

## ORIGINAL PAPER

# Sublingual immunotherapy in youngsters: adherence in a randomized clinical trial

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## Clinical and Experimental Allergy

### Summary

**Background** Adherence is essential for effective treatment. Although several trials on the efficacy of sublingual immunotherapy (SLIT) in youngsters have been published, few contain data on medication intake.

**Objective** We aimed to quantify adherence both to study protocol and medication intake as well as to identify factors that may influence adherence to SLIT in youngsters with rhinoconjunctivitis.

**Methods** Two hundred and four youngsters (6–18 years) with hayfever participated in a randomized controlled trial and used grass pollen extract or placebo for 2 years. The primary outcome of the trial was the mean daily total rhinoconjunctivitis symptom score in the second grass pollen season. Participants having completed the follow-up were considered adherent to the study protocol. Adherence to medication intake was assessed by weighing the study medication. Participants who completed the follow-up and used  $\geq 80\%$  of the prescribed medication were considered adherent to medication intake. Patient-, disease- and treatment-related factors were analysed.

**Results** One hundred and fifty-four youngsters completed the study. The main reason for discontinuation was the inability to take medication according to schedule. Drop-outs were older, had more difficulty following the medication instructions and their overall evaluation of the treatment effect was lower. The number and reasons for drop-out did not differ between treatment groups. In total, 77% of the participants was adherent to medication intake. Self-reported adherence was 99%. Non-adherent participants experienced more severe symptoms before the trial. Symptom scores did not differ between adherent and non-adherent participants. In adherent as well as non-adherent participants, no difference was found between verum and placebo group with respect to symptom scores.

**Conclusion** Adherence to both study protocol and medication intake was good. Drop-out was affected by age, evaluation of the treatment effect and medication instructions. Non-adherence to medication intake was influenced by the severity of the disease before the trial. The ineffectiveness of SLIT could not be explained by non-adherence.

**Keywords** adherence, adolescent, allergic rhinitis, child, compliance, grass pollen, sublingual immunotherapy

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### Introduction

The efficacy of sublingual immunotherapy (SLIT) in youngsters with rhinoconjunctivitis is still a subject of debate. An important issue in any discussion on the efficacy of a drug is adherence.

Adherence (or compliance) is generally defined as the extent to which patients use their medication as prescribed. Adherence is essential for the efficacy of a treatment to emerge. Medication intake can be assessed using direct or indirect methods. Direct methods measure the concentration of a drug or its metabolite in blood or

urine. Questionnaires and counting left-over tablets are examples of indirect methods. Age, severity of the disease and adverse events are a few factors that influence adherence [1].

The good safety profile and route of administration give SLIT the advantage of administration at home, taking away an important reason for non-adherence with the subcutaneous form [2–4]. On the other hand, self-administration and consequently lack of supervision might lead to incorrect or irregular use. Although several randomized placebo-controlled trials on the efficacy of SLIT in youngsters with rhinoconjunctivitis have been published [5–15], few contain data on medication intake. In some articles, compliance is mentioned, but the results do not refer to medication intake, but to the number of drop-outs [11–13] or it is not clear what the results represent [15]. Furthermore, where medication intake was registered [6, 10, 14], the results are not always presented [10] or are difficult to interpret, because compliance is not defined [14]. Only one study describes medication intake in detail [6]. Factors that could influence adherence have never been investigated.

As part of a randomized placebo-controlled trial on the efficacy of SLIT with grass pollen allergen in youngsters with rhinoconjunctivitis, we aimed to quantify adherence both to the study protocol and medication intake, as well as to identify factors that may influence adherence.

# Methods

## Participants and study design

A detailed description of the randomized double-blind placebo-controlled trial has been reported elsewhere [16]. The population and study design (Fig. 1) are summarized below.

**Participants.** Two hundred and four youngsters aged 6–18 years (114 boys/90 girls; mean age [SD] 12.9 [2.8] years) with hayfever were enrolled from general family practices in the Netherlands and randomly assigned to verum ( $n = 108$ ) or placebo treatment ( $n = 96$ ). All participants had IgE antibodies to grass pollen  $\geq 0.7$  kU/L (Phadia) and a history of rhinoconjunctivitis. The latter was assessed by a retrospective symptoms score: participants scored five 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  $\geq 5$  were included. Participants with daily pulmonary inhaled glucocorticoids during  $\geq 3$  months in the preceding year, or immunotherapy in the preceding 3 years were excluded. Other exclusion criteria were sensitization (specific IgE  $\geq 0.7$  kU/L) to pets present in the family home, nasal abnormalities requiring surgery and general contra-indications for immunotherapy [17].

