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Guiding principles of subcutaneous immunotherapy for allergic rhinitis in Japan

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ABSTRACT

Objective: In anticipation of the development of guidelines for antigen-specific subcutaneous immunotherapy (SCIT), we present recommendations that can serve as guiding principles based on a review of the scientific literature.
Methods: Clinical questions (CQs) concerning SCIT were prepared. Literature searches for publications between January 1990 and February 2011 were performed in PubMed, the Cochrane Library, and Japana Centra Revuo Medicina Web version 4. Qualified studies were analyzed and the results were evaluated, consolidated, and codified.
Results: We present answers for 13 CQs on the indications, methods, effectiveness and mechanisms of SCIT, with evidence-based recommendations.
Conclusion: The guiding principles are intended to be applied to children (≤15 years old) and adults (≥16 years old) with allergic rhinitis (AR). These principles can be used by otorhinolaryngologists for diagnosis of AR, evaluation of severity and rhinoscopic findings, performance of antigen challenge tests, and management of systemic anaphylactic reactions associated with SCIT.

1. Introduction

The incidence of allergic rhinitis (AR) is increasing in Japan. Spontaneous resolution of AR is relatively infrequent, except in elderly individuals, and its symptoms have marked adverse effects on quality of life (QOL). Evidence-based guidelines for use of antigen-specific subcutaneous immunotherapy (SCIT) for treatment of AR have been prepared [1,2]. Antigen extracts entered the Japanese market in 1963, and subsequently SCIT for AR was initiated. The present guiding principles were prepared based on research by the Japanese Rhinologic Society (JRS) [3] to provide accurate knowledge of immunotherapy for AR and contribute to development of this therapy.

The JRS is an independent academic organization that receives no sponsorship or funding from specific organizations or businesses. The JRS has not obtained funds for preparation of the present guidelines from any businesses, including those representing the pharmaceutical industry.

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2. Criteria for determining recommendation grades

Clinical questions (CQs) were prepared concerning the methods, effects, side effects, and mechanisms of SCIT. A comprehensive literature search was performed for studies published between January 1990 and February 2011. The databases used were PubMed, the Cochrane Library, and Japana Centra Revuo Medicina Web version 4. The search was executed primarily between October 2010 and July 2011, and used the primary index words "allergic rhinitis", "pollinosis", and "SCIT". Subsequently, two members were assigned to the task of collecting scientific evidence concerning each CQ from the selected papers. After a consensus was reached by the preparation committee, the results were evaluated, consolidated, and codified.

Levels of evidence I–IV were determined as follows: Ia, meta-analysis (with homogeneity) of randomized controlled trials; Ib, at least 1 randomized controlled trial; IIa, at least 1 well-designed, controlled study, but without randomization; IIb, at least 1 well-designed, quasi-experimental study; III, at least 1 well-designed, non-experimental descriptive study (e.g., comparative studies, correlation studies, case studies); IV, expert committee reports, opinions, and/or the experiences of respected authorities. The recommendation levels of the Medical Information Distribution Service (MINDS) were adopted as follows: A, strong scientific evidence, and implementation of the treatment is strongly recommended; B, scientific evidence, and implementation of the treatment is recommended; C1: no scientific evidence, but implementation of the treatment is recommended; C2: no scientific evidence, and implementation of the treatment is not recommended; D: evidence suggesting ineffectiveness or harm, and implementation of the treatment is not recommended.

These recommendation levels are not absolute and diagnostic or therapeutic decisions should be made based on the patient's condition and wishes, and the available resources of each medical facility. However, the guiding principles presented here can be applied tentatively in clinical settings. After evaluation of the results of this process and reviews by external experts, the principles will be developed into guidelines for diagnosis and treatment. The principles and handling of conflicts of interest will be reevaluated on the basis of the results of the preparation of guidelines by the JRS.

3. Indication and methods of SCIT

AR is defined as a type I allergic disorder of the nasal mucosa with 3 major manifestations: repetitive sneezing, watery rhinorrhea, and nasal obstruction [4]. The specific antigen should be determined prior to SCIT.

3.1. CQ01: What administration methods are used for SCIT and what are their advantages and disadvantages?

Administration methods used for SCIT for AR include the 50% incremental method, 100–200% incremental method, cluster method, and rush method. All can be performed until a maintenance dose is reached.

(1) The 50% incremental method is the commonly used method, in which the antigen concentration is increased 10 times from the threshold of the intradermal reaction using 7 injections (0.05, 0.07, 0.1, 0.15, 0.2, 0.3, and 0.5 mL) at a rate of 2 injections/week. This method has a high level of safety, but it requires frequent hospital visits over a long period until the maintenance dose is reached.
(2) The 100–200% incremental method is a rapid method in which the antigen concentration is increased 10 times from the threshold of the intradermal reaction using 3 injections (0.1, 0.3, and 0.5 mL) at a rate of 1 injection/week. The therapeutic effect of the 100–200% incremental method is comparable to that of the conventional 50% incremental method. No adverse reactions were noted while using the 100–200% incremental method with house-dust antigen extract [5] (Level IIb).
(3) In the cluster method, 3 injections are performed in one day at 1 h intervals and a maintenance dose is reached by repeating the treatment once weekly for approximately 5 weeks. The maintenance dose can be reached in a short period with a high level of safety. Moderate adverse reactions have been observed with the cluster method, but their frequency was lower than that with a placebo and the safety of the method was high [6] (Level Ib).
(4) In the rush method, the maintenance dose is reached in 3 days by repeating 5–6 injections every 2 h in one day. The rush method performed in hospitalization (3 days and 2 nights) is likely to produce effects in a short period and to be effective [7] (Level IIb). The nasal symptoms score was significantly better using the rush method compared to the rapid method. Systemic adverse reactions were observed in 40% of the patients, but none of these reactions were severe [8] (Level IIb).

