Allergology International. 2012;61:155-162
DOI: 10.2332/allergolint.11-OA-0342

ORIGINAL ARTICLE

A Randomized Control Trail of Stepwise Treatment with Fluticasone Propionate Nasal Spray and Fexofenadine Hydrochloride Tablet for Seasonal Allergic Rhinitis

Goro Takahashi[1,2], Zensei Matsuzaki[2], Atsushi Okamoto[2], Eiko Ito[2], Tomokazu Matsuoka[2], Takeo Nakayama[3] and Keisuke Masuyama[2]

ABSTRACT

Background: In Japan, oral antihistamines are frequently used as the initial treatment for seasonal allergic rhinitis (SAR), and intranasal steroids are added when nasal symptoms worsen. This study aimed to evaluate whether starting treatment with fluticasone propionate nasal spray (FP) from the beginning of pollinosis symptoms and adding fexofenadine hydrochloride tablet (FEX) when SAR is aggravated could achieve improved amelioration of nasal symptoms throughout the pollen season in comparison with a treatment that involves starting with FEX and later adding FP.

Methods: In this pragmatic, randomized, open-label, parallel-group trial, 51 Japanese cedar pollinosis patients (age, 16-85 years) were randomly divided and administered FP 100 mcg twice daily as an initial drug with FEX 60 mg twice daily as an additional drug and the same treatment in the reverse order. Nasal symptoms were evaluated in a daily dairy using a 4-point scale. The primary outcome was area under curve of the line representing the daily total nasal symptom score in the pollen season on a graph.

Results: Initial treatment with FP was significantly (P = 0.0015) more effective than initial treatment with FEX in improving the primary outcome. The average daily total nasal symptom score in the initial treatment with FP group was better than that in the initial treatment with FEX group throughout the pollen season.

Conclusions: Initiating treatment with FP and adding FEX might lead to improved outcomes for nasal symptoms in comparison with the same drugs administered in the reverse order.

KEY WORDS

back-up drug, histamine antagonists, initial drug, intranasal steroids, seasonal allergic rhinitis

INTRODUCTION

Allergic rhinitis (AR) is a common disease affecting over 500 million people worldwide.[1] AR is an IgE-mediated inflammation after allergen exposure to the nasal membrane and is characterized by four bothersome symptoms of runny nose, stuffy nose, itchy nose, and sneezing. AR influences the quality of life of the patient through impairment of daily activities, social function, emotions, and sleep patterns, although it is not a life-threatening disease.[2-5] Moreover, AR is a social burden in terms of medical expenditure. In the USA, the direct cost of this disease was estimated to be between $2 and $5 billion in 2003.[6]

[1]Department of Otolaryngology, Hamamatsu University School of Medicine, Shizuoka, [2]Department of Otorhinolaryngology and Head and Neck Surgery, Faculty of Medicine, Yamanashi University, Yamanashi and [3]Department of Health Informatics, School of Public Health, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Conflict of interest: KM has received fees for lectures from GlaxoSmithKline and Sanofi-Aventis. The other authors have no conflict of interest with any organizations related to the subject of this study.

This trial was conducted without any financial support.

Correspondence: Goro Takahashi, MD, MSc, Department of Otolaryngology, Hamamatsu University School of Medicine, 1–20–1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431–3192, Japan.
Email: gr–tkhs@umin.ac.jp

Received 2 June 2011. Accepted for publication 5 August 2011.

Cedar pollen is the most common outdoor allergen in Japan; it disperses in February and March every year. Epidemiological studies have demonstrated that the prevalence of seasonal allergic rhinitis (SAR) due to this pollen has risen from 16% in 1998 to 26% in 2008.[7]

Practical Guideline for the Management of Allergic Rhinitis in Japan recommends that clinicians treat SAR patients from the beginning of early symptoms, immediately after the start of pollen dispersal.[7,8] According to this recommendation, if the initial treatment fails to control the symptoms, additional medication is considered necessary. Oral antihistamines are considered the most frequently used drugs for the initial treatment of SAR in Japan,[9] and intranasal steroids are added for ameliorating the subsequent aggravation of nasal symptoms with increasing pollen dispersal as the season progresses. However, although certain studies have revealed that intranasal steroids have stronger effects on allergic rhinitis as compared to oral antihistamines,[10] the positioning of the two drugs in the initial and additional treatments remains unclear. We hypothesized that improved amelioration of nasal symptoms could be achieved throughout the pollen season by initiating treatment with an intranasal steroid followed by an oral antihistamine as a backup drug in comparison with the same treatment in the reverse order.