**Study design.** Participants entered the trial and started treatment after the grass pollen season, either in September–October 2001 or in September–October 2002. Both cohorts ended the trial 2 years later (in 2003 and 2004, respectively). Data were pooled at the end of the study.

The primary outcome of our trial 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. To evaluate the side-effects, participants recorded all complaints irrespective of the relationship with the study medication on a diary card.

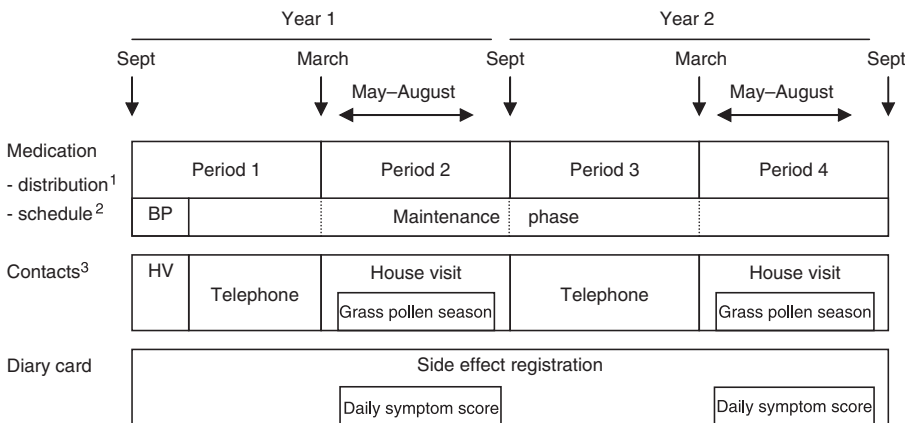


Fig. 1. Study design. (a) At the beginning of each period, four bottles were handed out; at the end of the period, the medication was handed in and weighed. (b) Build-up phase (BP): 20 days, daily intake, increasing with one drop. Maintenance phase: twice weekly intake, 20 drops. (c) Every 6 weeks, either by house visit (HV) or telephone.

Participants, parents, investigators and caregivers were unaware of the group assignment. Verum treatment consisted of a mixture of aqueous extracts of five grass pollen species (*Lolium perenne*, *Phleum pratense*, *Dactylis glomerata*, *Anthoxanthum odoratum*, *Holcus lanatus*; Oralgen Grass Pollen; Artu Biologicals, Lelystad, the Netherlands) in a glycerinated isotonic phosphate-buffered solution. Placebo treatment consisting of the solvent was delivered in such a way that neither participants, parents, investigators, nor caregivers could make a distinction between verum and placebo. Treatment started with a single drop and was increased with one drop daily until day 20. The maintenance dose was 20 drops twice weekly for 2 years. The drops were administered sublingually before breakfast (on an empty stomach) and kept there for at least 1 min before being swallowed.

A research assistant instructed the youngsters and their parents in the use of the study medication. Participants received written instructions, a schedule to record medication intake and an hourglass for timing the sublingual phase. They were contacted by a research assistant every 6 weeks during the 2-year follow-up, either by visits (March–October) or by telephone. The first follow-up contact took place in the final stage of the build-up phase. Medication use was checked during each contact and when necessary questions were answered and/or instructions repeated.

## Adherence

*Adherence to study protocol, i.e., drop-outs.* Participants having completed the study were considered adherent to the study protocol. Drop-outs were asked for the reason of discontinuing their participation in the study.

*Adherence to medication intake.* Because no methods for measuring blood- or urine-levels are available, medication intake was measured by weighing the study medication.

Every 6 months, the participants received a standard amount of study medication (four bottles). The study medication was handed in at the end of every 6-month period and the bottles were weighed. The participants were unaware of the fact that the study medication was being weighed. The second and fourth period included the grass pollen season.

