scores, and up-regulated specific IgG; however, a 2,500 SQ-T (0.5 μg Phl p 5) dose did not result in amelioration of the symptom and medication scores nor in the induction of IgG.[46] We previously reported that specific IgG4 was significantly increased in pollen season concomitant with improvement of the symptom medication score in the SLIT group compared to the placebo group.[47] The disagreement in results related to the induction of blocking IgG or IgG4 and the improvement of clinical symptoms may depend on the dose and/or the method of administration of the SLIT vaccine.

Other serological parameters have been recently reported to be useful as therapeutic biomarkers for SLIT. A 3-month course of pre-seasonal treatment of patients with grass pollen allergic rhinitis induced a reduction of the serum level of soluble human leukocyte antigen (sHLA)-G. The authors reported a significant relationship among the decrease of the sHLA-G serum level, the increase of interferon (IFN)-γ-producing cells, and the decrease of sHLA-A, -B, and -C after SLIT.[48] Furthermore, the changes of serum sHLA levels were significantly correlated with the clinical symptom score measured using a visual analogue scale (VAS) after SLIT.[49] In this preliminary open-labeled study, the authors suggested that sHLA molecules might be considered as possible biomarkers of the response to SLIT.

Recently, two reports investigated the change of serum reptin levels after SLIT. Leptin is primarily produced by adipocytes and has been reported to protect T lymphocytes from apoptosis, regulate T cell activation, and up-regulate adhesion molecules in endothelial cells.[50] Furthermore, leptin was reported to modulate the hyporesponsiveness and proliferation of human naturally occurring $Foxp3^+CD25^+CD4^+$ regulatory T (nTreg) cells.[51] After a 3-month course of SLIT against pollinosis, serum leptin levels were reported to significantly correlate with symptom severity as assessed by VAS of nasal symptoms in women, the number of peripheral eosinophils in men, the allergen threshold dose for allergen-specific nasal challenge in both men and women, and the medication score in women. This 3-month course of SLIT showed a tendency to increase serum leptin levels compared to the levels before the SLIT, albeit the increase was not significant.[52] After a 2-year course of SLIT, the serum leptin level was significantly increased in men.[53] The relationship between the up-regulation of leptin by SLIT and clinical symptoms remains unclear; however, the difference of the clinical therapeutic efficacy may depend on gender and the presence or absence of obesity.

The reduction of antigen-specific Th2 responses is considered to be an important biomarker for antigen-specific immunotherapy. The increase in the size of the specific Th2 clone, which produces IL4 after being stimulated with Cry j 1 (a major allergen of the Japanese cedar pollen), after pollen season was reported to be significantly reduced in the SLIT group compared with the placebo group in a double-blind, placebo-controlled study of Japanese cedar pollinosis. The increase of specific IL5-producing cells after pollen season was also reduced in the SLIT group, but the reduction was not statistically significant.[47] It has also been reported that after a 2-year course of SCIT against Japanese cedar pollinosis, B and T lymphocyte attenuator (BTLA) expression on $CD4^+$ T cells was down-regulated in untreated patients after Cry j 1 stimulation and up-regulated in SCIT-treated patients. Furthermore, the change of BTLA expression was negatively correlated with IL5 production. The authors concluded that BTLA-mediated coinhibition of IL5 production may contribute to the regulation of allergen-specific T cell responses by antigen-specific immunotherapy.[54]

The therapeutic biomarkers of SLIT in children also remain unclear. In a study of the administration of the SLIT treatment to children with seasonal allergic rhinoconjunctivitis to grass pollen, the authors reported that a 2-year course of SLIT using a standardized 5-grass mixture (1.5 μg/week) did not alter the systemic immunologic reaction of IL4, IL5, and IFN-γ cytokine production, nor the proliferation of PBMC after stimulation with allergens in the SLIT group compared to the placebo group, although a positive effect on rescue medication use was achieved by SLIT treatment.[55] However, another study reported the up-regulation of mRNA expression in PBMC during SLIT in children using SQ-standardized tree pollen extracts. The authors reported that after the stimulation of PBMC with allergen *in vitro*, the mRNA expression of signaling lymphocytic activation molecule (SLAM) was significantly increased from baseline after 1 year in the SLIT group receiving a high-dose (weekly dose of 200,000 SQ-U) treatment. This up-regulation was reported to be correlated with IL10 and transforming growth factor-β (TGF-β) mRNA expression. The IL18 mRNA expression was also increased in the high-dose group over a 1-year treatment compared to the placebo group and was reported to be inversely correlated with the late-phase skin reaction after the second study year. The authors reported that this up-regulation of SLAM and IL18 mRNA expression suggested the down-regulation of Th2-type inflammatory responses by increased Th1-type responses.[56] Another study of SLIT in children using SQ-standardized tree pollen extract (weekly dose of 200,000 SQ-T, 30 μg major allergen containing Bet v 1, Aln g 1, and Cor a 1) reported that specific allergen-induced Foxp3 mRNA expression after a 2-year course of SLIT treatment was significantly increased in PBMCs compared to the placebo group and compared to the level before treatment. Changes in allergen-induced Foxp3 expression that significantly correlated with IL10 mRNA expression

were reported in the whole study group, including the low-dose (weekly dose of 24,000 SQ-T) group and the placebo group, after 1- and 2-year courses of treatment, and correlated with TGF-β1 mRNA after 1 year of treatment. Furthermore, IL17A mRNA expression was significantly correlated with symptom-medication score (SMS) in the whole study group and especially in the high-dose treated group. The authors concluded that IL17 expression may be associated with a poor therapeutic outcome of SLIT.[57]

MECHANISMS OF ANTIGEN-SPECIFIC IMMUNOTHERAPY

Numerous data showing that antigen-specific Th2-type responses are down-regulated and, in contrast, Th1-type and/or regulatory T cell (Treg) responses are up-regulated by immunotherapy have been accumulated. The imbalance of the population among the antigen-specific Th1, dominant Th2, and Treg is considered to induce sensitization and subsequent allergic inflammation in response to invading allergens, and immunotherapy may correct the imbalance of these cells. Actually, the high frequency of IL4-secreting Th2 cells was reported in allergic individuals, as was, in contrast, the dominance of IL10-secreting Tr1 cells in healthy subjects.[58] These authors suggested that the balance between allergen-specific Tr1 cells and Th2 cells causes the development of the allergy.

IL10-producing regulatory cells are considered to play a crucial role in clinical therapeutic mechanisms in immunotherapy. In a study of SCIT using house dust mite (HDM) extract in patients allergic to HDM, SCIT induced the suppression of PBMC proliferation and the suppression of IFN-γ, IL5, and IL13 production in PBMC stimulated with Der p 1 (a major allergen of HDM) at 70 days after treatment compared to the levels before treatment. In contrast to the suppression of Th1 and Th2 cytokines, the production of both IL10 and TGF-β was significantly increased. The report also showed that the suppression of proliferation was dependent on IL10 and TGF-β and that the source of IL10 is $CD25^+CD4^+$ T cells.[59] It has also been reported that IL10 production was induced by SLIT against HDM. The authors also reported the suppression of the proliferation of PBMC stimulated with extract of mite (*Dermatophagoids farinae*) and the increase of IL10 production compared to non-treated subjects.[60] The IL10 production after 3 years of SLIT treatment was significantly correlated with the improvement of clinical symptoms as assessed by forced expiratory flow between 25% and 75% (FEF_{25-75}).[61]

In a report about the use of SLIT to treat birch pollinosis, the authors investigated the antigen-specific proliferation and mRNA levels of cytokines and Foxp3. They reported that 4 weeks of SLIT induced a reduction in Bet v 1-specific proliferation and induced mRNA expression of IL10 and Foxp3 in $CD3^+$ cells compared to the levels before SLIT. These up-regulations of IL10 and Foxp3 mRNA expression were not seen after 52 weeks after SLIT; however, IFN-γ mRNA expression was significantly induced at 52 weeks after SLIT. The reduced Bet v 1-specific proliferation was significant after both 4 and 52 weeks, and this down-regulation was dependent on IL10 at 4 weeks. It has also been reported that neither TGF-β levels nor cell-cell contact-mediated suppression of $CD25^+CD4^+$ cells were changed during the course of SLIT.[62] Another report shows the significant reduction of IL5 mRNA expression and increased IL10 expression compared to the placebo group after 1 and 2 years of SLIT at a weekly dose of 200,000 SQ-U (30 μg major allergen) in children with tree pollinosis. It has been reported that TGF-β expression remained low after 1 and 2 years of SLIT; however, TGF-β expression was inversely correlated with IL5 and positively correlated with IL10 expression after 1 year of SLIT.[63]