Fluticasone propionate aqueous nasal spray (FP) is an intranasal steroid commonly used for treating allergic rhinitis in adults and children.[11,12] It has been shown that FP is effective for improving both nasal and ocular symptoms associated with SAR.[13,14] Local adverse effects of FP, such as epistaxis and nasal dryness, are generally mild and temporal. Moreover, the low bioavailability of this drug is considered to be associated with fewer systemic adverse effects in cases of prolonged use.[15-17]

Fexofenadine hydrochloride tablet (FEX) is the active metabolite of terfenadine.[18] Certain clinical studies have demonstrated FEX to favorably influence nasal symptoms and the resultant quality of life.[19-21] FEX causes minimal sedation and does not interfere with concentration-intensive activities such as driving.[22] Moreover, FEX is considered a safe drug in view of cardiac toxicity.[23]

Our study aimed to evaluate whether initial treatment with FP followed by FEX as the additional treatment would lead to improved amelioration of the nasal symptoms of cedar pollinosis as compared to the same drugs administered in the reverse order.

METHODS

STUDY DESIGN

A pragmatic randomized, open-label, parallel-group study design was used. The target population of this study was asymptomatic AR patients or those with mild symptoms visiting a medical institute early in the cedar pollen season. This study was conducted at seven private ENT clinics and the ENT outpatient department of a general hospital in Yamanashi Prefecture, Japan, from January 1 to March 31, 2007.

POLLEN COUNTS

Cedar pollen grains were collected and measured by using a Durham sampler daily from January 1, 2007 at the University of Yamanashi Hospital. Pollen counts were expressed as a mean of grain per square centimeter. We defined "early cedar pollen season" as the period between the first day of identifying a cedar pollen grain and the second day of two consecutive days of identifying cedar pollen grains ≥1 grain/cm^2 for the first time in the season. "Full pollen season" was defined as the period between the end of the early pollen season until March 25.

PARTICIPANTS

The participants were recruited through physician referrals when patients visited a medical institute early in the pollen season. The following 4 inclusion criteria were considered: (1) age ≥16 years, (2) a history of Japanese cedar pollinosis for at least 2 seasons before study entry, (3) a positive allergy skin test to Japanese cedar pollen or Japanese cedar pollen-specific IgE RAST score ≥class 2, and (4) asymptomatic or mild symptoms (daily total nasal symptom score ≤2). Written informed consent was also necessary for participation in this study.

Patients were excluded if (1) they had taken any anti-allergy drugs at the beginning of the study; (2) had any other nasal/paranasal sinus disease, pharyngitis, laryngitis, respiratory tract infection, or asthma; (3) had a history of glaucoma, gastric ulcer, uncontrollable hypertension/diabetes, hepatitis, or malignant tumor; (4) were in a build-up phase of specific immunotherapy to Japanese cedar pollen; (5) had a history of nasal/paranasal sinus surgery; (6) had a history of hypersensitivity to fluticasone propionate or fexofenadine hydrochloride; and (7) were pregnant or lactating.

The physician contacted the data-collecting center after evaluating the eligibility criteria of the patient. Patients who matched the eligibility criteria were registered in the study and assigned in accordance with the computer-generated random allocation table with a block size of 4 and 6. To conceal the assignment sequence, central randomization was used, and the block size was not released.

