

The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis

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Abstract

Background: The minimally important difference (MID) has been defined as the smallest improvement considered worthwhile by a patient. The MID has not been estimated for the Rhinoconjunctivitis Total Symptom Score (RTSS).

Methods: In a prospective multicentre study, patients consulting for grass-pollen-induced allergic rhinitis (AR) recorded a 15-point global rating of change scale (GRCS) score and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score on a weekly basis and the individual symptom scores comprising the RTSS on a daily basis over two consecutive weeks. The MID in the RTSS was determined with anchor-based methods (using the GRCS and the RQLQ) and a distribution-based method [based on the RTSS' standard deviation (SD)].

Results: The study population comprised 806 patients (253 children, 250 adolescents and 303 adults). During the first week of the study, the mean $\pm$ SD RTSSs for these age groups were 6.5 ± 3.3 , 6.8 ± 3.4 and 7.0 ± 3.4 , respectively. For an improvement of 2 points in the GRCS or 0.5 points in the RQLQ score, the regression analysis yielded MIDs in the RTSS of 1.24 ± 0.17 and 1.12 ± 0.14 in children, 1.33 ± 0.14 and 1.20 ± 0.13 in adolescents and 1.13 ± 0.14 and 0.89 ± 0.12 in adults, respectively. When applying distribution-based methods, the MID ranged from 1.09 to 1.13 (based on 0.33 SDs of the first-week RTSS) and from 1.22 to 1.40 (based on 0.5 SDs of the difference in RTSSs between the first and second weeks).

Conclusion: The MID in the RTSS was consistently estimated as 1.1–1.3 (and could conceivably be rounded to 1) in patients with grass-pollen-induced AR.

Allergic rhinoconjunctivitis (AR) induced by grass pollen is a highly prevalent condition that can impair quality of life (QoL) (1–3). In clinical trials, symptom severity is evaluated using patient-reported outcomes such as a total symptom score (4, 5), a visual analogue scale (VAS) (6–8) or a disease-specific QoL scale (9–11).

The efficacy results are usually reported in terms of their statistical significance. According to Revicki et al. (12), information on the interpretation of changes or differences in patient-reported outcomes is based on the minimal important difference (MID), which denotes the smallest

score or change in score likely to be important from the patient's perspective.

In AR, the MIDs for a VAS and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) have already been estimated (13–15). Furthermore, the MID for the patient-based Rhinitis Control Assessment Test was recently estimated in individuals suffering from either allergic or nonallergic rhinitis (16). However, the most common efficacy endpoint used in clinical trials is the Rhinoconjunctivitis Total Symptom Score (RTSS). The RTSS has been validated through its widespread use, acceptance by the regulatory

authorities and recommendation in international guidelines (4, 17–19). There are no data on the MID in the RTSS (comprising four nasal and two ocular symptoms) for patients with seasonal AR. However, an attempt has been made to estimate the MID in a total nasal symptom score in adult patients with either seasonal or perennial AR (20). According to an international expert group (18), the minimal relevant magnitude of efficacy should be at least 20% (when comparing the efficacy scores in the active and placebo groups). In guidelines on the clinical development of allergen immunotherapy issued by the European Medicines Agency (4), an applicant seeking to register a new treatment must state the value of a clinically meaningful change in the primary efficacy endpoint and explain the basis for choosing this value.

Hence, this study sought to determine the MID in the RTSS in grass-pollen-induced AR in a population of children (aged 5–11), adolescents (aged 12–17) and adults (aged 18–65) seen in ‘real-life’ clinical practice.

Methods

Study design

We performed an observational, prospective multicentre study (‘Equinoxe 2’). Based on a comprehensive list of allergists, paediatricians, chest physicians and ear, nose and throat (ENT) specialists in France, 2300 practitioners were invited to participate in the study. To minimize bias due to geographical and seasonal parameters, a final sample of 298 practitioners across the country was selected.

Study population

Patients were included in the spring of 2011 after giving their verbal informed consent to the participation. The study protocol was approved by an independent ethics committee (IEC) (Paris IDF VIII). On the day of consultation, the physician filled out a questionnaire concerning sociodemographic data and information on the AR symptoms, the AR classification [according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (3)] and prescribed treatments. All patients met the following inclusion criteria: between 5 and 65 years of age, a diagnosis of grass-pollen-induced AR and consulting for AR. The four individual nasal symptoms (sneezing, rhinorrhoea, congestion and itching) and two ocular symptoms (tearing and itching) comprising the RTSS were scored using the four-point scale (0 = absence of symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms). The baseline RTSS had to be at least 6 of 18 on the day of the consultation and on the two previous days. Patients with a known disease that might interfere with the questionnaires (e.g. an ENT infection preceding the initial visit) or asthma symptoms were not included.

