

Original article

Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care

Esther Röder, MD,^{a,b} Marjolein Y. Berger, MD, PhD,^b Wim C. J. Hop, PhD,^c Roos M. D. Bernsen, PhD,^b Hans de Groot, MD, PhD,^a and Roy Gerth van Wijk, MD, PhD^a

Rotterdam, The Netherlands

Background: Sublingual immunotherapy (SLIT) is considered safer and more convenient than subcutaneous therapy and therefore has been proposed as especially suitable for children and in primary care. Most efficacy studies in children lack power to be conclusive, and all have been performed in referral centers.

Objective: To investigate the efficacy of SLIT with grass pollen allergen in children and adolescents with rhinoconjunctivitis in a primary care setting.

Methods: Youngsters aged 6-18 years with hay fever were enrolled from general practices and randomly assigned to receive placebo or grass pollen mix for 2 years. The primary outcome was the mean daily total symptom score (scale 0-15) comprising sneezing, itching nose, watery running nose, nasal blockage, and itching eyes during the months May-August of the second treatment year.

Results: Out of 204 youngsters randomized, 168 entered the intention-to-treat analysis (91 verum, 77 placebo). The mean daily total symptom score did not differ between participants allocated to verum and those allocated to placebo (difference for verum minus placebo: -0.08 , 95% CI, -0.66 - 0.50 ; $P = .78$). No differences were found for rescue medication-free days, disease-specific quality of life, and overall evaluation of the treatment effect. Local side effects were more frequent in the verum group (39% vs 17% of participants; $P = .001$).

Conclusion: Sublingual immunotherapy with grass pollen in a primary care setting is not effective in children and adolescents. **Clinical implications:** Currently, SLIT cannot be recommended for general practitioners as a therapeutic modality in youngsters with grass pollen allergy. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Immunotherapy, sublingual, grass pollen, allergic rhinitis, child, adolescent, primary care

From ^athe Section of Allergology, Department of Internal Medicine, ^bthe Department of General Practice, and ^cthe Department of Epidemiology & Biostatistics, Erasmus MC-University of Medical Center, Rotterdam, The Netherlands. Supported by Artu Biologicals, Lelystad, The Netherlands.

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Reprint requests: Prof. Dr. Roy Gerth van Wijk, Section of Allergology, Department of Internal Medicine, Erasmus MC, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: r.gerthvanwijk@erasmusmc.nl.

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Abbreviations used

AdolRQLQ: Adolescent Rhinoconjunctivitis Quality of Life Questionnaire

ANCOVA: Analysis of covariance

ARIA: Allergic Rhinitis and its Impact on Asthma

BU: Biological units

ISAAC: International Study of Asthma and Allergies in Childhood

PRQLQ: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire

SCIT: Subcutaneous immunotherapy

SLIT: Sublingual immunotherapy

In recent years sublingual immunotherapy (SLIT) has been proposed as an alternative to subcutaneous immunotherapy (SCIT). Owing to a convenient administration form and good safety profile,^{1,2} SLIT is particularly suitable for children. The evidence on the efficacy of SLIT in children is still inconclusive. Recent meta-analyses showed conflicting results, hampered by the significant heterogeneity in allergens, duration of treatment, and outcome measures of the included studies.³⁻⁵ The absence of serious side effects enables the administration of SLIT in primary care settings. Prescription of immunotherapy by general practitioners has the additional advantage of favoring introduction at an earlier stage of the disease, thereby potentially preventing the onset of asthma and the development of new sensitizations.^{6,7} From that perspective, SLIT is ideal to treat children seen in primary care. However, until now all clinical trials involving children have been performed in referral centers only.

We therefore designed a large randomized, double-blind, placebo-controlled trial in a primary care setting to evaluate the efficacy and safety of SLIT in children and adolescents with a grass pollen-induced allergic rhinoconjunctivitis.

