

Comparison of Six Different Allergen Extracts for Subcutaneous Specific Immunotherapy in Children: An Open-Labelled, Prospective, Controlled Observational Trial

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Keywords

Allergic rhinoconjunctivitis · Bronchial asthma · Children · Subcutaneous immunotherapy · Sublingual immunotherapy · Specific immunotherapy

Abstract

Background: Numerous products are available for subcutaneous (SCIT) and sublingual allergen-specific immunotherapy, but there are no information about the direct comparability regarding efficacy, safety, and tolerability of the different extracts. **Aims:** The aim of this open-labelled, prospective, controlled observational trial was to test the feasibility of a comparison of different products for SCIT in children. **Methods:** Pediatrician practices recruited patients with a confirmed diagnosis of a seasonal allergic rhinoconjunctivitis (AR) with or without asthma and an allergic sensitization against grass pollen allergen. Every patient was offered SCIT with one out of six allergen extracts: ALK SQ Depot, ALK Avanz, Allergovit, Depigoid, Purethal, Pollinex Quattro. Scores for symptoms and medications were calculated and the difference between treatment years and baseline were recorded. **Results:** In total, 284 were recruited and 255 chil-

dren (89.8%; mean age 10.4, SD 3.54 years; 65% males) participated in this trial. Overall, 49,649 patient days were recorded in the electronic database (mean 183.2 days/patient). There was no significant difference in the AR and asthma symptom score or the medication score between the six different SCIT preparations. Similarly, no differences were observed in terms of safety and tolerability. **Conclusion:** The comparison of different SCIT products using an online tool is feasible. Based on our preliminary data, all extracts indicated efficacy; however, larger groups would be necessary to demonstrate superiority or non-inferiority of one specific SCIT product.

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Introduction

Allergic rhinitis is the most common chronic disease in children and adolescents with a reported lifetime prevalence of 2–25% in children and adolescents and about 17–28% of adults in Europe [1–3]. It is commonly under-

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diagnosed and insufficiently treated, and the importance for health restrictions, comorbidities, and quality of life is underestimated. Allergen-specific immunotherapy is considered the only causative treatment that may alter the natural course of allergic diseases in children, adolescents, and adults [4]. Moreover, there is evidence from clinical trials in children that SIT might also influence the course of sensitization and asthma development in a preventive way [5–7]. In clinical routine, the efficacy and safety for subcutaneous (SCIT) and sublingual (SLIT) immunotherapy is well documented [8–11].

However, sufficient head-to-head comparative data are not available, neither for a comparison of SCIT and SLIT nor for different SCIT products [12]. Taking into account that numerous SCIT products are available, i.e., unmodified and modified extracts, which vary in allergen content and adjuvant composition, comparative trials are clearly an (urgent) unmet need. Therefore, a double-blind, controlled multicenter study would be highly appreciated. However, there are numerous obstacles which might get in the way of amounting the highest level of evidence. First, a direct comparison in a double-blind setting is hindered by different up-dosing regimes, comprising pre-seasonal and perennial treatment and ranging from three up to eleven recommended steps to achieve the maintenance allergen dose. Second, direct comparison of different products would require a large population, which would involve excessive costs.

Being aware of the fact that a double-blind, placebo-controlled multicenter study might not be possible, we aimed to approach the best achievable level of evidence. Therefore, we conducted an open-labelled, prospective, controlled observational pilot study to test the feasibility of a comparison of six different products for grass pollen SCIT in children and adolescents. Our primary goal was to test an online questionnaire, to identify key challenges for a subsequent clinical trial, and to collect information about a sufficient power calculation.

