

Analysis of allergen immunotherapy studies shows increased clinical efficacy in highly symptomatic patients

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Abstract

Background: The assessment of allergen immunotherapy (AIT) efficacy in the treatment for seasonal allergic rhinoconjunctivitis (SAR) symptoms is challenging. Allergen immunotherapy differs from symptomatic therapy in that while symptomatic therapy treats patients after symptoms appear and aims to reduce symptoms, AIT is administered before symptoms are present and aims to prevent them. Thus, clinical studies of AIT can neither establish baseline symptom levels nor limit the enrolment of patients to those with the most severe symptoms. Allergen immunotherapy treatment effects are therefore diluted by patients with low symptoms for a particular pollen season. The objective of this analysis was to assess the effect possible to achieve with AIT in the groups of patients presenting the most severe allergic symptoms.

Methods: Study centres were grouped into tertiles categorized according to symptom severity scores observed in the placebo patients in each centre (low, middle and high tertiles). The difference observed in the average score in each tertile in active vs placebo-treated patients was assessed. This allowed an estimation of the efficacy that could be achieved in patients from sites where symptoms were high during the pollen season.

Results: An increased treatment effect was observed in the most severe patients and was independent of the study analysed and symptom score used.

Conclusions: The use of a tertile approach to analyse efficacy in AIT in SAR clinical studies can give a more accurate assessment of potential clinical benefit.

The prevalence of seasonal allergic rhinoconjunctivitis (SAR) is on the rise with about 20% of the European population suffering from this disease, and approximately half of these individuals are allergic to grass pollen (1). Patients with SAR have bothersome nasal and eye symptoms.

Abbreviations:

AAdSS, Average Adjusted Symptom Score; AIT, allergen immunotherapy; ARTSS, Average Rhinoconjunctivitis Total Symptom Score; CI, confidence interval; EMA, European Medicines Agency; IR, index of reactivity; LS means, least square means; RTSS, Rhinoconjunctivitis Total Symptom Score; SAR, seasonal allergic rhinoconjunctivitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Moderate-to-severe SAR has a negative impact on the quality of life (2, 3) and may have significant economic implications (3, 4).

The severity of SAR symptoms correlates with the exposure to allergens in the environment (5). Symptomatic medications such as antihistamines and nasal corticosteroids are used, and allergen immunotherapy (AIT) is indicated when symptoms are severe. In contrast to symptomatic medication, AIT treats all rhinoconjunctivitis symptoms by tackling the underlying cause of SAR.

Clinical studies in SAR testing symptomatic medication and AIT have distinct features such as timing of patient randomization and enrolment, study duration, use of rescue medication and time of assessment of results. The main

difference between clinical studies testing symptomatic medication and AIT is that symptomatic medication is evaluated in patients with a threshold level of symptoms during the pollen season, whereas AIT starts months before the beginning of the pollen season, when patients are still asymptomatic and the intensity of the pollen season and the consequent symptom level are unknown. Therefore, if the intensity of the pollen season and the level of disease activity are low in parts of the patient population recruited in AIT studies, as a consequence, the efficacy of AIT can be underestimated, as a certain level of symptoms is necessary to demonstrate the activity of any therapy. In addition, AIT studies allow the use of rescue medication, further interfering with the assessment. In contrast, clinical trials assessing the efficacy of symptomatic therapies in patients with known symptom levels at the time of enrolment and without the use of rescue medication avoid the wide number of factors interfering with the assessment of treatment efficacy.

In an attempt to assess more precisely the benefit of AIT in patients with SAR, we tested a novel, post hoc approach analysing the primary efficacy results of three double-blind, randomized, placebo-controlled AIT studies. This approach used criteria that can be prespecified in a statistical analysis plan and included all patients recruited in the study. We propose that, by grouping the recruiting centres according to the symptom level observed in the placebo group, the magnitude of efficacy that can be achieved with AIT treatment can be assessed. Using this approach, we observe that the response to treatment is greater in patients who have been recruited in areas where the disease severity is the highest during the pollen season.