METHODS

Design

Using a randomized, double-blind, placebo-controlled trial design participants entered the trial and started treatment after the grass

pollen season either in September–October 2001 or in September–October 2002. At the end of the trial 2 years later (in 2003 and 2004, respectively) data were pooled. The ethics committee of the Dutch health authorities and the Erasmus MC–University Medical Center approved the study protocol. Written informed consents were obtained.

Participants

Youngsters aged 6 to 18 years with an International Classification of Primary Care code of R97 (hay fever/allergic rhinitis)⁸ were invited by their general practitioner and screened by a research assistant. Inclusion criteria were IgE antibodies to grass pollen ≥ 0.7 kU/L and a history of rhinoconjunctivitis, assessed by a retrospective symptom score: participants scored 5 symptoms (sneezing, itching nose, watery running nose, nasal blockage, and itching eyes) during the previous grass pollen season (May–August) on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe; maximum total score = 15). Participants with a retrospective total symptom score ≥ 5 were included. Exclusion criteria included the use of daily pulmonary inhaled glucocorticoids during ≥ 3 months in the preceding year, immunotherapy in the preceding 3 years, sensitization to pets in the family home (specific IgE ≥ 0.7 kU/L), nasal abnormalities requiring surgery, and contraindications for immunotherapy.⁹

Additionally, IgE antibodies to house dust mite, birch, and cat were determined to assess possible multisensitization. Specific questions on wheezing and dry cough at night from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire¹⁰ established the presence of lower airway symptoms during the last 12 months.

Intervention

Participants underwent verum treatment with a mixture of aqueous extracts of 5 grass pollen species (*Lolium perenne*, *Phleum pratense*, *Dactylis glomerata*, *Anthoxanthum odoratum*, and *Holcus lanatus*; Oralgen Grass Pollen; Artu Biologicals, Lelystad, The Netherlands) in a glycerinated isotonic phosphate-buffered solution. Placebo treatment consisted of the solvent. Treatment starting with a single drop containing 475 biological units (BU) of allergen was increased with 1 drop daily until day 20. The maintenance dose was 20 drops (9,500 BU; 21 μ g equivalent Lol p 5) twice weekly for 2 years, resulting in a mean cumulative dose of 1,976,000 BU (4.5 mg equivalent Lol p 5). The drops were administered sublingually and kept there for at least 1 minute before being swallowed. A research assistant instructed the participants and provided written instructions. A pharmacist allocated medication in accordance with a computer-generated randomization list stratifying for symptom score and participating general practice. Participants, parents, investigators, and caregivers were unaware of the group assignment and could not make a distinction between verum and placebo treatment.

Outcome measures

The primary outcome in this study was the mean daily total symptom score comprising sneezing, itching nose, watery running nose, nasal blockage, and itching eyes in the second treatment year. The symptoms were scored on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) and recorded on diary cards during the period May 1–August 31. Beforehand, several measures were taken to ensure that days with sufficient exposure to grass pollen would be analyzed (see Statistical Analysis). Daily pollen counts were obtained from the pollen-monitoring station in Leiden (Burkard pollen trap, Leiden University Medical Center). These counts represented the pollen exposure in the region where the participants were recruited and evaluated.

Secondary outcomes were the percentage symptom-free days, the percentage rescue medication-free days, the type of rescue medication used, disease-specific quality of life, overall evaluation of the treatment effect, and safety.

Rescue medication was recorded on diary cards during the period May 1 through August 31. Participants were provided with free cetirizine tablets, xylometazoline nose spray, and levocabastine eye drops. The use of other antiallergic drugs was allowed. Rescue medication was categorized as follows: cetirizine, xylometazoline, levocabastine eye drops, other oral antihistamines, nasal inhaled glucocorticoids, other nasal sprays, and other eye drops. Those days eligible for symptom score analysis were eligible for evaluation of rescue medication as well.

Rhinoconjunctivitis-specific quality of life was assessed with the validated Pediatric (6–11 years) and Adolescent (12–17 years) Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ and AdolRQLQ, respectively)^{11,12} at baseline and in June during the peak of the grass pollen season. The mean overall score and the mean score for the domains separately were calculated (scale 0–6, higher score represents lower quality of life).