Methods

Fifty-eight pediatrician practices, organized by the Pediatric Network Stuttgart (PädNetzS e.G.), recruited patients with a confirmed doctors' diagnosis of a seasonal allergic rhinoconjunctivitis (AR) with or without asthma and an allergic sensitization against grass pollen allergen confirmed by either a specific IgE (≥ 0.7 kU/L) or by a positive skin prick test result (allergen wheal diameter > 3 mm) from 2010 to 2015. For inclusion, children had to have typical clinical symptoms during at least two pollen seasons: runny or itchy nose, sneezing, nasal obstruction, or mucus discharge. Additionally, doctors' diagnoses of asthma and/or atopic dermatitis

were recorded. Children and adolescents were advised to record symptoms and medications in an internet-based electronic diary (<http://www.hyposensibilisierung-paed.de/>). After a baseline year with purely symptomatic treatment (e.g., local and/or systemic antihistamines, topical steroids, inhaled beta-agonists), every patient was offered SCIT with one out of six allergen extracts based on the habits of the pediatric practice: ALK Avanz ($n = 11$), ALK SQ Depot ($n = 49$), Allergovit ($n = 23$), Depigoid ($n = 86$), Pollinex Quattro ($n = 15$), Purethal ($n = 45$). Scores for symptoms and medications were calculated and the difference between treatment years and baseline was recorded. Data about the pollen counts were obtained from the German "Polleninformationsdienst."

Patients were advised to record their symptoms and medication use every year over a period of 72 days starting at the end of May (20/05) to the end of August (31/08). Symptom and medication scores were calculated for three periods: the entire observation period, the grass pollen season defined for each region, and the peak grass pollen season. The grass pollen season was defined for each pollen region using boundaries of three consecutive days with pollen counts > 10 grains/m³.

The global evaluation of treatment efficacy (1 = excellent, 2 = good, 3 = moderate, 4 = weak, 5 = worsened), overall evaluation of tolerability (1 = excellent, 2 = good, 3 = moderate, 4 = weak, 5 = bad), and side effects (1 = none; 2 = mild, 3 = moderate, 4 = mild systemic, 5 = severe systemic) was performed by the patients at the end of the treatment period.

Informed consent was obtained by all patients and their legal guardians. The study was approved by the local ethics committee of the University of Lübeck.

We calculated the maximum symptom and medication scores for allergic rhinitis and asthma as well as the median symptom scores for each individual during the pollen season. Score differences between groups in the first season were tested using Kruskal-Wallis tests. Possible differences over the course of the first 3 years between the groups were explored using nonparametric analyses of variance for repeated measures. Finally, group differences regarding tolerability and side effects were tested employing χ^2 tests for independence. All analyses were conducted in R using the additional package nparLD [13, 14].

Results

In total, 58 pediatrician practices recruited 284 patients with a confirmed diagnosis of a seasonal AR and an allergic sensitization against grass pollen allergen for this trial over a period of 5 years. Pediatrician practices were selected based on the ex ante assessment to be able to recruit at least 5 patients. However, nearly two-thirds of the selected pediatrician practices ($n = 36$, 62%) missed out on this and recruited only 1–3 patients (4–9 patients: $n = 14$, 24%; > 10 patients: $n = 8$, 14%). A total of 255 (89.8%; mean age 10.4, SD 3.5 years) patients recorded at least 1-day symptoms and medications in the electronic diary. Out of 229 patients treated with SIT, 136 provided diary data over 3 years (59.4%; Table 1). Overall, 49,649 patient

Table 1. Study population characteristics

	Control	Extract 1	Extract 2	Extract 3	Extract 4	Extract 5	Extract 6
<i>N</i>	26	86	23	45	15	49	11
Gender (male), <i>n</i> (%)	16 61.5%	50 58.1%	17 73.9%	33 73.3%	7 46.7%	34 69.4%	9 81.8%
Age (mean, STD)	9.2 4.3	10.1 2.9	10.5 2.5	10.1 3.4	13.6 1.6	11.1 4.2	10.1 3.6
Asthma, <i>n</i> (%)	11 42.3%	25 29.1%	5 21.7%	10 22.2%	1 6.7%	10 20.4%	5 45.5%
Neurodermitis, <i>n</i> (%)	5 19.2%	8 9.3%	2 8.7%	2 4.4%	1 6.7%	2 4.1%	0 0.0%
Additional allergic sensitizations, <i>n</i> (%)	9 34.6%	23 26.7%	15 65.2%	18 40.0%	4 26.7%	20 40.8%	2 18.2%
Diary data available over 3 consecutive years	na na	45 52.3%	12 52.2%	37 82.2%	3 20%	32 65.3%	7 63.3%