Assessments

Although this study did not influence the level or type of care provided to patients, the latter were asked to rate the

following scales: (i) the RTSS on a daily basis and (ii) a 15-point global rating of change scale (GRCS) (21) and a validated, age-specific RQLQ on a weekly basis (9–11). The GRCS is a standardized, symmetric scale on which the patients specify their level of agreement or disagreement that varies between -7 and $+7$ and reflects the patient’s perception of the change over time in his/her symptoms (Table 1) (21). The GRCS score obtained at the end of the second week of the evaluation period (i.e. the change in AR symptoms with respect to the first week) was defined as the ‘anchor’ value for the determination of the MID.

Ethics

In line with French legislation on clinical research and as validated by the study’s IEC, written consent was not required for this observational study because it did not influence the level or type of care provided to the patients. After reading an IEC-validated information sheet, each patient gave his/her verbal consent to participation in the study. The form was then included in the patient’s medical records, along with a brief note from the physician stating that consent had been requested and granted at the time of the consultation for allergic rhinitis.

Sample size

Given that the correlation between the GRCS and the RTSS was not available from previous studies, we could not estimate the sample size. Hence, based on previous observational studies with similar designs (and in which between 40% and 50% of questionnaires were returned with valid data), we estimated that the inclusion of approximately 1200 patients would yield a total sample size of 600 and thus about 200 patients per age group, that is a number that exceeds most prior publications on MID determination.

Table 1 The 15-point global rating of change scale (GRCS)

Score	Change
+7	A very great deal better
+6	A great deal better
+5	A good deal better
+4	Moderately better
+3	Somewhat better
+2	A little better
+1	Almost the same, hardly any better at all
0	No change
−1	Almost the same, hardly any worse at all
−2	A little worse
−3	Somewhat worse
−4	Moderately worse
−5	A good deal worse
−6	A great deal worse
−7	A very great deal worse

Table 2 Demographic and clinical characteristics of the study groups

	Children aged 5–11 (<i>n</i> = 253)	Adolescents aged 12–17 (<i>n</i> = 250)	Adults aged 18 and over (<i>n</i> = 303)
Male (<i>n</i> , %)	157 (62.1)	144 (57.6)	99 (32.7)
Age (years), mean $\pm$ SD	9 $\pm$ 2	15 $\pm$ 2	34 $\pm$ 11
ARIA classification (<i>n</i> , %)			
Mild intermittent	8 (3.2)	12 (4.8)	4 (1.3)
Moderate-to-severe intermittent	22 (8.7)	20 (8.0)	17 (5.6)
Mild persistent	17 (6.7)	18 (7.2)	13 (4.3)
Moderate-to-severe persistent	203 (80.2)	195 (78.0)	267 (88.1)
Time since diagnosis (years)	3.4 $\pm$ 1.7	5.7 $\pm$ 3.1	12.5 $\pm$ 9.1
RTSS at the inclusion visit	9.8 $\pm$ 2.6	9.8 $\pm$ 2.8	10.1 $\pm$ 2.9
Average RTSS week 1	6.5 $\pm$ 3.3	6.8 $\pm$ 3.4	7.0 $\pm$ 3.4
RQLQ score at the inclusion visit	4.3 $\pm$ 1.0	2.5 $\pm$ 1.0	2.7 $\pm$ 1.0
RQLQ score week 1	4.8 $\pm$ 1.1	2.1 $\pm$ 1.1	2.2 $\pm$ 1.2
Concomitant comorbidities (<i>n</i> , %)			
Asthma	22 (8.7)	30 (12.0)	17 (5.6)
Sinusitis	11 (4.3)	14 (5.6)	38 (12.5)
Atopic dermatitis	62 (24.5)	38 (15.2)	26 (8.6)
Food allergy	20 (7.9)	25 (10.0)	23 (7.6)
Treatments for AR on the day of the consultation (<i>n</i> , %)			
Oral antihistamines	189 (74.7)	186 (74.4)	237 (78.2)
Nasal corticosteroids	65 (25.7)	76 (30.4)	95 (31.4)
Nasal antihistamines	24 (9.5)	28 (11.2)	28 (9.2)
Leukotriene receptor antagonist	18 (7.1)	19 (7.6)	10 (3.3)
Decongestants	0 (0)	2 (0.8)	9 (3.0)
Ocular chromone	63 (24.9)	52 (20.8)	7 (2.3)

Results are given as the number (percentage) or the mean $\pm$ SD.