At the end of the study, both participants and their parents evaluated the overall effect of the treatment on a 6-point scale (1 = much worse, 2 = worse, 3 = unchanged, 4 = better, 5 = much better, 6 = no complaints any more).

To evaluate side effects, participants recorded all complaints irrespective of the relationship with the study medication. The complaints were grouped as follows: oral pharyngeal irritation/swelling, gastrointestinal complaints, rhinitis, conjunctivitis, shortness of breath/cough, eczema/itch/rash, allergy (not specified), and other.

Compliance was determined by weighing the returned study medication and calculating the medication intake during the study period. The participant was considered compliant if the medication intake was $\geq 80\%$ of prescribed.

A research assistant contacted the participants every 6 weeks during the 2-year follow-up either by visits (March–October) or by telephone.

Statistical analysis

The primary outcome was the mean daily total symptom score during the months May–August of the second treatment year. The sample size was based on an earlier trial among adults.¹³ A difference in primary outcome between treatment groups of at least 30% was considered to be the minimal clinically important difference.¹⁴ To detect a difference of 30%, 70 participants were required in each treatment group (2-sided $\alpha = 0.05$; power = 90%). To allow for dropouts, we aimed to randomize 100 participants to each group.

The protocol incorporated several measures to ensure that only days with sufficient exposure to grass pollen were analyzed. First, a minimum mean seasonal grass pollen count of 20–30 pollen grains/m³ was required for the efficacy of grass pollen immunotherapy to emerge.¹⁵ Therefore, if the mean daily pollen count was less than 25 pollen grains/m³ during the period of May 15–June 30 of a particular year, that year was considered a lost season and would not be evaluated. Second, only those days that exceeded the median pollen count of that year were considered as pollen-relevant days and consequently evaluated. Finally, an often-used and straightforward intention-to-treat procedure, the last observation carried forward (LOCF) method, was used to impute missing data. Thus, if a participant left the study before the second year or the diary card assessed during the second year was incomplete (ie, <50% of pollen-relevant days were filled out), the first year would be analyzed, provided that the first year diary was sufficiently complete (ie, $\geq 50\%$ of pollen-relevant days were filled out).

Univariate comparison of the primary outcome, all secondary outcomes, and compliance was done by the Mann-Whitney test or χ^2 test in case of percentages.

The main evaluation of the primary end point was done using analysis of covariance (ANCOVA) with the *a priori* defined covariates “age,” “sensitization to house dust mite,” “sensitization to birch

pollen,” and “retrospective total symptom score” included in the model. “Gender” was also included as a covariate, because the girls/boys ratio at baseline differed between both groups. Appropriate interaction terms were used to investigate whether these baseline variables modified the treatment effect.

To estimate the maximal effect of the intervention in this population, the 95% confidence interval for the ratio (verum/placebo) of the adjusted mean of the daily total symptom score was determined using the bootstrap method.

Preplanned ANCOVA analysis with the covariate “use of nasal inhaled glucocorticoids in the month prior to the evaluated season” and with the covariate “cohort” (ie, the year of inclusion) also included were performed.

Preplanned ANCOVA subgroup analyses were performed according to age ($<$ or $\geq$ the median) and the retrospective total symptom score ($\leq$ or $>$ the median).

All analyses were done according to the intention-to-treat principle. A per-protocol analysis of the primary outcome was also performed, excluding participants with either an incomplete or a missing diary card in the second year and participants who were noncompliant (ie, medication intake $<80\%$ of prescribed).

$P = .05$ (2-sided) was considered to be the limit of significance in all analyses.