Number of participants per group, mean age and standard deviation (STD), gender distribution, doctor diagnosis of asthma and/or atopic eczema, and number of participants with other allergic sensitizations were reported. Extract E1 = Depigoid®, E2 = Allergovit®, E3 = Purethal®, E4 = Pollinex Quattro®, E5 = ALK-SQ Depot®, E6 = ALK-Avanz®; na = not applicable.

days were recorded in the electronic database (mean 183.2 days/patient).

Of the 255 participants, 166 were males (65.1%) and 240 were Caucasians (94.1%). Details of the study population are outlined in Table 1. Sixty-seven (26.3%) had a doctors' diagnosis of bronchial asthma, 22 (8.1%) a comorbid atopic dermatitis, and 96 (35.4%) at least one additional allergic sensitization (Table 1).

Two hundred and twenty-nine children and adolescents received one of the six SCIT products. We calculated the maximum symptom and medication scores for allergic rhinitis and asthma as well as the median symptom scores for each individual during the pollen season. There was no significant difference in AR symptom score, AR medication score, or asthma symptom or medication score during the first year of SCIT treatment between the different SCIT extracts (Fig. 1). Similarly, the symptom and medication scores showed no differences between the tested extracts in the second and third year of SCIT treatment (Fig. 2).

Overall, SCIT was well tolerated and side effects were only mild to moderate. Again, no differences were observed between the different SCIT products. The global evaluation of treatment efficacy showed an excellent, good, or moderate effect for all SCIT products. No insufficient treatment response or worsening of symptoms was reported during SCIT treatment (Fig. 3).

Discussion

To our best knowledge, this is the first observational pilot study to prospectively collect data comparing the efficacy and safety of six different SCIT products in children with AR sensitized to grass pollen. We were able to show that our approach is feasible in a real-life setting and that our internet-based electronic diary provides sufficient data to evaluate symptom and medication scores over a period of up to 3 years.

SCIT is underutilized in grass pollen-sensitized children with AR. Published data indicate that about 1–5% of European children with AR are treated with specific immunotherapy [12]. In light of the given efficacy, safety, and secondary preventive qualities of specific immunotherapy in children, these figures are alarming. There is an unmet need to better understand decision paths and patient preferences in order to improve the access of patients with allergic diseases to the only causal treatment option. Our data provide indirect evidence that a patient registry could help to identify knowledge gaps and to define scientific issues for a better acceptance and adherence to specific immunotherapy in children. Moreover, long-term data about treatment efficacy and safety obtained by a patient register might help to identify hallmarks for individuals with a good or excellent response to SCIT.