ARIA, Allergic Rhinitis and its Impact on Asthma; RTSS, Rhinoconjunctivitis Total Symptom Score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

Statistical analysis

All statistical analyses were performed with SAS software (version 9.2, SAS Institute Inc., Cary NC, USA).

The MID in the RTSS was determined for each age group using two distinct but widely adopted approaches: anchor-based methods and distribution-based methods.

The anchor-based approach consisted in comparing the difference between the mean RTSSs for the first and second weeks (Δ RTSS) with the change in the GRCS score (the anchor). The MID then corresponds to the mean Δ RTSS in patients having scored -3 , -2 , $+2$ or $+3$ for the anchor at the end of the second week (15, 21, 22). The MIDs for the improvement and worsening are determined separately because differences between the two cannot be ruled out *a priori* (i.e. nonsymmetrical changes). This methodology has already been used to determine the MID in the QoL score [as measured by the RQLQ and validated by Juniper (15)] in moderate-to-severe ragweed-induced AR. The relationship between Δ RTSS and the GRCS score can also be analysed in a linear regression, with residual analysis being used to find the best model. In this regression-based method, the whole data set is considered (i.e. not just values of -3 , -2 , $+2$ or $+3$); the MID for the improvement is then determined as the value of Δ RTSS that corresponds a score of $+2$ on the GRCS

regression line. Furthermore, receiver operating characteristic (ROC) curves were used to identify the Δ RTSS with the best sensitivity and specificity, to discriminate between 'improved' and 'unchanged' patients (based on a GRCS score change of $+2$). Youden's index was used to confirm the cut-off value established with the ROC curves.

Although most of the MID estimations in the literature have used anchor-based strategies, distribution-based approaches have also been applied (23). These approaches rely on the statistical distributions of the score (such as the SD) and seek to identify the smallest change in the score that is not likely to be due to random variation in measurement (also referred to as a 'minimum detectable change') (24). The distribution-based approach uses different proportions (e.g. 0.2, 0.33 and 0.5) of the SD of the baseline score (5, 24–29) or 0.5 SD of the mean change in the score (12, 24, 27).

Furthermore, the MID in the RTSS was estimated using two different anchor-based methods (a regression method and the ROC-based procedure), with the RQLQ as the anchor and a threshold value of 0.5 as the MID in the RQLQ (15).

Results

Valid data sets for the estimation of the MID in the RTSS were obtained for 806 patients (253 children, 250 adolescents

Table 3 Estimated changes in the RTSS for each GRCS category and each age class

Global rating of change	Children		Adolescents		Adults	
	<i>n</i>	Change in the RTSS (mean ± SD)	<i>n</i>	Change in the RTSS (mean ± SD)	<i>n</i>	Change in the RTSS (mean ± SD)
[+6, +7]	19	2.89 ± 3.92	17	3.03 ± 1.76	26	2.88 ± 2.49
[+4, +5]	38	2.61 ± 2.62	27	2.77 ± 1.81	39	2.22 ± 2.61
[+2, +3]	48	1.19 ± 2.85	53	1.73 ± 2.51	43	1.66 ± 2.14
[-1, 0, +1]	90	0.52 ± 1.95	104	0.35 ± 1.97	123	0.21 ± 2.38
[-3, -2]	24	-0.69 ± 2.11	24	-1.10 ± 1.83	30	-0.94 ± 1.63
[-5, -4]	9	-1.69 ± 2.91	9	-1.75 ± 1.96	28	-1.19 ± 2.51
[-7, -6]	8	-2.61 ± 2.39	2	-0.71 ± 0.20	8	-3.49 ± 1.24

RTSS, Rhinoconjunctivitis Total Symptom Score; GRCS, global rating of change scale; SD, standard deviation. The line in bold type (i.e., a GRCS score of +2 or +3), corresponds to the minimal important improvement.

and 303 adults). The baseline characteristics of each age group are shown in Table 2. On the day of the consultation, about 90% of the patients were rated by the physician as having moderate-to-severe AR [according to the ARIA criteria (3)]. All patients were taking one or more types of symptomatic medication for AR (Table 2).