RESULTS

From 64 general practices, 1,590 children and adolescents received written invitation to participate. 829 youngsters (52%) responded, of which 384 were not interested in participating, mainly because of a lack of symptoms ($n = 117$). After adding 42 extra youngsters (29 from a pilot study and 13 siblings), 487 participants entered the screening procedure (Fig 1). Two hundred eighty-three children (58%) were excluded, mainly because of the use of daily pulmonary inhaled glucocorticoids during ≥ 3 months in the preceding year ($n = 63$) and IgE antibodies to grass pollen <0.7 kU/L ($n = 54$). Finally, 204 youngsters were randomly assigned to verum ($n = 108$) or placebo ($n = 96$) treatment. All participants started treatment. Fifty participants (25%) did not complete the 2-year follow-up; 26 of them withdrew before the first grass pollen season. No statistically significant or clinically relevant difference between groups was found for the number of drop-outs and the reasons for discontinuation. The main reason for discontinuation was the inability either to take the study medication according to schedule or to complete the diary card ($n = 31$).

One hundred sixty-eight participants were included in the intention-to-treat analysis (91 verum, 77 placebo). The baseline characteristics of the intention-to-treat population are shown in Table I. The treatment groups were comparable for age, severity of symptoms, specific IgE, multisensitization, and lower airway symptoms. By chance, relatively more boys were randomized to verum treatment. The same distribution was observed in the intention-to-treat and per-protocol population.

All seasons could be evaluated, because the prespecified limits of the grass pollen counts were met. During each pollen season of 123 days, 61 days met the criterion of a pollen count above the median. A diary card could be

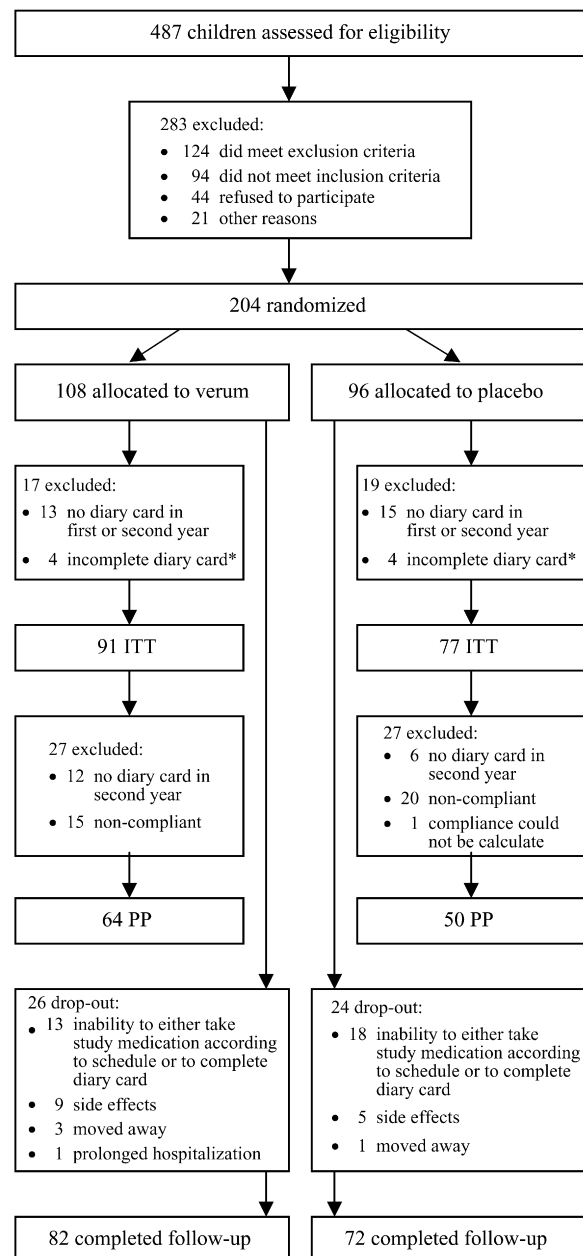


FIG 1. Trial profile. In the per-protocol analysis, participants with a diary card in the first year only and participants who were noncompliant (ie, medication intake $<80\%$ of prescribed) were excluded. *Incomplete diary card: $<50\%$ of the evaluated days were filled out. *ITT*, Intention-to-treat analysis; *PP*, per-protocol analysis.

evaluated if at least 50% (ie, 31 days) was filled out properly. The average evaluated days (SD) was 55 (7) and 54 (8) days in the verum and placebo group, respectively ($P = .45$).