In addition to IL10-secreting Tr1 cells, $Foxp3^+$ Treg cells are also considered to play a crucial role in the therapeutic effects achieved by immunotherapy (Fig. 2). It has been reported that 2 years of SCIT against hay fever significantly induced an increase in the number of $Foxp3^+CD25^+$ and $Foxp3^+CD4^+$ cells in the nasal mucosa compared to the number before SCIT and the number in untreated patients out of season. Twenty per cent of $CD3^+CD25^+$ cells were reported to also be Foxp3-positive, and 18% of $CD3^+$IL10-expressing cells were Foxp3-positive in the nasal mucosa after immunotherapy. This report suggested that the increase of $Foxp3^+CD25^+CD3^+$ cells in the nasal mucosa was associated with the clinical efficacy and suppression of seasonal allergic inflammation. This report also suggested the involvement of different types of regulatory T cells, namely IL10-secreting Tr1 cells and adaptive or induced Foxp3-positive Treg, in the therapeutic mechanisms of immunotherapy.[64] The involvement of Treg cells in immunotherapy was also reported in SCIT against hymenoptera venom allergy. In this report, the authors showed that the numbers of peripheral Treg cells defined as $Foxp3^+CD25^{bright}CD4^+$ T cells were significantly increased by venom immunotherapy, and the increase of circulating Treg cells was significantly correlated with the venom specific IgG4/IgE ratio.[65]

Antigen-specific Tr1 and Treg cells are considered to be involved not only in the suppression of Th2 cells but also, directly or indirectly, in the suppression of peripheral allergic inflammation[24] (Fig. 3). It has been reported that $CD25^+CD4^+$ Treg cells, more than 90% of which are $Foxp3^+$, directly inhibited the FcεR1-dependent mast cell degranulation after crosslinking of IgE, and this inhibition was dependent on cell-cell contact involving OX40-OX40L interactions between Treg and mast cells in the mouse.[66] Furthermore, al-

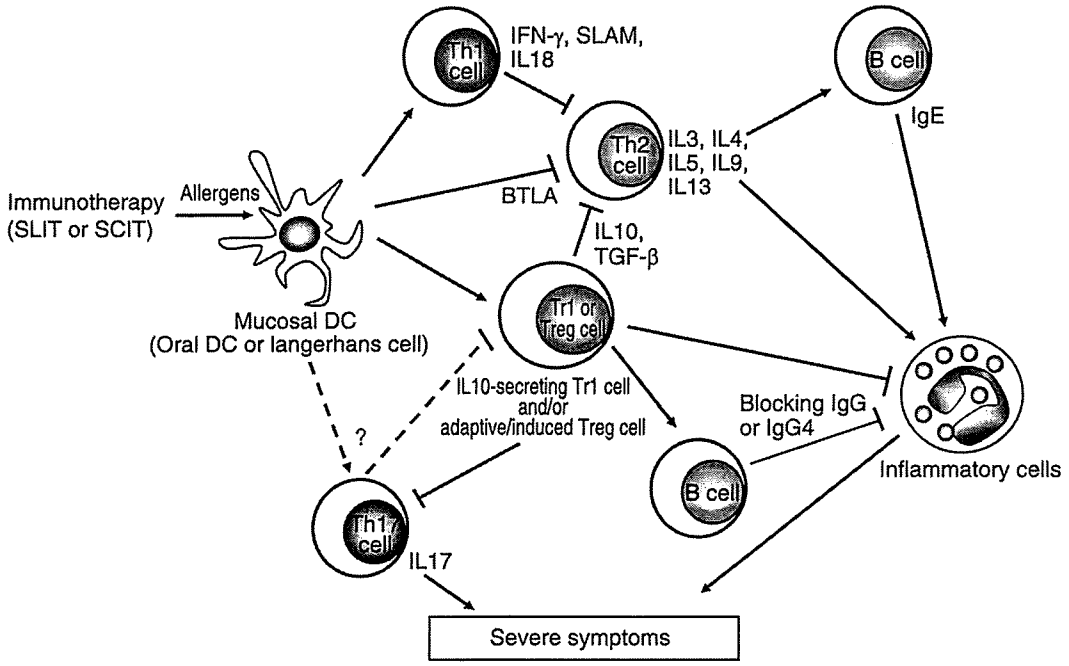

Fig. 2 T cells in antigen-specific immunotherapy. Antigen-specific immunotherapy induces regulatory T cells and Th1 cells via antigen-presentation by mucosal dendritic cells (DC). Th17 cells may be induced in a non-responder population by immunotherapy. The induced Th1 cells and/or regulatory T cells down-regulate the activation of Th2 cells and subsequently the activation of inflammatory cells such as eosinophils and mast cells. The regulatory T cells also activate B cells to produce blocking IgG or IgG4, and the blocking antibody inhibits binding between allergen and surface IgE on inflammatory cells to prevent the secretion of inflammatory chemical mediators.

lergic human eosinophils in peripheral blood and chronically inflamed nasal tissues were reported to express CD40, and the cross-linking of CD40 and CD40L enhanced the survival of eosinophils and induced the release of granulocyte/macrophage colony-stimulating factor (GM-CSF). In this report, IL10 down-regulated the constitutive expression of CD40 mRNA expression in eosinophils.[67] The induction of IL10-producing Tr1 or Treg cells in the nasal mucosa may play an important role in the reduction of nasal symptoms via cross-talk down-regulation of mast cells and eosinophils.

In a reports on the rush protocol of SCIT against Japanese cedar pollinosis using standardized pollen extract, the percentage of $CD203c^{high}$ cells in $CD3^-$ $CRTH2^+$ basophils after allergen stimulation was reported to be down-regulated after rush immunotherapy without a decrease of the serum specific IgE titer. Furthermore, the percentage of $CD203c^{high}$ on basophils after *in vitro* stimulation was reported to be significantly correlated with symptom score.[68] The mechanisms which attenuate the sensitivity of peripheral basophils without a change in serum specific IgE remain unclear; however, this attenuation may be partially due to the up-regulation of inhibitory blocking antibody on the surface of basophils.

ANTIGEN-SPECIFIC IMMUNOTHERAPY AGAINST JAPANESE CEDAR POLLINOSIS

In Japan, Japanese cedar pollinosis is one of the most prevalent types of seasonal allergic rhinitis, with a prevalence estimated to be 26.5%.[2] Two clinical trials described the therapeutic effects of SLIT against Japanese cedar pollinosis.[47,69] In both trials, standardized Japanese cedar pollen extract was used at a monthly cumulative dose of 8,000 JAU, which contains approximately 10 μg of Cry j 1. This dosage is less than that reported in Europe, where a dose of 75,000 SQ-T (15 μg of a major grass allergen Phl p 5) was administered once daily for 18 weeks.[46] Unless the monthly cumulative dose is approximately $1/40^{th}$ of the amount required to be considered a major allergen (10/450 μg as a major allergen) in Japan, SLIT with an active treatment group against Japanese cedar pollinosis is still effective for improving quality of life and significantly ameliorates patients' SMS and symptom score during the pollen season. The up-regulation of the IL4-producing clone size specific to epitopes from Cry j 1 and Cry j 2[70] was reported to be significantly attenuated, and Cry j 1-specific IgG4 production was also significantly induced by active SLIT.[47] Furthermore, IL10-producing Tr1 cells were

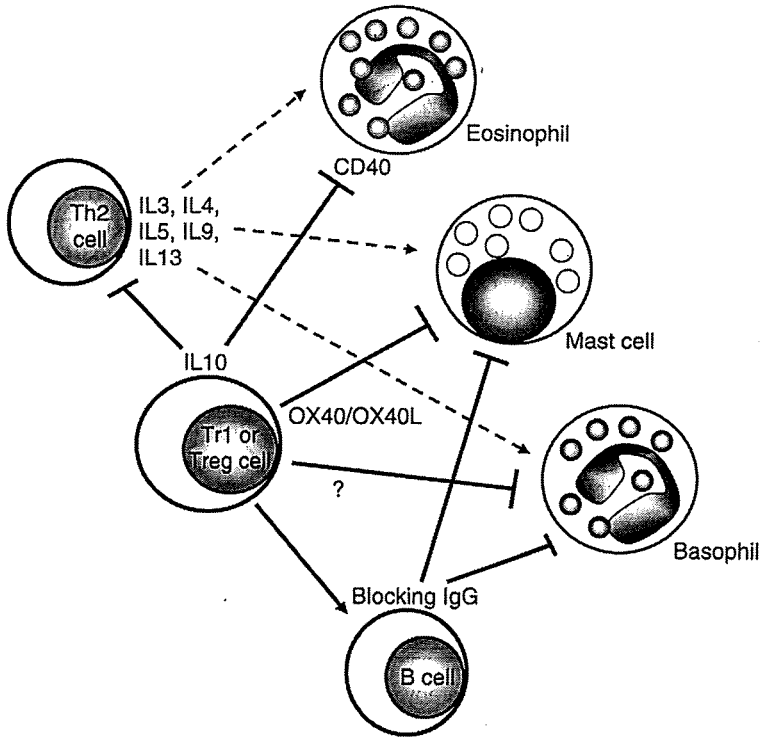

Fig. 3 Proposed roles of regulatory T cells on inflammatory cells in allergen-specific immunotherapy. Regulatory T cells, namely IL10-secreting Tr1 cells or adaptive/induced Treg cells, down-regulate inflammatory cells, directly or indirectly. Regulatory T cells down-regulate the activation of Th2 cells and subsequently Th2-type cytokine secretion. Regulatory T cells suppress the activation of inflammatory cells directly via their surface molecules and by secreting cytokines, and indirectly via the down-regulation of cytokine production in Th2 cells and by the activation of B cells to produce blocking IgG.