Estimation of the MID in the RTSS using the GRCS in the anchor-based method

A change of +2 (for the improvement) represents a 28% change on the 7-point GRCS and is considered to be clinically significant (5, 15, 21, 22). For each rating of the GRCS, the corresponding Δ RTSS (when comparing the first and second weeks) is shown in Table 3. For patients who experienced a minimal clinically important improvement (i.e. a GRCS score of +2 or +3), the mean (median) reductions in the average RTSS were 1.19 (1.14) in children, 1.73 (1.71) in adolescents and 1.66 (1.57) in adults. The results for the improvement and worsening were not symmetrical and thus prevented us from combining the results for a more precise estimate. The results of the Δ RTSS vs GRCS regression analysis were significant for each age group, with Pearson's correlation coefficients higher than the recommended correlation threshold of 0.30–0.35 (based on Cohen's rules of

thumb) for an acceptable association between the anchor and a patient-reported change in score (12). The slope of the regression line gives an overall estimate of the Δ RTSS corresponding to the change in the GRCS score (Table 4).

We also used a ROC curve anchor-based method to estimate the MID in the RTSS. The area under the curve (AUC) of the ROC curves represents the probability with which the RTSS correctly discriminates between improved and unimproved patients (based on the GRCS). An AUC of 0.7–0.8 corresponds to an acceptable degree of the discrimination (30). Our results show a ROC AUC over 0.71 in all three age groups (Table 4). By calculating Youden's index (the point on the ROC curve that is farthest from the diagonal line of equality), we found that the RTSS cut-off changes associated with a change of +2 in the GRCS score ranged from 1.05 to 1.28 in the three age groups (Table 4).

Estimation of the MID in the RTSS with two distribution-based methods

The distribution of the average RTSS during the first week of the study was used to calculate the SD. The MID in the RTSS corresponding to different proportions of the SD (0.2, 0.33 and 0.5) of the baseline score (from the first week) is shown in Table 5. In the three age groups, the MID in the

Table 4 The MIDs in the RTSS, estimated for the improvement in the GRCS score of +2 using the regression (mean ± SD) and the ROC curve methods

Regression	Children (<i>n</i> = 236)	Adolescents (<i>n</i> = 236)	Adults (<i>n</i> = 297)
Change in RTSS	1.24 ± 0.17	1.33 ± 0.14	1.13 ± 0.14
Pearson's correlation coefficients	0.47*	0.55*	0.53*
ROC curve	Children (<i>n</i> = 101)	Adolescents (<i>n</i> = 81)	Adults (<i>n</i> = 82)
RTSS cut-off change†	1.28	1.14	1.05
Sensitivity/specificity	0.58/0.77	0.71/0.79	0.68/0.73
ROC AUC [95% CI]	0.71 [0.64–0.78]	0.79 [0.72–0.86]	0.77 [0.69–0.84]

MID, minimally important difference; RTSS, Rhinoconjunctivitis Total Symptom Score; GRCS, global rating of change scale; ROC AUC, area under the receiver operating characteristic curve; CI, confidence interval.

**P* < 0.0001.

†Youden's index (*J*), defined as $J = \max [(sensitivity(c) + specificity(c) - 1)]$.

Table 5 The MID in the RTSS, estimated with the distribution-based methods as a function of the proportion of the SD

	Children (<i>n</i> = 250)	Adolescents (<i>n</i> = 247)	Adults (<i>n</i> = 301)
SD of the RTSS during the first week	3.30	3.44	3.41
0.5 SD	1.65	1.72	1.70
0.33 SD	1.09	1.14	1.13
0.2 SD	0.66	0.69	0.68
0.5 SDs of the mean change in the RTSS (first vs second week)	1.40	1.22	1.34

MID, minimally important difference; RTSS, Rhinoconjunctivitis Total Symptom Score; SD, standard deviation.

RTSS ranged from 1.09 to 1.13 (based on 0.33 SDs of the baseline score). When based on 0.5 SDs of the mean change (i.e. first week vs second week), the MID ranged from 1.22 to 1.40 (Table 5).

Estimation of the MID in the RTSS using the RQLQ score as the anchor

The results of the Δ RTSS vs Δ RQLQ regression analysis were significant for each age group ($P < 0.0001$). Pearson's correlation coefficients for the children, adolescents and adults were 0.33, 0.38 and 0.41, respectively. The coefficient in children is between the recommended correlation thresholds (0.30–0.35) for considering an association between the anchor and a patient-reported change in a score to be acceptable (12), and the coefficients in adolescents and adults were above that range. The Δ RTSS associated with the improvement of 0.5 in the RQLQ score ranged from 0.89 to 1.20 (Table 6).