The mean daily total symptom score (SEM) in the verum group was 3.1 (0.2) compared with 3.4 (0.2) in the placebo group ($P = .398$; Table II). Analysis of covariance (ANCOVA), allowing for the prespecified covariates plus “gender,” was performed with the mean daily total symptom score as outcome parameter (Table III, total

TABLE I. Baseline characteristics of the intention-to-treat population

	Verum n = 91	Placebo n = 77
Age (y)		
Mean (SD)	12.9 (2.6)	12.5 (2.9)
Median (range)	13.0 (7-17)	13.0 (6-17)
Gender, number of male participants	61 (67%)	34 (44%)
Retrospective symptom score		
Total [mean (SD)]*	8.7 (2.6)	9.0 (2.4)
Nose [mean (SD)]†	6.7 (2.2)	7.0 (2.1)
Eye [mean (SD)]‡	2.0 (0.8)	2.0 (0.9)
IgE grass pollen, kU/L [median (range)]	75.8 (0.8->100)	76.8 (1.6->100)
No. of participants with multisensitization§	69 (76%)	57 (74%)
No. of participants with lower airway symptoms	52 (57%)	46 (60%)

*Scale 0-15; †scale 0-12; ‡scale 0-3.

§Sensitization (IgE antibodies ≥ 0.7 kU/L) to house dust mite and/or birch and/or cat.

||In the last 12 months (ISAAC questionnaire).

group). The adjusted difference in mean daily total symptom score was small and equaled 0.1 on a scale of 15, in favor of the verum group. The resulting adjusted mean daily total symptom scores for verum and placebo were 3.2 and 3.3, respectively. The ratio of both means (verum/placebo) equaled 0.97 (95% CI, 0.82-1.16). The covariates “gender” and “retrospective total symptom score” had a significant effect on the outcome parameter. Further analysis showed that none of the baseline variables affected the treatment effect. Inclusion of the covariate “cohort” (ie, the year of inclusion) or “use of nasal inhaled glucocorticoids in the month before the evaluated season” (3 verum, 5 placebo) did not affect the outcomes of the ANCOVA. Age (<13 years and ≥ 13 years) and the retrospective total symptom score (≤ 8 and >8) categories equally affected the adjusted difference of the means (Table III, subgroups).

Per-protocol analysis of the primary end point also did not reveal a significant difference between both treatment groups.

As shown in Fig. 2, symptom scores and pollen counts in both treatment groups parallel each other closely. Study days of the second year were grouped according to the daily pollen counts (<25, 25-50, 51-100, >100 grains/ m^3), and within each category the mean daily total symptom score was determined for each participant. Fig 3 clearly shows an increase in mean daily total symptom scores with increasing pollen count. No significant differences between treatments within pollen count categories were observed (all 4: $P \geq .30$).

In line with these findings, analyses of the secondary outcome measures shown in Table II did not reveal statistically significant differences between treatment groups. No significant difference was found for the total days on which rescue medication was used. Analyzing categories

TABLE II. Results of the univariate analyses of the primary and secondary outcome measures (intention-to-treat analysis)

	Verum n = 91	Placebo n = 77	P value
Mean daily total symptom score (0-15)	3.1 (0.2)	3.4 (0.2)	.398
Percentage symptom-free days (0-100)	27.7 (3.0)	24.1 (3.0)	.398
Percentage rescue medication free days (0-100)	69.3 (3.4)	74.2 (3.2)	.674
Overall evaluation (1-6)			
Participant	3.9 (0.1)	3.8 (0.1)	.143
Parent*	3.7 (0.1)	3.7 (0.1)	.643
PRQLQ (6-11 y)	n = 30	n = 26	
Total score (0-6)	1.7 (0.2)	1.4 (0.1)	.799
AdolRQLQ (12-17 y)	n = 56	n = 47	
Total score (0-6)	1.7 (0.2)	2.1 (0.2)	.272

PRQLQ, Pediatric rhinoconjunctivitis quality of life questionnaire;

AdolRQLQ, adolescent rhinoconjunctivitis quality of life questionnaire.

