Yamanashi Med. J. **34**(1), 17 ～ 26, 2019

Original article

Comparison of Regular and As-needed Use of Mometasone Furoate Hydrate Nasal Spray for the Treatment of Japanese Cedar Pollinosis

Kaname SAKAMOTO[1)], Goro TAKAHASHI[2)], Takaaki YONAGA[1)], Shota TANAKA[1)], Tomokazu MATSUOKA[1)] and Keisuke MASUYAMA[1)]

[1)] *Department of Otorhinolaryngology and Head and Neck Surgery, Faculty of Medicine, Graduate Faculty of Interdisciplinary Research, University of Yamanashi, Yamanashi, Japan*

[2)] *Yamahoshi ENT clinic, Shizuoka, Japan*

Abstract: Background: Intranasal glucocorticosteroids (INSs) are the first-line treatment for allergic rhinitis. However, it is not clear whether regular use of INSs during the pollen season is necessary for patients with Japanese cedar pollinosis (JCP). We conducted a randomized, open-label, parallel-group study to compare the efficacy of regular and as-needed use of INSs.
Method: Between January and May 2009, we recruited patients with Japanese cedar pollinosis and divided them into regular and as-needed use groups. Participants were asked to record nasal and ocular symptom scores every day, and after the start of the trial, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores were evaluated for three different days.
Result: A total of 123 patients joined this trial. Patients in the regular-use group had significantly improved non-hay fever symptom, nasal symptom, and emotional scores than those in the as-needed group during the first half of the season. The number of days with minimal nasal symptoms in the regular-use group was significantly higher than that in the as-needed group during the entire season (P=0.0261).
Conclusion: Continued use of INSs during the pollen season leads to improvement of symptoms of patients with Japanese cedar pollinosis. Guidance on the appropriate use of INSs is necessary.

Key Words: cedar pollinosis, intranasal steroids, regular or as-needed use

INTRODUCTION

Allergic rhinitis (AR) is a global health care problem that affects the daily activity, work productivity, learning efficiency, and sleep quality of patients of all ages[1)]. In Japan, a nationwide epidemiological survey was conducted in 1998 and 2008. The prevalence of AR has increased over the past decade. In particular, the prevalence of JCP was 28.8%, higher than those of other types of AR in 2008. Recent data showed that 40% of adults and 45% of children in developed countries suffer from AR[2)]. A survey of patients with JCP was conducted by the Tokyo Metropolitan Government in 2016. The estimated prevalence of JCP was 48.8%.

In Japan, a large number of patients with JCP experience more severe symptoms for longer periods of time compared to those for other pollen allergies. Between February and April, Japa-

University of Yamanashi, 1110 Shimokato, Chuo City, Yamanashi, Japan
Received February 25, 2019
Accepted April 11, 2019

nese cedar pollen is dispersed in large quantities over long distances and can remain airborne for more than 12 hours[1]. Furthermore, pollen from the Japanese cypress, which has cross antigen with Japanese cedar, is dispersed in April and May. Therefore, allergic symptoms may last for as long as four months, from February to May. During this period, about ninety percent of those patients are classified as having moderate-to-severe based by nasal symptom scores[1]. Because of the severe symptoms and the duration of symptoms, it is necessary to use INSs continuously to maximize the treatment effect during the period of cedar pollinosis.

A number of drugs are available for the treatment of AR. Most recent guidelines recommend INSs as a first choice in adults and children because of its higher efficacy and lower incidence of side effects compared to those of other drugs[3–5]. While INSs are the most effective remedy, it is important to determine the correct usage to maximize its efficacy. The onset of action of INSs starts at time points ranging from 3-5 to 36 hours after the initial dosing[3]. Previous studies suggested that the continuous use of INSs was more effective than as-needed use[3,4]. However, in previous research, a number of AR patients failed to use INSs continuously, which contributed to unsatisfactory treatment outcomes[6,7].

