^b	1.13 (0.17)	1.70 (0.23)	0.67 (0.21) ^b	0.48 (0.12) ^h	1.61 (0.22)	1.00 (0.21)	1.48 (0.27)	1.39 (0.21)	0.21 (0.12)	0.80 (0.24)	0.70 (0.18)
11	0.40 (0.16) ^f	0.79 (0.18) ^g	1.52 (0.16)	0.48 (0.18) ^b	0.92 (0.16)	1.43 (0.22)	0.48 (0.16) ^b	0.50 (0.13) ^g	1.35 (0.26)	0.40 (0.12) ^b	0.92 (0.19)	1.22 (0.22)	0.08 (0.06) ^c	0.43 (0.16)	0.57 (0.15)
12	0.60 (0.17)	0.68 (0.19)	1.30 (0.23)	0.56 (0.15)	0.72 (0.16)	1.00 (0.23)	0.32 (0.11) ^c	0.36 (0.11) ^e	0.91 (0.25)	0.28 (0.12)	0.56 (0.17)	0.83 (0.22)	0.12 (0.9)	0.24 (0.13)	0.70 (0.25)

Abbreviations: EIT, early interventional treatment; POT, postonset treatment.

^aData were expressed as the mean (SEM). Analysis of covariance was used to compare data among the groups.

^b $P < .01$ in EIT vs placebo.

^c $P < .05$ in EIT vs placebo.

^d $P < .05$ in EIT vs POT.

^e $P < .05$ in POT vs placebo.

^f $P < .001$ in EIT vs placebo.

^g $P < .01$ in POT vs placebo.

^h $P < .001$ in POT vs placebo.

ⁱ $P < .01$ in EIT vs POT.

Discussion

Preseasonal prophylaxis or early intervention is recommended for patients with pollinosis in both domestic and international guidelines.^{1,2} Several systemic reviews provide level Ia evidence for the efficacy of medications, including antihistamines, antileukotrienes, and INSs in the treatment of pollinosis; however, there have been no DB-RCTs to show whether and by what mechanism EIT is superior to POT for the treatment of pollinosis.^{15–17} We believe that this is the first DB-RCT demonstrating the efficacy of EIT with INSs in pollinosis compared with POT.

Compared with the control groups, EIT with INSs delayed the significant exacerbation of allergy symptoms for 2 weeks. EIT with antihistamines, antileukotrienes, or INSs has been reported to delay the onset of AR.^{4,6,8,18} Our results are consistent with the report by Graft et al demonstrating that EIT with mometasone furoate nasal spray and beclomethasone dipropionate aqueous nasal spray resulted in a longer duration to the first occurrence of a nonminimal symptom (16.5 days) than the placebo group.⁶ MPI, characterized by the presence of inflammatory cells (eosinophils and neutrophils) and increased intercellular adhesion molecule 1 expression on epithelial cells in the nasal mucosa, seems to be present before the major onset of symptoms.^{3,19} Because the first dispersion of Japanese cedar pollen occurred on January 28, the delayed exacerbation for 2 weeks in the EIT group compared with controls may be mediated by suppressing MPI by INSs in February. However, we did not confirm whether there was MPI in the present study because we could not collect nasal tissues during the pollen season due to ethical reasons. Noninvasive and reliable biomarkers to monitor MPI should be established in the future.

After the start of pollen counts being high on consecutive days, EIT with INSs not only delayed the onset of exacerbation but also alleviated the severity of naso-ocular symptoms compared with the placebo treatment and also to POT with INSs. Throughout the study period, the mean TSS in the EIT group was significantly lower than that in the POT group. More importantly, this significance was especially seen in weeks 5 to 8, when both the EIT and POT groups received the same active treatment. Together with the finding that it takes mometasone time to work, the present study suggests that EIT with INSs is superior to POT in controlling pollinosis.⁹ After the onset of pollinosis, the priming effect is a major factor that exacerbates the pathophysiology of pollinosis by decreasing the threshold for subsequent allergic reaction on rechallenge and increasing the responsiveness of nasal mucosa.²⁰ Because the priming effect is at least partially caused by increased mediator release from the influx of inflammatory cells, including eosinophils and metachromatic cells, INSs are known to suppress the priming effect.²¹ The present result suggests that EIT with INSs has more potency in controlling the priming effect than POT with INSs. Alternatively it takes time for mometasone to work and to control or minimize the nasal inflammation.

No significant difference in the proportion of patients experiencing on-demand use of loratadine was seen among the 3 groups. In addition, the mean dose of loratadine was also similar among the groups, with the exception of week 11, when the placebo group took significantly more loratadine than the EIT group. These results suggest that the efficacy of EIT with mometasone furoate nasal spray on end points was mainly reflected in the potency of mometasone furoate nasal spray with negligible effect of rescue medication.

On the basis of the duration of nasal symptoms, the ARIA classification subdivides patients with AR into intermittent or persistent disease groups.¹ In the present study, patients were monitored

during a 12-week period that covered almost the entire pollen season. Thus, we could classify patients as having either intermittent or persistent disease. All patients in both the placebo and POT groups had persistent rhinitis. On the other hand, a significant proportion of intermittent rhinitis was seen in the EIT group. This result is similar to our previous report from 2010, suggesting that EIT with INSs 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.⁸

Initial differences in TNSS, TSS, TOS, or individual naso-ocular symptoms at week 0 were not statistically significant between groups except for rhinorrhea, in which a significant difference was seen between the POT group and EIT group ($P < .05$). The reason was unclear because the central registry and computer-generated block randomization was performed. Therefore, ANCOVA was chosen for statistical comparison between groups.

Nasal ECP levels have been shown to increase after allergen exposure and are considered to be one of the biomarkers that reflect allergic inflammation in the nose.^{22,23} In addition, a recent report demonstrated that nasal ECP level was one of the biomarkers noted during INS treatment in AR patients.²⁴ The present findings suggest that both EIT and POT with mometasone furoate nasal spray can control eosinophilic inflammation in the nose, and the former is more potent. On the other hand, nasal smear looking for eosinophils is also a valuable method to monitor the local eosinophilic inflammation and can be considered to be used for future trial.

In conclusion, EIT is superior to POT in controlling not only the nasal but also the ocular symptoms even when both of the treatments used active mometasone furoate nasal spray. These results may provide a basis for therapeutic approaches targeting MPI in pollinosis. To progress this conclusion, future investigation may be considered, in which a 4-armed, parallel group trial is performed, with one additional group receiving placebo after 4 weeks of INSs.

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