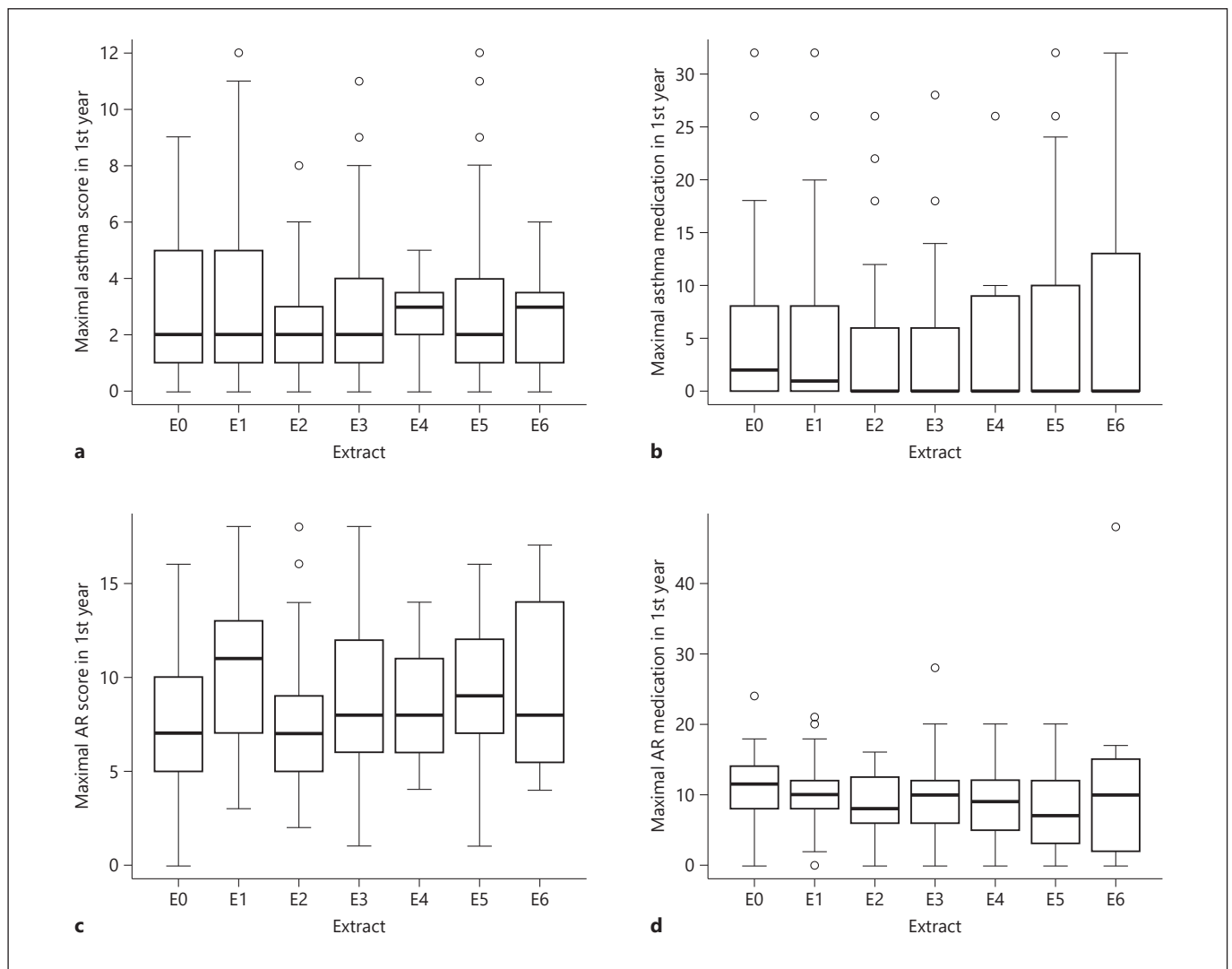


Fig. 1. Symptom and medication use in children and adolescents receiving SCIT during the first year. Extract E0 = control, E1 = Depigoid®, E2 = Allergovit®, E3 = Purethal®, E4 = Pollinex Quattro®, E5 = ALK-SQ Depot®, E6 = ALK-Avanz®. The median

(bars), 25th and 75th percentiles (box), and the 5th and 95th percentiles (range) are presented. **a** Maximal asthma symptom score. **b** Maximal asthma medication score. **c** Maximal AR symptom score. **d** Maximal AR medication score.

Up to now, the standard of care for poorly controlled seasonal allergic rhinitis in children and adolescents is SCIT with allergen extracts, administered in a physician's office. For children with a grass pollen allergy, SLIT can be considered as an alternative option for patients with seasonal allergic rhinitis. Until today, mainly indirect comparisons about SCIT and SLIT are published [15]. While available products for SCIT differ in total allergen concentration and in dosing protocols, no data comparing efficacy and safety of different SCIT products are available. We focused on children and adolescents with

grass pollen allergy given the fact that this is the most common seasonal allergy in this age group causing AR.

