Allergology International. 2013;62:487-493
DOI: 10.2332/allergolint.13-OA-0570

ORIGINAL ARTICLE

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

Takaya Higaki[1], Mitsuhiro Okano[1], Shin Kariya[1], Tazuko Fujiwara[1], Takenori Haruna[1], Haruka Hirai[1], Aya Murai[1], Minoru Gotoh[2], Kimihiro Okubo[2], Shuji Yonekura[3], Yoshitaka Okamoto[3] and Kazunori Nishizaki[1]

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

[1]Department of Otolaryngology-Head & Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, [2]Department of Otorhinolaryngology, Nippon Medical School, Tokyo and [3]Department of Otorhinolaryngology-Head and Neck Surgery, Chiba University Graduate School of Medicine, Chiba, Japan.

Conflict of interest: MO receives honoraria from Kyowa Hakko Kirin, MSD, Sanofi and Taiho Pharmaceutical. YO receives honoraria from GlaxoSmithKline, Kyorin Pharmaceutical, Kyowa Hakko Kirin, MSD, Shionogi and Torii Pharmaceutical. The rest of the authors have no conflict of interest.

Correspondence: Mitsuhiro Okano, MD, Department of Otolaryngology-Head & Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2–5–1 Shikatacho, Okayama 700–8558, Japan.
Email: mokano@cc.okayama–u.ac.jp

Received 16 April 2013. Accepted for publication 13 June 2013.

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).

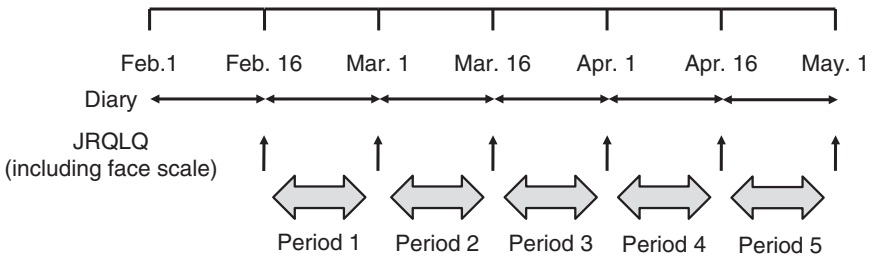

Fig. 1 Calculation of MCID. The MCIDs for symptom and QOL scores were determined based on face scale score changes before and after 6 time points (February 16, March 1 and 16, April 1 and 16, and May 1).

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

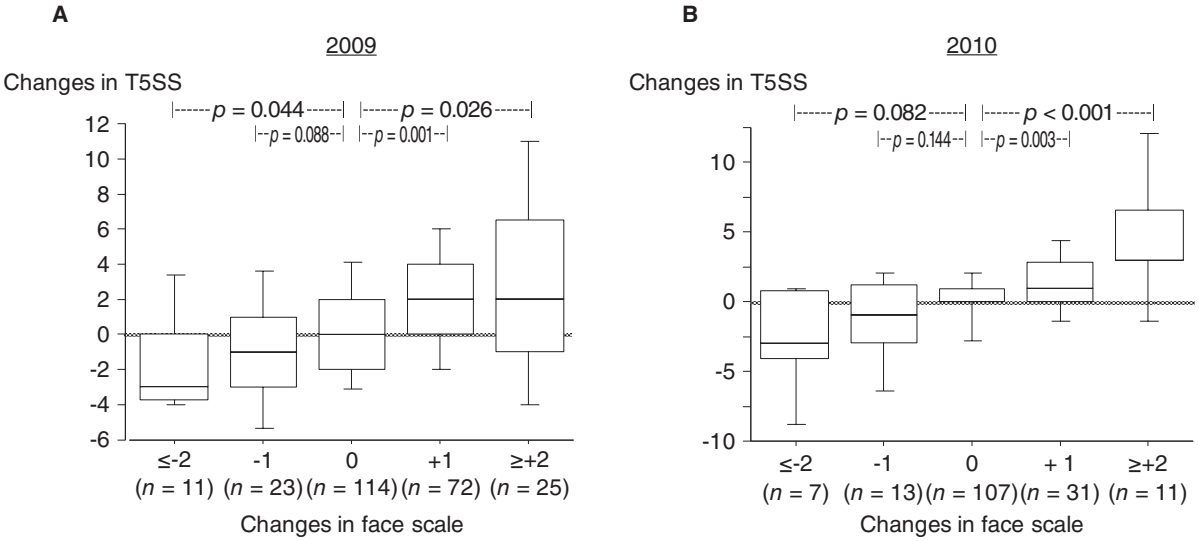

Fig. 2 T5SS changes on the diary cards based on face scale score changes, in 2009 (**A**) and 2010 (**B**). The rectangle includes the range from the 25th to the 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to 90th percentiles. *P*-values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