INTERVENTIONS

FP group intervention: One fluticasone 50 μg per nostril twice a day (total 200 μg/day) was administered from the beginning of pollinosis symptoms as the initial drug. Sixty mg of fexofenadine orally twice a day (total 120 mg/day) was started as an additional drug for treating the exacerbation of nasal symptoms. Ex-

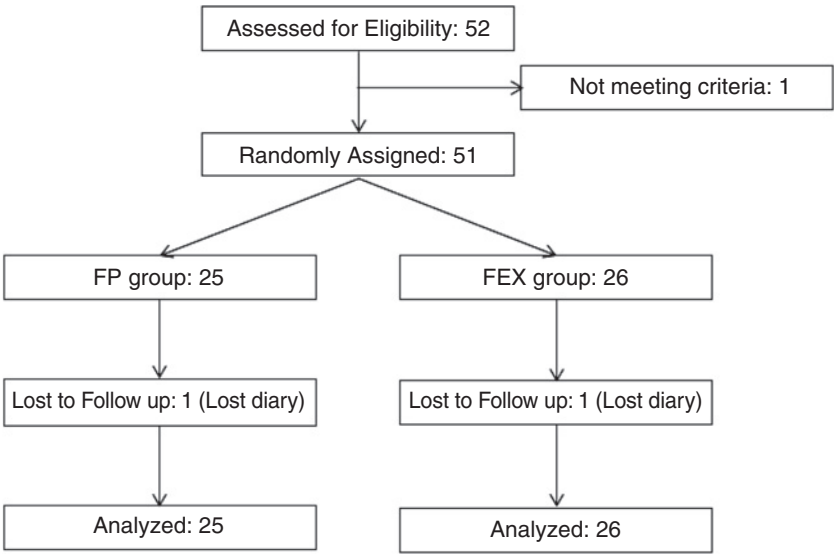

Fig. 1 Schematic summary of the flow of participants in the study.

acerbation was defined as a daily total nasal symptom score of 4 more for 4 times a week.

FEX group intervention: Oral fexofenadine 60 mg twice a day (total 120 mg/day) was administered from the beginning of pollinosis symptoms as the initial drug. One fluticasone 50-μg puff per nostril twice a day (total 200 μg/day) was started as the additional drug for treating the exacerbation of nasal symptoms as mentioned above.

Sodium cromoglicate 2% eye drops were given for administration on an as-needed basis to alleviate ocular symptoms to both patient groups.

OUTCOMES MEASURED

Participants assessed 4 nasal symptoms, i.e., runny nose, stuffy nose, sneezing, and itchy nose, and 3 ocular symptoms-tearing, redness, and itchy eyes on the basis of a 4-point scale in a daily dairy during the study as follows: 0, no symptom evident; 1, symptom present but not bothersome; 2, definite symptom that is bothersome but tolerable; and 3, symptom that is hard to tolerate. Participants also filled a Japanese version of the rhinoconjunctivitis quality of life questionnaire (RQLQ) every time when they visited the medical institute.

The primary outcome was the area under the curve (AUC) of the line representing the total nasal symptom score (TNSS) in the full pollen season on a graph. Secondary outcomes were AUC of the 4 nasal and total ocular symptom scores in full pollen season on a graph and the change in the overall and 7 domain scores of RQLQ at the peak of the pollen season from the time of registration in the study (i.e., baseline).

The drug dosage for each participant was also noted from their daily dairy. Adverse events were also recorded from the daily dairy and from clinical examination records.

Table 1 Participants characteristics

	FP group (n = 25)	FEX group (n = 26)
Age, years	39 (29, 45)	43 (31, 53)
Male/Female, n	10/15	7/19
Age of JCP onset, years	20 (15, 32)	20 (16, 38)
JCP in 2006, n		
Severity		
none	0	1
mild	16	18
moderate	5	2
severe	0	1
unknown	4	4
Treatment		
OAH	7	9
INS	3	2
OAH + INS	3	4
unknown	5	3
no treatment	7	8
Immunotherapy, n	1	0
Overall RQLQ score	0.38 (0.00, 0.78)	0.47 (0.18,1.22)
Date of registration	1/31 (1/25, 2/2)	1/30 (1/27, 2/1)

Median (25 percentile, 75 percentile).

FP, fluticasone propionate nasal spray; FEX, fexofenadine hydrochloride tablet; JCP, Japanese cedar pollinosis; OAH, Oral antihistamines; INS, Intranasal steroids.