reported to be significantly increased in patients treated with SLIT compared with the levels in untreated patients and healthy subjects, and the proliferation of $CD4^+$ leukocytes stimulated with Cry j 1 and Cry j 2 was significantly suppressed by SLIT treatment in an IL10-dependent manner.[71] Supplementation with recombinant or native Cry j-allergens and/or updosing of the extract by bio-engineering may lead to more effective SLIT for treating pollinosis.

Another approach to safer immunotherapy is the use of oral immunotherapy using transgenic rice seed accumulating Cry j 1.[72] The generated transgenic rice plants expressed recombinant, structurally disrupted Cry j 1 peptides but spanned the entire Cry j 1 region as fusion proteins with the major rice storage protein glutenin. These fusion proteins aggregated with cysteine-rich prolamin and were deposited in endoplasmic reticulum-derived protein body I in rice seed. Transgenic rice expressing T cell epitopes from Cry j 1 and Cry j 2 successfully suppressed antigen-specific Th2-mediated IgE responses in a mouse model of allergic rhinitis.[73] Further clinical trials are needed to develop a rice-based edible vaccine as a tool for oral immunotherapy to control allergies.

An immunoregulatory liposome encapsulating the recombinant fusion protein of Cry j 1-Cry j 2 was manufactured as a novel vaccine for Japanese cedar pollinosis without risk of anaphylaxis.[74] The hybrid fusion allergen is expected to provide safer and more effective vaccines for immunotherapy. Vaccines using only T cell epitopes are also safer than native allergens, but there is wide variation among individual T cell epitopes. The fusion protein of major allergens covers all sequential T cell epitopes but is expected to have less IgE-binding capacity because its three-dimensional structure is disrupted in some B cell epitopes. Recombinant hybrid molecules using major allergens of timothy grass pollen induced stronger proliferation of PBMC in timothy-allergic patients than did mixtures of corresponding allergens, but still possess IgE-binding capacity and induce IgG production in sensitized mice.[75] In a mouse model sensitized with native Cry j 1 and Cry j 2, the vaccine that con-

tained Cry j 1-Cry j 2 fusion protein in the immunoregulatory liposome showed suppression of IgE and IgG antibody responses after being challenged with the allergens. Furthermore, oral administration of the vaccine showed efficient suppression of IgE antibody production.[74]

CONCLUSIONS

The standardization of a vaccine enables us to compare the results from varied clinical trials with respect to dose, clinical effects, and changes in biological parameters. Many reports have shown positive clinical therapeutic effects and suppressed effector/inflammatory responses. It is considered that IL10-producing Tr1 and/or adaptive or induced Treg cells may be involved in the suppression of the antigen-specific Th2-responses and local inflammation. However, how immunotherapy induces suppressor cells like Tr1 and Treg cells remains unclear, although the involvement of mucosal dendritic cells has been proposed. High-quality clinical studies are indispensable to clarify the therapeutic biomarkers and the mechanisms of induction of suppressor cells, and the resultant data from the studies may enable us to develop safer and more effective immunotherapy through the modification of the allergens, optimum dose, or administration regimen of a vaccine.

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ORIGINAL ARTICLE

Beneficial Effects of Leukotriene Receptor Antagonists in the Prevention of Cedar Pollinosis in a Community Setting

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Abstract

Background: In recent years, many countries have experienced an increase in the prevalence of allergic rhinitis. No effective approach is currently available to prevent the onset of symptoms in allergic individuals. Pranlukast, a leukotriene receptor antagonist with a good safety and efficacy record for the management of allergic inflammation, may be appropriate for early intervention in the management of pollinosis.
Objective: To investigate the efficacy of pranlukast as an early intervention in the control of cedar pollinosis.
Methods: In a double-blind comparative study, pranlukast (n=102) or placebo (n=91) was administered to cedar pollinosis patients immediately before the start of the dispersion season and continued for 4 weeks. Subsequently, pranlukast was administered to all patients for 2 weeks until the end of the cedar pollen dispersion season (mid-March). All patients were carefully monitored for severity of nasal symptoms, symptom scores, medication scores, symptom-medication scores, and quality of life (QOL).
Results: Compared with placebo, therapy with pranlukast before and during the dispersion of cedar pollen in these patients significantly improved nasal symptoms (paroxysmal sneezing, rhinorrhea, and nasal congestion), symptom scores, and symptom-medication scores. The drug also significantly reduced deterioration of QOL, and improved nasal symptoms and QOL throughout the dispersion period.
Conclusion: Administering pranlukast immediately before the beginning of cedar pollen dispersion is effective in reducing symptoms of allergic rhinitis throughout the dispersion period.

Key words: Allergic rhinitis. Cedar pollinosis. Early intervention. Leukotriene receptor antagonist.

Resumen

Antecedentes: En los últimos años, muchos países han experimentado un aumento en la prevalencia de la rinitis alérgica. No está disponible actualmente ningún abordaje eficaz para prevenir el comienzo de los síntomas en los individuos alérgicos. Pranlukast, un antagonista del receptor de los leucotrienos con buena seguridad y récord de eficacia para el manejo de la inflamación alérgica podría ser apropiado como intervención precoz en el manejo de la polinosis.
Objetivo: Investigar la eficacia del pranlukast como intervención precoz en el control de la polinosis por cedro.
Métodos: En un estudio doble ciego comparative, se administró pranlukast (n=102) o placebo (n=91) a pacientes con polinosis por cedro inmediatamente antes de comenzar la polinización del cedro y continuaron durante 4 semanas. Posteriormente, se administró pranlukast a todos los pacientes durante 2 semanas hasta el final de la época de polinización del cedro. De todos los pacientes se controló cuidadosamente la gravedad de los síntomas nasales, la puntuación de los síntomas, la puntuación de la medicación, puntuación de síntomas-medicación y la calidad de vida (CV).

Resultados: Comparado con el placebo, la terapia con pranlukast antes y durante la polinización del cedro en estos pacientes mejora significativamente los síntomas nasales (estornudos paroxísticos, rinorrea y congestión nasal), la puntuación de síntomas, y la puntuación de síntomas-medicación. El fármaco también redujo significativamente el deterioro de la CV, y mejoró los síntomas nasales y la CV durante todo el período de polinización.
Conclusión: La adminitración de pranlukast inmediatamente antes y en el comienzo de la polinización del cedro es eficaz en la reducción de síntomas de la rinitis alérgica durante toda la época de polinización.

Palabras clave: Rinitis alérgica. Polinosis por cedro. Intervención precoz. Antagonista del receptor de leucotrienos.

Introduction

Recent observations suggest a significant worldwide increase in the prevalence of allergic rhinitis and cedar pollinosis [1]. In Japan, extensive dispersion of cedar pollen has also led to increased incidence of pollinosis, and it is estimated that over 16% of the population are now affected by cedar pollinosis [2,3]. Seasonal dispersion of cedar pollen normally starts in early February in the south Kanto area (Chiba and Tokyo), peaks from late February to early March, and terminates in the middle of March. The status and magnitude of pollen dispersion in Japan is determined by the Ministry of the Environment, and an annual forecast of the initiation date and the probable pollen count is made available to the public in January. Pollen counts in Japan are generally determined using the gravimetric method with a Durham sampler (Nishiseiki Co. Ltd., Funabashi, Japan), whereas in Western countries the volumetric method with a Burkard sampler (Burkard Manufacturing Co. Ltd., Rickmansworth, United Kingdom) is used. Direct comparison of the counts using both methods is difficult, and counts are often influenced by local meteorological conditions and the type of pollen. In a study conducted in the Chiba prefecture in 2005, the amount of pollen in the air counted with a Burkard sampler was about 12 times higher than that detected with a Durham sampler [4].