3.2. CQ02: How should the maintenance dose and administration period for SCIT be determined?

The effect of SCIT is insufficient at low doses, but systemic adverse events increase at high doses. For many antigens, administration as a single injection of 5–20 μg as the major antigen is recommended. If a long-term effect is required, it is generally necessary to continue the therapy for 3 years [9] (Level Ia). Three-year SCIT (32 subjects, maintenance dose 20 μg, timothy antigen) was effective for 3 years after discontinuation of treatment [10] (Level Ib). SCIT administered over 3 years (20 subjects, maintenance dose 12 μg, ragweed antigen Amb a1) suppressed antigen-evoked responses in the nasal mucosa [11] (Level Ib). One-year SCIT (35 subjects) reduced the total nasal symptom score (TSS) and medication score (MS) [6] (Level Ib). Three-year SCIT in 147 children aged 6–14 years old was effective for 7 years after the end of the therapy [12] (Level Ib). In 28 patients with a cat allergy, in whom the effects of the cat antigen Fel d 1 were compared using maintenance doses of 0.6, 3, and 15 μg, nasal symptoms were alleviated in a dose-dependent manner [13] (Level Ib). The TSS was significantly lower in 5-year SCIT (239 subjects, maintenance dose 3.6 μg, mite antigen Der p1) than in 3-year SCIT [14] (Level IIa). In patients with mite-induced asthma, the recurrence rate 3 years after discontinuation of treatment was lower in those who underwent SCIT for ≥3 years (19 patients) than in those treated for <3 years (21 patients) [15] (Level III). Recommendation level is A.

3.3. CQ03: What are the types and frequencies of the side effects of SCIT and how are they managed?

SCIT has a risk of systemic adverse reactions and anaphylaxis, with prompt treatment required after 0.13% of treatments (19/14,085 subcutaneous inoculations) [9,10] (Level Ia). Systemic adverse reactions have also been observed after 0.025% of inoculations [16] (Level Ia). Severe anaphylactic reactions due to SCIT for SAR occurred in 5.4 of 1,000,000 injections (0.0005%) and were most frequently observed during the pollen season (46%). In most cases, the cause of anaphylaxis was an error in the dose (25%) and epinephrine was administered within 20 min as a life-saving treatment [17] (Level III). The incidence of local adverse reactions to SCIT using a standardized mite or weed allergen was 10.5% and

that of systemic reactions was 4.8% (0.37% of all injections). Adverse systemic reactions occurred significantly more frequently in patients with asthma, in those sensitized to mites, and when the dose of antigen extract was increased [18] (Level III). Recommendation level is B.

3.4. CQ04: What kinds of patients are not indicated for SCIT?

Adverse reactions are more likely to occur in patients with AR complicated by asthma than in those with AR alone [19] (Level III). Malignant diseases, autoimmune disorders, patients under treatment with β-blockers, patients who are pregnant at the start of SCIT, asthmatic patients with FEV1 <70%, and patients with acute infections such as a cold are contraindicated for SCIT for AR. SCIT should also not be performed in patients aged <5 years old [20] (Level IV). Pregnancy is not a specific contraindication for SCIT, but the dose or concentration of drugs used for SCIT must not be increased during pregnancy to avoid the possibility of anaphylaxis. Initiation of new SCIT is not recommended in patients who are pregnant [21] (Level IV). SCIT is contraindicated for patients with severe cardiovascular diseases; those using β-blockers; those with severe asthma, irreversible chronic airway obstructions, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, and immunodeficiencies; those with psychiatric disorders, and those who cannot follow instructions concerning the therapy. Beginning SCIT during pregnancy is also a contraindication and a very young patient is a relative contraindication. Patients with mild AR that can be sufficiently managed by occasional medication and those who cannot understand explanations of SCIT are considered to be inappropriate for SCIT. In addition, patients with nasal polyps are not expected to respond markedly to SCIT [22] (Level IV). Recommendation level is C2.

4. Effectiveness of SCIT

4.1. CQ05: Can AR in children (including QOL) be improved by SCIT?

We searched the literature for randomized studies of SCIT against AR in children published since 1990 and found 2 small-scale studies: 1 on perennial AR (PAR), and the other on SAR. Symptoms were alleviated by SCIT relative to administration of a placebo [23,24] (Level Ib). SCIT for 1 year significantly lowered the TSS and MS in children with PAR [23] (Level Ib). Many of the adverse reactions were mild, but systemic adverse reactions must be managed appropriately [23,25] (Level Ia). SCIT significantly reduced symptoms and drug scores in children with AR or asthma due to a fungal allergy [26] (Level Ib). SCIT administered over 3 years significantly controlled the symptoms of SAR in children for 7 years following completion of the therapy [12] (Level IIa). The efficacy of antihistamines and topical nasal steroids was higher in children with PAR for 2 years after the start of treatment, but was surpassed by the efficacy of SCIT after 3 or more years [27] (Level IIb). Recommendation level is B.