All values are means (SEMs). Data between brackets represent the scales of the various items. PRQLQ-AdolRQLQ: numbers do not add up to 91 and 77, because of occasional missing data (verum 5/91, placebo 4/77).

*Missing evaluation parent: verum 2, placebo 3.

of rescue medication, no difference between verum and placebo group regarding the mean percentage of days with cetirizine (18.9% vs 17.2%), levocabastine eye drops (8.6% vs 6.9%), and nasal inhaled glucocorticoids (6.0% vs 4.0%) use was observed. Only the use of xylometazoline differed significantly between treatment groups (verum 3.4% vs placebo 5.9% of days; $P = .022$).

Separate PRQLQ and AdolRQLQ domains also did not differ between treatment groups.

Regarding possible side effects, only local oral pharyngeal reactions were more frequently recorded in the verum group (verum 39% vs placebo 17% of participants; $P = .001$; see Table E1 in this article's Online Repository at www.jacionline.org). These reactions were mild. Systemic anaphylactic reactions did not occur. Hospital admissions (none related to study medication) were noted in 13 children (9 verum, 4 placebo).

The percentage of compliant participants did not differ significantly between both groups (80% [73/91] verum vs 71% [55/77] placebo; $P = .312$).

DISCUSSION

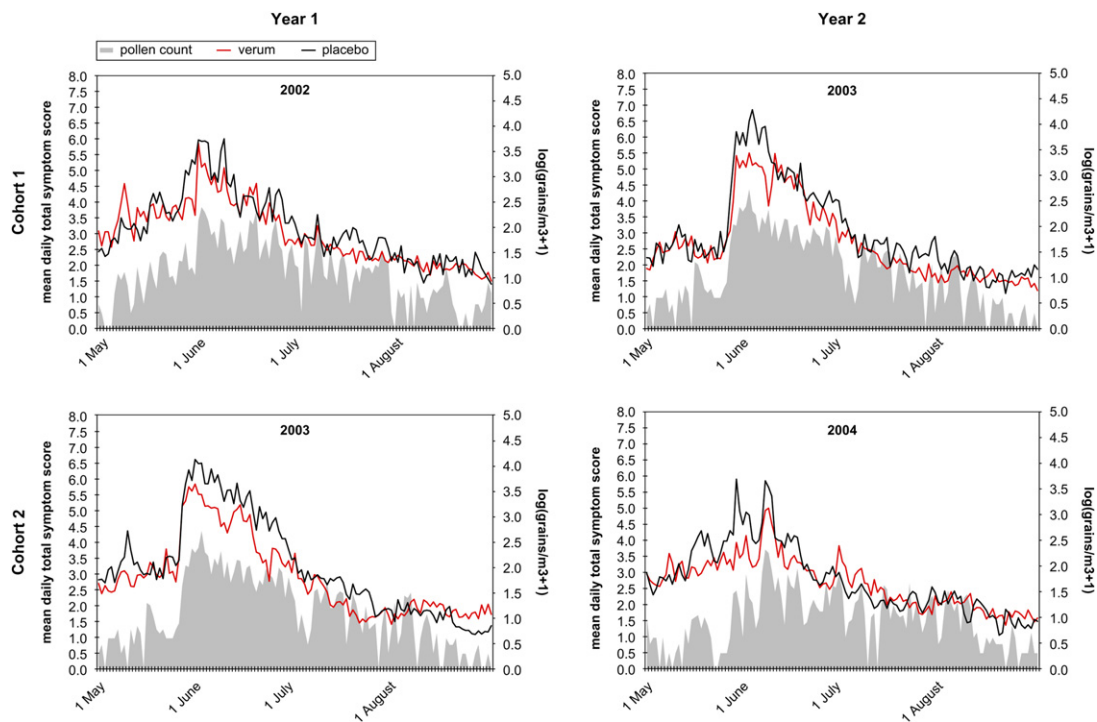
This is, at present, the largest study with SLIT in children and the first performed in a setting that is considered ideal for the use of SLIT. In this study we demonstrated that, when used in a primary care setting, SLIT with grass pollen is not effective in reducing symptoms and medication use in youngsters with rhinoconjunctivitis. Until now, all trials have been performed in referral centers and the evidence resulting from these relatively small and heterogeneous studies is conflicting.¹⁶⁻²⁵ The 2 large randomized, double-blind, placebo-