Based on consumption numbers in the recruitment centers, we decided to include six SCIT products commonly used in Germany. Every pediatric office or outpatient clinic using one or more of this SCIT products on a regular basis was invited to participate in this trial. Baseline data 1 year before starting SCIT were obtained and symptoms as well as medication scores were reported over the grass pollen season. Overall, symptom and medication scores did not differ between the six SCIT products. This

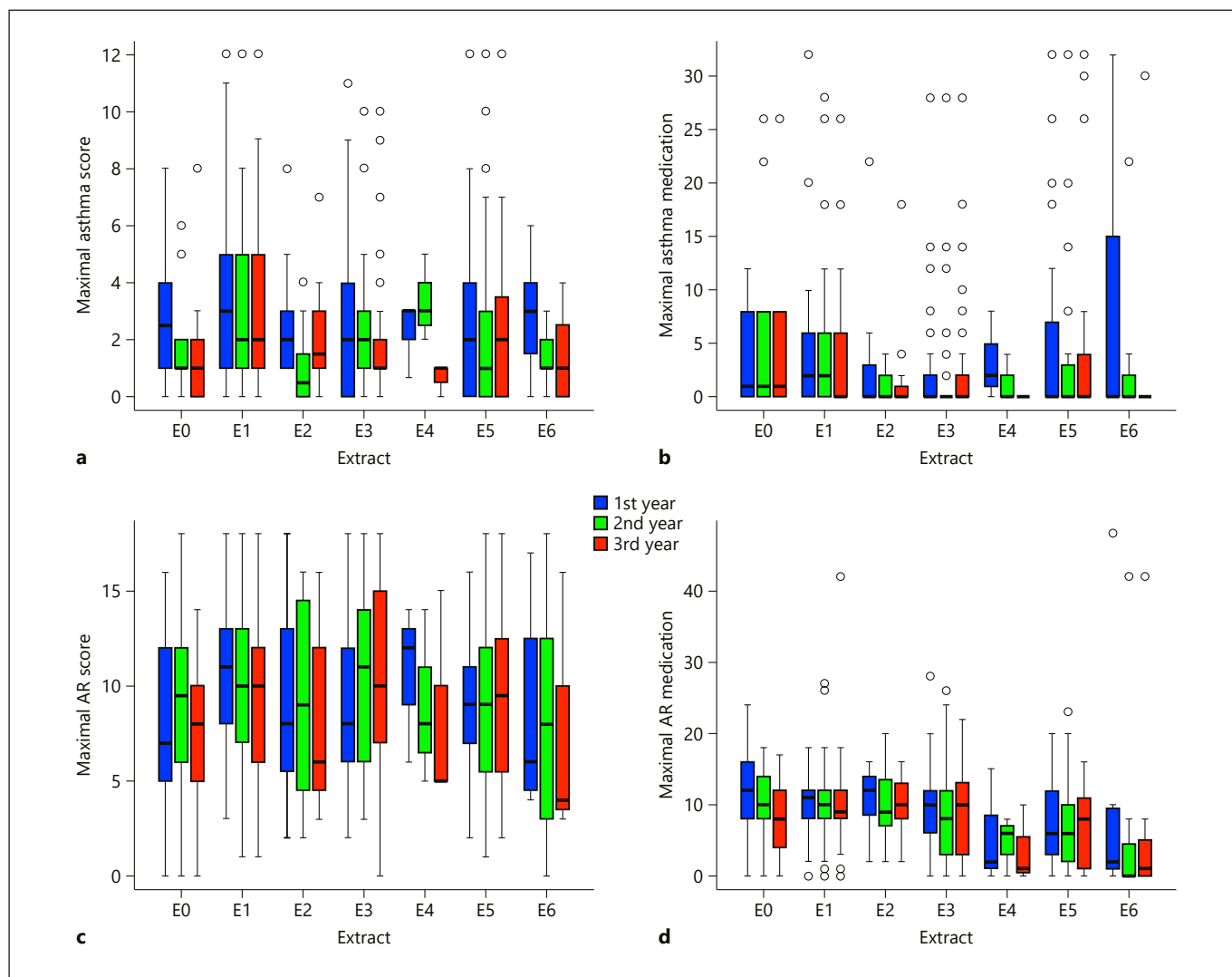


Fig. 2. Symptom and medication use in children and adolescents receiving SCIT during the treatment period of 3 years. Extract E0 = control, E1 = Depigoid®, E2 = Allergovit®, E3 = Purethal®, E4 = Pollinex Quattro®, E5 = ALK-SQ Depot®, E6 = ALK-Avanz®. The median (bars), 25th and 75th percentiles (box), and the 5th

and 95th percentiles (range) are presented. T1 = first year, blue bars; T2 = second year, green bars; T3 = third year, red bars. **a** Maximal asthma symptom score. **b** Maximal asthma medication score. **c** Maximal AR symptom score. **d** Maximal AR medication score.

is not surprising because our pilot study could not recruit enough patients to achieve the power necessary for demonstrating superiority or non-inferiority of a specific SCIT product, but to allow statements about the feasibility of our approach, to identify obstacles, and to provide data for a rational power analysis. Nevertheless, symptom scores and medication scores were reduced in all children with AR sensitized against grass pollen receiving SCIT.

Our study has several strengths and limitations. To our knowledge, this is the first trial which directly compared

six different SCIT products in children. We followed the recommendations of the ARIA guidelines [16] and collected data on symptoms as well as medication scores in our study population. To verify our results, we analyzed efficacy and safety not only during the first pollen season after initiation of SCIT but also rechecked our data during the second and third treatment year. Moreover, we included a baseline season and had a straightforward definition on allergic rhinitis and other comorbid diseases, i.e., atopic eczema and asthma, which gives us certainty that