Mometasone furoate nasal spray (MFNS) is an effective and convenient drug to treat seasonal and perennial AR in both adults and children[8–10]. The continuous use of beclomethasone dipropionate and fluticasone propionate nasal sprays were shown to be better than as-needed use for the treatment of AR[11,12]. However, other reports suggested the efficacy of fluticasone propionate nasal spray in the treatment of seasonal AR, even when used on an as-needed basis[13,14]. It remains unclear the effectiveness of continuous or as-needed use of INSs for JCP, which has more severe symptoms and longer duration than those of other hay fevers. We hypothesized that the continuous use of INSs for JCP would be more effective than as-needed use. The purpose of this study was to compare the effects of as-needed use of MFNS with those of continuous use on the quality of life (QOL) in the treatment of patients with JCP.

METHODS

Trial design

This randomized, open-label, parallel-group study was conducted at two medical hospitals (University of Yamanashi Hospital and Fujiyoshida Municipal Medical Center) in Yamanashi prefecture, Japan, from January 17 to March 28, 2009. The participants were randomly assigned in a 1:1 ratio to regular or as-needed groups based on MFNS use. This trial was registered with University of Yamanashi Hospital and was approved by the ethics committee at each participating institution.

Participants

The participants were recruited at the two medical hospitals from January 17 to 31 by advertising the clinical trial in a local newspaper and by sending notices of the trial to patients with JCP who had previously visited these hospitals. The inclusion criteria were as follows: (1) age, ≧16 years; (2) history of JCP in previous pollen seasons; (3) positive skin test for Japanese cedar pollen or Japanese cedar pollen-specific immunoglobulin E (IgE) based on a radioallergosorbent test (RAST) score ≧2. Written informed consent was obtained from all participants in this trial.

Patients were excluded if they (1) had used immunosuppressant or systemic corticosteroids within 6 months before recruitment; (2) had

used antibiotics, antihistamines, antileukotrienes, or corticosteroids or intranasally administered antihistamines or corticosteroids within 2 weeks before recruitment; (3) were in the build-up phase of immunotherapy for Japanese cedar pollen; (4) had excessive nasal polyps, sinusitis, or nasal septum deviation that influenced the nasal symptoms; (5) had pharyngitis, laryngitis, respiratory tract infection, or asthma; (6) had severe heart, hepatic, kidney, or hemal disease; (6) had a history of hypersensitivity to mometasone furoate, loratadine, or sodium cromoglycate; (7) had taken erythromycin or cimetidine at the beginning of the trial; or (8) were lactating or pregnant.

Patients who fulfilled the eligibility criteria were provided a daily diary to record baseline data on nasal and ocular symptoms for at least 7 days.

Visit 0 (baseline) occurred in the first week of February. The participants visited the hospital otorhinolaryngology department with their symptom diaries and were assessed using the Japanese version of the RQLQ. After collecting their diaries and RQLQ responses, the participants were re-confirmed to meet the eligibility criteria and randomly assigned to the two groups. They were provided another daily diary to record their nasal and ocular symptoms, drug usage, and any adverse events during the trial. The participants returned in the third week of February (visit 1), the second week of March (visit 2), and the last week of March (visit 3).

Intervention

Regular-use group: Two puffs of mometasone furoate (50 μg) per nostril once daily (total 200 μg per day) administered from the beginning of the nasal symptoms of pollinosis.

As-needed use group: Two puffs of mometasone furoate (50 μg) per nostril once daily when required to relieve nasal symptoms of pollinosis.

Sodium cromoglycate (2%) eye drops were used on an as-needed basis to alleviate ocular symptoms in both groups. One loratadine tablet (10 mg) was taken up to once a day as a rescue medicine.