We also used a ROC curve to estimate the MID in the RTSS with the RQLQ score as the anchor. The ROC curve based on a 0.5-point improvement in the RQLQ score provided an acceptable degree of the discrimination, because the AUC was over 0.75 in all three age groups (Table 6) (30). By

Table 6 Estimated MID in the RTSS using the regression and ROC curve methods with the RQLQ as the anchor

	Children	Adolescents	Adults
Regression method	1.12 $\pm$ 0.14 (<i>n</i> = 242)	1.20 $\pm$ 0.13 (<i>n</i> = 237)	0.89 $\pm$ 0.12 (<i>n</i> = 297)
ROC curve	1.62	0.88	1.17
Cut-off changes*	AUC = 0.75 (<i>n</i> = 111)	AUC = 0.83 (<i>n</i> = 99)	AUC = 0.84 (<i>n</i> = 117)

MID, minimally important difference; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; ROC, receiver operating characteristic.

*Youden's index (*J*), defined as $J = \max [(sensitivity(c) + specificity(c) - 1)]$.

calculating Youden's index, we found that the cut-off for the change in the RTSS was close to 1 unit in adolescents and adults and 1.6 units in children (Table 6). Furthermore, the ROC curve for the whole population (AUC = 0.81, n = 194) indicated a cut-off for the change in the RTSS change of 1.14 (data not shown).

Discussion

The present prospective study used three different anchor-based methods (with a GRCS as the external criterion) and two distribution-based methods to estimate the MID in the RTSS in children, adolescents and adults suffering from grass-pollen-induced AR. Furthermore, the MID in the RTSS was estimated using two different anchor-based methods with RQLQ as the external criterion. The estimates provided by each of the different methods in the different age groups ranged from 0.88 to 1.73, with most of the values ranging consistently from 1.0 to 1.2. A change of at least 1 RTSS unit can thus be considered as the MID in this population. In the present observational study, the patients were treated according to normal clinical practice in a 'real-life' setting. The main inclusion criteria were a baseline RTSS ≥ 6 , to give sufficient room for the improvement and thus avoid floor effects related to low initial levels of symptom intensity.

Anchor-based methods are generally recommended for estimating MIDs, whereas distribution-based methods are considered to be useful for providing supportive evidence (5, 12). The anchor-based methods use either a patient-reported outcome (such as the widely used 15-point GRCS (15, 21, 22) in the present study) or previously established study outcomes (31, 32) to directly establish the importance of changes perceived by the patient. The use of patient-reported retrospective measures of change as 'external' anchors for the estimation of the MID was initiated by researchers at McMaster University (Hamilton, Canada) (5). Juniper et al. (15) established the MID in the RQLQ score by applying the anchor-based method to a group of 28 adult patients with a GRCS score of [+2, +3] for the improvement or [−3; −2] for worsening. In the present study, the same anchor-based method was used on twice as many patients in each of the three age groups to estimate the MID in RTSS. The regression and ROC curve methods take into account the data from all the patients (not only the data from the group of patients with a GRCS score of [+2, +3]) and thus are expected to provide more accurate estimates of the MID. In adolescents and adults, the MIDs in the RTSS estimated with the regression and ROC curve methods were somewhat lower than those calculated using the 'small improvement group' method. A threshold of 2 GRCS units was used for both the regression method and the ROC curve method because this value was previously employed to estimate the MID for validated QoL questionnaires in AR (15) and in asthma (21, 33). Use of a GRCS score as the anchor is not ideal because this metric reflects a patient's subjective assessment of change. However, given that the lack of satisfactory objective measurements in AR and the GRCS's good sensitivity to change, the GRCS is

currently the most appropriate choice for this disease. Furthermore, recall bias constitutes a limitation for GRCS-based methods. In an attempt to minimize this shortcoming, changes in AR symptoms were assessed with the GRCS over two consecutive weeks. Lastly, we used RQLQ as the anchor to complete the estimation of the MID in the RTSS; with the exception of the result of the ROC method in children, the five other estimations ranged from 0.88 to 1.20.