4.2. CQ06: Can AR in adults (including QOL) be improved by SCIT?

SCIT is likely to be effective with use of a sufficient amount of standardized allergen [9,28,29] (Level Ia). For many allergens, the optimal dose of the primary allergen is 5–20 μg per administration [28,29] (Level Ia). The efficacy of SCIT as a treatment for AR is also enhanced in combination with other drug therapies [29] (Level Ia). Using the Cochrane Collaboration, 1111 papers were evaluated, and 15 of 51 papers fulfilling the criteria of scientific assessment were used in a meta-analysis, in which SCIT was found to be effective based on the TSS. Using the MS, SCIT was also found to be effective in a meta-analysis of 13 papers. However, the degree of efficacy varied and was not easily evaluated [25] (Level Ia). There is a risk of an anaphylactic reaction as a systemic side effect; although rare, appropriate management is required should this reaction occur [28,29] (Level Ia). In a domestic evaluation of SAR, SCIT was more effective than drug therapy alone for improving symptoms and QOL scores [30] (Level III). Recommendation level is B.

4.3. CQ07: Is addition of SCIT effective in patients not responding to regular drug therapy?

Drug therapy is the most widely used method for treatment of AR, but some patients do not respond to this therapy. Therefore, studies have been performed to examine whether symptoms can be alleviated and whether the quantity of drugs administered can be reduced by additional SCIT in such patients. In a randomized, double-blind, placebo controlled study (RCT) of SCIT in 40 patients with severe SAR that was poorly controlled by antihistamines, topical nasal steroids, and disodium cromoglycate in the previous year, improvements in TSS, MS, and VAS scores were observed in the active group [31] (Level Ib). In an RCT of SCIT in 36 patients with severe PAR that was not sufficiently controlled by standard antiallergic medicine, improvements in TSS and MS were observed in the SCIT group [32] (Level Ib). Recommendation level is C1.

4.4. CQ08: Does SCIT suppress the occurrence of asthma in nonasthmatic children?

The results of a 3-year open study comparing the incidence of asthma between SCIT and control drug therapy in 205 children with SAR showed that SCIT significantly suppressed the occurrence of asthma [33] (Level IIa). A 2-year follow-up of the patients in this study (183 patients) indicated that the occurrence of asthma was significantly lower in the SCIT group than in the control group [24] (Level IIa). Follow-up at 7 years after completion of SCIT (147 patients) showed that the occurrence of asthma was still significantly lower in the SCIT group, and that asthma and airway hypersensitivity were significantly alleviated [12] (Level IIa). Recommendation level is C1.

4.5. CQ09: Can sensitization to novel allergens be suppressed by SCIT in patients (children/adults)?

In children sensitized to house dust-mite antigen alone (including those with AR), the percentage of those sensitized to new antigens was significantly lower after SCIT for 2 years (22 patients) [34] and 3 years (75 patients) [35], compared to age-matched controls (Level IIa). In 147 children with AR and asthma, the percentage of those sensitized to new antigens was significantly lower in the SCIT group than in the control group [36] (Level IIa). In a retrospective study in 8396 patients with an airway allergy (asthma, AR) sensitized to house dust antigen alone, the percentages of those sensitized to new antigens at 4 years and 7 years were significantly lower in the SCIT group compared to the control group (23.8% vs. 68.0% at 4 years, and 27.0% vs. 76.8% at 7 years) [37] (Level III). Recommendation level is C1.

4.6. CQ10: How long are the effects of SCIT sustained in children?

The total symptom score was significantly lower in 13 children with SAR who underwent SCIT for 3 years than in 10 age-matched controls after 6 [38] and 12 [39] years (Level IIa). Improvements in the condition of 25 children with PAR and 12 with SAR who underwent SCIT for ≥2 years were sustained over a long period of ≥17 years, compared to children who received drug therapy [40,41] (Level III). Recommendation level is C1.

4.7. CQ11: How long are the effects of SCIT sustained in adults?

The duration of the SCIT effect after discontinuation of therapy depends on the duration of treatment and responses to a skin test [42] (Level III). The effect of the therapy in 32 patients who underwent SCIT for SAR due to grass pollen persisted for 3 to 4 years regardless of whether SCIT was continued for more than 3 years [10] (Level Ib). In 108 patients who underwent SCIT for 3 to 4 years, symptoms exacerbated in 2.7%, 16.7%, 30.6% and 32.8% of the patients at 1, 2, 3 and 4 years after therapy discontinuation, respectively [43] (Level III). The therapeutic effect in 36 patients who underwent SCIT for tree pollinosis for 3 years was maintained in 86% of those with rhinitis and 68% of those with asthma at 6 years after discontinuation of treatment [44] (Level III). In patients with AR/conjunctiva, reactivation at 2 years after discontinuation of SCIT occurred in 36% of 87 patients treated for 4 years and in 18% of 61 patients treated for 6 years [45] (Level III). Recommendation level is C1.

4.8. CQ12: Can the systemic adverse effects of SCIT be prevented by pretreatment with antiallergic drugs?

In a double-blind trial, systemic adverse reactions occurred in 7 (33%) of 21 patients who received loratadine prior to subcutaneous injection and in 19 (79%) of 24 patients who received a placebo. Thus, the incidence of severe adverse reactions was reduced by premedication with an antihistamine [46] (Level Ib). Another study showed a reduced incidence of severe adverse reactions after administration of an antihistamine before subcutaneous injection [47] (Level IV). Recommendation level is C1.