Outcomes

Participants recorded the severity of four nasal symptoms (rhinorrhea, nasal obstruction, sneezing, and itchy nose) and three ocular symptoms (tearing, redness, and itchy eyes) in their daily diary based on a four-point scale, as follows: 0, no evident symptom; 1, slight symptom that is not bothersome; 2, definite symptom that is bothersome but tolerable; 3, severe symptom that is hard to tolerate. The participants also completed an RQLQ at every hospital visit. The primary outcome was the overall RQLQ score during the trial. The secondary outcomes were the seven domain scores of the RQLQ and the number of minimal nasal symptom days (MNSD) during the trial. MSND was defined as a day with a total score of $\leqq 2$ for four nasal symptom scores.

Statistical analysis

We used STATA 12 for statistical analysis. Analysis of the baseline characteristics followed the intention-to-treat principle. Wilcoxon rank-sum tests were used for comparisons between the two groups of MNSD. Statistical analysis of least-square means (LSM) with 95% confidence intervals (CI) was conducted using a repeated measurement ANCOVA with the baseline QOL score as a covariate.

Results

Of 160 people who participated in the briefing session, 123 fulfilled the inclusion criteria.

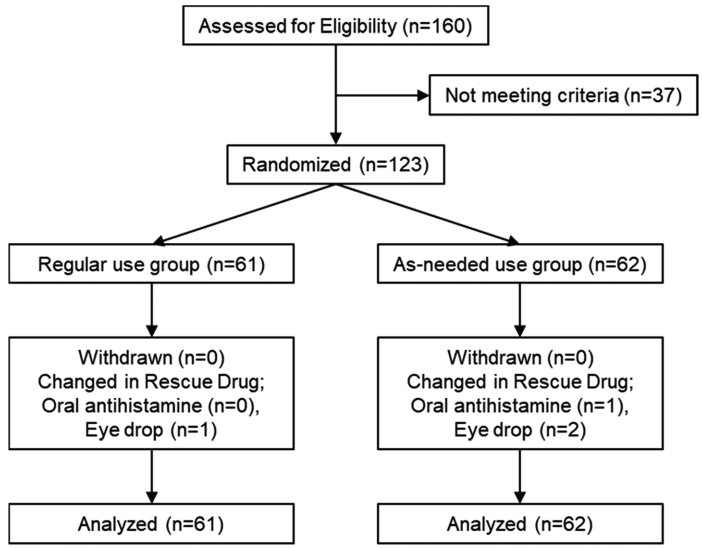

Figure 1. Schematic summary of the flow of participants in the trial.
The 123 participants were randomly divided into two groups. Drop-outs from the trial were not observed in either group.

Table 1. Baseline participant characteristics

	Regular use group (n=61)	As-needed use gropu (n=62)	p value
Male/Female, No.	24/37	29/33	0.468
Age, mean (SD), y	37.8(10.1)	39.7(9.9)	0.2877
Onset age, mean (SD), y	21.3(9.1)	23.5(9.7)	0.1962
Severity, No.			
Mild	8	10	
Moderate	39	38	0.931
Severe	14	13	
Allergic disease, No.			
Asthma	4	3	
Atopic dermatitis	6	8	
Food allergy	9	4	0.217
Others	3	0	
None	41	49	

They were randomly assigned to the regular-use (n=61) and as-needed use (n=62) groups. No trial dropouts were observed in either group (Figure 1). Clinical features at baseline (Visit 0) did not differ significantly between the two groups (Table 1). Cedar pollen grains were collected and measured using a Durham sampler daily from January 1, 2009, at the University of Yamanashi Hospital. Cedar pollen was detected from February 5. The total pollen count for the season was 2,518/cm^2. The average of total nasal symptom score (TNSS) and total ocular symptom score (TOSS) are shown in the graph, together with the spread of Japanese pollen. In

