

Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care

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Summary

Background Allergic rhinitis (AR) severity is evaluated using scores such as Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) and total symptom score (TSS). However, a simple assessment is needed to enable physicians to evaluate the severity of the AR and the efficacy of the treatment.

Objective The main objective was to validate visual analogue scale (VAS) as a simple quantitative tool to assess the burden of AR in primary care.

Methods The study was multi-centre prospective observational conducted in patients consulting general practitioners for symptomatic rhinitis. VAS, RQLQ and TSS6 were assessed at the consultation day and 14 days later, and changes were analysed using paired test. Correlations between VAS, RQLQ and TSS6 were assessed. Cut-off levels for VAS, which discriminate significant from insignificant changes, were established using Receiver Operating Characteristic curves.

Results A total of 990 patients were included in the study. According to allergic rhinitis and its impact on asthma classification, mild intermittent rhinitis was diagnosed in 20% patients, mild persistent in 17%, moderate/severe intermittent in 15% and moderate/severe persistent in 48%, at the consultation day. At day-14, rhinitis symptoms and QoL improved significantly in almost all patients. Impairment incurred by AR and assessed with VAS improved also. The established cut-off variation of 23 mm for VAS was associated with a cut-off variation of 0.5 for RQLQ. Sensitivity analysis with RQLQ and TSS6 scales confirmed the aptitude of the cut-off value (23 mm) to discriminate changes in symptoms and QoL.

Conclusion and Clinical Relevance The VAS can detect with high sensitivity the variations of symptoms and QoL in patients with AR.

Keywords allergic rhinitis, ARIA, observational study, rhinoconjunctivitis quality-of-life questionnaire, total symptom score, visual analogue scale

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Introduction

Allergic rhinitis (AR) comprises classical symptoms such as nasal and ocular symptoms, and impairment in quality-of-life (QoL) [1, 2]. QoL and symptoms severity can be evaluated using scores such as Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) and total symptom score (TSS) respectively. However, a simple test is needed to enable physicians to evaluate the severity of AR and to assess treatment efficacy for this disease.

Visual analogue scale (VAS) is a simple quantitative measure largely used to assess the severity of AR [3–5].

The VAS was proposed by the Joint Task Force on Practice Parameters for the symptom severity assessment of AR [5]. This simple instrument was shown to correlate significantly with the severity of rhinitis, assessed by the allergic rhinitis and its impact on asthma (ARIA) criteria and by RQLQ score [3, 6–8]. VAS was also used in the evaluation of the efficacy of AR treatments [3, 5, 9–12]. Nevertheless, still there is no robust evaluation of this scale value and assessment of other patient-reported outcomes (PROs) is encouraged [13]. A *post hoc* analysis of a randomized cluster trial had compared the responsiveness of VAS score with RQLQ and TSS, at baseline

and after 15 days of treatment [14]. This analysis showed that VAS is highly sensitive to changes. However, these results are issued from post hoc analysis and prospective studies are still required.

Such as in asthma [15–18], a new concept including disease control and treatment responsiveness has just emerged for AR [19–22]. Although most patients have controlled symptoms during treatment, some are still uncontrolled leading to the concept of severe chronic upper airway disease (SCUAD) [23]. A *post hoc* analysis to investigate SCUAD in AR was carried out in a cluster randomized trial. Using VAS levels and ocular symptoms, uncontrolled rhinitis after 2 weeks of treatment was found in around 18.9% of patients [24]. However, these results need validation in prospective real life studies.

A French observational prospective multi-centre study (EVEIL: Echelle Visuelle analogiquE dans la rhinite allergique) was carried out to evaluate the responsiveness of VAS in patients consulting general practitioners (GPs) for AR and treated as per clinical practice. The main objective of this study was to validate VAS as a simple quantitative tool to assess the burden of AR in primary care.