Rhinitis tends to be severe in patients with cedar pollinosis and is often associated with significant impairment of quality of life (QOL). Early intervention in such patients may be beneficial and greatly influence the severity and outcome of symptoms during the peak pollen season. Such approaches are recommended in the Clinical Guidelines for the Management of Allergic Rhinitis in Japan [3].

Leukotriene receptor antagonists have proven to be effective in the treatment of nasal congestion [5,6]. These drugs also reduce allergic inflammation by inhibiting eosinophil secretion in the airway [7-9]. Recent studies have shown that leukotriene receptor antagonists are as effective as antihistamines for the treatment of allergic rhinitis, without the sedative side effects frequently observed with antihistamines. It has been suggested that leukotriene receptor antagonists are less effective than nasal corticosteroids [10-12], which effectively reduce sneezing, rhinorrhea, and nasal obstruction. However, adherence is sometimes poor in Japan, because patients prefer oral medication. Leukotriene receptor antagonists are suitable for early intervention because of their anti-allergic inflammatory effects and safety. In Japan, pranlukast is the only leukotriene receptor antagonist currently recommended for use in the treatment of allergic rhinitis [13]. Therefore, we conducted a double-blind placebo-controlled comparative study of the efficacy of early intervention with pranlukast in patients with cedar pollinosis.

Methods

Participants

The study population consisted of patients with cedar pollinosis who lived in the south Kanto area from February to March 2007. Age ranged from 20 to 65 years and participants met the following inclusion criteria: a positive allergen-specific skin test (wheal diameter ≥10 mm) to a standardized cedar pollen extract (Torii Pharmaceutical Co. Ltd., Tokyo, Japan) and a serum cedar pollen–specific immunoglobulin (Ig) E levels score of ≥2 by the CAP radioallergosorbent test (CAP-RAST; SRL, Tokyo, Japan). The exclusion criteria were as follows: complications including nasal polyps and chronic sinusitis; continuous use of antihistamines, antiallergic drugs, or nasal corticosteroid drops; immunotherapy; pregnancy, women of childbearing potential, and nursing mothers; and other patients deemed inappropriate for the study by the investigator. Informed written consent was obtained from participants after they received a detailed explanation of the study and of the possible side effects. The study adhered to the Ethical Guidelines for Clinical Studies and Good Clinical Practice (GCP), and the Declaration of Helsinki (revised in 2000).

Study Protocol

Specially designed capsules containing 112.5 mg of pranlukast hydrate per capsule or placebo capsules were used. Participants were selected in late January based on a skin test for cedar pollen to confirm the presence of cedar pollinosis. The study was initiated before the beginning of cedar pollen dispersion, which was forecast to be in early February, and administration of pranlukast or placebo was started according to the study schedule outlined in Figure 1. Two capsules were administered bid (after breakfast and dinner) for 4 weeks (double-blind comparative study period). Subsequently, all patients took pranlukast for an additional 2 weeks (pranlukast administration period). A total of 193 subjects completed the study (Table). The pranlukast group included 102 patients (57 males and 45 females; mean age, 36.5 years). Of these, about 28.4% had perennial allergic rhinitis. The placebo group included 91 patients (49 males and 42 females; mean age, 36.1

Table. Baseline Characteristics of the Patients

	Pranlukast Group n=102	Placebo Group n=91
Mean (SD) age, y	36.5 (11.6)	36.1 (12.1)
Female sex (%)	45 (44.1)	42 (46.2)
Mean duration of cedar pollinosis, y	9.7	9.4
Type of allergic rhinitis		
Cedar pollinosis with perennial symptoms	29	25
Cedar pollinosis only	73	66
Additional allergy history		
History of asthma symptoms	2	5
Current asthma symptoms	0	0
History of allergic conjunctivitis	102	91
Cedar pollen RAST score, mean (SD)	3.9 (0.9)	4.0 (1.2)
Cedar pollen skin test score, mean (SD)	2.0 (0.8)	1.9 (0.7)
Peak of daily total nasal symptoms score in the last pollen season	5.2	5.0

Abbreviation: RAST, radioallergosorbent test.

years; perennial allergic rhinitis in 27.5%). The symptoms of perennial allergic rhinitis were mild, and none of the enrolled patients required treatment. There were no significant differences in sex, age, age at onset, duration of disease, or frequency of complications between the 2 groups.

For assignment of participants to the 2 study groups, limited randomization was performed in subgroups of 6 patients with no differences in sex or age, and 3 participants in each subgroup were assigned to the pranlukast group or to the placebo group.

Other antihistaminic drugs were administered concomitantly as follows: in the last 2 weeks of the double-blind comparative period, an oral antihistamine (loratadine), nasal vasoconstriction drops (tetrahydrozoline hydrochloride), or chemical mediator release–suppressing eye drops (sodium cromoglycate) was administered for eye and nasal symptoms based on the patient's self-judgment of symptom severity. In the pranlukast administration period, the same drugs and a nasal corticosteroid spray (fluticasone propionate) were permitted depending on symptom severity, as described in the Clinical Guidelines for the Management of Allergic Rhinitis in Japan [3]. Use was also based on patient self-judgment.

Pollen Counts

Cedar pollen dispersion was measured using a gravimetric method with a Durham sampler.

Symptom Scoring

Each participant completed the Japanese rhinoconjunctivitis QOL questionnaire (JRQLQ) survey form 4 times every 2 weeks [14-16]. Participants also kept a nasal allergy diary record. Symptoms, medication, and symptom-medication scores were based on daily nasal allergy diary records using the following criteria. For nasal symptoms, the severity of paroxysmal sneezing (number of sneezes per day), runny nose (number of times participants blew their nose per day), nasal congestion, and the degree of interference with daily life were evaluated on a 5-point scale (0-4) based on the Clinical Guidelines for the Management of Allergic Rhinitis in Japan [3], as follows: 0, no sensation; 1, mild; 2, moderate; 3, severe; and 4, extremely severe. Episodes of sneezing and nose blowing (rhinorrhea) per day were rated from 0 to 4 as follows: 0, none; 1, 1-5 episodes; 2, 6-10 episodes; 3, 11-20 episodes; and 4, >21 episodes. Eye itching and watering were evaluated using a 5-point scale. Eye itching was rated as follows: 0, none; 1, itching but not necessary to scratch; 2, scratching occasionally; 3, scratching frequently; and 4, more frequently. Eye watering was rated as follows: 0, none; 1, not necessary to wipe; 2, wiping sometimes; 3, wiping frequently; and 4, more frequently. The medication score was based on the required amounts of the 4 concomitant drugs according to Japanese practice guidelines. The following scores were applied each day of the pollen season: 0, if no intake of concomitant medication; 1, one oral antihistamine, nasal vasoconstriction drops, or chemical mediator release–suppressing eye drops; 2, nasal corticosteroid spray. For each patient, the medication scores and the symptom-medication scores (by adding the symptom scores to the medication scores) were calculated. The QOL scores were also evaluated on a 5-point scale (0-4). The symptom-medication score was used as the primary outcome parameter and other criteria were used as secondary outcome parameters.

Statistics

Data were analyzed using 2-tailed tests at a significance level of 5%, the chi-square test, Fisher exact test, 2-sample *t* test, and

paired *t* test. The analysis was performed using SAS v. 8.02 (Cary, North Carolina, USA).

Results

Pollen Counts

Cedar pollen started to disperse in the study region on February 6th (day 3 of drug administration) and the first week included 2 days before and 5 days after pollen dispersion began. Pollen counts of >50/cm²/d occurred almost daily for about 3 weeks from February 19th (week 3 of drug administration) to March 9th. The pollen count then decreased to <50/cm²/d and was almost undetectable on March 20th (Figure 1).

Nasal Symptom Score

The nasal symptom score in the pranlukast group increased by less than 0.48 (<0.5), and was significantly lower (Figure 2). The sneezing scores in the placebo group increased by more than 0.63 (≥0.5) between week 3 and week 5, compared to the scores observed initially in week 1; however, the severity of sneezing in the pranlukast group was significantly milder than in the placebo group during weeks 3, 4, and 5. Compared to week 1, the rhinorrhea score increased by ≥0.5 from weeks 3 to 6 in the placebo group and by ≥1 in week 4, whereas the increase was lower (<0.5) in the pranlukast group. The severity of rhinorrhea in the pranlukast group was significantly milder than that observed in the placebo group in week 4. The nasal congestion score increased by ≥0.5 in weeks 4 and 5 in the placebo group, compared to week 1, and exceeded 1, whereas the score increased by <0.5 throughout the study in the pranlukast group, although it did not exceed 1. No significant increase was observed in the score at week 4 in the pranlukast group compared to week 1. The severity of nasal congestion in the pranlukast group was significantly milder than in the placebo group in weeks 4 and 5, as shown in Figure 2.