Adherence was determined for the total 2-year study period and for each of the four 6-month periods separately. In the absence of a clear-cut definition of adherence, we applied a cut-off level of  $\geq 80\%$  [18]. First, the weight of the drops that were prescribed was calculated (prescribed). Second, the weight of the returned bottles was subtracted from the weight of the full bottles and the weight of the consumed drops computed (consumed). Finally, if the participant completed the follow-up and the amount of consumed study medication was  $\geq 80\%$  of the amount that

was prescribed  $[(\text{consumed/prescribed}) \times 100\%]$  the participant was considered adherent to medication intake. Adherence in a certain period could only be calculated if a participant returned all bottles. Only those periods in which all bottles were returned were considered eligible for the determination of the adherence in the total study period.

Additionally, the youngsters were asked during each contact to report the number of drops they forgot to take since the last contact to determine the self-reported adherence for the total study period and for each period separately. If a participant stated that  $\geq 80\%$  of the amount that was prescribed was taken, the participant was considered self-reported adherent.

*Factors influencing adherence.* All data, with the exception of multi-sensitization, were collected using structured questionnaires.

- (1) Patient-related factors
  - (a) Age
  - (b) Gender
  - (c) Expected treatment allocation: at the end of the study, the participants were asked if they thought they received the grass pollen extract or placebo
  - (d) Overall evaluation treatment effect: at the end of the study, the youngsters judged 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).
- (2) Disease-related factors
  - (a) Duration of disease: parents reported the age at which symptoms first occurred
  - (b) Severity of the disease: retrospective total symptom score (as described in 'Methods')
  - (c) Multi-sensitization: IgE antibodies  $\geq 0.7$  kU/L to house dust mite and/or birch and/or cat
- (3) Treatment-related factors
  - (a) Complexity of the instructions: participants were asked if they considered the following instructions difficult (yes/no) – time of day (before breakfast, on an empty stomach); sublingual application (getting and keeping the drops under the tongue); counting drops; built-up phase (daily intake, increasing with one drop); maintenance phase (twice-weekly intake of 20 drops); keeping medication refrigerated. Also, the total number of instructions that was considered difficult was calculated.
  - (b) Local side-effects: the presence of oral pharyngeal irritation/swelling.

Additionally, at the end of the study, the participants were asked if they had suggestions to enhance adherence in future users.

### Statistical analysis

Univariate comparison was done by the Mann–Whitney test or  $\chi^2$ -test in case of percentages.  $P = 0.05$  (two-sided) was considered the limit of significance.

## Results

### Adherence to the study protocol, i.e., drop-outs

Fifty participants (25%; 26 verum, 24 placebo) did not complete the 2-year follow-up; 26 (52%) of them withdrew before the first grass pollen season. The mean duration of participation of the drop-outs was 231 days ( $SD = 183$ ). The main reason for discontinuation was the inability to take the study medication according to schedule ( $n = 26$ ; Table 1). Neither the number of drop-outs nor the reasons for discontinuation for the total study period as well as for the periods separately differed between youngsters allocated to verum and those allocated to placebo.

Participants who discontinued the study, compared with participants having completed the study were slightly older, had more difficulty in following the instructions and their overall evaluation of the treatment effect was lower (Table 2a).

Eighty percent (24/30) of the drop-outs reported forgetting drops during the build-up phase compared with 37% (55/150) of the youngsters who completed the follow-up period ( $P < 0.0001$ ). No difference was found between groups considering forgetting drops during the maintenance phase, e.g., 72% (110/152) complete follow-up vs. 73% (22/30) drop-outs.

### Adherence to medication intake

One hundred and fifty-four youngsters completed the study (82 verum, 72 placebo). One hundred and one participants returned all bottles in four periods, 40 participants in three periods, 10 participants in two periods and two participants in one period. One participant failed to

hand in a complete set of study medication in all periods and therefore adherence could not be calculated. Disposal of an empty or broken bottle was the main reason for not returning study medication. The average weight of the provided medication (in four full bottles) and the prescribed medication was 94.5 and 57.5 g, respectively.

Seventy-seven percent (118/153) of the participants were considered adherent in the 2-year follow-up (Figs 2 and 3). These adherent participants used on average 100% ( $SD = 15$ ) of the prescribed study medication. The percentage adherent participants did not differ significantly between both treatment groups (82% [67/82] verum vs. 72% [51/71] placebo). Adherence in the first, second, third and fourth 6-month periods were 87%, 74%, 66% and 68%, respectively (Figs 2 and 3). Considering the 101 participants who returned all 16 bottles, 78% of these youngsters were adherent for the total study period. They used on average 94% ( $SD = 20$ ) of the prescribed medication. The non-adherent participants used on average 68% ( $SD = 11$ ) of the prescribed study medication.