Methods

Study design

This study was an observational prospective multicenter and carried out throughout France (EVEIL: Echelle Visuelle analogiquE dans la rhinite allergique). The primary outcome was to validate VAS as a simple quantitative tool to assess the burden of AR in primary care. This validation was performed by assessing the correlation and the cut-off change in VAS associated with the clinically minimal change in RQLQ over 15 days. Secondary outcomes included the correlation between VAS and TSS and the cut-off change in VAS associated with clinically significant changes in both RQLQ and TSS over 15 days. GPs were randomly selected by means of geographic stratification. Physicians filled a questionnaire on the consultation day including socio-demographic data, diagnostic history, rhinitis symptoms, concomitant diagnosed pathologies and treatment prescription. The management of AR was on the physician's discretion.

Study population

Patients were included in the study after oral informed consent was obtained and after approval of the protocol by the Ethics Committee of Montpellier, France. Patients were enrolled during a year (February 2010–January 2011) and were selected from all regions of France to rule out any geographic or seasonal parameter. All

patients fulfilled the following inclusion criteria: patients over 18 years of age with a diagnosis of AR and presenting clinical symptoms of AR on the consultation day.

Outcome measures

Outcome measures such as TSS, RQLQ and VAS were assessed by the patients on the consultation day and 14 days later.

Total symptom score 6. Patients recorded symptom severity ratings in a form for six individual AR signs/symptoms (Nasal symptoms: sneezing, rhinorrhoea, nasal pruritus, nasal congestion and non-nasal symptoms: ocular symptoms (including itchy, red and watery eyes) and itchy ears and/or palate). A score ranging from 0 to 3 was used for each symptom: 0, no symptoms; 1, mild symptoms (symptoms clearly present but minimal awareness, easily tolerated), 2, moderate symptoms (awareness of bothersome but tolerable symptoms); and 3, severe symptoms (symptoms hard to tolerate and/or cause interference with activities of daily living, sleeping or both). The TSS6 was the sum of nasal and non-nasal symptoms ratings ranging from 0 (absence of symptoms) to 18 (very severe).

Quality-of-life. QoL was assessed using the disease-specific RQLQ score. In this 28-item questionnaire, patients evaluated their QoL impairment during the previous week. Items were rated from 0 (no impairment) to 6 (maximal impairment). The questionnaire provided an overall score and scores in seven domains: limitation of activities, sleep, non-hayfever symptoms, practical problems, nasal symptoms, eye symptoms and emotions. The total RQLQ score ranged from 0 to 6.

Visual analogue scale. The patients expressed the global discomfort caused by their AR during the previous week using a VAS. Scores ranged from 'not at all bothersome' (0 mm) to 'intolerable bothersome' (100 mm).

Sample size

Assuming a correlation between VAS and RQLQ of 0.4–0.5, with a risk of 0.05 and a precision less than 0.33, 1100 evaluable patients were needed for this analysis. Taking into consideration that 50% of patients would be lost to follow-up, 2200 patients were expected to be recruited for this study.

Statistical analysis

Qualitative data were expressed in percentages and frequencies, and quantitative data in means and standard

deviations (SD). The analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA) with a significance level of 5%.

The changes of RQLQ, TSS6 and VAS were observed between consultation day and 14 days later. Absolute values were computed to take positive and negative evolutions into account. Correlations (Spearman rank test) were assessed between VAS, RQLQ and TSS6. In the global RQLQ score, 0.5 is demonstrated as clinically minimal change on a scale ranging from 0 to 6 [25]. Using receiver operative characteristic (ROC) curves [26], VAS cut-off change was established with RQLQ minimal change of 0.5 (primary outcome). Youden index (J), defined as $J = \max \{Se(c) + Sp(c) - 1\}$ was also used to confirm the cut-off value established with the ROC curve. The sensitivity of VAS cut-off values (Se) was calculated for different cut-offs of RQLQ and TSS6 scales.