Symptom Scores, Medication Scores, and Symptom-Medication Scores

The symptom score increased by ≥0.5 from week 2 to week 6 in the placebo group and by ≥1 in week 4, compared to week 1, whereas the increase was <0.5 in the pranlukast group. The score in the pranlukast group was significantly lower than that in the placebo group in weeks 4 and 5 (Figures 3 and 4). The medication scores showed that the oral antihistamine was used significantly more often in the placebo group in weeks 3 and 4 and that the nasal vasoconstrictor was used significantly more often in the placebo group in week 4. The symptom-medication score increased by ≥2 in weeks 4 and 5 in the placebo group, compared to week 1, whereas the increase was <2 in the pranlukast group. In week 4 the symptom-medication score in the pranlukast group was significantly lower than in the placebo group. Regarding eye symptoms, there was no significant difference in eye itching or watering between the placebo and pranlukast groups (data not shown). The score for the degree of interference with daily life increased by ≥0.5 from week 3 to week 5 in the placebo group, compared to week 1, whereas the increase was <0.5 in the pranlukast group. The score in the pranlukast group was significantly lower than in the placebo group in week 4 (Figure 4).

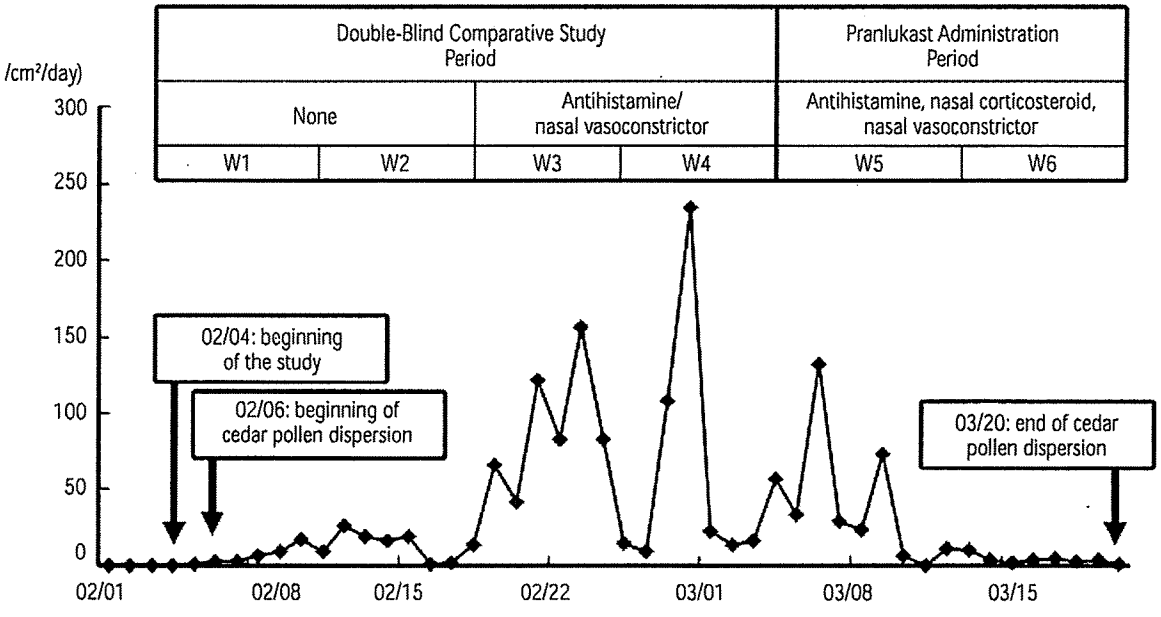

Figure 1. The study schedule and the 2007 cedar pollen counts.

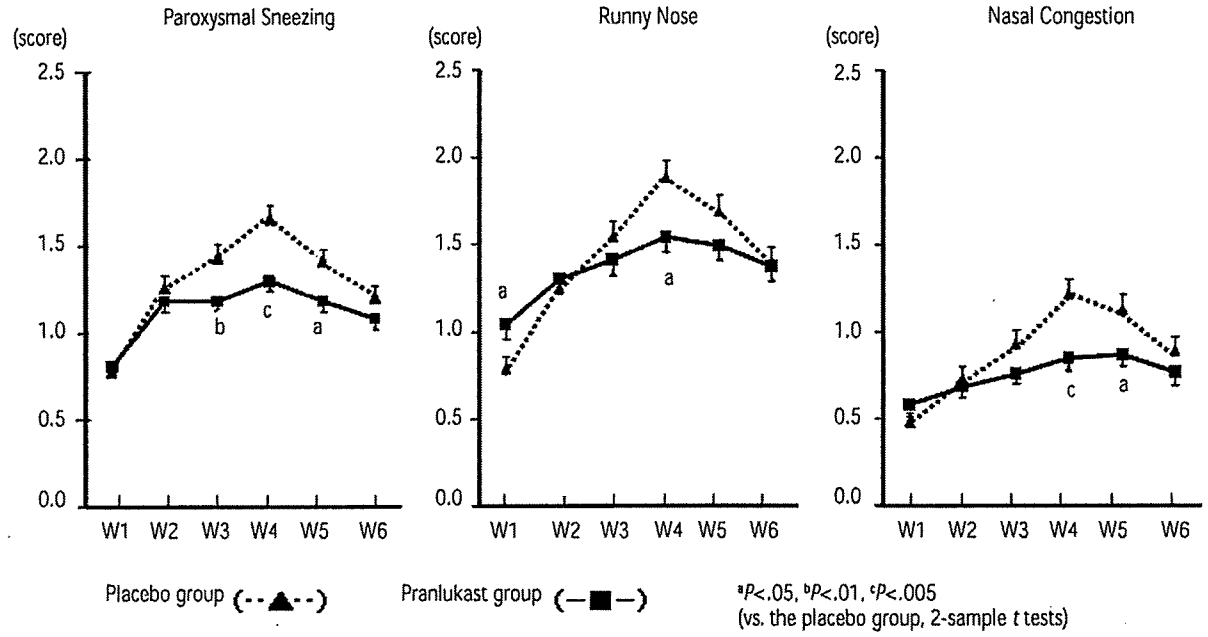

Figure 2. Effects on nasal symptoms.

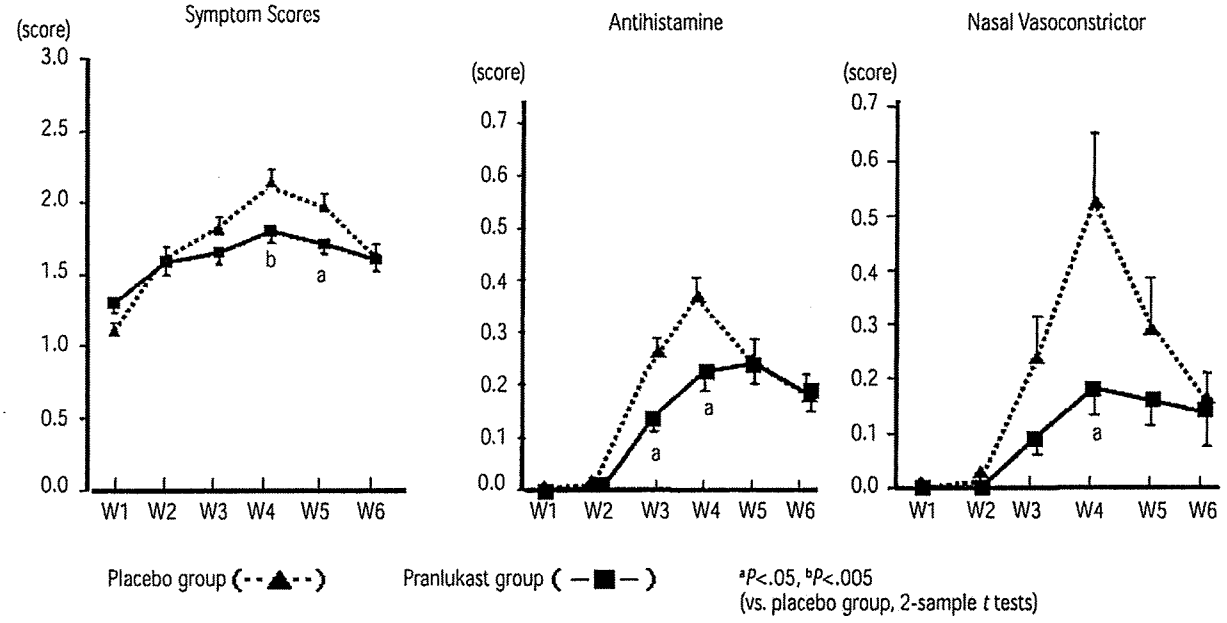

Figure 3. Symptom scores and medication scores.