TABLE III. Results of the analysis of covariance of the mean daily total symptom score (intention-to-treat analysis)

Total group—all covariates		Effect*	95% CI	P value
Treatment (verum minus placebo)		−0.08	−0.66-0.50	.778
Age (per year)		0.01	−0.10-0.11	.927
Gender (female minus male)		0.76	0.17-1.35	.012
Sensitization to house dust mite (yes minus no)		−0.54	−1.11-0.03	.062
Sensitization to birch pollen (yes minus no)		0.35	−0.22-0.91	.230
Retrospective total symptom score (per point)†		0.14	0.03-0.26	.014
Subgroups—covariate treatment	n (verum/placebo)	Treatment effect*	95% CI	P value
Age				
<13 y	36/38	0.12	−0.62-0.87	.744
≥13 y	55/39	−0.02	0.92-0.88	.963
Retrospective total symptom score†				
≤8	47/38	0.03	−0.77-0.83	.934
>8	44/39	−0.14	−1.05-0.76	.756

*Difference in mean daily total symptom score (verum minus placebo).

†Scale 0-15.

**FIG 2.** Mean daily total symptom scores and grass pollen counts during the first and second years of treatment according to cohort.

controlled trials using grass pollen allergen in children with rhinoconjunctivitis demonstrated moderate effects only. Bufe et al,¹⁶ using a composite symptom-medication score, showed no difference between active and placebo treatment after one year follow-up. After another 2 years in an open setting, in which all children received SLIT, post hoc analysis showed a favorable effect of SLIT in a subgroup of patients with severe symptoms.¹⁶ Rolinck-Werninghaus et al¹⁷ demonstrated an effect on medication scores only, without apparent influence on symptoms.

In contrast, the present study showed no effect of SLIT. Moreover, we did not identify subgroups that might benefit from this treatment. The lower limit of the ratio (verum/placebo) of the mean daily total symptom scores amounted to 0.82, representing at most an 18% reduction in symptom scores. Therefore, we could not reach the minimal clinically acceptable improvement of 30%.¹⁴ Before accepting these results, we have to address several issues.

The present large trial—the only one in children in a primary care setting—has the advantage that results

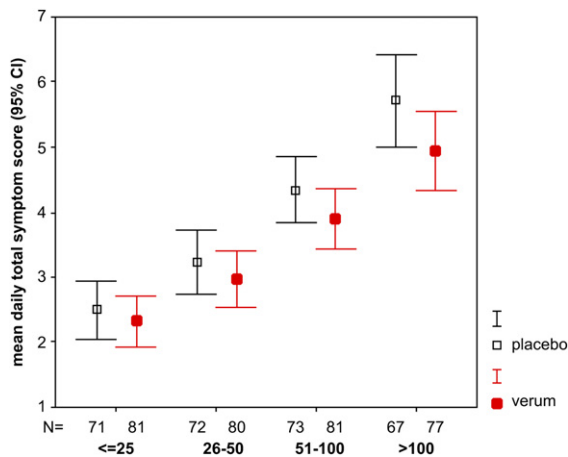


FIG 3. Mean daily total symptom scores (with 95% CI) according to grass pollen count category (grains/m³) and treatment. Data represent outcomes for the second year of treatment. N, Number of participants.

are relevant and applicable for children with hay fever presenting to general practitioners. An issue to be addressed is whether efficacy could be demonstrated in these patients from a primary care setting. Two large studies showed that approximately 90% of the patients consulting general practitioners have moderate/severe rhinitis.^{26,27} Apart from the retrospective symptom score, we do not have an indication of symptom severity before the study. However, as the quality-of-life data obtained during the trial demonstrated that participants experienced practical problems and daily life activity impairments, rhinitis severity could be labeled at least as moderate,²⁸ whereas the percentage of days with symptoms (verum 72.3% and placebo 75.9%) refers to persistent rhinitis.²⁸ Moreover, patients were independently selected by researchers from the University Hospital according to predefined criteria taking the degree of grass pollen sensitization and the level of symptom severity into account. Therefore, the study population should be appropriately composed to detect treatment effects. Especially in a pediatric population, there is reluctance to use (long-term) pharmacologic treatment. Not only are such patients good candidates for immunotherapy according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines,²⁸ SLIT with its good safety profile might be particularly tailored to the needs of these patients.