Post hoc assessment of SCUAD

Criteria for SCUAD assessment were based on a previous cluster randomized trial [24]. Uncontrolled SCUAD allergic rhinitis was defined as VAS level ≥ 50 mm and/or presence of ocular symptoms (ranked ≥ 2) at the end of the 2-week treatment. Ocular symptoms were evaluated using the corresponding item of the TSS6, ranging from 0 to 3.

Results

A total of 191 GPs throughout France participated in the study and 161 enrolled at least one patient. A number of 990 consecutive patients consulting for AR were included.

Baseline characteristics of patients

Among the 990 subjects included in the study, 981 (99%) patients were analysed. Two patients were excluded from this analysis. Patient flow is presented in Fig. 1.

The baseline characteristics of patients are presented in Table 1. Half of patients ($n = 477$, 49%) had a proven diagnosis of allergy using skin prick tests (80% of patients with a documented diagnosis) and/or serum allergen specific IgE (73.5% of patients with a documented diagnosis).

The majority of patients (76%) were sensitized for at least one allergen. Tree pollens (49%) and grasses (44%) were the most common allergens.

On consultation day, all the patients received treatment prescription: 919 patients (94%) received H1 antihistamines (6% of cases were nasal administration, 84% oral administration and 10% both routes of administration), 734 patients (75%) received corticosteroids (88% nasal, 8% oral and 4% both), 197 patients (20%) were treated with decongestants (86% nasal, 13.5% oral and 1.5% both), 294 patients (30%) were treated with ocular H1 antihistamines, 70 patients (7%) were treated with cromoglycate-like drugs (83% ocular and 17% nasal), 68 patients (7%) with an anti-leukotriene and 53 patients (5%) with other treatments.

Changes in clinical outcomes evaluated with RQLQ, TSS6 and VAS

QoL, symptoms and the global discomfort caused by AR assessed with RQLQ, TSS6 and VAS, respectively, improved significantly after 14 days. Improvement of the clinical outcomes is presented in Fig. 2 as means

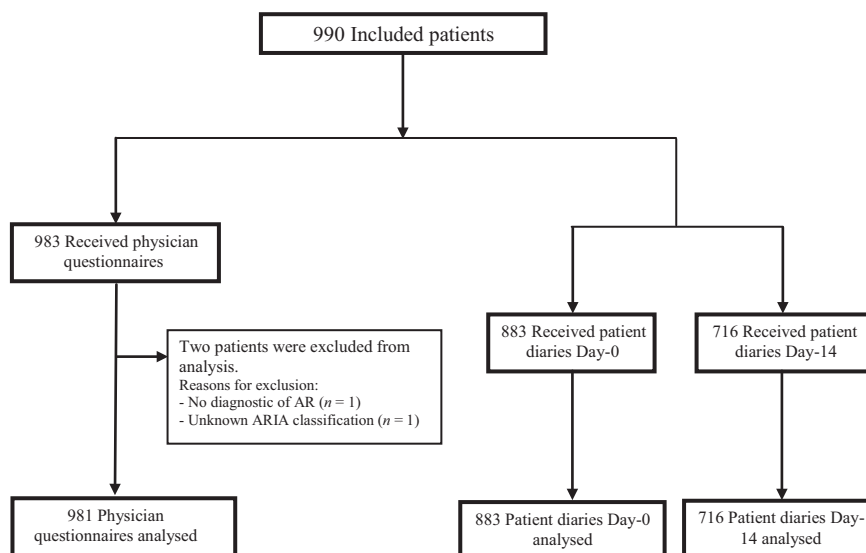


Fig. 1. Patient flow.