The self-reported adherence was 99% (151/153) in the total study period and 95%, 99%, 96% and 96% in the first, second, third and fourth periods, respectively (Fig. 2). The overlap between calculated (non-)adherence and self-reported (non-)adherence was 78% (120/153) in the total study period and 85%, 74%, 67% and 69% in the first, second, third and fourth periods, respectively (Fig. 2). In adherent participants, the overlap varied from 97% to 100%, whereas the overlap in non-adherent participants ranged from 3% to 12% (Fig. 2). Similar results were found for the 101 participants returning all bottles in all periods. Adherent and non-adherent youngsters reported comparable results on forgetting drops during the build-up phase (37% [42/115] adherent vs. 35% [12/34] non-adherent) or during the maintenance phase (72% [83/116] adherent vs. 74% [26/35] non-adherent). Adherent participants reported to miss 0.03% of the intakes, whereas non-adherent participants missed 0.06%. Most participants were supervised by their parent(s), only 8% (10/118) of the adherent and 11% (4/35) of the non-adherent youngsters were solely responsible for medication intake.

Table 1. Adherence to study protocol: drop-out according to reason and time

|                                                                                          | Period 1 | Period 2 | Period 3 | Period 4 | Total     |
|------------------------------------------------------------------------------------------|----------|----------|----------|----------|-----------|
| Inability to take study medication according to schedule                                 | 8 (16%)  | 1 (2%)   | 3 (6%)   | 1 (2%)   | 13 (26%)  |
| Inability to complete the diary cards                                                    | 0 (0%)   | 4 (8%)   | 1 (2%)   | 0 (0%)   | 5 (10%)   |
| Inability to take study medication according to schedule and to complete the diary cards | 4 (8%)   | 5 (10%)  | 3 (6%)   | 1 (2%)   | 13 (26%)  |
| Side-effects                                                                             | 12 (24%) | 1 (2%)   | 0 (0%)   | 1 (2%)   | 14 (28%)  |
| Prolonged hospitalization                                                                | 0 (0%)   | 0 (0%)   | 0 (0%)   | 1 (2%)   | 1 (2%)    |
| Moved away                                                                               | 2 (4%)   | 1 (2%)   | 1 (2%)   | 0 (0%)   | 4 (8%)    |
| Total                                                                                    | 26 (52%) | 12 (24%) | 8 (16%)  | 4 (8%)   | 50 (100%) |

Number of participants (percentage of total number of drop-outs,  $n = 50$ ).

Periods 2 and 4 included the grass pollen season.