To include participants with sufficient symptoms and to ensure stratification of the treatment groups as to disease severity, we used a post-season retrospective instead of a run-in-season symptom score. Although a retrospective score cannot be considered a substitute for baseline evaluation, Bodtger et al²⁹ showed that even though post-season assessment using a 4-point scale tends to overrate average severity it could be used as the basis of randomization. We could exclude a possible effect of overrating, because participants with a retrospective total symptom score higher than the median did not show significant treatment effect.

It is often suggested that multisensitized patients might not benefit from specific immunotherapy as much as monosensitized patients, but, as indicated in the ARIA guidelines, further research on this subject is needed.²⁸ In our study we included both mono- and multisensitized participants. About 75% of the participants were multisensitized, possibly representing the average allergic population seen both in general and in hospital-based practice. Analysis of the subgroup of monosensitized participants showed no significant difference between the verum and the placebo group (data not shown). In line with this observation, we did not see any effect from cosensitization in the ANCOVA.

To assess efficacy, only days with sufficient pollen counts were analyzed. Symptoms fluctuated with the level of exposure, and even on days with high exposure and therefore higher symptom scores there was no significant difference between the treatment groups. It is not very likely that rescue medication, in particular nasal steroids, have masked efficacy, because the use of concomitant medication was low and well balanced between groups. According to the protocol, all days regardless of the pollen count were analyzed as well (data not shown). In that analysis we also could not demonstrate an effect of SLIT on the primary outcome or on medication use. Although participants were enrolled in 2 consecutive years, analysis showed that this did not affect the outcome.

One of the great advantages of SLIT is a good safety profile. In our study, minor side effects only were reported in both treatment groups. Not unexpectedly, significantly more local reactions in the oral pharyngeal cavity were reported in the verum group. In a study among adults enrolled from general practices, common but well tolerated side effects led to the conclusion that SLIT is safe to use in a community setting.³⁰

Data on compliance with SLIT are seldom reported.^{16-18,23,24} Those studies do not predefine compliance, and it is often unclear whether the results represent compliance to medication intake or to the study protocol. Moreover, they lack information on data collection or use patient reports instead of investigator-verified medication intake. The overall compliance to medication intake in our study was good, especially considering the age of the participants and the duration of the study. In daily clinical practice where patients are not intensively supervised, compliance might drop.

The issue of optimal dosage has not been solved yet. The wide range of allergen preparations used and a lack of information concerning the dose expressed in micrograms of major allergen make it difficult to compare studies. In the present study, the total dose was 4.5 mg equivalent Lol p 5 given over 24 months. The only 2 other studies in children using grass pollen allergen and reporting the dose of major allergen in micrograms used different dosages: 0.188 mg major grass pollen allergen given over 32 months¹⁷ and 9.6 mg equivalent Phl p 5 given over 36 months.¹⁶ Nevertheless, it cannot be excluded that a higher dosage may lead to better results. A recent study with grass pollen SLIT in adults suggested a dose-related response.

Treatment with the highest dose of 1.9 mg equivalent Phl p 5 given over 4.5 months, however, did not lead to a clinically relevant reduction in symptom scores.³¹

In conclusion, in this large randomized, double-blind, placebo-controlled study in a primary care setting, SLIT with grass pollen was not effective in children and adolescents with seasonal allergic rhinoconjunctivitis. Currently, SLIT cannot be recommended for general practitioners as a therapeutic modality in children or adolescents with grass pollen allergy.

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