SAMPLE SIZE

The clinically significant difference for daily TNSS was determined to be 0.5 in late February, 0.75 in

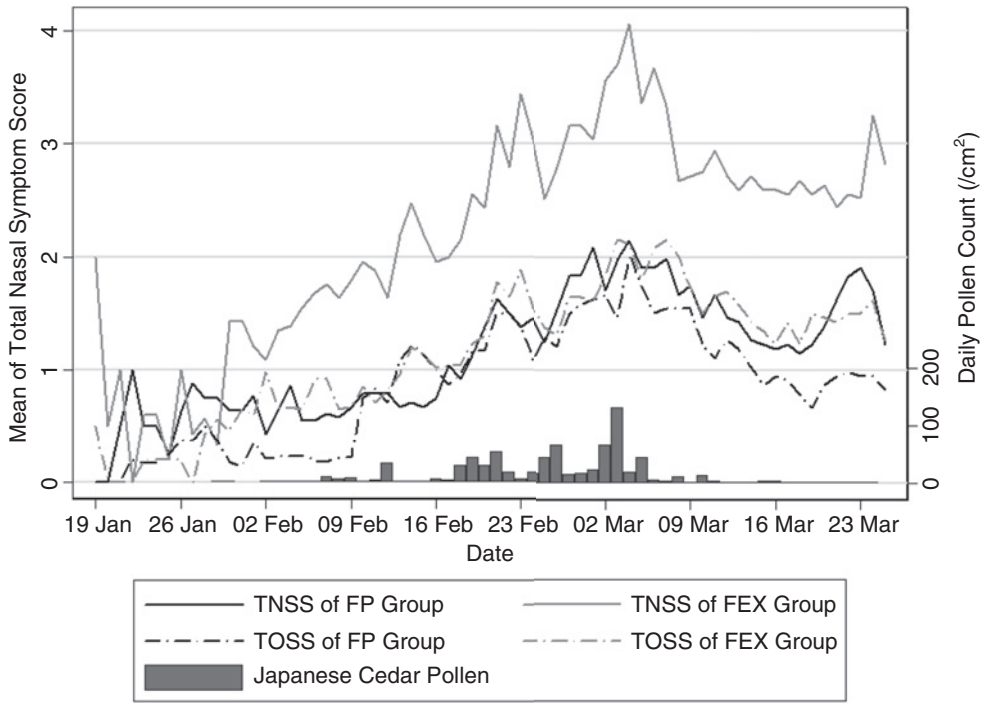

Fig. 2 Average daily total nasal symptom score and pollen counts during the study period. Participants were registered and randomly assigned to fluticasone propionate nasal spray (FP) and fexofenadine hydrochloride tablet (FEX) groups between January 19 and February 9, 2007. In both the groups, the peak of the average daily total nasal symptom score (TNSS) was recognized in early March.

early March, and 1.0 in late March. Assuming the least expected difference in the AUC of TNSS between the two groups to be 26 and a standard deviation of 50 as derived in our previous study,[24] a two-sided alpha of 0.05, and power of 0.8 with equal allocation, the estimated sample size needed to be 52 in each group. Taking into account a 20% dropout rate, we needed 120 participants in total.

STATISTICAL METHODS

We compared the two groups in terms of the AUC of the symptom scores and the change in RQLQ scores by Wilcoxon's rank-sum test. These analyses were based on intent-to-treat. Missing data of daily symptom scores were predicted to be caused as the result of participants dropping out or insufficient measurement. Therefore, we utilized an imputation method for determining the missing data in the trial protocol. In brief, the missing data could be replaced by the mean of the available data of the participant's assigned treatment group from the first day of the full pollen season to the day of the maximum pollen dispersal and by the last observational data noted by the subject from the day following the maximum pollen dispersal until March 25. The clinical characteristics of the participants and the drug dosage were summarized as representative values for each group.

The statistical software package used to analyze the data was Stata Software version 11 (Stata Corporation, College Station, Texas, USA).