Table 1. Demographic and clinical characteristics at baseline

	N = 981
Male gender	432 (44)
Age (years)	42 ± 16
Allergy diagnosis*	477 (49)
ARIA classification	
Mild intermittent	197 (20)
Moderate to severe intermittent	150 (15)
Mild persistent	166 (17)
Moderate to severe persistent	466 (48)
TSS6	9.74 ± 3.81
RQLQ	2.71 ± 1.08
VAS level (mm)	60.9 ± 19.8
Concomitant pathologies	
Asthma	191 (19)
COPD	18 (2)
Sinusitis	66 (7)
Urticaria	41 (4)
Eczema	100 (10)
Treatments prescribed on consultation day	
Oral antihistamines	865 (88)
Nasal antihistamines	146 (15)
Nasal corticosteroid	644 (66)
Decongestant	197 (20)
Ocular antihistamines	394 (10)
Cromone	70 (7)

Results are given in numbers and percentages *n* (%) or means ± SD.

*Allergy diagnosis made by skin prick tests and/or serum specific IgE. ARIA, allergic rhinitis and its impact on asthma; TSS6, total symptom score; RQLQ, Rhinoconjunctivitis Quality-of-Life Questionnaire; VAS, visual analogue scale; COPD, Chronic obstructive pulmonary disease.

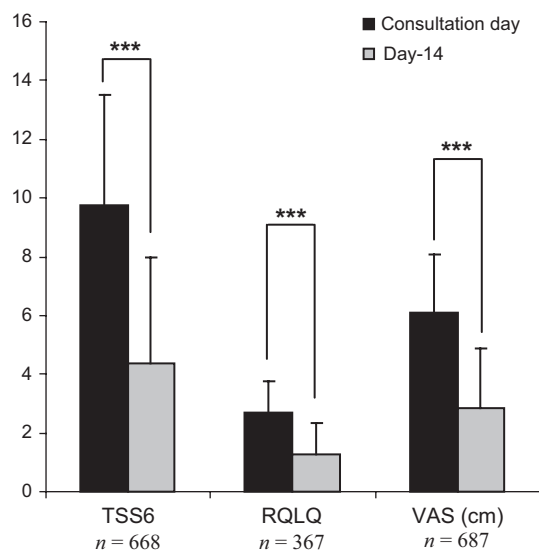


Fig. 2. Changes in clinical outcomes and scores between consultation day and 14 days later (*** $P < 0.001$). Total symptom score (TSS6), Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) and visual analogue scale (VAS) values were available at baseline and at Day-14 in 668 patients, 367 patients and 687 patients respectively.

Table 2. Correlation between VAS, RQLQ and TSS6 scores

	Change over 15 days	
	RQLQ	TSS6
VAS change over 15 days	0.77 ($P < 0.0001$)	0.80 ($P < 0.0001$)

Analysis was performed with Spearman rank correlation.

TSS6, total symptom score; RQLQ, Rhinoconjunctivitis Quality-of-Life Questionnaire; VAS, visual analogue scale.

and SD. TSS6, RQLQ and VAS values were available at baseline and at day-14 in 668 patients, 367 patients and 687 patients respectively.

Considering a clinically relevant minimal change of 0.5 in RQLQ score, the majority of patients (81%) had a significant improvement in QoL at day-14. However, 15% had an unchanged QoL between consultation day and day-14, and 4% had a significant worsening in QoL at day-14.

Correlations between changes in VAS and RQLQ and, VAS and TSS6 over 15 days were positive and significantly strong (Table 2).

Determination of VAS cut-off change

Using ROC curve and Youden index, the VAS cut-off change associated with the clinically relevant minimal change of 0.5 point in RQLQ is evaluated at 23 mm (Area under the curve (AUC) 0.887, $P < 0.0001$). This cut-off change is defined as the minimal important difference (MID) of VAS associated with a clinically relevant change in QoL. ROC curves are shown in Fig. 3.

This VAS cut-off change was independent from the initial severity of AR. The VAS cut-off change was 23 mm in patients with mild persistent and intermittent AR ($n = 327$, AUC = 0.8455, $P < 0.0001$) and 22 mm in patients with moderate to severe persistent and intermittent AR ($n = 550$, AUC = 0.9122, $P < 0.0001$).