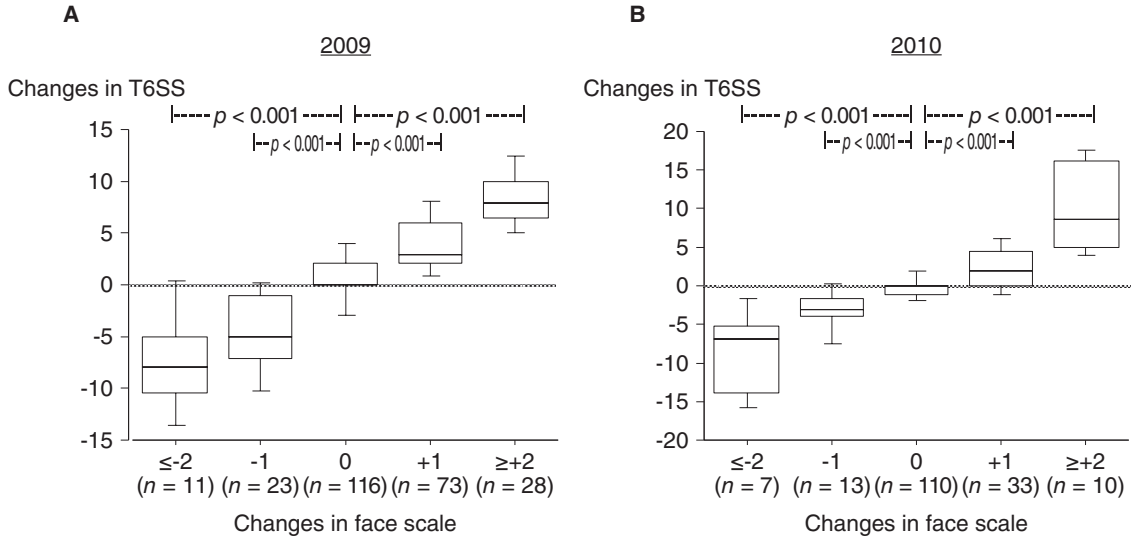

Fig. 3 T6SS changes on the JRQLQ based on face scale score changes, in 2009 (**A**) and 2010 (**B**). The rectangle includes the range from the 25th to the 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to 90th percentiles. *P*-values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