INSTITUTIONAL REVIEW BOARD AND CLINICAL TRIAL REGISTRATION

The Institutional Review Board of the Faculty of Medicine, University of Yamanashi, had approved the protocol of this study in December 2006. The clinical trial registration number is UMIN000000575 (www.umin.ac.jp/ctr/index/htm).

RESULTS

The period of the enrollment and random assignment was from January 19 to February 9, 2007 in accordance with pollen count as measured by the Durham sampler. We followed up the participants until the last week of March 2007.

Fifty-one participants were randomly assigned to either the FP group or the FEX group. We could not collect the diary of one participant from each group (Fig. 1). Baseline clinical characteristics of both the treatment groups are shown in Table 1. These groups were comparable with respect to their demographic background. Medication use for cedar pollinosis in the 2006 season was almost identical in both the groups.

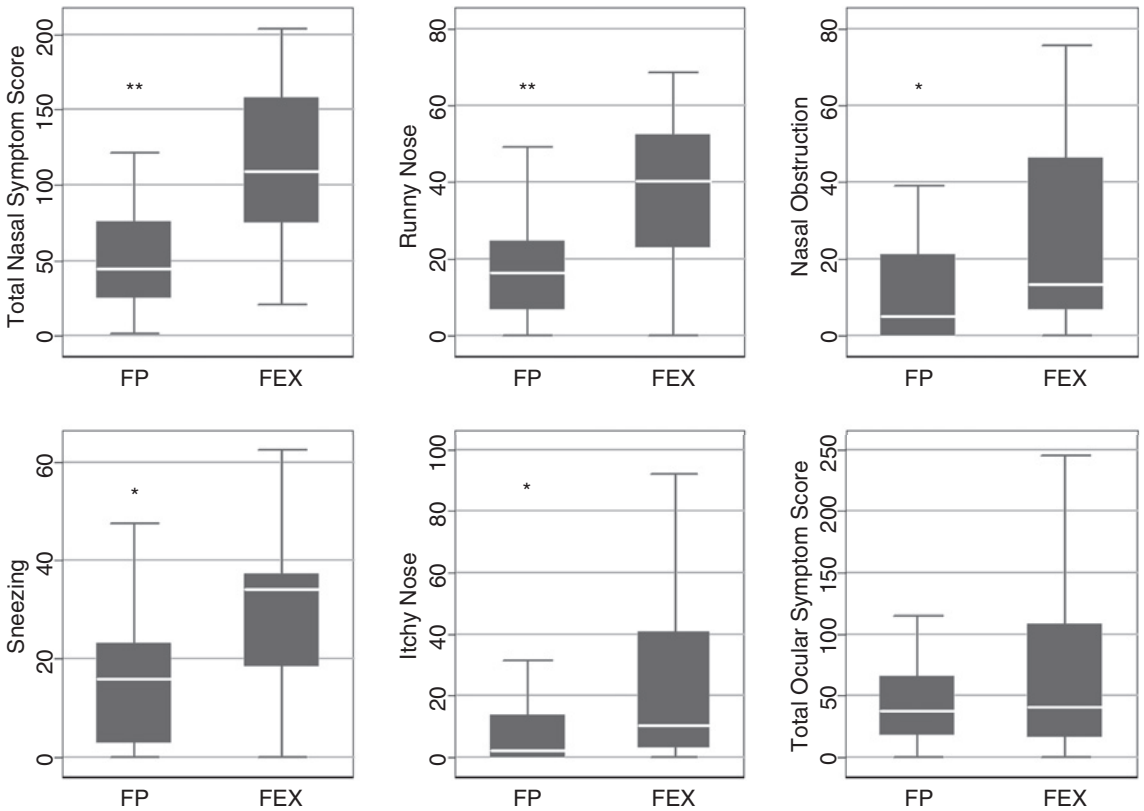

Fig. 3 The area under the curve (AUC) for each symptom score during full pollen season. Median symptom scores are indicated with horizontal bars. The vertical bars indicate the range from lower to upper adjacent values, and the horizontal boundaries of the boxes represent the 25% and 75% percentile. Full pollen season was between February 10 and March 25, 2007. *P < 0.05. **P < 0.01. P values (2-sided) are derived from Wilcoxon's rank-sum test for group comparisons.