VAS cut-off change associated with RQLQ and TSS6 minimal significant changes

As RQLQ and TSS6 do not assess the same dimensions, a VAS composite cut-off variation was established for the RQLQ and TSS6 combination (RQLQ change ≥ 1 and TSS6 change ≥ 5). In most trials, patients under placebo have a mean improvement of RQLQ around 1 point [9, 23, 24, 27–29], we therefore considered a score change of 1 point as a clinically significant change of RQLQ. The TSS6 was considered to be improved if patients had a 50% change in symptoms improvement [28–34]. The baseline TSS6 was close to 10 in our study and we considered an *a priori* change of 5 points, on a scale ranging from 0 to 18, as a clinically relevant improvement of symptoms.

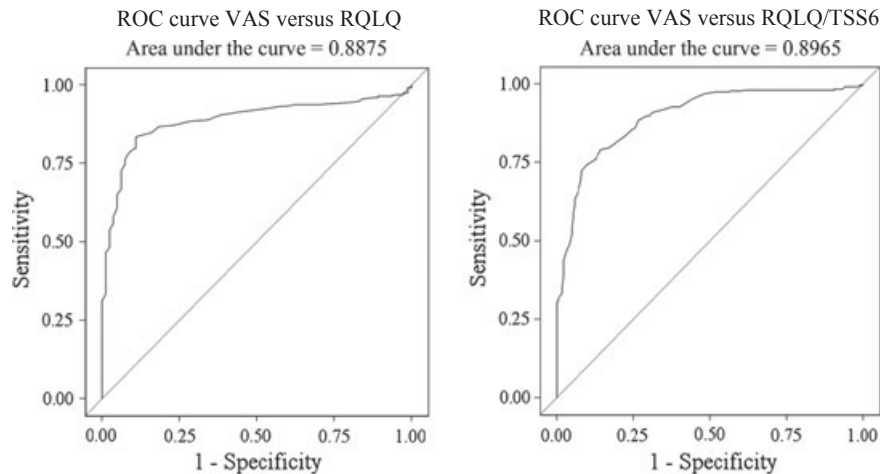


Fig. 3. Receiver operative characteristic (ROC) curves evaluating the visual analogue scale (VAS) cut-off change.

Table 3. Sensitivity of VAS cut-off variations associated with RQLQ alone (23 mm) and RQLQ/TSS6 (36 mm)

	Cut-off variations				
	RQLQ			TSS6	
	0.57	0.89	1.19	4	6
VAS cut-off variations					
23 mm	0.862	0.910	0.940	0.894	0.952
36 mm	0.626	0.694	0.761	0.660	0.784

TSS6, total symptom score; RQLQ, Rhinoconjunctivitis Quality-of-Life Questionnaire; VAS, visual analogue scale.

VAS cut-off change associated with the clinical significant change of RQLQ = 1 and TSS6 = 5 was also established: 36 mm (AUC 0.896, $P < 0.0001$). This cut-off change is defined as the minimal significant change of VAS associated with a clinically relevant change in QoL and symptoms, simultaneously (Fig. 3).

Sensitivity (Se) of both values (23 mm and 36 mm) was calculated with different cut-off variations of RQLQ and TSS6. Results are showed in Table 3. The RQLQ cut-off variations of 0.57, 0.89 and 1.19 correspond to minimal change, moderate change and large change, respectively, as reported by Juniper et al. The cut-off values 4 and 6 of TSS6 were chosen as closer values to 5. These analyses showed that VAS cut-off variation of 23 mm carries a high sensitivity to discriminate clinically relevant changes in QoL and symptoms. VAS cut-off variation of 36 mm, composite of RQLQ and TSS6 variations, showed lesser sensitivity than 23 mm.