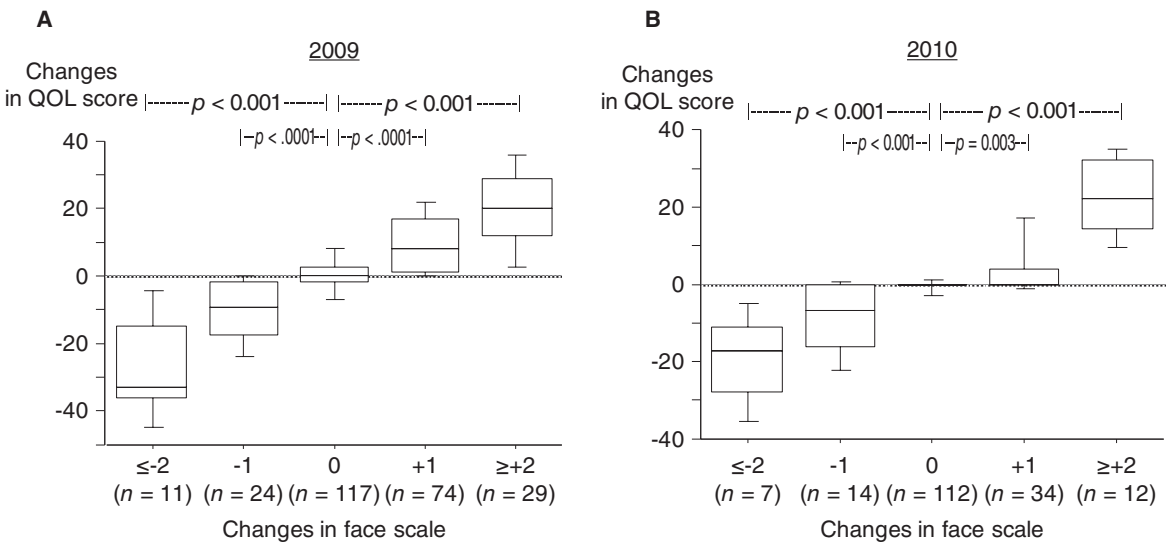

Fig. 4 QOL score changes on the JRQLQ based on the face scale score changes, in 2009 (**A**) and 2010 (**B**). The rectangle includes the range from the 25th to the 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to 90th percentiles. *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

hand, severity of nasal blockade in the diary is classified into 5 scales as follows: 0, no troublesome nasal blockade; 1, nasal blockade without oral breathing; 2, severe nasal blockade causing occasional oral breathing in a day; 3, severe nasal blockade causing prolonged oral breathing in a day; and 4, completely obstructed all day.

The MCIDs for the sum of QOL scores in JRQLQ results were determined to be 10.469 (0.616 in each item) and 6.026 (0.354 in each item) in 2009 and 2010, respectively. This result suggests that a 8.2-unit difference in the sum of QOL score and a 0.5-unit difference in each item are considered clinically meaningful. Although items, scales or anchors are different, this result is consistent with the report by Juniper showing that a 0.5-unit difference in each item on the RQLQ represents the MCID.[8] These values also can be used to evaluate whether differences in QOL scores among treatment groups are clinically meaningful. For example, we have previously reported a distinct randomized double-blind comparative study of sublingual immunotherapy for Japanese cedar pollinosis. In this study, the mean changes of QOL score from baseline data in February to peak data in the peak pollen dispersal period were 1.10 and 0.58 for the placebo and active treatment groups, respectively, showing that active sublingual immunotherapy significantly alleviated an deterioration of QOL ($p < 0.05$).[15] In addition, the difference of the mean change of QOL score between the two groups (0.52) is more than the estimated value of the MCID for QOL score (0.5). Furthermore, there was no difference in the number of medication used during the season between active and placebo treatment, suggesting that the sublingual immunotherapy is clinically efficacious and meaningful.

Subjects were allowed to use antihistamines and eye drops for rescue medication on demand. All subjects were enrolled in this study irrespective of use of the rescue medications. We investigated whether rescue medication affects MCID. In 2009, rescue medications were used in 133 out of 245 samples. Median change of T5SS at 1-point improvement in face scale was -1.0 and -1.0 in subjects with and without rescue medications, respectively ($p = 0.868$ by Mann-Whitney U test). Median change of T5SS at 1-point exacerbation in face scale was 2.0 and 2.0 in subjects with and without rescue medications, respectively ($p = 0.407$). In fact, MICD for T5SS is 1.496 (0.299 per item) and 1.493 (0.299 per item) in samples with and without rescue medications, respectively. Similar result was seen in 2010. In 2010, rescue medications were used in 56 out of 169 samples. Median change of T5SS at 1-point improvement in face scale was -3.0 and -1.0 in subjects with and without rescue medications ($p = 0.482$). Median change of T5SS at 1-point exacerbation in face scale was 1.0 and 1.5 in subjects with and without rescue medications ($p = 0.256$). MICD for T5SS was 1.885 (0.377 per item) and 1.333 (0.267 per item) in samples with and without rescue medications, respectively, in 2010. These results suggest that taking medications had minimal effect on MICD.

One concern regarding the present study is whether the estimated value of the MCID strictly reflects "minimal" differences, since we used a face scale with a 5-point scale as an anchor. Previous reports used the global rating of change scale with a 15-point scale as an anchor.[8,9] For example, Juniper *et al.* estimated that a change in score of 0.5 per item represents the MCID based on a change of 2 (a little better), 3 (somewhat better), -2 (a little worse) or -3 (somewhat worse) on the global rating of change scale.[8] Future investigations using an independent questionnaire as an anchor that includes the global rating of change scale will be required in order to determine the precise MCID for symptom and QOL scores. Since a 1 scale-point change of face scale score seems to correlate with a substantial alteration, as compared with a 1 scale-point change on the global rating of change scale, the values reported in the present study may represent clinically "meaningful," but not "minimally," important differences.