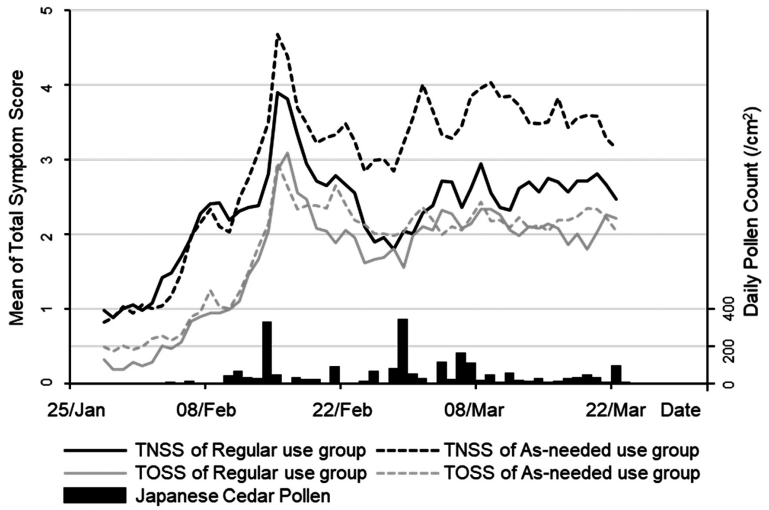

Figure 2. Mean total symptom score and daily pollen count.
Cedar pollen grains were collected and measured daily using a Duhram sampler from January 1, 2009 at the University of Yamanashi Hospital. Cedar pollen was counted from February 5 at University of Yamanashi Hospital. The total pollen count for the season was 2,518 per square centimeter. The total symptom score was calculated from patients' daily diaries. TNSS: total nasal symptom score; TOSS: total ocular symptom score.

Table 2. Differences in scores of the overall QOL and seven QOL domains of the RQLQ between the two groups at each visit

	Visit	Least square mean	95% confidence interval		P value		Visit	Least square mean	95% confidence interval		P value
Overall QOL	1	-0.27	-0.52	-0.02	0.037	Practical problems	1	-0.28	-0.65	0.09	0.142
	2	-0.2	-0.46	0.06	0.113		2	-0.29	-0.67	0.08	0.12
	3	-0.2	-0.45	0.06	0.115		3	-0.36	-0.73	0.01	0.057
Activity limitation	1	0.03	-0.37	0.42	0.897	Nasal symptom	1	-0.5	-0.83	-0.17	0.003
	2	-0.17	-0.56	0.22	0.383		2	-0.36	-0.69	-0.03	0.032
	3	-0.27	-0.68	0.12	0.171		3	-0.32	-0.65	0	0.063
Sleep impairment	1	-0.22	-0.48	0.03	0.081	Eye symptom	1	-0.05	-0.42	0.31	0.772
	2	-0.08	-0.34	0.17	0.512		2	0.07	-0.29	0.44	0.698
	3	-0.05	-0.3	0.2	0.679		3	-0.06	-0.42	0.3	0.746
Non hay fever symptom	1	-0.39	-0.63	-0.15	0.002	Emotional function	1	-0.31	-0.61	-0.01	0.044
	2	-0.28	-0.53	-0.04	0.022		2	-0.26	-0.56	0.03	0.082
	3	-0.2	-0.44	0.04	0.11		3	-0.19	-0.49	0.11	0.208

Note: The coefficient of 'living alone' could not be analysed for male data.
Abbreviation: IADL, instrumental activities of daily living; CI, confidence interval; Ref, reference category.

both groups the symptom scores were correlated with the amount of scattering of cedar pollen. There were no significant differences between regular-use group and as-needed group in TNSS and TOSS (Figure 2). In Figure 3 and Table 2, the LSM with 95%CI showed a difference