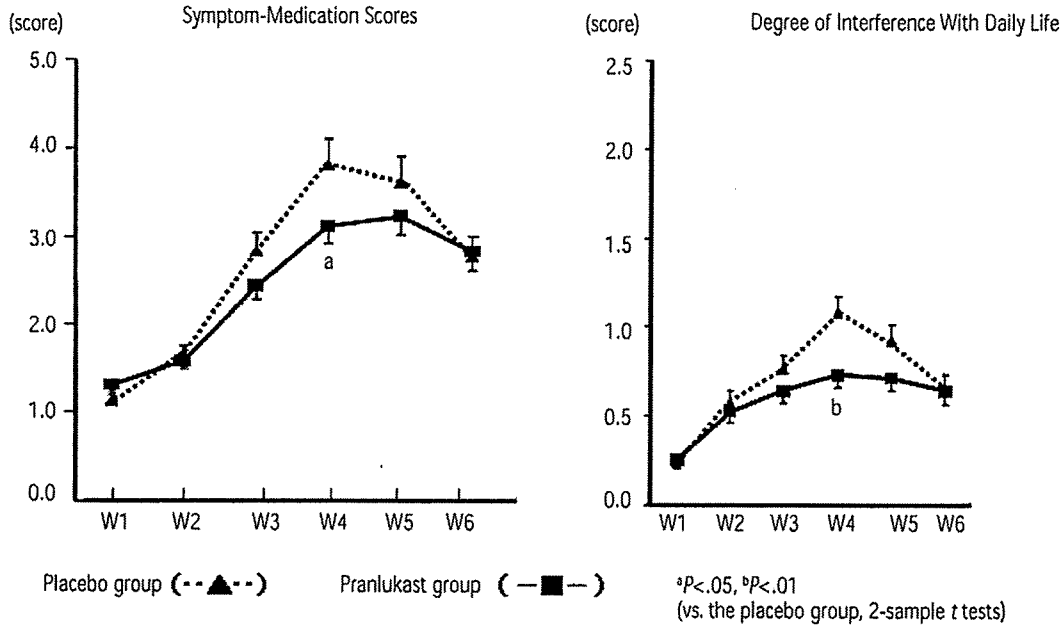

Figure 4. Symptom-medication scores and the degree of interference with daily life.

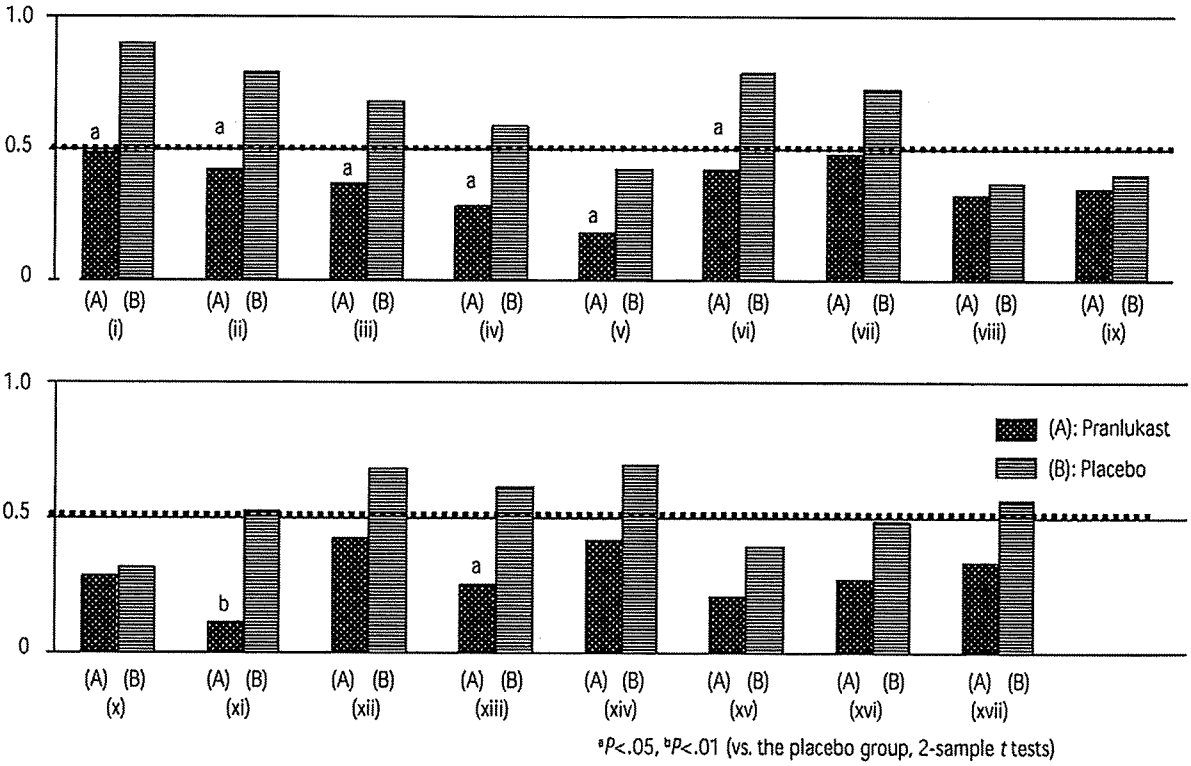

Figure 5. Change in QOL scores at 4 weeks from baseline (at 0 weeks).

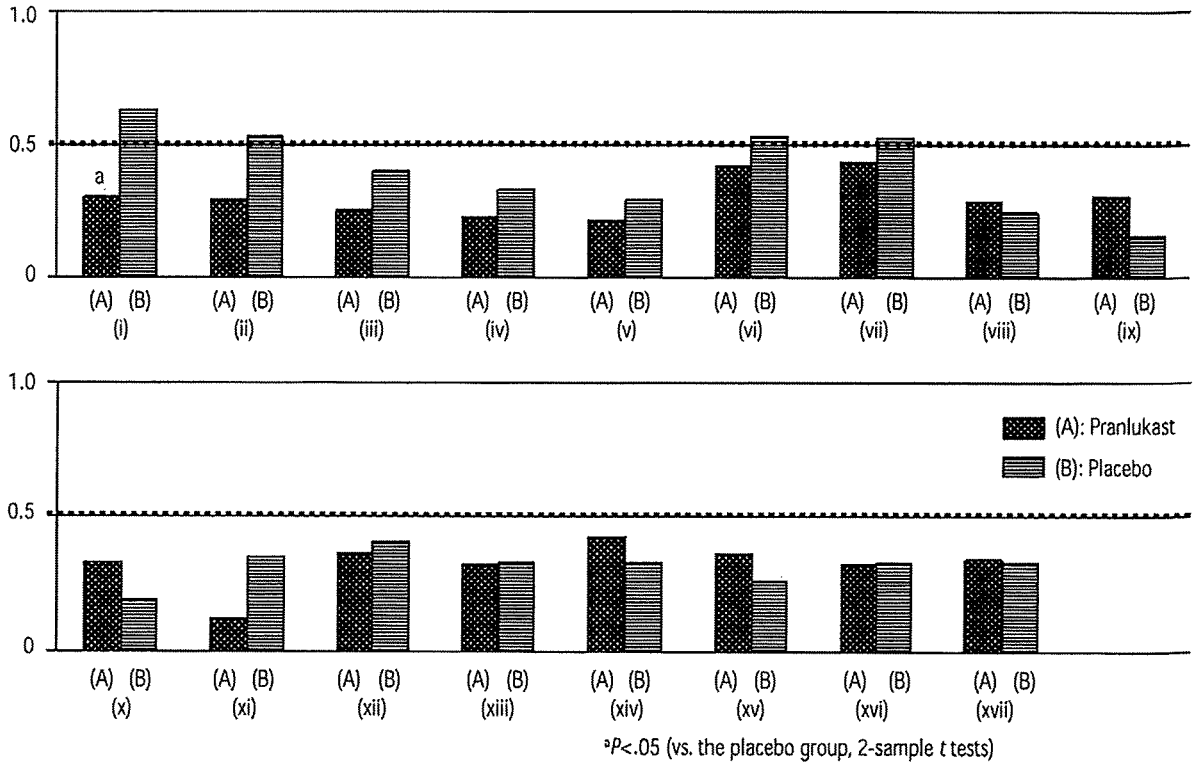

Figure 6. Change in QOL scores at 6 weeks from baseline (at 0 weeks).