Methods–studies

The measure efficacy of AIT in allergic rhinoconjunctivitis studies is commonly based on the Rhinoconjunctivitis Total Symptom Score (RTSS) as a scoring system. The efficacy of active treatment is assessed by a decrease in the RTSS relative to placebo. Four nasal and two ocular symptoms are evaluated: nasal itching, sneezing, rhinorrhea, nasal obstruction, ocular itching and lacrimation. Patients score each

individual symptom as follows: 0 – no symptoms; 1 – mild symptoms; 2 – moderate symptoms; and 3 – severe symptoms (6). The daily RTSS is the sum of the individual symptom scores (i.e. with six symptoms, the total score will be between 0 and 18). The Average Rhinoconjunctivitis Total Symptom Score (ARTSS) is calculated as the average of the daily RTSS during the observation period.

The European Medicines Agency Guidelines (7) and the World Allergy Organisation (WAO) (8) recommend AIT studies in SAR should include a measure of rescue medication use as well as symptoms. The widely used RTSS does not reflect the true disease activity, because when rescue medication is taken, it decreases the RTSS. Different scores have been proposed to combine symptom and rescue medication scores. However, as most rescue medications have long-lasting effect, their effects are still evident in the following day; the Average Adjusted Symptom Score (AAdSS) based on the RTSS and adjusted for the use of rescue medication has been recently proposed (9, 10). It takes into account the highest RTSS on the preceding day and applies it for the day the rescue medication was taken and the following day. This adjustment for rescue medication intake reflects the treatment effect more precisely than the RTSS alone (10).

Data from 1539 patients suffering from SAR, who were included in three European studies with the 5-grass-pollen 300IR SLIT tablet (Oralair®), were used for this post hoc analysis: the adult VO34 (11), the paediatric VO52 (12) and the first season of the long-term adult VO53 (9) studies (Table 1). All three studies used similar basic designs (randomized, multinational, double-blind and placebo-controlled), the treatments were given in a pre- and coseasonal schedule (i.e. before and during the pollen season). One study tested a variety of doses (VO34), and another one (VO53) tested two preseasonal dosing schedules (VO53) (i.e. treatment beginning 2 or 4 months prior to the start of the pollen season). For consistency, the present work only used the data in the groups of patients treated with the 300IR dosage and for 4 months prior to the start of the pollen season. The two different symptom scoring methods were used as primary endpoints, ARTSS was used in studies VO34 and VO52 and the AAdSS in study VO53 (Table 1). However, ARTSS and

Table 1 Clinical studies used in the analysis of allergen immunotherapy according to symptom tertiles

Study	No. of patients	Treatment duration	Design	Dates	Efficacy endpoint
VO34	628 (18–45 years)	3 × daily; 7–8 months	Randomized, multinational, double-blind, placebo-controlled, three 5-grass tablet doses (100IR, 300IR and 500 IR)	2004–2005	Primary: ARTSS Secondary : AAdSS
VO52	278 (5–17 years)	1 × daily; 6–7 months	Randomized, multinational, double-blind, placebo-controlled, one 5-grass tablet dose (Oralair® 300IR)	2006–2007	Primary: AAdSS Secondary: ARTSS
VO53; Year 1	633 (18–50 years)	1 × daily; 6–7 months	Randomized, multinational, double-blind, placebo-controlled, two 5-grass tablet dosages (Oralair® 300IR given 2 and 4 months prior to pollen season)	2007	Primary: AAdSS Secondary: ARTSS

ARTSS, Average Rhinoconjunctivitis Total Symptom Score; AAdSS, Average Adjusted Symptom Score.

AAdSS were, respectively, used as secondary endpoints in studies VO53, and studies VO34 and VO52.