Pollen counts and average daily TNSS of the treatment groups are shown in Figure 2. The average daily TNSS of the FP group was lower than the score of the FEX group throughout full pollen season.

The area under the TNSS curve for the FP group (median = 45; interquartile range = 25 to 75) was significantly lower than that for the FEX group (median = 109; interquartile range = 75 to 158; P = 0.0015). For the 4 nasal symptoms, i.e., runny nose, stuffy nose, sneezing, and itchy nose, the AUC for the FP group was significantly lower than that for the FEX group (P = 0.0008, 0.0175, 0.0128, and 0.0166, respectively) (Fig. 3). No significant difference was noted for the area under the TOSS curve between the two groups (P = 0.8358).

We did not observe any significant differences between the two treatment groups in the degree of change in the overall RQLQ score at the peak of the pollen season from baseline (FP: median = 0.13; interquartile range = 0.02 to 1.06; FEX: median = 0.44; interquartile range = -0.16 to 1.21; P = 0.3946). No significant difference was recognized between the two groups in the analyses of the 7 domain scores for RQLQ (data not shown).

Throughout the study, 67% of the FP group (n = 16) and 40% of the FEX group (n = 10) used only the initial drug. The backup drug was taken by 33% (n = 8) and 60% (n = 15) of the FP and FEX groups, respectively. The timing of starting the backup drug was also different between the two groups. Participants who started the backup drug at earlier timing than instructed were 25% of the FP group (n = 6) and 8% of the FEX group (n = 2). Though 4 participants of the FP group and 16 of the FEX group met the requirement of starting the backup drug, 2 (50%) of the 4 of FP group and 12 (75%) of the 16 of the FEX group were late to start the backup drug or did not use the backup drug. The use of sodium cromoglicate eye drops was similar in both the groups (Table 2).

Nasal bleeding was the most frequently reported adverse effect by 4 (16%) of the 25 participants from the FP group; none of the FEX group participants reported the same. No adverse events leading to the discontinuation of the treatment were observed.

DISCUSSION

Our study evaluated the difference in the outcomes

Table 2 Medications used in this trial

	FP group (n = 24)	FEX group (n = 25)
Date of starting drug therapy	2/2 (1/31, 2/7)	2/1 (1/30, 2/2)
Number of participants using drugs, *n* (%)		
FP only	16 (67)	0 (0)
FEX only	0 (0)	10 (40)
FP + FEX	8 (33)	15 (60)
Number of doses		
FP†	100 (91, 105)	11 (0, 50)
FEX‡	0 (0, 8)	101 (95, 108)
SCED§	20 (1,78)	28 (0, 72)
Timing of additional drug, *n* (%)		
Not requiring additional drug with the low tnss	14 (58)	7 (28)
Not using additional drug despite the rise of tnss	2 (8)	3 (12)
Starting additional drug at later timing than instructed	0 (0)	9 (36)
Starting additional drug as instructed	2 (8)	4 (16)
Starting additional drug at earlier timing than instructed	6 (25)	2 (8)

Median (25 percentile, 75 percentile).

FP, fluticasone propionate nasal spray; FEX, fexofenadine hydrochroride tablet; SCED, Sodium cromoglicate eye drop; tnss, total nasal symptom score.

† One fluticasone puff per nostril twice a day was counted as two times.

‡ Intake of fexofenadine hydrochroride tablets was counted.

§ Number of ocular instillation was counted.

for nasal symptoms of cedar pollinosis in a Japanese population depending on the order of drugs (FP and FEX) used as the initial and additional treatment for SAR.

In the primary outcome, we noted the area under the TNSS curve for the FP group to be significantly lower than that for the FEX group. Moreover, the curve for the FP group tended to be lower than that for the FEX group throughout the pollen season. We therefore considered that first-line treatment with FP, backed up by FEX, would be more effective for treating the nasal symptoms of seasonal allergic rhinitis as compared to the reverse order of the same drugs from the beginning of the pollen season to its end.