Quality of Life

QOL scores were determined using the JRQLQ questionnaire. The total QOL score after 4 weeks of drug administration was significantly lower in the pranlukast group. In the placebo group, the QOL scores for 11 out of a total of 17 items on the JRQLQ increased by ≥0.5 at week 4 compared to week 0 (Figure 5). The QOL scores for all 17 items improved at week 6 (the end of the cedar pollen dispersion period) and did not increase by ≥0.5 at week 6 compared to week 0, before the pollen season in the pranlukast group (Figure 6). However, in 4 items (reduced productivity at work/home/school; poor concentration; limitation to participating in outdoor activities; and limitation to leaving one's house) in the placebo group, the scores were still ≥0.5; therefore, the improvement was limited. In particular, there was no significant increase in impaired sleeping scores following initiation of pranlukast, and sleep was not disturbed in the pranlukast group throughout the study.

Side Effects

Pranlukast was safe and no significant side effects were noted. However, in 2 cases, mild diarrhea was observed on day 16 of administration. In 1 case, the diarrhea stopped when administration was interrupted for 2 days. No further problems occurred when administration was restarted. In the other case, abdominal pains occurred on day 16 of drug administration. However, administration of the drug was continued and the symptom disappeared 2 days later.

Discussion

Recent randomized controlled trials comparing leukotriene receptor antagonists with antihistamines or nasal corticosteroids in patients with pollinosis have shown that the use of leukotriene receptor antagonists significantly improved the nasal symptoms score. The effectiveness of such therapy was determined in part by pollen levels in the community [11,17]. Earlier studies have shown that leukotriene receptor antagonists are as effective as oral antihistamines alone, but significantly inferior to nasal corticosteroids [12,18-20]. The results of the present study were similar.

Our results show only limited improvement in nasal symptoms and impaired QOL scores in patients treated with placebo for the first 4 weeks of pollen dispersion, even after combined administration of pranlukast with nasal corticosteroids and antihistamines. In addition to the expected symptom control during the initial period (when the pollen count was still low and associated with mild symptoms and

moderate hyperreactivity of the nasal mucosa), the effects of early intervention with pranlukast persisted during the whole season, including during peak pollen dispersion.

The lasting effects of pranlukast during peak pollen dispersion reported here may be due to its anti-inflammatory properties. Allergic inflammation in the airway is induced by leukotriene, and this leads to eosinophilic infiltration and degranulation during active inflammation, stimulation of type 2 helper T-cell production, and proliferation and hyperplasia of goblet cells and mucus glands, resulting in hypersecretion [7-9]. Cysteinyl leukotriene receptor antagonists such as pranlukast have potent inhibitory effects on the inflammatory cascade [21-23].

The antihistamine used in this study, loratadine, acts quickly with a very low sedative effect, and was administered on demand; however, exacerbation was still observed in the placebo group. It has been shown that treatment with antihistamines only during peak cedar pollen dispersion results in a poor outcome [3]. Various anti-inflammatory effects of antihistamines have been shown in vitro and in animal studies, but have yet to be clarified clinically beyond H_1-receptor antagonism [24]. Similarly, lasting effects of an antihistamine were not obtained in the present study.

Nasal corticosteroids are generally very effective in preventing or reducing rhinorrhea and sneezing, as well as in reducing the severity of nasal obstruction. Thus, intranasal corticosteroids provide significant resolution of these symptoms and are advantageous for early intervention. However, adherence to intranasal corticosteroids is sometimes poor [25], since many patients prefer to use oral medication. A comparative study with leukotriene receptor antagonists and corticosteroids in patients with allergic rhinitis may further clarify these important issues. Allergen-specific immunotherapy has been evaluated and shown to be an effective approach to modifying the course of allergic rhinitis [26,27]. The combination of early intervention with drugs and specific immunotherapy may be beneficial for the management of pollinosis.

These observations show that administration of pranlukast in cedar pollinosis patients initiated just before and continued during the entire pollen dispersion season in high-risk communities is effective in improving clinical symptoms and quality of life. The efficacy of early intervention with pranlukast must be compared with that of other drugs, while taking into account the cost-benefit ratio.

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分担研究報告書

スギ花粉飛散数とスギ花粉症患者のQOLと睡眠障害

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研究要旨
スギ花粉症は、通年性アレルギー性鼻炎とは異なり、特定の時期に大量の花粉が飛散することによって非常に強い局所症状のみならず全身症状を引き起こす。近年スギ花粉症の患者数は急増し、国民の約20%を超えると報告されており、現代社会においてこの疾患の治療は重要性を増している[1]。スギ花粉症に罹患する患者層は若年層が多く、治療はくしゃみ、鼻汁、鼻閉などの鼻、眼の症状だけではなく、倦怠、集中力の低下など日中のパフォーマンスが労働や就学に及ぼす影響があるためにQOLを考慮した治療が求められている。しかし、スギ花粉の飛散数とスギ花粉症患者のQOLと睡眠障害の関連については十分な検討がなされていない。そこで今回、われわれはスギ花粉飛散数とスギ花粉症患者のQOLおよび睡眠障害について検討した。その結果、スギ花粉症患者ではスギ花粉飛散数の増加に連動して、QOLが低下するだけでなく、睡眠障害のスコアが有意に上昇しており、睡眠が著しく障害されている可能性が示唆された。特に、睡眠の質と入眠時間が障害されていた。スギ花粉症患者の治療に対する満足度は高くなく、患者の満足度を高めるためには眼鼻の症状を抑制するだけなく、夜間睡眠や日常生活のQOLを低下させないためにリアルタイムモニターを十二分に利用して、よりきめ細かなセルフケアと治療に応用できると考えられた。

A. 研究目的：

スギ花粉症に罹患する患者層は若年層が多く、治療はくしゃみ、鼻汁、鼻閉などの鼻、眼の症状だけではなく、倦怠、集中力の低下など日中のパフォーマンスが労働や就学に及ぼす影響があるためにQOLを考慮した治療が求められている。しかし、スギ花粉の飛散数とスギ花粉症患者のQOLと睡眠障害の関連については十分な検討がなされていない。そこで今回、われわれはスギ花粉飛散数とスギ花粉症患者のQOLおよび睡眠障害について検討した。

B. 研究方法：

対象：2009年2月から4月のスギ花粉飛散前と飛散中に受診した15歳以上のスギ花粉症患者で本試験の参加に同意を得られた84例を対象とした。性別は男性30例、女性52例、年齢は21歳から83歳であった。スギ花粉症の診断は、問診，鼻内所見、鼻汁中好酸球検査、皮膚反応、血中特異的ＩｇＥ検査（CAP－RAST）によった。これらのアレルギー検査は奥田の判定基準により判定し，CAP－RASTはスコア1以上を陽性とした。また、健常人２０例をコントロールとし患者群と同様に花粉飛散初期とピーク時に後述する質問票を用いて鼻症状およびQOLについて検討を行った。

スギ花粉飛散数の測定：スギ花粉飛散数は、リアルタイムモニター(KH300)およびダーラム型花粉捕集器を用い，山形県山形市の山形大学医学部屋上にて測定した。

観察項目および評価方法

症状スコア：アレルギー疾患治療ガイドラインの重症度分類に基づく鼻閉とくしゃみ発作または鼻汁の程度の分類に最重症として++++を加え、日本アレルギー学会アレルギー性鼻炎委員会が作成したsymptom scoreの基準によって重症度の点数付けを行った。

QOLおよび睡眠障害の検討：奥田らの作成したJRQLQ(No1およびNo2)調査票を用いた。JRQLQ(No1)調査票は、鼻症状4項目(鼻汁、くしゃみ、鼻閉、鼻のかゆみ)、眼症状2項目（かゆみ、流涙)、QOLは6因子17項目、すなわち①日常生活（5項目)、②戸外活動（2項目)、③社会活動（3項目)、④身体（2項目)、⑤精神生活（4項目)、⑥睡眠（1項目）から構成されている。また、鼻・眼以外の症状の評価のためにJRQLQ(No2)調査票を用いて検討を行った。JRQLQ(No2)調査票は、鼻症状4項目(鼻汁、くしゃみ、鼻閉、鼻のかゆみ)、眼症状2項目（かゆみ、流涙)、QOLは6因子15項目、すなわち①気道（4項目)、②のど（2項目)、③鼻閉（2項目)、④口耳皮膚（4項目)、⑤全身（2項目)、⑥睡眠（1項目）から構成されている。JRQLQの評価はそれぞれの重症度を0から4の5段階でスコア化し各々の障害の程度を分析、さらに総合スコアを求めて評価を行った。また、睡眠