The analysis of the results by the tertile approach is based on the symptom severity data observed in the placebo-treated patients in each study site during the pollen season. This placebo reference value indicates the level of the disease activity during the evaluation period for the placebo group population in the corresponding area. To determine the tertiles, the following method was applied: pooled centres were ranked from the lowest mean considered score (AAdSS or ARTSS) in the placebo group to the highest mean considered score in the placebo group and gathered in three clusters or tertiles including approximately one-third of patients. The grouping of centres by tertiles is prespecified but retrospectively assigned, as the centres cannot be assigned to tertiles until the placebo results for each centre are known for that particular pollen season.

Statistical methods

The AAdSS and ARTSS during the pollen period while on treatment were analysed by tertile using an ANCOVA with treatment and pooled centre as main effects, and age, gender, asthma status and sensitization status as covariates (gender, asthma status and sensitization status being qualitative covariates; age being quantitative covariates). A point estimate and 95% CI for the difference in the adjusted LS means between each active treatment group and the placebo group were calculated. The relative difference was calculated as

follows: relative LS mean difference = $(\text{LS mean}_{\text{active}} - \text{LS mean}_{\text{placebo}}) / \text{LS mean}_{\text{placebo}} \times 100$. All analyses were performed using the SAS System® for Windows version 8.02 (or higher) (SAS Institute, Cary, NC, USA).

Results

The characteristics of the population of allergic patients included in the three studies have been previously published (9, 11, 12). For each study, the number of patients as well as the ARTSS and AAdSS for each tertile is indicated in Table 2. The mean ARTSSs in the placebo arm in the adult (studies VO34 and VO53) and in the paediatric (study VO52) populations during the entire pollen season were 4.93, 4.73 and 4.51, respectively. These values reflect the mean seasonal disease activity observed in the entire study populations. There was an absolute LS mean difference between the 5-grass-pollen tablet and placebo ARTSS of 1.35 in study VO34, of 0.51 in study VO53 and of 1.26 in study VO52.

In each study, when the centres were stratified according to the disease activity in the placebo group and analysed, there were substantial differences in the treatment effect observed in the tertiles with low symptom scores and in those with high symptom scores. In studies VO34 and VO53 (Table 2, Fig. 1A,B), the relative reduction in symptom levels in the 300IR 5-grass-pollen tablet vs placebo was, respectively, 29% and 10% for the total population but was 40% and 19% for the high tertile compared to only 14% and even

Table 2 Average Rhinoconjunctivitis Total Symptom Score and Average Adjusted Symptom Score by symptom tertiles for the three clinical studies

		Treatment group	N	ARTSS LS mean (SE)	Relative difference in LS Means vs placebo	P ^b	N	AAdSS LS Mean (SE)	Relative difference in LS Means vs placebo	P
VO34	Low	Placebo	51	3.72 (0.515)			40	3.91 (0.576)		
		300IR	45	3.19 (0.546)	−14.2%	0.3497	36	4.20 (0.572)	+7.3%	0.6901
	Medium	Placebo	50	5.12 (0.467)			53	6.09 (0.601)		
		300 IR	47	3.71 (0.457)	−27.6%	0.0153	49	3.62 (0.609)	−40.6%	0.0003
	High	Placebo	47	6.22 (0.676)			55	7.61 (0.674)		
		300 IR	44	3.72 (0.760)	−40.3%	0.0006	51	4.98 (0.700)	−34.6%	0.0007
VO53 ^a	Low	Placebo	73	3.49 (0.354)			73	4.81 (0.488)		
		300 IR (4 M)	64	3.62 (0.384)	+3.7%	0.7757	63	4.76 (0.527)	−0.9%	0.9448
	Medium	Placebo	62	4.54 (0.469)			66	6.34 (0.541)		
		300 IR (4 M)	56	4.26 (0.465)	−6.2%	0.5686	56	4.97 (0.556)	−21.6%	0.0350
	High	Placebo	70	6.64 (0.429)			66	9.58 (0.597)		
		300 IR (4 M)	68	5.41 (0.443)	−18.6%	0.0185	69	7.28 (0.599)	−24.0%	0.0005
VO52	Low	Placebo	45	3.53 (0.454)			45	4.72 (0.568)		
		300 IR	45	3.03 (0.444)	−14.0%	0.3765	45	3.67 (0.557)	−22.1%	0.1383
	Medium	Placebo	44	4.63 (0.486)			46	6.17 (0.712)		
		300 IR	43	3.45 (0.538)	−25.5%	0.0353	45	5.06 (0.733)	−18.0%	0.1614
	High	Placebo	46	5.56 (0.568)			44	7.33 (0.715)		
		300 IR	43	3.74 (0.552)	−32.7%	0.0076	41	4.27 (0.708)	−41.8%	0.0003