In the secondary outcomes, the AUC for each of the 4 nasal symptom scores for the FP group was significantly lower than that for the FEX group. This finding supported our abovementioned recommendation derived from the primary outcome. However, no significant differences were noted in the area under the TOSS curve and the RQLQ scores between the two treatment groups.

In the medication usage, participants who used only the initial drug were 67% of the FP group and 40% of the FEX group. In terms of medication cost, starting treatment for mild AR with FP and backed up by FEX in the case of AR aggravation might be better than treatment with the same drugs in the reverse order.

The timing of using the backup drug is also important point to generalize the results of this pragmatic trail into clinical practice. Participants starting the backup drug at earlier timing than instructed were 25% in the FP group and 8% in the FEX group. Proportion of the participants starting the backup drug at later timing than instructed or using no backup drugs in the population who needed backup drug were 50% in the FP group and 75% in the FEX group. These data may reflect that Japanese cedar pollinosis patients prefer anti-histamine tablets as an additional drug rather than intranasal steroids.

The following reasons may account for our results of primary endpoint from this trial. First, starting treatment with FP may be more effective as compared to FEX against minimal persistent inflammation with low pollen counts.[25] Second, backup therapy with FP nasal spray may not be entirely effective because of ineffective nasal diffusion caused by inferior turbinate swelling with the progress of the pollen season. Third, the backup drug was used early in the FP group as compare to the FEX group.

Studies regarding the stepwise treatment of SAR are few. Juniper and colleagues conducted a randomized clinical trial for seasonal ragweed rhinoconjunctivitis comparing initial treatment with FP backed up by terfenadine and initial treatment with terfenadine backed up by FP,[26] wherein participants were advised to start their medication either before pollen was expected in the air or immediately after experiencing their first symptoms, with RQLQ scores being the primary outcome. They concluded that there was little difference in the therapeutic benefit between the two

approaches, as the difference in the overall RQLQ score between the two groups was on the borderline of statistical significance with the mean difference in RQLQ scores not being clinically important. Similarly, we did not note a statistically significant difference in the RQLQ scores between the FP and FEX groups. However, this may have been due to the lack of statistical power for detecting differences in the RQLQ scores between the two groups with small sample sizes.

The control of ocular symptoms is an important point in treating pollinosis. Bernstein and colleagues showed that FP reduced ocular symptoms more than or equal to the effect of loratadine tablets in the treatment of SAR.[14] We noted no differences between the two intervention groups for either TOSS or the usage of sodium cromoglicate eye drops, suggesting that FP had an ameliorating effect on ocular symptoms comparable to that of FEX.

Our study has certain limitations. The small sample size may have decreased the statistical power. However, we successfully determined a statistically significant difference between the two intervention groups in the AUC of TNSS, i.e., the primary outcome. This was possible because the therapeutic effect of the initial treatment with FP and additional FEX on the primary outcome was greater than that assumed before starting this trial. Further, as our study did not involve placebo controls, a bias in each participant's memory regarding the effect of previous SAR medication, including FP and FEX, may have affected the daily symptom scores. However, no definite difference was noted for SAR medication in the 2006 season between the two groups. We therefore considered that such a bias would have little impact on the results. Additionally, our study did not involve any blinding processes, which may have led to a potential bias in the results. To resolve these limitations, a larger randomized controlled trial would be necessary in the future to further elucidate our results.

In conclusion, we consider that initiating treatment with FP and adding FEX might lead to improved outcomes for nasal symptoms in comparison with the same drugs administered in the reverse order.

ACKNOWLEDGEMENTS

The authors would like to express their appreciation to the following clinical collaborators: Jun Ogino, MD, Masashi Ozawa, MD, Tsutomu Nakazawa, MD, and Kazuo Watanabe, MD. The research protocol of this trial was drawn up when GT was enrolled at the Master of Clinical Research course, School of Public Health, Kyoto University Graduate School of Medicine.

REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA (2) LEN and AllerGen). *Allergy* 2008;**63** (Suppl 86):8-160.
2. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;**21**:77-83.
3. Blanc PD, Trupin L, Eisner M *et al*. The work impact of asthma and rhinitis: findings from a population-based survey. *J Clin Epidemiol* 2001;**54**:610-8.
4. Leger D, Annesi-Maesano I, Carat F *et al*. Allergic rhinitis and its consequences on quality of sleep: An unexplored area. *Arch Intern Med* 2006;**166**:1744-8.
5. Stuck BA, Czajkowski J, Hagner AE *et al*. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. *J Allergy Clin Immunol* 2004;**113**:663-8.
6. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004;**22**:345-61.
7. Okuda M, Ishikawa T, Baba K *et al*. *Practical Guideline for the Management of Allergic Rhinitis in Japan,* 6th edn. Tokyo: Life Science, 2008.
8. Okubo K, Kurono Y, Fujieda S *et al*. Japanese guideline for allergic rhinitis. *Allergol Int* 2011;**60**:171-89.
9. Takahashi G, Matsuzaki Z, Nakayama T, Masuyama K. Patterns of drug prescription for Japanese cedar pollinosis using a clinical vignette questionnaire. *Allergol Int* 2008;**57**:405-11.
10. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998;**317**:1624-9.
11. Howland WC 3rd, Hampel FC Jr, Martin BG, Ratner PH, van Bavel JH, Field EA. The efficacy of fluticasone propionate aqueous nasal spray for allergic rhinitis and its relationship to topical effects. *Clin Ther* 1996;**18**:1106-17.
12. Grossman J, Banov C, Bronsky EA *et al*. Fluticasone propionate aqueous nasal spray is safe and effective for children with seasonal allergic rhinitis. *Pediatrics* 1993; **92**:594-9.
13. DeWester J, Philpot EE, Westlund RE, Cook CK, Rickard KA. The efficacy of intranasal fluticasone propionate in the relief of ocular symptoms associated with seasonal allergic rhinitis. *Allergy Asthma Proc* 2003;**24**:331-7.
14. Bernstein DI, Levy AL, Hampel FC *et al*. Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. *Clin Exp Allergy* 2004;**34**:952-7.
15. Vargas R, Dockhorn RJ, Findlay SR, Korenblat PE, Field EA, Kral KM. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol* 1998;**102**: 191-7.
16. Howland WC 3rd. Fluticasone propionate: topical or systemic effects? *Clin Exp Allergy* 1996;**26** (Suppl 3):18-22.
17. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. *Clin Otolaryngol Allied Sci* 1998;**23**:69-73.
18. Russell T, Stoltz M, Weir S. Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. *Clin Pharmacol Ther* 1998;**64**:612-21.
19. Bernstein DI, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine

hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;**79**:443-8.

20. Meltzer EO, Casale TB, Nathan RA, Thompson AK. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1999; **83**:311-7.

21. Okubo K, Gotoh M, Shimada K, Ritsu M, Okuda M, Crawford B. Fexofenadine improves the quality of life and work productivity in Japanese patients with seasonal allergic rhinitis during the peak cedar pollinosis season. *Int Arch Allergy Immunol* 2005;**136**:148-54.

22. Vermeeren A, O'Hanlon JF. Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance. *J Allergy Clin Immunol* 1998;**101**:306-11.

23. Pratt CM, Mason J, Russell T, Reynolds R, Ahlbrandt R. Cardiovascular safety of fexofenadine HCl. *Am J Cardiol* 1999;**83**:1451-4.

24. Takahashi G, Ito E, Matsuoka T, Endo S, Matsuzaki Z, Masuyama K. [A comparison of fluticasone propionate aqueous nasal spray and olopatadine hydrochloride as initial treatment for Japanese ceder pollinosis: a pilot study]. *Jibi Meneki* 2008;**26**:277-83(in Japanese).

25. Ricca V, Landi M, Ferrero P *et al*. Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;**105**:54-7.

26. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. First-line treatment of seasonal (ragweed) rhinoconjunctivitis. A randomized management trial comparing a nasal steroid spray and a nonsedating antihistamine. *CMAJ* 1997;**156**: 1123-31.