Table 2. Factors influencing adherence

|                                                        | Complete follow-up<br>( <i>n</i> = 154) | Drop-out<br>( <i>n</i> = 50)     | <i>P</i> -value   |
|--------------------------------------------------------|-----------------------------------------|----------------------------------|-------------------|
| (A) Complete follow-up vs. drop-outs                   |                                         |                                  |                   |
| Patient                                                |                                         |                                  |                   |
| Age (mean SD)                                          | 12.6 (2.7)                              | 13.7 (2.8)                       | <i>P</i> < 0.001  |
| Gender ( <i>N</i> male participants)                   | 88 (57%)                                | 26 (52%)                         | ns                |
| Expected treatment allocation ( <i>N</i> verum)        | 64 (43%)*                               | 16 (52%) <sup>†</sup>            | ns                |
| Overall evaluation of treatment effect (mean SD) [1–6] | 3.9 (0.9)                               | 3.2 (1.1) <sup>‡</sup>           | <i>P</i> < 0.0001 |
| Disease (baseline)                                     |                                         |                                  |                   |
| Duration (year)                                        | 5.9 (3.5)                               | 6.3 (3.7)                        | ns                |
| Severity (mean SD) [0–15]                              | 8.8 (2.5)                               | 9.2 (2.4)                        | ns                |
| Multi-sensitization <sup>§</sup> ( <i>N</i> )          | 115 (75%)                               | 33 (66%)                         | ns                |
| Treatment                                              |                                         |                                  |                   |
| Verum                                                  | 82 (53%)                                | 26 (52%)                         | ns                |
| Instructions considered difficult <sup>†</sup>         |                                         |                                  |                   |
| Time of day ( <i>N</i> )                               | 61 (40%) <sup>¶</sup>                   | 23 (74%)                         | <i>P</i> < 0.001  |
| Sublingual application ( <i>N</i> )                    | 64 (42%)                                | 16 (52%)                         | ns                |
| Counting drops ( <i>N</i> )                            | 20 (13%)                                | 7 (23%)                          | ns                |
| Build-up phase ( <i>N</i> )                            | 56 (36%)                                | 18 (58%)                         | <i>P</i> < 0.05   |
| Maintenance phase ( <i>N</i> )                         | 24 (16%)                                | 14 (47%) <sup>¶</sup>            | <i>P</i> < 0.001  |
| Keeping medication refrigerated ( <i>N</i> )           | 25 (16%)                                | 7 (23%)                          | ns                |
| Total number (mean SD) [0–6]                           | 1.6 (1.3) <sup>¶</sup>                  | 2.8 (1.2) <sup>¶</sup>           | <i>P</i> < 0.0001 |
| Local side-effects ( <i>N</i> )                        | 45 (29%)                                | 13 (26%)                         | ns                |
| Complete follow-up <sup>  </sup>                       | Adherent<br>( <i>n</i> = 118)           | Non-adherent<br>( <i>n</i> = 35) | <i>P</i> -value   |
| (B) Complete follow-up – adherent vs. non-adherent     |                                         |                                  |                   |
| Patient                                                |                                         |                                  |                   |
| Age (mean SD)                                          | 12.5 (2.9)                              | 13.0 (1.9)                       | ns                |
| Gender ( <i>N</i> male participants)                   | 70 (59%)                                | 17 (49%)                         | ns                |
| Expected treatment allocation ( <i>N</i> verum)        | 49 (43%)*                               | 15 (43%)                         | ns                |
| Overall evaluation of treatment effect (mean SD) [1–6] | 3.9 (0.9)                               | 3.8 (1.0)                        | ns                |
| Disease (baseline)                                     |                                         |                                  |                   |
| Duration (year)                                        | 6.0 (3.6)                               | 5.7 (3.2)                        | ns                |
| Severity (mean SD) [0–15]                              | 8.6 (2.6)                               | 9.4 (2.0)                        | <i>P</i> < 0.05   |
| Multi-sensitization <sup>§</sup> ( <i>N</i> )          | 88 (75%)                                | 26 (74%)                         | ns                |
| Treatment                                              |                                         |                                  |                   |
| Verum                                                  | 67 (57%)                                | 15 (43%)                         | ns                |
| Instructions considered difficult                      |                                         |                                  |                   |
| Time of day ( <i>N</i> )                               | 43 (37%) <sup>¶</sup>                   | 18 (51%)                         | ns                |
| Sublingual application ( <i>N</i> )                    | 49 (42%)                                | 14 (40%)                         | ns                |
| Counting drops ( <i>N</i> )                            | 16 (14%)                                | 4 (11%)                          | ns                |
| Build-up phase ( <i>N</i> )                            | 42 (36%)                                | 14 (40%)                         | ns                |
| Maintenance phase ( <i>N</i> )                         | 19 (16%)                                | 5 (14%)                          | ns                |
| Keeping medication refrigerated ( <i>N</i> )           | 18 (15%)                                | 7 (20%)                          | ns                |
| Total number (mean SD) [0–6]                           | 1.6 (1.3) <sup>¶</sup>                  | 1.8 (1.3)                        | ns                |
| Local side-effects ( <i>N</i> )                        | 36 (31%)                                | 9 (26%)                          | ns                |

*N*, number of participants.

\*Five missing.

<sup>†</sup>Drop-out *n* = 31, 19 drop-outs refused to fill out the questionnaire.

<sup>‡</sup>Six missing.

<sup>§</sup>Additional sensitization (specific IgE ≥ 0.7 kU/L) to house dust mite, birch and/or cat.

<sup>¶</sup>One missing.

<sup>||</sup>Adherence could not be calculated for one participant.

\*\*Four missing.