5. Mechanisms of SCIT

5.1. CQ13: What are the mechanisms underlying the effects of SCIT for AR?

Regulatory $Foxp3^+$ $CD4^+$ and $Foxp3^+$ $CD25^+$ T cells are significantly increased in the nasal mucosa in patients treated with SCIT [48]. Antigen-specific serum IgG in patients receiving SCIT inhibits binding of antigen IgE to B cells [49] and SCIT suppresses IL-4 production by $CD4^+$ T cells [50]. Expression of IL-5 mRNA in peripheral blood mononuclear cells (PBMCs) stimulated with Cry j 1 was significantly lower in patients with a marked response to SCIT compared to an untreated group and patients who did not respond to SCIT [51]. Expression of the co-inhibitory molecule BTLA in PBMCs stimulated with Cry j 1 was significantly higher in the SCIT group than in the control group. The increase in the serum cedar-specific IgE antibody level during the pollen dispersion season was suppressed by SCIT [52]. IgG antibodies (particularly IgG4) are increased by SCIT and have been reported to act as a blocking antibody and to correct the tilt to Th2 dominance by suppressing Th2 cytokines and Th2 cells. Recently, SCIT has also been reported to induce regulatory T cells and control allergic reactions via production of regulatory cytokines such as IL-10 and TGF-β.

6. Conclusion

Administration of SCIT for AR involves use of the 50% incremental, 100–200% incremental, cluster, and rush methods until a maintenance concentration is reached, but there has been no direct comparison of the effectiveness of these methods. A major antigen dose of 5–20 μg is recommended to minimize adverse reactions. The incidence of systemic adverse reactions including anaphylaxis is about 1 in 1000–4000 inoculations, and prompt and appropriate treatment is required for such reactions. The risk of systemic adverse reactions might be reduced by oral premedication with an antihistamine. SCIT administered to children with AR significantly improved the total symptom score and significantly reduced the medication score. The effect of SCIT for children with AR is also likely to continue over a long period after discontinuation of the therapy. Sensitization to new allergens can be prevented by SCIT. SCIT for adults with AR is recommended because it alleviates nasal symptoms and reduces the quantity of required drugs. In patients not responding to drug therapy, SCIT can also alleviate symptoms and reduce the use of other drugs. SCIT for AR significantly suppresses the occurrence of asthma and its effect is likely to persist after completion of SCIT. We recommend that SCIT is continued for 3 years or longer. The effect of SCIT is sustained over a long period, even after its discontinuation, and the duration of the effect of SCIT after discontinuation is related to the duration of the treatment.

Conflicts of interest

Any organizations or businesses that have provided research funding (for contract research, joint research, clinical trials, etc.), scholarship donations, and monetary compensations for lectures, manuscripts, and pamphlets to members of the guideline preparation committee are listed. (The period of interest is between January 2010 and December 2011). Astellas Pharma Inc., AstraZeneca KK, Eisai Co., Ltd., Merck & Co., Inc., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., GlaxoSmithKline KK, Kowa Pharmaceutical Co., Ltd., Sanofi Aventis KK, Shionogi Co., Ltd., Senju Pharmaceutical Co., Ltd., Daiichi sankyo Co Ltd, Dainippon Sumitomo Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Nikken Chemical Laboratory Co., Ltd., Nippon Shinyaku Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Bayer Yakuhin, Ltd, Pfizer Japan Inc, Meiji Seika Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd.

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ORIGINAL ARTICLE

Determining Minimal Clinically Important Differences in Japanese Cedar/Cypress Pollinosis Patients

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ABSTRACT

Background: Statistically significant results of medical intervention trials are not always clinically meaningful. We sought to estimate the minimal clinically important difference (MCID) (the smallest change in a given endpoint that is meaningful to a patient) during seasonal alteration of Japanese cedar/cypress pollinosis (JCCP).

Methods: Results of a double-blinded, placebo-controlled trial of JCCP patients conducted between 2008 and 2010 were analyzed using an anchor-based method in which a face scale for Japanese rhinoconjunctivitis quality-of-life questionnaire (JRQLQ) was set as an anchor. MICDs were calculated as changes of average scores, including those for naso-ocular symptoms with 5 items in diary cards (T5SS), naso-ocular symptoms with 6 items (T6SS) and QOL with 17 items on the JRQLQ when face scale scores either improved or deteriorated by one point.

Results: In 2009 and 2010, 3,698 and 374, respectively, grains/cm^2 of pollens were dispersed. The MCIDs for T5SS in 2009 and 2010 were 1.426 (0.285 per item) and 1.441 (0.288), respectively. The MCIDs for T6SS were 4.115 (0.686) and 3.183 (0.531) in 2009 and 2010, respectively. The MCIDs for QOL were 10.469 (0.616) and 6.026 (0.354) in 2009 and 2010, respectively.

Conclusions: For T5SS in the diary, T6SS and QOL in JRQLQ, unit differences of 1.5 (0.3 per item), 3.6 (0.6) and 8.2 (0.5), respectively, were considered clinically meaningful by JCCP patients. The MCID for symptoms recorded in the diary was stable irrespective of the dispersed pollen level.