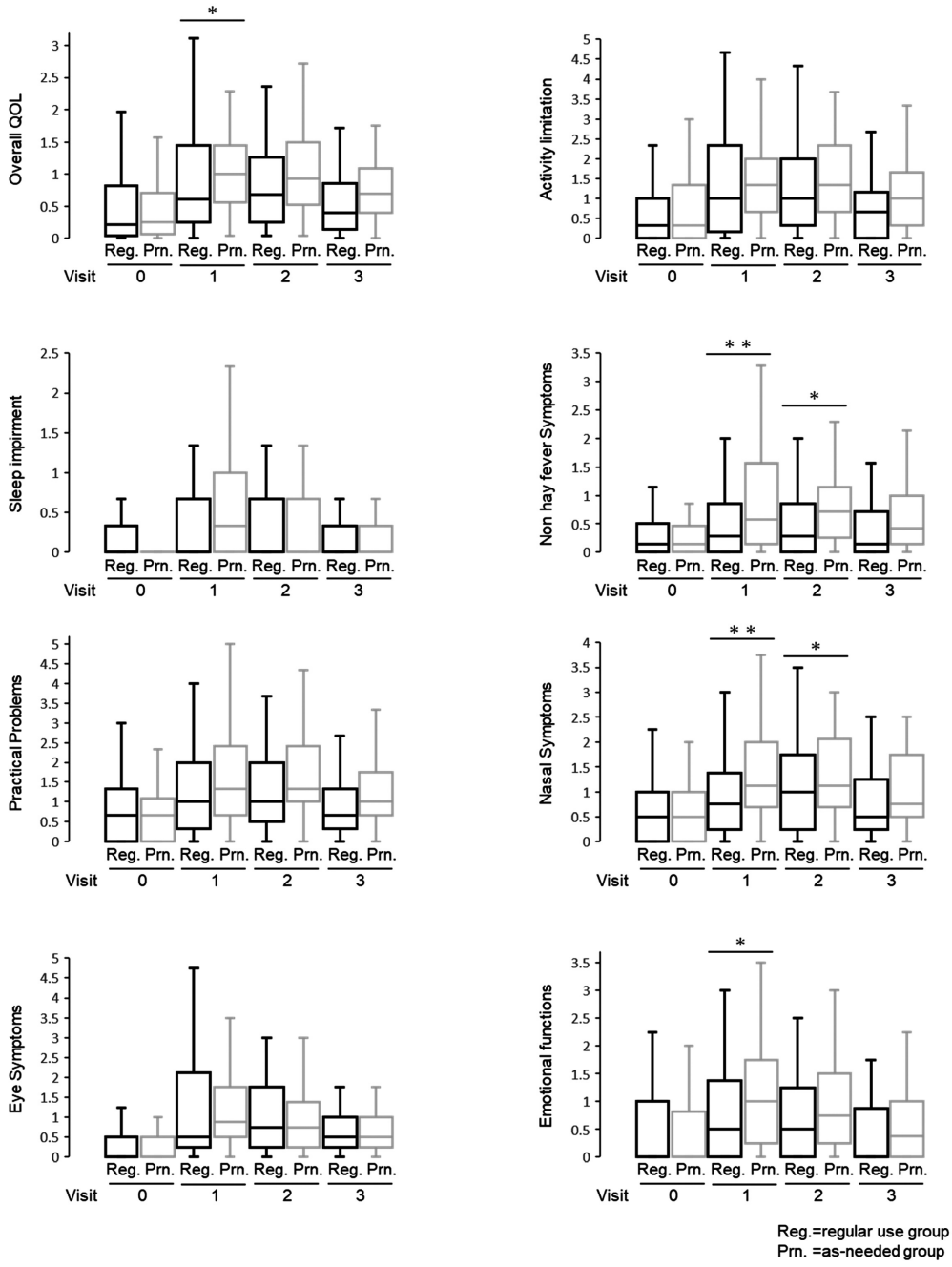

Figure 3. Box and whisker plots of overall QOL scores.
The vertical bars indicate the range from lower to upper adjacent values. The horizontal boundaries of the boxes represent the first and third quartiles. The horizontal bar in the boxes indicates the medians. LMS with 95% CI was generated using a repeated measurement ANCOVA model. (*P <0.05; **P<0.01) Reg: regular-use group; Prn: as-needed use group.