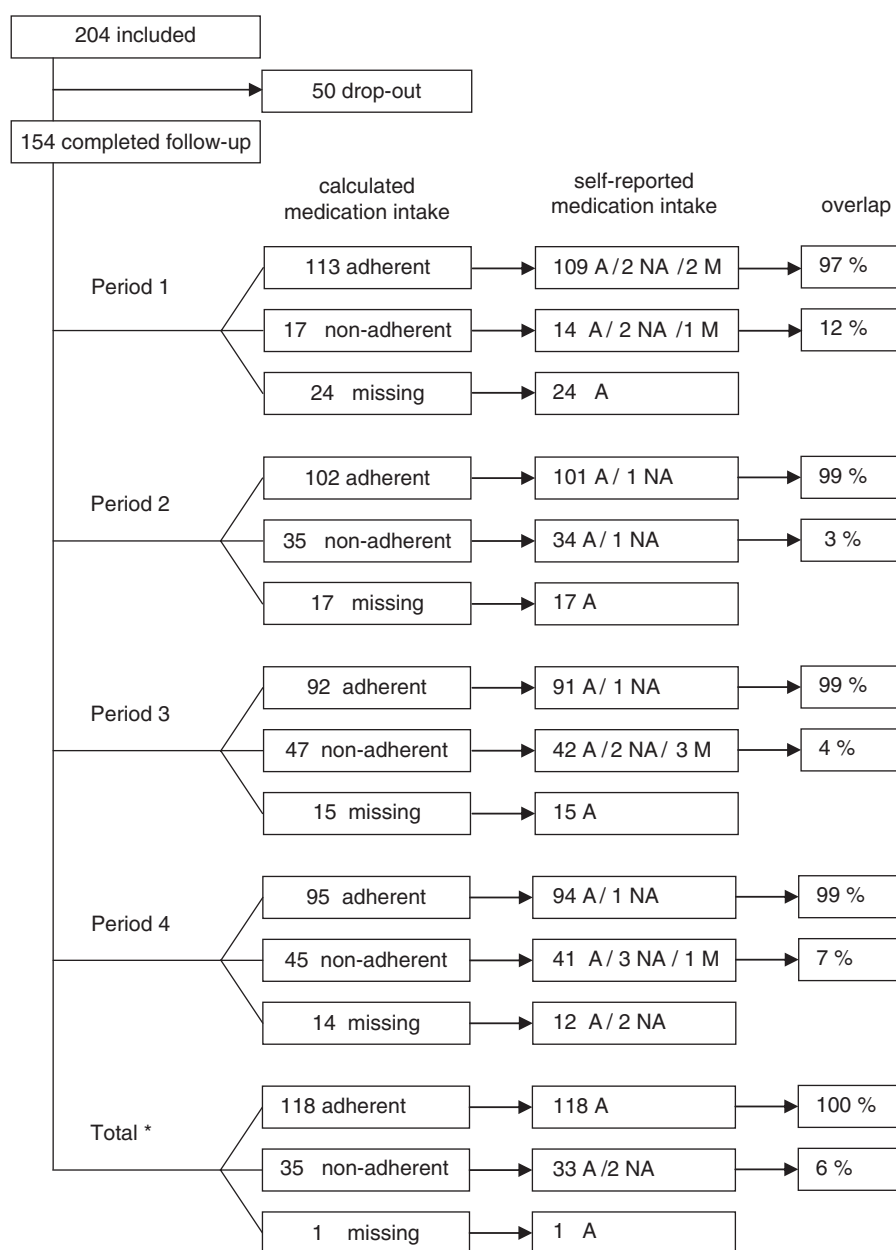


Fig. 2. Calculated and self-reported adherence to medication intake. Adherent (A), medication intake  $\geq 80\%$  of prescribed; non-adherent (NA), medication intake  $< 80\%$  of prescribed; missing (M),  $\geq$  one bottle not returned (calculated intake) or missing data (self-reported intake). \*For the total study period, only those periods in which all bottles were returned (calculated intake) or all data were available (self-reported intake) were considered. Periods 2 and 4 included the grass pollen season.

Adherent participants could be distinguished from non-adherent participants in severity of the disease before the study only. Non-adherent youngsters experienced more severe symptoms in the season preceding the trial (Table 2b).

The mean daily total rhinoconjunctivitis symptom score (SD), the primary outcome of our study, did not differ between adherent and non-adherent participants (3.2 [1.8] vs. 3.5 [2.3]). If considered separately, in adherent as well as non-adherent participants, no difference

was found between the verum and placebo group with respect to the symptom scores.