KEY WORDS

face scale, minimal clinically important difference, pollinosis, quality of life, symptom score

INTRODUCTION

In order to evaluate the efficacy of interventions for allergic rhinitis (AR), setting specific endpoints is required. The total nasal symptom score, which is the sum of 4- or 5-point scaled scores for sneezing, rhinorrhea and nasal congestion as recorded in an allergy dairy, is generally used as a primary endpoint in Japan. Secondary endpoints are often defined, including quality of life (QOL), as determined by the Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ), the ocular symptom score and the naso-ocular symptoms score (especially for seasonal AR), work productivity, sleepiness, impaired performance and safety.[1-5]

The efficacy of various medical interventions is usually estimated by statistical significance. However, statistically significant differences do not always reflect clinically meaningful differences. For example, a clinical trial of a therapy involving a large patient

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population may result in a statistically significant finding that nevertheless has no clinical relevance.[6] Thus, clinically meaningful differences should be determined.[7] In fact, the minimal clinically important difference (MCID) of endpoints for various therapies for AR has been examined in a few studies.[8,9] For example, Juniper *et al.* interpreted the data obtained using Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and set a value of 0.5 change of score from baseline as the MCID.[8] Barnes *et al.* determined, by using the global rating of change scale, that an MCID is 0.4 and 0.55 unit change of the Mini RQLQ and total nasal symptom scores, respectively.[9] However, to our knowledge, determining an MCID for AR has not been done in Japan.

In the self-reported Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ), a patient's general state is monitored by a 5-point face scale, depicting facial emotions ranging from "fine" to "crying".[10,11] In the present study, we utilized this face scale with an anchor-based method, and determined the units of total symptom and QOL score changes resulting in 1 face scale unit change, as the MCID.[12] We believe that the present findings may provide a basis for understanding the clinical meaning of results of medical interventions for Japanese cedar/cypress pollinosis (JCCP), or facilitate AR research in Japan.

METHODS

SAMPLE

We calculated MCIDs using an "anchor-based" method.[12] We used data from a randomized, double-blinded, placebo-controlled trial for the efficacy of sublingual immunotherapy for Japanese cedar/cypress pollinosis (JCCP) conducted between 2008 and 2010 in our hospital. This trial was approved by the institutional review board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Rinri-1204). In this trial, 55 patients with JCCP (17 males and 38 females, age range 23-79 [mean 53.1 ± 11.9] years) were enrolled in 2008, and then received sublingual immunotherapy with active or placebo extract of Japanese cedar pollen (Torii Pharmaceutical, Tokyo, Japan). Naso-ocular symptoms and QOL were monitored in the dispersal season of Japanese cedar and cypress pollen in 2009. Subsequently, 36 of the enrolled patients (10 males and 26 females, age range 31-75 [mean 55.4 ± 9.6] years) continued to receive the same treatment in the 2009-2010 season, and then the identical assessment was performed in the 2010 pollen dispersal season. Prior to participation in the study, all patients provided written informed consent.

NASO-OCULAR SYMPTOMS AND QOL

During the pollen dispersal season, subjects completed the JRQLQ twice a month for a total of 6 times (February 16, March 1 and 16, April 1 and 16, and May 1). The JRQLQ contains 3 sections, as follows: naso-ocular symptoms with 6 items (sneezing, rhinorrhea, nasal congestion, itchy nose, itchy eyes and watery eyes), rhinitis-related QOL with 17 items; and a global status determined by a 5-point face scale depicting emotions ranging from "fine" to "crying".[10] In addition, subjects' daily naso-ocular symptoms were recorded by filling in diary cards. On these cards, the presence and intensity of three nasal symptoms (sneezing, rhinorrhea, and nasal congestion) and two ocular symptoms (watery and itchy eyes) were recorded in a 5-point scale using Okuda's modified classification.[11]

CALCULATION OF MCID

The MCID was determined based on the changes of face scale scores before and after the 6 time points when the JRQLQ was completed. Thus, 5 time periods were investigated for each subject enrolled. Because the subjects were asked to choose the face scale item that best described their general status in the past 1-2 weeks, the average of all the T5SS scores (naso-ocular symptom score with 5 items) recorded in the diary (during 6 time periods: February 1 to 15, February 16 to 28, March 1 to 15, March 16 to 31, April 1 to 15 and April 16 to 30) was calculated (Fig. 1).[10] Data were excluded when there were missing values. The changes of face scale scores were classified into 5 grades: greater than or equal to 2 scale-points improvement, ≤-2; 1 scale-point improvement, -1; no change, 0; 1 scale-point exacerbation, +1; and greater than or equal to 2 scale-points exacerbation, ≥+2. The MCIDs were calculated as changes in the average symptom and QOL scores when the face scale score was either improved or exacerbated by 1 point. The actual calculating formula used is as follows: MCID = $(|a - b| + |c - b|)/2$; a, b and c represent mean changes in the T5SS, T6SS, or QOL scores when the grade of the mean face scale change is -1,0 and +1 during each time period, respectively (Table 1).

MEASUREMENT OF POLLEN DISPERSAL

The daily amount of Japanese cedar and Japanese cypress pollen dispersal was measured from January 20 to May 10 of both 2009 and 2010 using a Durham sampler that was installed on the rooftop of the Okayama University Hospital building.[5]

STATISTICAL ANALYSIS

The nonparametric Mann-Whitney U test was used to compare data between groups. *P* values of less than 0.05 were considered to be statistically significant. Statistical analyses were performed with SPSS software (version 11.0 SPSS, Chicago, IL, USA).