The distribution-based method mostly relies on a threshold of 0.5 SDs (5, 12, 26). However, it has been considered that the MID of 0.5 SDs is both clinically significant and meaningful but not necessarily minimal (12). Half of an SD is also the effect size used to estimate the MID in control questionnaires in AR and asthma (16, 31). A fifth of the SD (i.e. 0.2 SDs) is considered to represent a small effect and 0.5 SDs approximate a moderate effect (5, 12, 20, 34). In this context, it has been suggested that 0.33 SDs are a good approximation of the MID (12, 25, 29, 32). In the present study, the MIDs in the RTSS estimated using 0.33 SDs were around 1.2 units. This value is close to the estimations made with the other distribution-based method (0.5 SDs of the mean change in the RTSS).

In the literature, more weight is given to MIDs estimated using anchor-based methods because the distribution-based approach (i) bears no relation to individual patient assessments, (ii) depends closely on the variability of the score in the population studied and (iii) is influenced by the sample size (5, 12, 27). Concordance between methods is, however, an important factor in confirming the choice of an MID. Hence, in the present study, the MID in the RTSS ranged from 1.0 to 1.2 units in children, adolescents and adults. If the value is rounded to the nearest whole number [as performed conventionally (35)], the MID for the improvement in the RTSS would be 1 unit. As the MID may be influenced by disease severity (12, 30), this value should be considered as the lower bound of the MID for the population studied here, that is patients with an RTSS of 5–8.

The MIDs in the mini-RQLQ score and in a four-component nasal symptom score (T4NSS) have been previously estimated in 204 adults with mild-to-moderate seasonal or perennial AR by pooling nine different small studies (20). The MID in the T4NSS was calculated using (i) anchor-based methods (either in a subset of patients with a GRCS score of +1 or +2 or by linear regression to determine the change in T4NSS associated with a score of 1.5 units in the GRCS) and (ii) a distribution-based method (0.2 SD). These thresholds for clinical importance were lower than those used in the present study and other previous studies (5, 10, 15). The choice of these thresholds resulted in low estimates for the MID in the T4NSS (0.28 units and 0.23 units using the anchor-based methods and 0.59 units using the distribution-based method) and the MID in the mini-RQLQ score (relative to the value published by Juniper et al.) (36). Although these latter values correspond to the MIDs for four individual symptoms (rather than six for the RTSS), they are clearly lower than the rounded-down value of 1 RTSS unit estimated in the present study.

Due to the large number of investigating centres, we cannot rule out a risk of heterogeneity in the way the questionnaires

were administered by the physicians and/or interpreted by the patients. In an attempt to reduce this risk, data collection was standardized through the use of booklets containing comprehensive instructions on filling out the questionnaires. The investigators were experienced physicians involved in allergic rhinitis management, and all had the expertise required to explain the booklet's questionnaires and answer any related questions.

In conclusion, our results suggest that the MID for the improvement of the RTSS in grass-pollen-induced AR is at least 1 unit in children, in adolescents and in adults. This value appears to be the smallest meaningful change in the RTSS.

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Authors contribution

Philippe Devillier made substantial contributions to study conception and design and data acquisition and analysis. He drafted the article. Olivier Chassany made substantial contributions to study conception and design and data acquisition and analysis. He also revised the article critically for important intellectual content. Eric Vicaut made substantial contributions to study conception and design and data acquisition and analysis. He also revised the article critically for important intellectual content. Olivier de Beaumont made substantial contributions to study conception and design and revised the article critically for important intellectual content. Jean-François Dreyfus made substantial contributions to study conception and design and data acquisition and analysis. He revised the article critically for important intellectual content. Bruno Robin made substantial contributions to study conception and design and data acquisition and analysis. He helped to draft the article. Philippe-Jean Bousquet made substantial contributions to the study conception and design and data analysis and interpretation. He revised the article critically for important intellectual content. All the above-cited individuals gave their final approval of the version to be published.

Conflicts of interest

Philippe Devillier has received consulting fees, honoraria for lectures and/or research funding from MSD Schering-Plough, GlaxoSmithKline, AstraZeneca, ALK, Meda Pharma and Stallergenes. Olivier Chassany has received consulting fees, honoraria for lectures and/or research funding from Stallergenes. Eric Vicaut has received consulting fees, honoraria for lectures and/or research funding from Stallergenes. Olivier de Beaumont is an employee of Stallergenes SA. Jean-François Dreyfus has received consulting fees from Stallergenes. Bruno Robin is an employee of Stallergenes SA. Philippe-Jean Bousquet has received consulting fees, honoraria for lectures and/or research funding from Stallergenes, Phadia-Thermo-Fisher and MSD Schering-Plough.

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