in QOL score between the 2 groups. In the primary outcome, the overall QOL score at visit 1 was significantly lower in the regular-use group than that in the as-needed use group (p=0.037). The overall QOL scores at visits 2 and 3 did not differ significantly between the two groups. In the secondary outcome, statistically significant differences were found for non-hay fever symptoms, nasal symptoms, and emotional aspects at some visits. However, in other QOL domains significant differences were not found (Figure 3 and Table 2). The percentage of MNSD which indicates a day with few symptoms of hay fever during the trial was statistically significantly higher in the regular-use group than that in the as-needed use group (P=0.0261) (Figure 4). The dosage of loratadine tablets and cromoglycate eye drops which were used as rescue medicines were correlated with the amount of scattering of cedar pollem. Amounts of using loratadine tablets and cromoglycate eye drops were similar in both groups (Figure 5).

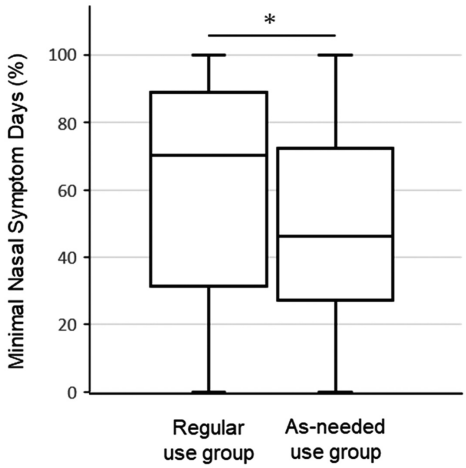

Figure 4. Percentage of MNSD during the trial. MNSD was defined as a day with a total score of ≦2 for all four nasal symptom scores. The difference between the two groups was analyzed by Wilcoxon rank-sum test. (*P=0.0261)

Nasal bleeding was the most frequently reported adverse effect experienced by 6 (9.8%) of the 61 participants in the regular-use group

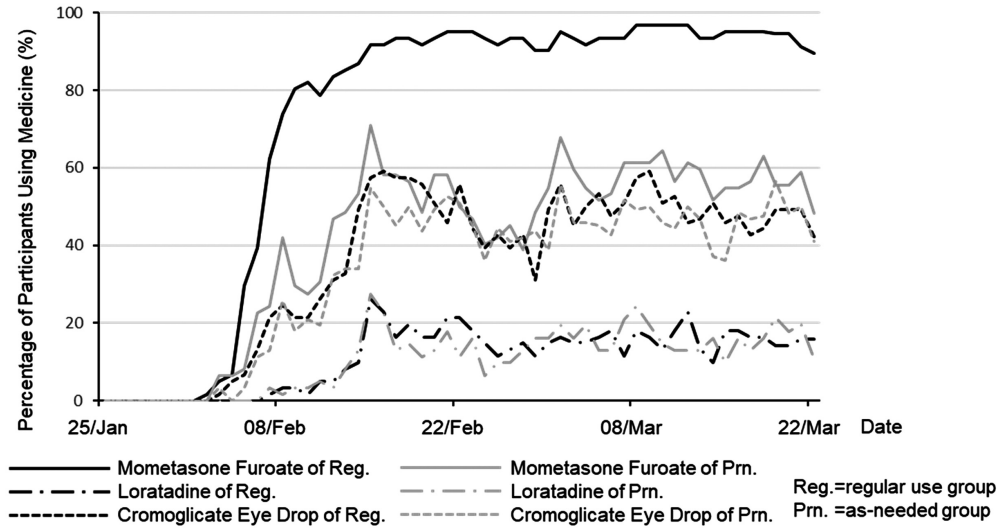

Figure 5. Percentages of participants using medications during the trial. The drug dosages of loratadine tablets and cromoglicate eye drops are similar in both groups.

and one (1.6%) of the 62 participants in the as-needed group. No adverse effects leading to discontinuation of the intervention were observed.