^aThe data are given only for the group of patients treated for 4 months (4 M) before the pollen season.

^bValues in bold indicate statistical significance.

AAdSS, Average Adjusted Symptom Score; ARTSS, Average Rhinoconjunctivitis Total Symptom Score; SE, Standard error.

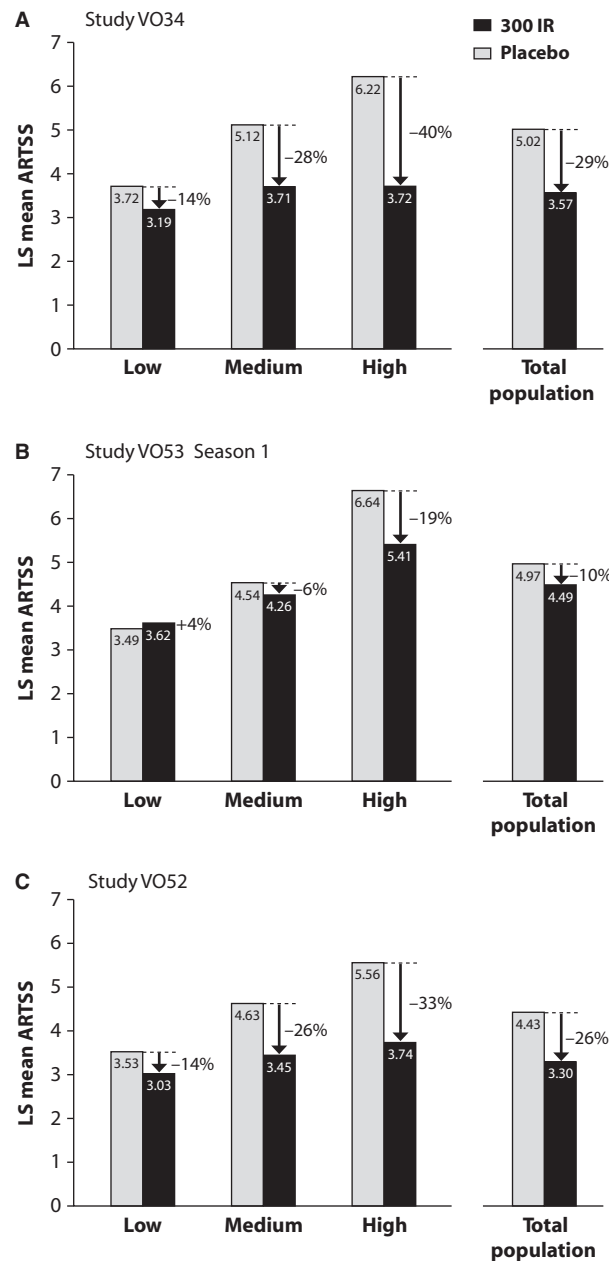


Figure 1 Treatment effect increases with greater disease severity – Average Rhinoconjunctivitis Total Symptom Score by tertiles in three clinical studies. ARTSS, Average Rhinoconjunctivitis Total Symptom Score; IR, index of reactivity.

a relative increase of 4% for the low tertile, respectively. Similarly, in study VO52 (Fig. 1C), the difference between active and placebo was 26% for the total population but was 33% for the high tertile compared to only 14% for the low tertile.