## Discussion

### *Adherence to study protocol*

The drop-out rate in our trial (25%) was comparable to other trials using pollen extracts. Seasonal allergen trials (all year treatment) seem to have higher drop-out rates

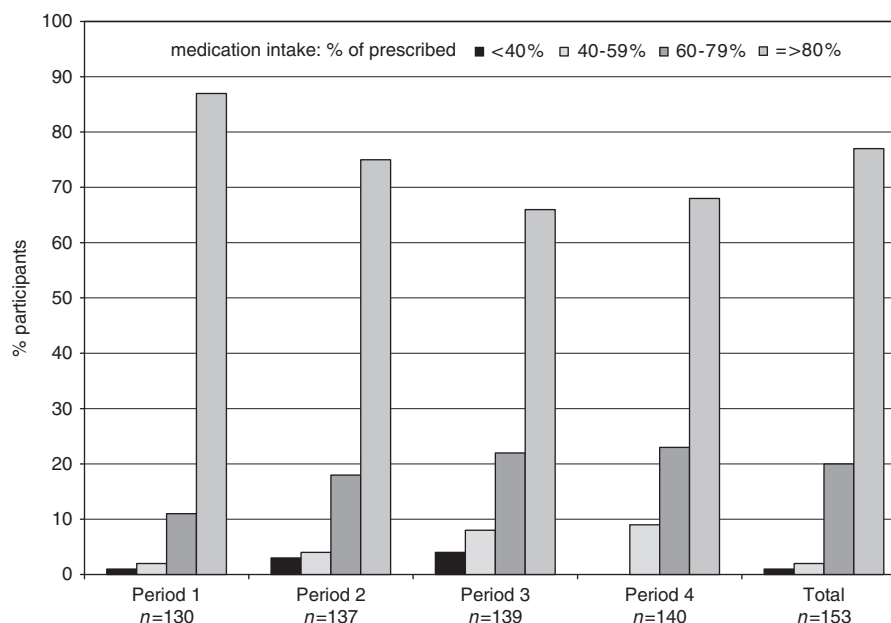


Fig. 3. Compliance to medication intake in participants having completed the follow-up period. Periods 2 and 4 included the grass pollen season.

(mean 14%, range 0–23%) [8, 9, 12–15] compared to trials using house dust mite extracts (mean 4%, range 0–12%) [5, 6, 10, 11]. Possible explanations could be that, in general, seasonal allergen trials last longer than trials using a perennial allergen and that house dust mite patients have complaints throughout the year, which might keep them motivated.

The number and reasons for drop-outs did not differ between treatment groups. Therefore, it is unlikely that drop-out influenced the results on efficacy.

The main reason for discontinuing the study was difficulty in following the treatment schedule. Most drop-outs already forgot to take their medication in the first weeks of treatment. Several preparations from various manufacturers are available in the market. These preparations differ in administration form (drops/vials/tablets) and instructions. However, most preparations have one instruction in common, that being the medication has to be taken before breakfast, an instruction that was considered difficult by 74% of the drop-outs.

All trials on the efficacy of SLIT in youngsters report the number of drop-outs for each treatment group and the reasons for discontinuation are in general clearly stated. No data are available from other trials on factors influencing drop-outs. In one observational study only, Pajno et al. investigated the drop-out rate and the reasons for stopping immunotherapy in children (6–15 years) using subcutaneous immunotherapy (SCIT), SLIT or local nasal immunotherapy (LNIT). The drop-out rates after 3 years were 11%, 21.5% and 73% for SCIT, SLIT and LNIT, respectively [19]. Most participants discontinued SCIT because they considered the treatment expensive or time-consuming. High costs, followed by the ineffectiveness of

the treatment, were the main reason for discontinuing SLIT. More than 50% of the youngsters using LNIT stopped treatment due to the unpleasant nasal reactions. The authors concluded that SCIT is the most suitable immunotherapy form and route of administration in children and adolescents. It is, however, difficult to compare these data to our study as our study was placebo-controlled, the participants were more frequently supervised and the study medication was free of charge.