Evolution of VAS depending on RQLQ and/or TSS

A *post hoc* analysis was done to assess the VAS change in three categories of patients:

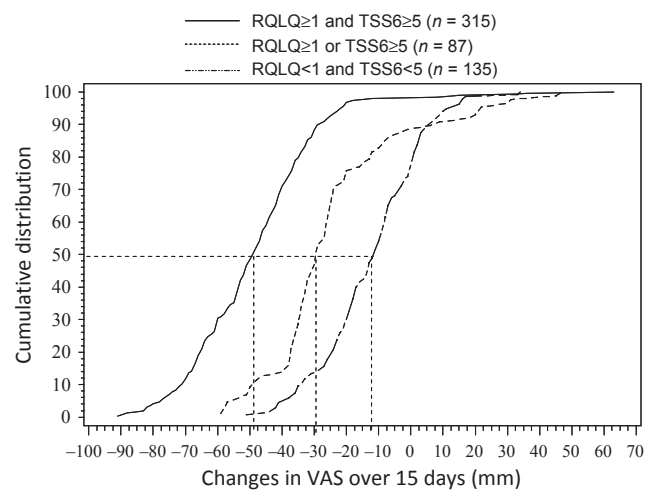


Fig. 4. Cumulative distribution of visual analogue scale (VAS) score changes depending on Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) and total symptom score (TSS6) changes.

- Patients with clinically significant improvement: improvement in RQLQ ≥ 1 and TSS6 ≥ 5 ($n = 315$)
- Patients with clinically moderate improvement: improvement in RQLQ ≥ 1 only or in TSS6 ≥ 5 only ($n = 87$)
- Patients without improvement: change in RQLQ < 1 and TSS6 < 5 ($n = 135$).

Cumulative distribution of changes in VAS is showed in Fig. 4. VAS variation was found to be dependent of the clinical change. Patients with no improvement ($n = 135$) had the lowest reduction in VAS levels (11 mm), patients with a clinically relevant improvement in QoL only or symptoms only ($n = 87$), had an intermediate reduction in VAS levels (29 mm) and patients with a clinically significant improvement in

QoL and symptoms ($n = 315$) had a mean reduction of 49 mm in VAS.

Uncontrolled rhinitis at day-14 and SCUAD patients

At day-14, there were 105 patients (15%) with a VAS > 50 mm and 114 patients (16%) with bothersome ocular symptoms (ranked ≥ 2 on a scale ranging from 0 to 3). Of these, 159 patients (22%) had a VAS > 50 mm and/or bothersome ocular symptoms.

Discussion

This study evidenced that VAS is valid in measuring the burden of AR in patients consulting GPs and treated as per clinical practice. The VAS is a self-reporting tool widely used to measure subjective perceptions. In addition to be effective in assessing the burden of AR, it is a very simple instrument (continuous scale ranging from 0 to 100 mm) allowing quick assessment. Changes in VAS greater than 23 mm (MID) can be considered of clinical importance, and thus may reflect the responsiveness to treatments. Data from a placebo-controlled, randomized, trial in patients treated for AR showed that VAS changes in placebo group were 12.7 mm (± 1.50) at day-29 and 18.0 mm (± 1.61) at day-85 [12]. Although the methodology and the assessment time differ from our study, these placebo VAS values were lower than our finding and thus clinically not significant.

In the *post hoc* analysis of a randomized cluster trial assessing VAS at baseline and after 15 days of treatment, the optimal cut-off in VAS was shown to be 30 mm [14]. This slight difference (7 mm) from our cut-off could be explained as follows: (1) the cut-off was calculated on the basis of RQLQ and TSS scores; (2) the patients in the mentioned investigational study were selected and randomized to receive treatment based on the ARIA guidelines or to the free-choice treatment group; (3) the patient population at baseline included a majority of severe rhinitis (more than 80%). Thus, our study might be more representative of the patients consulting in primary care and more valuable in clinical practice.

The changes in VAS values, after 14 days of treatment, were strongly correlated with changes in RQLQ and TSS6, meaning that these measures are similarly responsive to changes at the single-patient level. The VAS can detect, with high accuracy, the changes in AR-specific QoL and symptoms. The highest variations of VAS were observed in patients with a significant clinical improvement in QoL and symptoms (Change in RQLQ ≥ 1 and in TSS6 ≥ 5). The patients without any improvement are easily discriminated from those with clinically significant improvement. These results are in line with previous studies [14]. Compared with

RQLQ which is validated at the population level, the VAS is now validated at the single-patient level, and can be used in further prospective studies to better guide the treatment of AR patients in a stepwise manner.