With the AAdSS scoring method (10), relative reductions in symptom levels in the 300IR 5-grass-pollen tablet vs placebo in studies VO34 and VO53 were, respectively, 30% and 18% for the total population but was 35% and 24% for the high tertile compared to an increase of 7% (VO34) and to

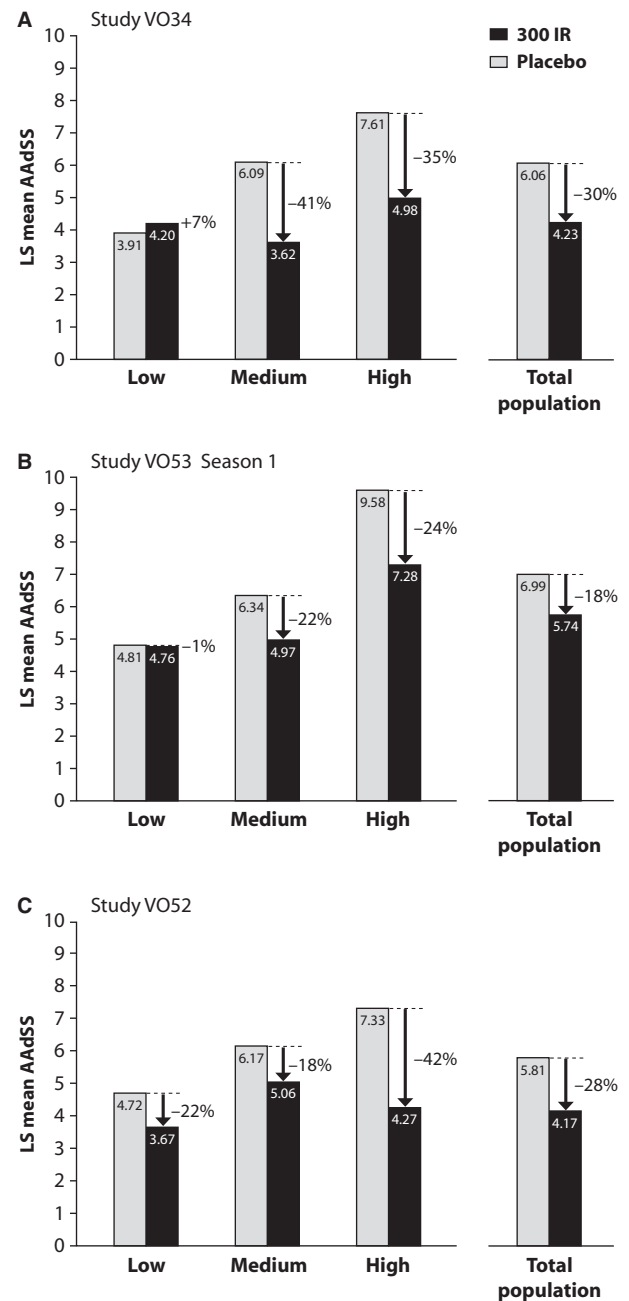


Figure 2 LS mean Average Adjusted Symptom Score by tertiles of pooled sites according to placebo mean in three clinical studies. IR, index of reactivity.

the absence of effect (1% reduction, VO53) for the low tertile, respectively (Table 2, Fig. 2A,B). Similarly, in study VO52 (Fig. 2C), the relative reduction was 28% for the total population but was 42% for the high tertile compared to 22% for the low tertile. Within a study, the ranking of the centres according to the AAdSS or ARTSS in the placebo group may differ, leading to a different gathering in the three tertiles, which can explain that the relative differences

between 300IR 5-grass-pollen tablet and placebo differ (Table 2).