DISCUSSION

Many people experience AR worldwide, leading to declines in QOL. INSs are reported to be the most effective treatment for AR and are widely recommended as a first-line drug[1,3–5]. In order to use INSs effectively, it is necessary to use them continuously; however, adherence to INSs use is lower adherence than that for oral chemical mediator receptor antagonists[6,15]. In addition, JCP has a long disease duration and high severity. Therefore, while more effective treatment is required, the differences in therapeutic effect for JCP between the continuous and as-needed use of INSs have not been verified in Japan. Therefore, this trial was conducted to assess the effectiveness of the continued use of INSs for cedar pollen allergy and to improve the INSs adherence by comparing the effects of continuous and as-needed use.

A previous study compared the therapeutic effects of continuous-use and as-needed use beclomethasone for AR, in which continuous use showed a superior therapeutic effect[11,12]. However, another comparative test of the therapeutic effect of a placebo and as-needed fluticasone[13,14] use for AR suggested that the QOL was better in the as-needed group than that for a placebo. Although we used mometasone furoate in the present study, to our knowledge, no studies have used MFNS to assess the treatment effects of as-needed use for AR. In our study, the nasal symptom score of the RQLQ was significantly lower in the continuous use group at visits 1 and 2. MNSD is defined as days with nasal symptom scores of 2 or less and the ratios of MNSD are often compared to examine the drug effect on AR. In addition, the percentage of MNSD was significantly higher in the continued-use group than that in the as-needed use group. Several days are required to reach the maximum therapeutic effect of INSs; therefore nasal symptoms were significantly suppressed in the continuous use group[3].

Among patients with seasonal AR, not only nasal symptoms but also the general QOL are more improved if INSs are used continuously[8,16]. In our study, the total QOL score in the regular-use group was significantly higher than that in the as-needed group at visit 1. In term of nasal symptoms, non-hay fever symptoms and emotions, the QOL of the regular-use group was significantly higher in visit 1. However, there was no significant difference in any of the QOL scores in subsequent visits. The total spread of cedar pollen in 2009, when we conducted research, was 2,518/cm^2, which was higher than the yearly average[17,18]. Therefore, the symptoms of JCP, which tended to be more severe, became stronger in the second half of the season. when pollen exposure increased, and symptoms other than nasal symptoms could not be suppressed with INSs alone. In addition, even in the regular-use group, there were days in which the participants forget to use INSs, one of the reasons to explain why the INSs usage rate was not 100%. Nosebleeds are the most frequent side effect of INSs and were experienced by seven people in the present trial. However, the bleeds were mild enough that use was not discontinued. Systemic side effects like those for antihistamine do not occur; thus, INSs can be safely used for long periods of time[19].

The causes of reduced compliance to treatments for AR are various. However, most patients did not use drugs because they had no symptoms. It certainly seems efficient to use medicines only when symptoms are present[6].

In addition, the spread of JCP is sustained and long-term and may be larger than expected depending on the year[20]. JCP-induced allergic inflammation in the nasal mucosa even in asymptomatic patients. Even without symptoms, inhalation of the antigen is serious. In order to suppress symptoms throughout the season, it is important to continue to use medications even when there are no symptoms. Continuous use of treatments, regardless of the presence or absence of symptoms, suppresses inflammation throughout the pollen season and improves symptoms.

Previous studies showed that as-needed use is effective for AR. However, these studies were in comparison to placebos[13,14]. In our study, the QOL in the continuous use group was improved compared to that in the as-needed use group. However, the normal-use group had better QOL scores in some respects as well as more MNSD. Therefore, for better control, continued use of INSs enhances the treatment effect and suppresses symptoms. Based on our findings, we not only prescribe INSs but also explain to patients the necessity and effectiveness of continued use, the nature of JCP, and try to increase treatment compliance[21,22].