TSS6 had been largely used in studies to evaluate the change in AR symptoms. In previous placebo-controlled randomized trials [28–31], a mean reduction of 50% in TSS was observed in the active group, whereas it was of 20–35% in the placebo group. The mean baseline TSS6 was almost 10 in our study, on a scale ranging from 0 to 18, 5 points (or change of 50%) as a clinically relevant improvement of symptoms is consistent with the previous results [28–31].

Juniper et al. proposed 0.5 point as a clinically minimal change in RQLQ score, ranging from 0 to 6 [35]. Our data showed that 5-point reduction in TSS6 was correlated with 0.89 and 1.19-point improvement in RQLQ score. Therefore, 1-point improvement in RQLQ and 5-point in TSS6 were considered a significant clinical improvement. A cut-off value of 36 mm was associated with a clinical improvement in QoL and in AR symptoms.

Despite treatments, some patients remained with uncontrolled rhinitis defined as severe chronic upper airway disease (SCUAD). SCUAD, a newly described phenotype of AR, applies only to patients who, despite adequate treatment, present a VAS ≥ 50 and/or significant ocular symptoms. The percentage of patients with uncontrolled rhinitis was 22% in this study. This result is in agreement with previous *post hoc* analysis showing 18.9%, the prevalence of SCUAD [24]. This prevalence was lower (11.4%) in a prospective study validating a self-assessment global score for AR control (five items scored from 1 to 5 assessing the rhinitis over the 2 previous weeks). This may be due to the different tools assessing the AR control. Nevertheless, special therapies are required for patients with SCUAD to alleviate their symptoms and their QoL impairment. Of note, a rhinitis classification taking into consideration the therapy necessary for control achievement is highly encouraged by the GA(2)LEN taskforce [13].

There are multiple approaches to determine the MID such as the distribution- and anchor-based approaches. These approaches examine the relationship between scores on the instrument whose interpretation is under question (the target instrument) and some independent measure (an anchor). In this study, single anchor-based method was used: the MID of the VAS was estimated using ROC curves based on RQLQ (the anchor) for which the MID has been established before [35]. Of note, linear regression could be also used but appears to be less sensitive than ROC curves. Other approach could be the 'Between-Patient Global Ratings'. A published paper in asthma assessed the use of a global

rating obtained from patients, rather than a validated anchor to determine changes in a questionnaire score [36]. They found that the alternative anchors lead to different estimates of small, moderate and large differences in questionnaire score. They concluded that the wording of the global question can affect the definition of meaningful change in the score. Therefore, to identify meaningful changes, we preferred to use a validated anchor rather than a global question that could be incorrectly understood.

Some limitations may exist in this trial, such as a number of recruited patients ($n = 990$) slightly lower than expected ($n = 1100$). However, analysis was enough powered to show significant changes ($\alpha = 0.05$). Of note, sample size was calculated with high accuracy (precision less than 3%).

In conclusion, our findings indicate that the VAS is a practical, sensitive and valid tool to monitor the burden of AR in clinical practice. Changes in VAS greater than 23 mm, or simply 2 cm (relatively easy to use in clinical practice), should be considered of clinical impor-

tance. Characteristics and outcomes of patients with SCUAD should be assessed in further larger prospective studies.

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Conflict of interest

Jean Bousquet has received Honoraria for scientific and advisory boards, lectures during meetings, press conferences from Stallergènes, Actelion, Almirall, AstraZeneca, Chiesi, GSK, Merck, MSD, Novartis, OM Pharma, Sanofi-Aventis, Schering Plough, Teva, Uriach. No other conflicts of interest.

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