Discussion

In the three studies analysed, large and statistically significant differences in symptom score were demonstrated in patients receiving AIT compared to placebo. The greatest improvement was observed in the tertiles (in the medium and particularly in the high tertile), where symptom scores in the placebo group were high enough to show a clinically relevant difference in active treatment group. The results were almost independent of which of the two symptom scores (ARTSS or AAdSS) was used in the analysis. The centres with low level of symptoms (grouped in the lower tertile) showed no or limited clinical benefit with the AIT treatment. Interestingly, the symptoms in patients treated with the 5-grass-pollen tablets were at approximately similar levels for all three tertiles (i.e. there was a large decrease in the high tertile, a moderate decrease in the middle tertile and almost no difference in the low tertile), suggesting that the magnitude of the effect is dependent on the severity of the allergic symptoms. Studies of SAR pose unique challenges to the investigation into AIT efficacy. Patients who are included in the trial are required to conform to a set of inclusion criteria and have experienced sufficient disease severity in the previous pollen seasons in which a therapy effect can be demonstrated. Allergen immunotherapy starts months before the beginning of the pollen season, when patients are asymptomatic, and the intensity of the coming pollen season and symptom levels are unknown. Natural pollen exposure varies within a season, from year to year and over the same season in different geographical areas, making it difficult to demonstrate the treatment efficacy (7).

Several guidelines (7, 8) propose a baseline period of observation, e.g. one pollen season prior to the study, but such approach fails to ensure that patients will have a sufficient level of symptoms in a lower pollen season during the study. Retrospective scoring of AR severity is inherently unreliable because patients have difficulty in accurately recalling how they felt (7, 13). Demonstration of the response to treatment by comparing baseline pretreatment with post-treatment values in the studied season is clearly not possible with AIT, for which the therapeutic action starts quite early (14) and entails a decrease in symptoms already at the beginning of the pollen season (15).

There is a relationship between the presence of pollen grains in the atmosphere and allergic rhinoconjunctivitis symptoms, and high pollen counts influence the symptom scores (Fig. 3). In the VO34 study, it was shown that the mean RTSS was related to the daily pollen counts, and with higher pollen exposure, the RTSS values were higher in both the active and placebo groups (Fig. 4). In addition, when there was higher mean RTSS in the placebo group, greater differences between the placebo-treated and the 5-grass-pollen-tablet-treated groups were observed (11, 12).

The analysis using the tertiles approach showed that the efficacy of AIT for ARTSS ranged between 19% (VO53) and

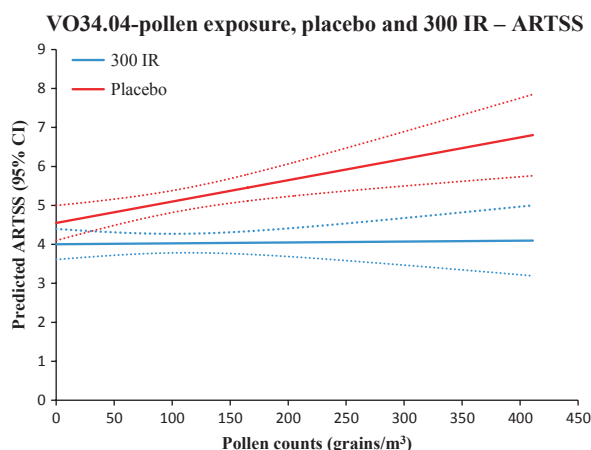


Figure 3 The allergen immunotherapy treatment efficacy increases when the symptoms related to the pollen exposure are higher (study VO34). ARTSS, Average Rhinoconjunctivitis Total Symptom Score; CI, confidence interval; IR, index of reactivity.

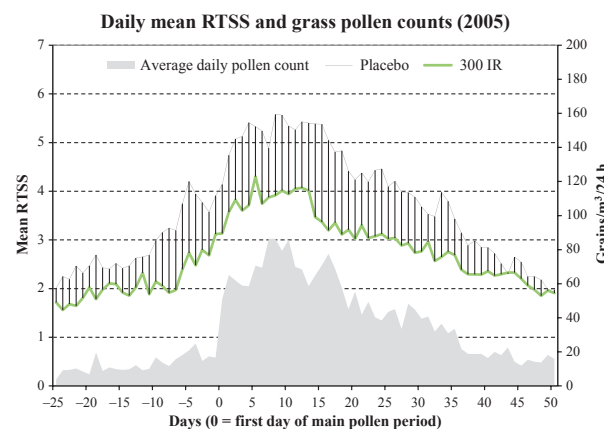


Figure 4 Daily mean symptom scores and grass pollen counts (data from study VO34). IR, index of reactivity; RTSS, Rhinoconjunctivitis Total Symptom Score.