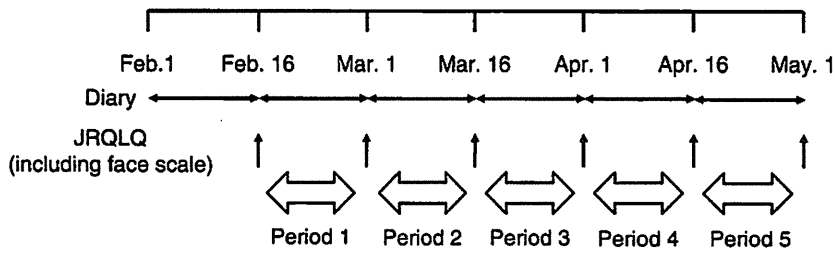

Fig. 1 Calculation of MCID. The MCIDs for symptom and QOL scores were determined based on face scale score changes before and after 6 time points (February 16, March 1 and 16, April 1 and 16, and May 1).

Table 1 Formula to calculate MCID

$$\frac{\left\|\left[\begin{array}{l}\text{changes of symptom/QOL}\\ \text{scores at 1 improvement}\\ \text{in face scale score}\end{array}\right]-\left[\begin{array}{l}\text{changes of symptom/QOL}\\ \text{scores at no change in}\\ \text{face scale score}\end{array}\right]\right\|+\left\|\left[\begin{array}{l}\text{changes of symptom/QOL}\\ \text{scores at 1 exacerbation}\\ \text{in face scale score}\end{array}\right]-\left[\begin{array}{l}\text{changes of symptom/QOL}\\ \text{scores at no change in}\\ \text{face scale score}\end{array}\right]\right\|}{2}$$

RESULTS

DISPERSAL OF JAPANESE CEDAR AND CYPRESS POLLEN IN 2009 AND 2010

A total of 3,698 grains/cm^2 of Japanese cedar/cypress pollen were dispersed in 2009. On the other hand, only 374 grains/cm^2 of Japanese cedar/cypress pollen were dispersed in 2010. The amounts of cedar/cypress pollen grains observed in 2009 and 2010 were 228.1% and 23.1%, respectively, of the average amount observed at our hospital from 2001 to 2010, which was 1,621 grains/cm^2.

THE MCID IN T5SS (TOTAL NASO-OCULAR SYMPTOM SCORE WITH 5 ITEMS) RECORDED ON DIARY CARDS

In 2009, the year with high pollen dispersal, 245 eligible diary card samples were analyzed: 11, 23, 114, 72, and 25 samples were classified as ≤-2, -1, 0, +1, and ≥+2, respectively. These improvements and exacerbations, as scored by face scale, lead to a symmetrical decrease and increase, respectively, of T5SS, as recorded on diary cards. Statistically significant differences in the change of T5SS were observed when the face scale score change was +1 (p = 0.001), greater than or equal to +2 (p = 0.026) and greater than or equal to -2 (p = 0.046) (Fig. 2A).

In 2010, the year with low pollen dispersal, 169 eligible diary card samples were analyzed: 7, 13, 107, 31, and 11 samples were classified as ≤-2, -1, 0, +1, and ≥+2, respectively. Statistically significant differences in the T5SS score change were seen for face scale scores of +1 (p = 0.003) and ≥+2 (p < 0.001) (Fig. 2B).

The MCID was calculated based on a 1-point improvement or deterioration of T5SS score recorded in the diary for each time period. In 2009 and 2010, the MCIDs of T5SS were determined to be 1.426 ([|-1.130 - 0.351| + |1.772 - 0.351|]/2: 0.285 per item) and 1.441 ([|-1.462 - 0.009| + |1.419 - 0.009|]/2: 0.288 per item), respectively (Table 2).

MCID IN T6SS (TOTAL NASO-OCULAR SYMPTOM SCORE WITH 6 ITEMS) BY JRQLQ RESULTS

In 2009, 251 eligible JRQLQ samples were investigated; 11, 23, 116, 73, and 28 samples were classified as ≤-2, -1, 0, +1, and ≥+2, respectively. In 2010, 173 eligible samples were classified as ≤-2 (n = 7), -1 (n = 13), 0 (n = 110), +1 (n = 33), and ≥+2 (n = 10). Compared with the T5SS, as determined by the diary recordings, the face scale score changes did correlate with a more robust and significant alteration of T6SS as determined by the JRQLQ (T6SS) in both 2009 and 2010 (p < 0.001, Fig. 3). Based on the calculation shown above, the MCIDs for T6SS by JRQLQ were determined to be 4.115 ([|-4.174 - 0.629| + |4.055 - 0.629|]/2: 0.686 per item) and 3.183 ([|-3.308 - (-0.163)| + |2.788 - (-0.163)|]/2: 0.531 per item) in 2009 and 2010, respectively (Table 2).