#### *Adherence to medication intake*

The overall adherence to medication intake in our trial was good. Previously reported average adherence to treatment by children and adolescents was 58% [1]. In our study, 97% (148/153) of the youngsters used more than 58% of the prescribed medication. Self-reported medication intake was overestimated, as has previously been shown for inhaled steroids in children with asthma, also a long-term preventive therapy [20]. Medication intake decreased gradually, but appeared to stabilize after 1 year. Grass pollen exposure and concomitant symptoms did not influence medication intake. Only one difference between adherent and non-adherent participants could be found. Non-adherent youngsters experienced more severe symptoms in the season preceding the trial. A possible explanation could be that youngsters with more severe symptoms might have had more symptoms because they were also non-adherent to pharmacotherapy in previous seasons. Another reason could be that these youngsters had higher expectations of the treatment.

Adherence and efficacy are inter-related. Non-adherence compromises efficacy and inefficacy may lead to

non-adherence. However, in our study, SLIT was ineffective, but the adherence to medication intake was good and comparable in both intervention groups. Therefore, the ineffectiveness of SLIT could not be explained by non-adherence.

In three randomized placebo-controlled trials in youngsters with allergic rhinitis, participants recorded their medication intake on a diary card [6, 10, 14]. Bahçeciler *et al.* did not present the results [10]. Rolinck-Werninghaus *et al.* reported the number of drop-outs due to non-compliance, but it was not clear how compliance was defined [14]. Hirsch *et al.* presented a detailed report of the medication intake and showed that 53% (8/15) and 67% (10/15) of the participants (6–15 years) in the SLIT and placebo group, respectively, reported complete regular intake [6].

In a non-controlled study, participants were called unannounced after 3 and 6 months of treatment and asked to count the left-over mono-dose vials [21]. Passalacqua *et al.* reported that 69% (49/71) and 66% (37/56) of the participants (2–13 years) used more than 90% of prescribed after 3 and 6 months, respectively [21].

Indirect methods (e.g., weighing, counting, diary card) have been used in all studies to measure adherence. A major disadvantage of these indirect methods is that there is no guarantee that the medication was indeed consumed. For instance, in our trial, the liquid could have been thrown away. Moreover, the average rate of adherence in clinical trials is higher than in daily practice, due to the selection of participants and the attention participants receive during the study. Therefore, the actual percentage of adherent participants in daily clinical practice will be lower. Although measuring medication intake in a trial may overrate adherence, the results are essential for the interpretation of the (in)efficacy of a treatment.

### *Enhancing adherence*

We received several suggestions from the youngsters to enhance adherence. One of the major problems was taking the medication before breakfast, the busiest time of the day according to the youngsters. Participants indicated that it would be easier if the medication could be used during the day. Most participants used a reminder. They placed the schedule on a visible location (e.g., on the refrigerator), put the hourglass on their breakfast plate or set an alarm. Some youngsters preferred to receive a message on their mobile phone on the day of medication intake. Counting drops was not a major problem, but a large number of participants considered it difficult to get and keep the drops under their tongue. Several youngsters suggested the use of a tablet. Keeping medication refrigerated was not considered very difficult, however, participants reported that keeping the medication cool when travelling and on holiday was problematic. Although

other preparations can be kept at room temperature (15–25 °C), one still has to take measures to keep the medication at this temperature during the summer and on holiday.

### *Practical implications*

In our study, adequate adherence was obtained. The procedures and results from this study could be used in daily clinical practice. Before starting treatment, the instructions and preventive nature of the treatment (no instant relief of symptoms) should be explained to create realistic expectations. Measures to enhance adherence may include the use of reminders and attention to the timing of intake. Adherence is a dynamic process and therefore patients should be monitored regularly from the beginning to the end of treatment to check medication intake, and evaluate symptoms and side-effects. Although serious systemic side-effects have never been reported, incorrect use is a potentially life-threatening risk. One should be aware that self-reported medication intake over-estimates adherence. Special attention should be paid to patients with serious complaints before treatment (as they might have been non-adherent to therapy before), the first months of treatment (as the chance of drop-out is highest then) and to the holiday season (as logistic problems may appear and patients might want to discontinue treatment for a while).

### *Future research*

Adherence affects the effectiveness of a treatment. Therefore, every randomized clinical trial investigating the efficacy of a drug should not only report the number and reason for drop-out, but also assess (either by questionnaire and/or more objective means) and report on medication intake.

Adherence is influenced by a large interactive complex of factors. Our study is the first to investigate factors that affect adherence to SLIT in youngsters. More research is needed to gain more insight in the influence of other factors, for instance, socioeconomic status and the doctor–patient relationship, to optimize adherence.

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