40% (VO34) and for AAdSS between 24% (VO53) and 42% (VO52) in the high tertile. In the low tertile, either no efficacy (even an apparent increase in symptoms) with the ARTSS (study VO53) or a small reduction with the AAdSS (VO34) was observed. The tertiles analysis indicated that a highly clinically relevant difference can be observed when patients are exposed to a level of allergen capable of eliciting severe allergic symptoms. The differences between 300IR 5-grass-pollen tablet and placebo in the higher tertiles were in the range of the difference observed in an allergen challenge chamber (mean reduction in ARTSS of 29% vs placebo) where patients are recruited based on their symptom levels in response to the challenge and do not use rescue medication (i.e. ARTSS = AAdSS in that situation) (15). The results in the high tertile give an indication of the effect that is possible to achieve with the AIT. If a clinical study has a population with many centres with low pollen exposure, the treatment

effect might be underestimated for the patients suffering from more severe AR symptoms. In addition, the tertiles analysis in the adult VO34 study and in the paediatric VO52 study showed that there was no difference in results for the paediatric and adult populations.

Our approach presents a prespecified, post hoc analysis, which uses the results in the placebo group after the pollen season to identify the third of all study centres with the highest symptom load owing to the highest pollen exposure. It is important to note that the tertiles approach includes all patients in the centres, regardless of their individual response, and accounts for both interpatient variability in symptoms and geographical variation in pollen counts (14). It can be contrasted with that of a post hoc identification of patients with the best response (responder analysis) and an analysis of the magnitude of the effect in the responders. What we propose is an identification of sites where the most severe symptoms are observed in the placebo control population.

There is a general perception of somewhat lower efficacy results for AIT therapies compared with symptomatic therapies, which are applied only in highly symptomatic patients after the onset of full-blown rhinoconjunctivitis symptoms and consequently have the potential for higher levels for improvement. Symptomatic medication studies also do not allow the use of other relief therapy, to avoid confounding results. Wilson and colleagues (16) reported that the clinical effect size of pharmacotherapy for allergic rhinitis when compared with placebo was 18% for corticosteroids, 7% for antihistamine and 5% for leukotriene modifiers. In a recent meta-analysis (17), the efficacy of symptomatic medications expressed as median percentage changes from baseline for total nasal symptom score for SAR was -15.0% for placebo, -23.5% for oral antihistamines and -40.7% for intranasal steroids.

According to the WAO, the relative difference in the combined symptom score between active and placebo groups in AIT studies should be at least 20% (8). In the studies that we have analysed, the relative improvements in the high-

symptom tertile ranged from 27 to 37% and represented relative differences vs placebo largely beyond what is normally reported for symptomatic treatments such as antihistamines and nasal corticosteroids.

Conclusions

The tertiles approach applied to AIT clinical studies can help overcome the difficulty of demonstrating efficacy in a field where many variables interact strongly. The analysis, which was based on the placebo population symptom score in each centre, was tested using two types of rhinoconjunctivitis symptom scores and allowed a more accurate assessment of the actual patient benefit obtained with AIT. We propose that future studies of AIT in SAR include an analysis based on tertiles to estimate the benefit of the treatment.

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Conflict of interest

In the past 5 years, Dr. Philippe Devillier received fees for speaking, organising education or consulting from ALK, AstraZeneca, GlaxoSmithKline, Stallergenes, Schering-Plough, Merck Sharp & Dohme, and Sanofi-Aventis. Dr. Howarth, Dr. Molimard and Dr. Malling are consultants for and have received research support from Stallergenes.

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