MCID OF QOL SCORE BY JRQLQ

In 2009, 255 eligible samples were investigated; 11, 24, 117, 74, and 29 samples were classified as ≤-2, -1, 0, +1, and ≥+2, respectively. In 2010, 179 eligible samples were classified as ≤-2 (n = 7), -1 (n = 14), 0 (n = 112), +1 (n = 34), and ≥+2 (n = 12). Similar to T6SS results, the changes of face scale score significantly correlated with alteration of the QOL score with 17 items as determined by JRQLQ responses, in both 2009 and 2010 (p < .0001, except for one exacerbation in 2010 where the p value was 0.003) (Fig. 4). The MCIDs of

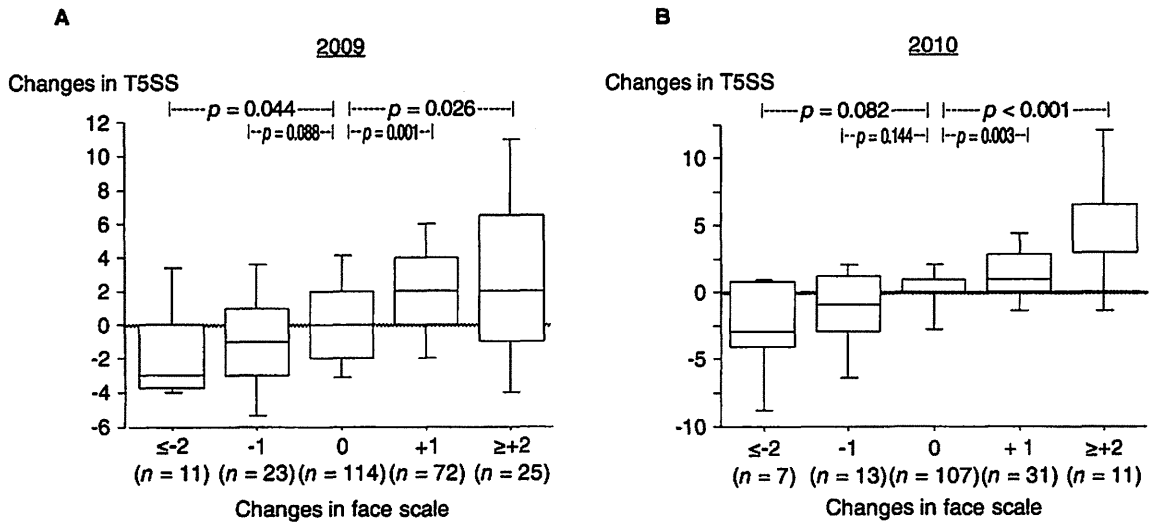

Fig. 2 T5SS changes on the diary cards based on face scale score changes, in 2009 (**A**) and 2010 (**B**). The rectangle includes the range from the 25th to the 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to 90th percentiles. *P*-values were determined by using the Mann-Whitney U test.

Table 2 Calculated MCID based on the minimal change of face scale

Endpoint type	Year	MCID	
		at total score	per 1 item
Symptom scores			
diary (5 items)	2009	1.426	0.285
	2010	1.441	0.288
JRQLQ (6 items)	2009	4.115	0.686
	2010	3.183	0.531
QOL scores			
JRQLQ (17 items)	2009	10.469	0.616
	2010	6.026	0.354

the QOL score on the JRQLQ were determined to be 10.469 ([|-11.000 - 1.034| + |9.937 - 1.034|]/2: 0.616 per item) and 6.026 ([|-8.400 - (-0.379)| + |3.652 - (-0.379)|]/2: 0.354 per item) in 2009 and 2010, respectively (Table 2).

DISCUSSION

In the present study, we have applied an anchor-based approach to derive the MCIDs for major endpoints in an assessment of Japanese cedar/cypress pollinosis, the major type of allergic rhinitis in Japan. Although a few previous studies had shown such MCIDs in allergic rhinitis,[8,9] we believe that this is the first report calculating the MCIDs for symptoms and QOL scores in Japanese patients with allergic rhinitis.

We calculated MCIDs in two consecutive seasons. In 2009, high pollen dispersal was observed. On the contrary, pollen dispersal was extremely low in 2010. The amount of pollen exposure affects the severity of rhinitis.[5,13,14] For example, we performed a double-blinded placebo-controlled trial to determine whether early interventional treatment with mometasone furoate nasal spray is effective for Japanese cedar/cypress pollinosis in 2010 (total 374 grains/cm^2) and 2011 (total 1,973 grains/cm^2).[5,14] The T5SSs in the placebo group at the peak of Japanese cedar pollen dispersal were 3.12 and 7.33 in 2009 and 2010, respectively. This study advantageously resulted in a comparison of MCIDs during high and low pollen dispersal seasons.

The MCIDs for T5SS in the diary cards in 2009 and 2010 were 1.426 (0.285 per item) and 1.441 (0.288 per item), respectively. This result suggests that a 1.5-unit difference in the 5-point T5SS scale and a 0.3 unit difference in each symptom score were clinically meaningful in this population, regardless of the amount of allergen exposure. These results can be used to evaluate whether differences in symptom scores among treatment groups are clinically meaningful or not. For example, our recent randomized, double-blinded, placebo-controlled trial for Japanese cedar/cypress pollinosis has shown that the average T5SS throughout the study period (February to April) in patients with early interventional treatment with mometasone was 2.3, which was statistically lower than in patients with placebo treatment (score, 5.0; $p < 0.01$) and those with post-onset treatment with mometasone (score, 3.9; $p = 0.03$).[14] Based on the MCIDs calculated in the present study, the efficacy of early interventional treatment with mometasone is not only statistically significant but also clinically meaningful, as compared to post-onset treatment with mometasone or placebo administration.