References

1) Yamada T, Saito H, Fujieda S: Present state of Japanese cedar pollinosis: The national affliction. American Academy of Allergy, Asthma & Immunology, 133: 632–639, 2014.
2) Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW: Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. Allergy, 63: 1280–1291, 2008.
3) Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, *et al.*: Clinical Practice Guideline: Allergic Rhinitis. American Academy of Otolaryngology-Head and Neck Surgery, 152(1S): S1–S43, 2015.
4) Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, *et al.*: Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision. ALLERGIC RHINITIS AND ITS IMPACT ON ASTHMA GUIDELINES: V. 9/8/2010, 2010.
5) Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, *et al.*: Japanese guidelines for allergic rhinitis 2017. Allergology International, 66: 205–219, 2017.
6) Loh CY, Chao SS, Chan YH, Wang DY: A clinical survey on compliance in the treatment of rhinitis using nasal steroids. Allergy, 59: 1168–1172, 2004.
7) Yonezaki M, Akiyama K, Karaki M, Goto R, Inamoto R, Samukawa Y, *et al.*: Preference evaluation and perceived sensory comparison of fluticasone furoate and mometasone furoate intranasal sprays in allergic rhinitis. Auris Nasus Larynx, 43: 292–297, 2016.
8) Makihara S, Okano M, Fujieda T, Kimura M, Higaki T, Haruna T, *et al.*: Early Interventional Treatment with Intranasal Mometasone Furoate in Japanese Cedar/Cypress Pollinosis: A Randomized Placebo-Controlled Trial. Allergology international, 61: 295–304, 2012.
9) Graft D, Aaronson D, Chervinsky P, Kaiser H, Mekamed J, Pedinoff A, *et al.*: A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. Journal of Allergy and Clinical Immunology, 98: 724–731, 1996.
10) Bielory L, Chun Y, Bielory BP, Canonica GW: Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. Allergy, 66: 686–693, 2011.
11) Juniper EF, Guyatt GH, Byrne PM, Viveiros M: Aqueous beclomethasone diproprionate nasal spray: Regular versus "as required" use in the treatment of seasonal allergic rhinitis. The Journal of Allergy and Clinical Immunology, 86: 380–386, 1990.
12) Juniper EF, Guyatt GH, Archer B, Ferrie PJ: Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. The Journal of Allergy and Clinical Immunology, 92: 66–72, 1993.
13) Jen A, Baroody F, Tineo M, Haney L, Blair C, Naclerio R: As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. Journal of Allergy and Clinical Immunology, 105: 732–738, 2000.

14) Dykewicz MS, Kaiser HB, Nathan RA, Goode-Sellers A, Cook CK, Witham LA, *et al.*: Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). Annals of Allergy, Asthma and Immunology, 91: 44–48, 2003.
15) Matsubara A, Futai K, Shirasaki T, Nagaki T, Ikeno K, Tanita J, *et al.*: Medication compliance of oral anti-allergic drugs to perennial allergic rhinitis. jibi to rinsho, 55: 39–45, 2009. (in Japanese)
16) Rodrigo GJ, Neffen H: Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. Clinical & Experimental Allergy, 41: 160–170, 2011.
17) Isono M, Oto T, Ozawa H, Shimada K, Fujimori I, Horiuchi H, *et al.*: The situation of Yumanashi prefecture's 2009 cedar and cypress pollen dispersion. ENT Report Yamanashi, 27: 49–53, 2009.
18) Kishikawa R, Kotoh E, Oshikawa, Soh N, Shimoda T, Saito A, *et al.*: Longitudinal monitoring of tree airborne pollen in Japan — regional distribution and annual change of important allergic tree pollen —. Japanese Journal of Allergology, 66: 97–111, 2017. (in Japanese)
19) Rosenblut A, Bardin PG, Muller B, Faris MA, Wu WW, Caldwell MF, *et al.*: Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. Allergy, 62: 1071–1077, 2007.
20) Prediction study work report on pollinosis in 2016. Weather Service Co., Ltd. 2017 (in Japanese)
21) Skadding GK, Richrds DH, Price MJ: Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clinical Otolaryngology & Allied Sciences, 25: 551–557, 2000.
22) Gani F, Pozzi E, Crivellaro MA, Senna G, Landi M, Lombardi C, *et al.*: The role of patient training in the management of seasonal rhinitis and asthma: clinical implications. Allergy, 56: 65–68, 2001.