In conclusion, we have derived the MCIDs for symptom scores in the diary (0.3 unit per item), symptom scores on the JRQLQ (0.6 unit per item) and QOL scores (0.5 unit per item). Among these, we think that MCID for T5SS recorded in the diary seems to be most reliable and reflect the patient's condition because the MCIDs for T5SS in 2009 (0.285 unit per item) and 2010 (0.288 unit per item) were similar as compared with those for T6SS in JRQLQ (0.686 and 0.531 unit per item in 2009 and 2010, respectively) and QOL scores in JRQLQ (0.616 and 0.354 unit per item in 2009 and 2010, respectively). These values can enable physicians to interpret research findings regarding both statistical and clinical significance of allergic rhinitis treatment, especially treatment of Japanese cedar/cypress pollinosis. On the other hand, since the values are the average of the MCIDs of 2009 and 2010 and might be variable in another year depend on the amount of pollen, additional analysis using data from another years with different pollen dispersal will conduce to a more significance of the value.

ACKNOWLEDGEMENTS

The authors would like to thank Fumiyo Higaki and Yuko Okano for their editorial assistance. This work was supported in part by grants from Ministry of Health, Labour and Welfare, Japan.

REFERENCES

1. Gotoh M, Suzuki H, Okubo K. Delay of onset of symptoms of Japanese cedar pollinosis by treatment with a leukotriene receptor antagonist. *Allergol Int* 2011;**60**:483-9.

2. Yonekura S, Okamoto Y, Yamasaki K *et al*. A randomized, double-blind, placebo-controlled study of Ten-Cha (Rubus suavissimus) on house dust mite allergic rhinitis. *Auris Nasus Larynx* 2011;**38**:600-7.

3. Yamamoto H, Yamada T, Sakashita M *et al*. Efficacy of prophylactic treatment with montelucast and montelucast plus add-on laratadine for seasonal allergic rhinitis. *Allergy Asthma Proc* 2012;**33**:e17-22.

4. Takahashi G, Matsuzaki Z, Okamoto A *et al*. A randomized control trail of stepwise treatment with fluticasone propionate nasal spray and fexofenadine hydrochloride tablet for seasonal allergic rhinitis. *Allergol Int* 2012;**61**: 155-62.

5. Makihara S, Okano M, Fujiwara T *et al*. Early interventional treatment with intranasal mometasone furoate in Japanese cedar/cypress pollinosis: a randomized placebo-controlled trial. *Allergol Int* 2012;**61**:295-304.

6. Akerlund A, Andersson M, Leflein J, Lildholdt T, Mygrid N. Clinical trial design, nasal allergen challenge models, and considerations of relevance to pediatrics, nasal polyposis, and different classes of medication. *J Allergy Clin Immunol* 2005;**115**:S460-82.

7. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;**10**:407-15.

8. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996;**98**:843-5.

9. Barnes ML, Vaidyanathan S, Williamson PA, Lipworth BJ. The minimal clinically important difference in allergic rhinitis. *Clin Exp Allergy* 2010;**40**:242-50.

10. Okubo K, Kurono Y, Fujieda S *et al*. Japanese guideline for allergic rhinitis. *Allergol Int* 2011;**60**:171-89.

11. Fujieda S, Kurono Y, Okubo K *et al*. Examination, diagnosis and classification for Japanese allergic rhinitis: Japanese guideline. *Auris Nasus Larynx* 2012;**39**:553-6.

12. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003;**56**:395-407.

13. Brito FF, Gimeno PM, Carnes J *et al*. Olea europaea pollen counts and aeroallergen levels predict clinical symptoms in patients allergic to olive pollen. *Ann Allergy Asthma Immunol* 2011;**106**:146-52.

14. Higaki T, Okano M, Makihara S *et al*. Early interventional treatment with intranasal corticosteroids is superior to post-onset treatment in pollinosis. *Ann Allergy Asthma Immunol* 2012;**109**:458-64.

15. Okubo K, Gotoh M, Fujieda S *et al*. A randomized double-blind comparative study of sublingual immunotherapy for Japanese cedar pollinosis. *Allergol Int* 2008;**57**:265-75.