障害についてはピッツバーグ睡眠問診票（PSQI）を用いた[6),7)]。PSQIは主観的な睡眠の質を評価分析する自記式質問票で、①睡眠の質、②入眠時間、③睡眠時間、④睡眠効率、⑤睡眠困難、⑥眠剤の使用、⑦日中の覚醒困難の7つの項目から構成されている。評価方法であるが、睡眠時間以外は重症度を0から3の4段階で評価し、さらに通常総合スコアを用いて睡眠障害の程度について評価した。

統計学的解析：初期治療群および発症後投与群の症状改善度，全般改善度などの比較はWilcoxonの順位和検定およびpaired t検定を用いた。検定における有意水準は両側危険率5%以下とした。

C. 結果：

2009年の山形市のスギ花粉の飛散状況であるが、飛散開始日は2月27日、総花粉飛散数は7638個／m^3であった。3月下旬と4月上旬に2つの花粉飛散ピークを認める例年にない稀なパターンであった。JRQLQの症状と各QOLの項目を合わせた23項目のスコアは、スギ花粉飛散初期には健常人とスギ花粉症患者で有意な差は認められなかったが、スギ花粉症患者ではスギ花粉飛散数の増加に伴って上昇し、花粉飛数ピーク時には健常人と比較して有意な差を認めた。健常人とスギ花粉症患者のJRQLQ(No1)の各サブスケール別スコアを比較検討した。花粉飛散初期には、日常生活、野外活動、社会生活、睡眠、身体、精神生活のいずれのサブスケールにおいても健常人とスギ花粉症患者との間で有意な差は認められなかった。しかし、花粉飛散ピーク時期では、日常生活、野外活動、社会生活、睡眠、身体、精神生活のいずれのサブスケールにおいてもスギ花粉症患者で有意なスコアの上昇が認められた。スギ花粉飛散ピーク時のJRQLQ(No1)の全項目について、健常人とスギ花粉症患者のスコアを比較検討すると、水っぱな、くしゃみ、鼻づまり、鼻のかゆみ、目のかゆみ、涙目のすべての症状のスコアがスギ花粉症患者で上昇し、日常生活や野外活動だけでなく、社会生活や睡眠などほぼすべての項目でスコアの有意な場が認められQOLが大きく低下していることが確認された。次に、眼鼻以外の症状を主に検討するJRQLQ(No2)の各サブスケール別スコアを比較検討した。花粉飛散初期には、気道、のど、鼻閉、口耳皮膚、全身、いびきのいずれのサブスケールにおいても健常人とスギ花粉症患者との間で有意な差は認められなかった。しかし、花粉飛散ピーク時期では、気道、のど、鼻閉、口耳皮膚、いびきのサブスケールにおいてスギ花粉症患者で有意なスコアの上昇が認められた。スギ花粉飛散ピーク時のJRQLQ(No2)の全項目について、健常人とスギ花粉症患者のスコアを比較検討すると、眼鼻の症状が増悪するだけでなく、気道、のど、口耳皮膚、全身に影響が及ぶことが確認された。

健常人とスギ花粉症患者の睡眠障害についてPSQIを用いて比較検討した。花粉飛散初期には、健常人とスギ花粉症患者で明らかな差は認められなかった。しかし、花粉飛散ピーク時期では、健常人は睡眠スコアの有意な上昇は認められなかったのに対して、スギ花粉症患者では有意な上昇が認められ、睡眠が障害されている可能性が示唆された。スギ花粉飛散初期とピーク時でスギ花粉症患者のPSQIのサブスケールを検討した結果、睡眠の質、入眠時間、睡眠困難および日中覚醒困難のスコアの有意な上昇が認められた。

D. 考察：

スギ花粉症は発症の低年齢化と自然寛解率が低いため、その患者数が非常に増加している。いわゆる働き盛りの世代に患者が多く日常生活のQOLが著しく低下すると報告されている。我々はスギ花粉飛散数とスギ花粉症患者の症状、QOLおよび睡眠障害について健常人と比較検討した。その結果、スギ花粉症患者ではスギ花粉飛散数の増加に連動して、QOLが低下することが確認された。また、アレルギー性鼻炎の症状が労働や学業を障害し、睡眠障害の原因となる可能性についても報告されている。スギ花粉症に罹患することによって労働生産性にも影響が生じることも懸念されている。今回の検討でも、スギ花粉症患者では健常人と比較して、スギ花粉飛散数に伴って睡眠障害のスコアが有意に上昇しており、睡眠が著しく障害されている可能性が示唆された。特に、睡眠の質と入眠時間が障害されていたが、アレルギー性鼻炎の睡眠障害に関する検討では、鼻症状の悪化が明らかに睡眠を障害し、特に鼻閉が大きく関与していると報告されている。本年度はスギ花粉飛散数も多い大量飛散年における検討であるため、症状は充全型の割合も多く鼻閉がQOLの低下および睡眠障害の主要な原因となっていると考えられる。今回の検討でスギ花粉飛散数の増加に伴ってスギ花粉症患者の鼻および眼の症状が増悪し、QOLが低下するだけでなく、睡眠も障害される実態があることが示唆された。スギ花粉症患者の治療に対する満足度は高くなく、患者の満足度を高めるためには眼鼻の症状を抑制するだけなく、夜間睡眠や日常生活のQOLを低下させない工夫が必要であると考えられる。今回の結果を踏まえて、スギ花粉症患者の治療にあたっては、重症度に応じた薬剤選択を行うと同時にQOLと睡眠障害も念頭に置いた治療戦略を考える必要があると考えられた。

E. 結論：

スギ花粉飛症の治療では、飛散散数の増加に伴って鼻眼の症状の増悪と QOL の低下、さらに睡眠障害の増悪があることを念頭に重症度に応じた薬剤選択を行う治療戦略を考える必要があると考えられた

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G. 知的所有権の取得状況

1. 特許取得 なし
2. 実用新案登録 なし
3. その他

アレルギー 58(12),
1619-1628, 2009(平21)

原　著

山形市におけるアレルギー性鼻炎患者の花粉抗原陽性率の検討

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【背景・目的】花粉症の原因抗原としてはスギ・イネ科が有名であるが，その他の花粉症も注目されている．今回我々は当科を受診したアレルギー性鼻炎患者の花粉抗原陽性率について調査・検討したので報告する．
【対象・方法】対象はアレルギー性鼻炎症例の男性90例，女性61例．ハウスダスト・ダニ・スギ・カモガヤ・チモシー・ブタクサ・ヨモギ・カナムグラ・アルテルナリア・カンジタ・アスペルギルスに加え，シラカンバ・クルミ・ヒメスイバ・コナラ・ヤナギのエキスを用いてスクラッチテストを施行した．
【結果】スギ花粉陽性率（45%）よりもカモガヤ花粉陽性率（51%）のほうが高く，シラカンバ・クルミ・ヒメスイバ・コナラ・ヤナギ花粉はそれぞれ13%，8%，9%，11%，10%とスギ・イネ科花粉に比べると低いが真菌より高い陽性率であった．
【考察】イネ科花粉や，イネ科花粉と飛散時期の重なるシラカンバ・クルミ・ヒメスイバ・コナラ・ヤナギ花粉は陽性率が高く重要な抗原と考えられた．重複陽性率も高い傾向があり，抗原間の交差反応性の検索も必要と考えられた．

Key words: allergic rhinitis —— overlapping positive ratio —— positive ratio of pollen antigen —— scratch test

1. 緒　言

アレルギー性鼻炎は患者数が多く，その症状も強くQOLも低下することなどにより近年大きな社会的注目を集めている．原因抗原の全国平均陽性率はハウスダスト・ダニが53.0%，スギ42.0%，イネ科16.4%と報告され，主要な抗原であると考えられる[1]．

しかし，スギ，イネ科以外に花粉症の原因となる花粉には多くのものがあり，季節や地域によっては様々な花粉が飛散している．本邦でI型アレルギー疾患の抗原として，花粉抗原が約60種，職業性抗原が約80種，ハウスダスト・ダニ・真菌抗原・ペット抗原など合わせて20種以上が報告されている[1]．

地域に根ざしたアレルギー性鼻炎の診療を考えるとき，その地域特性を知っておく必要がある．山形県は首都圏と異なりスギ花粉症患者よりもイネ科花粉症患者のほうが多い傾向があり[2]，その他様々な花粉が季節ごとに飛散している．山形県では山形県衛生研究所のホームページにて各種花粉飛散予想，各種花粉飛散開花情報，スギ花粉の

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