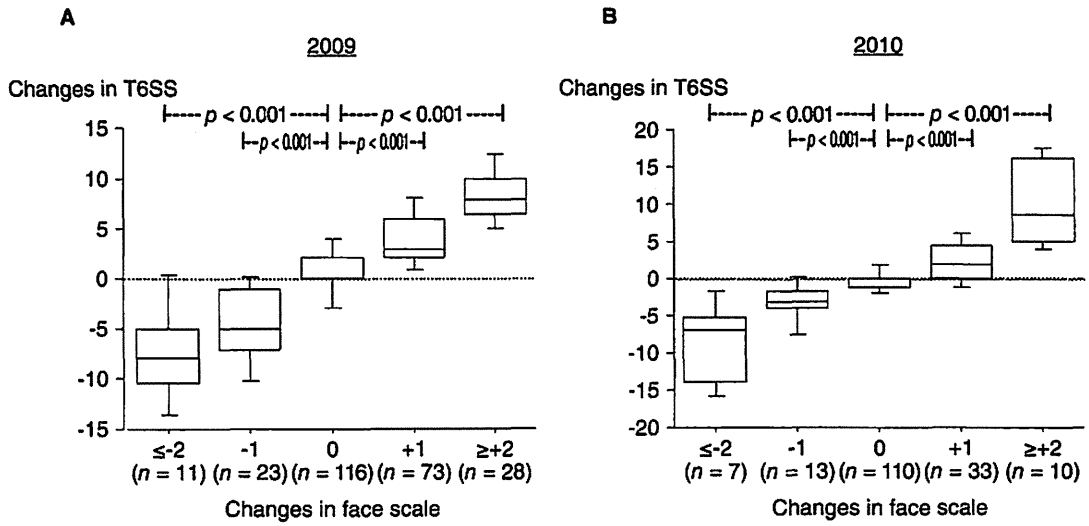

Fig. 3 T6SS changes on the JRQLQ based on face scale score changes, in 2009 (**A**) and 2010 (**B**). The rectangle includes the range from the 25th to the 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to 90th percentiles. *P*-values were determined by using the Mann-Whitney U test.

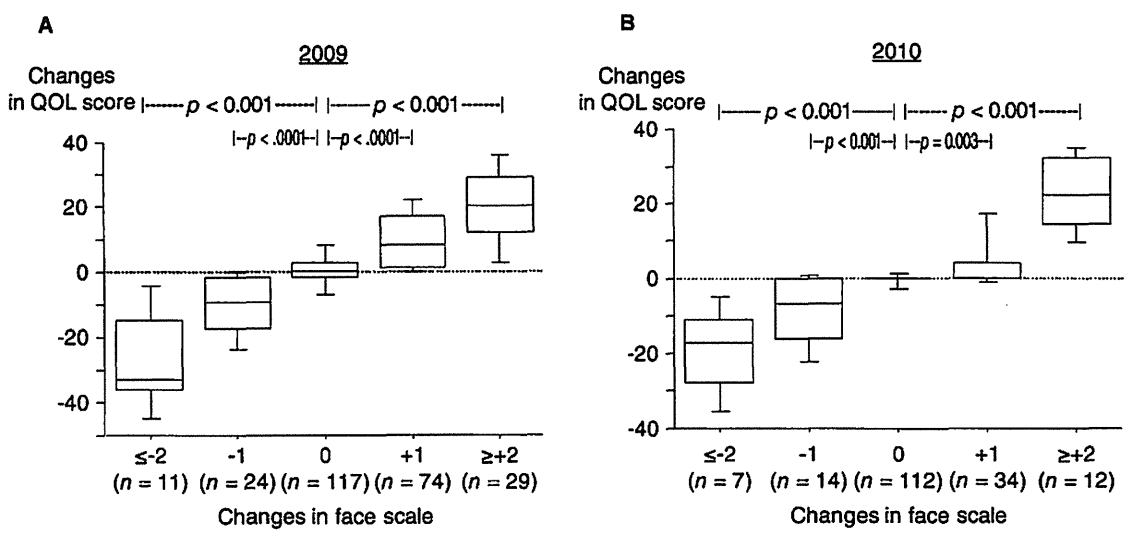

Fig. 4 QOL score changes on the JRQLQ based on the face scale score changes, in 2009 (**A**) and 2010 (**B**). The rectangle includes the range from the 25th to the 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to 90th percentiles. *P*-values were determined by the Mann-Whitney U test.

The MCIDs for T6SS by JRQLQ were determined to be 4.115 (0.686 in each symptom) and 3.183 (0.531 in each symptom) in 2009 and 2010, respectively. This result suggests that a 3.6-unit difference in T6SS and a 0.6-unit difference in each symptom score were clinically meaningful. However, these MCIDs by JRQLQ responses are relatively variable year to year, and seem to be influenced by the amount of pollen exposure, as compared to T5SS results from the diary cards, by which the MCIDs were almost equal in 2009 and 2010. Although the 5-point scale for nasoocular symptoms is set in both the diary and the JRQLQ, the specific criteria of the scales differ.[10] We think the one of the reasons why there were no significant changes of in T5SS value among the changes in face scale in 2009 and 2010 is that T5SS consists of more precise scale criteria for each symptom. For example, severity of nasal blockade in JRQLQ is simply divided into 5 scales as follows: 0, none; 1, mild; 2, moderate; 3, severe; and 4, very severe. On the other