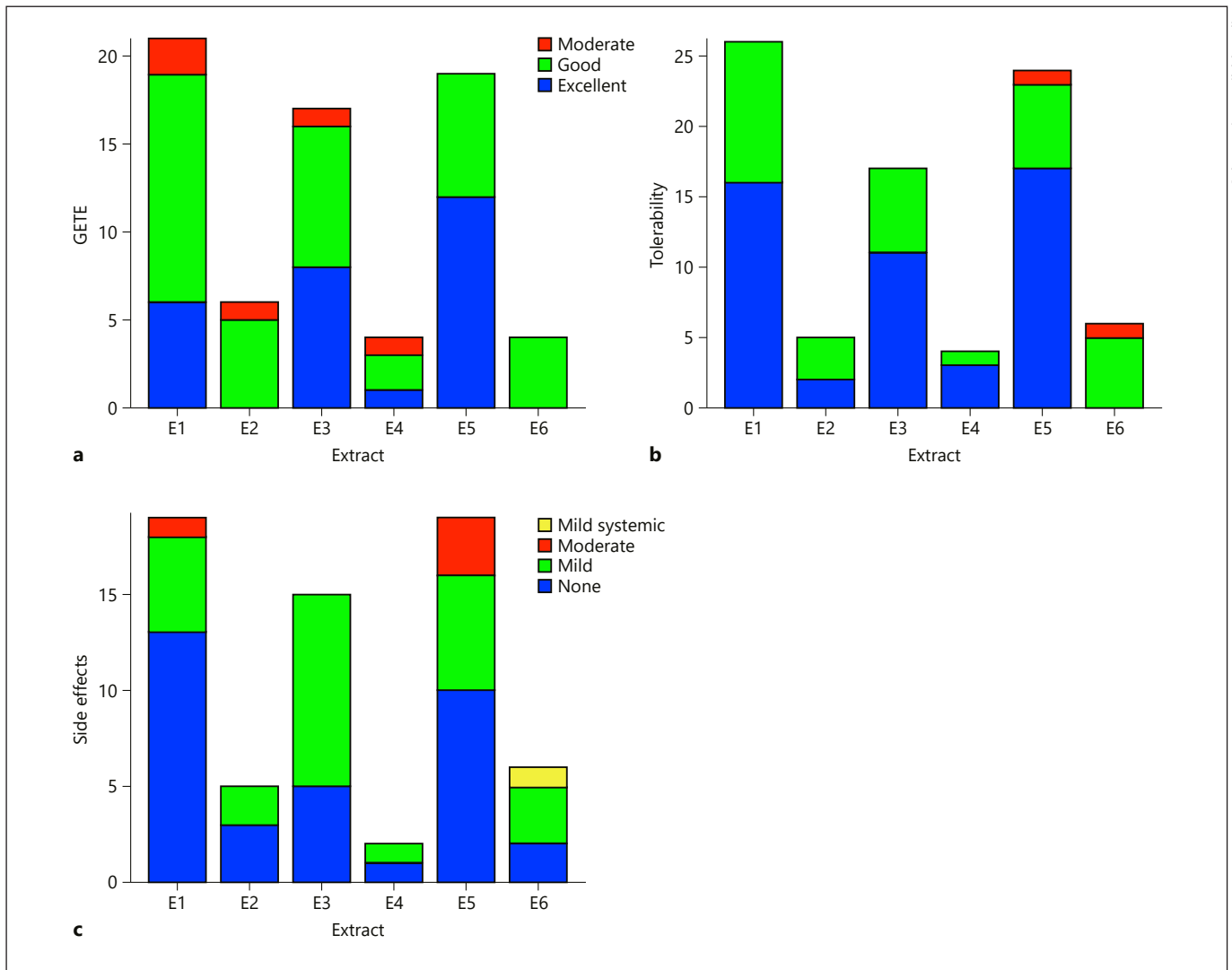


Fig. 3. Global evaluation of treatment efficacy (GETE; 1 = excellent, 2 = good, 3 = moderate, 4 = weak, 5 = worsened) (a), tolerability (1 = excellent, 2 = good, 3 = moderate, 4 = weak, 5 = bad) (b), and side effects by the patients (1 = none; 2 = mild, 3 = moderate, 4 = mild systemic, 5 = severe systemic) (c) on a five-point scale after the first treatment year. Extract 0 = control, E1 = Depigoid®,

E2 = Allergovit®, E3 = Purethal®, E4 = Pollinex Quattro®, E5 = ALK-SQ Depot®, E6 = ALK-Avanz®. The width of the bars corresponds to the number of patients in each group, and the height corresponds to the number of patients choosing 1 (upper bar), 2, or 3 (lower bars).

we have included a relevant population with atopic complaints.

We were not able to randomize our children in different treatment groups but left the decision about the SCIT product to the single practitioner. This resulted in different numbers of SCIT-treated patients in our different groups. Moreover, even if we had recruited a substantial number of patients, low numbers of children in certain SCIT groups would have occurred. Therefore, we were not able to sufficiently test for different efficacies of the

SCIT products. However, our data provide information about the group size, which would be necessary to do so. Finally, our results might be biased by center effects. Nearly two-thirds of the selected pediatrician practices recruited only 1–3 patients, while only 14% recruited more than 10 patients. Possible reasons for the disappointing recruitment rate in our trial are (1) work intensification in the pediatrician practices in everyday life, (2) limited administrative resources in the pediatrician practices, (3) limited experience to carry out an observational

trial, and (4) overestimation of the availability of patients. Based on the results of this pilot study, the pediatrician practices must be better selected for future clinical trials. In this trial, we provided standardized instructions given by the Paed-Netz-Stuttgart, which might scale down the risk for center effects. In light of the potential bias and given the fact that we were not able to use a population-based approach, one should beware of generalizing our results. Nevertheless, our trial may be helpful to identify knowledge gaps, i.e., the low number of already identified children who received SIT.

In conclusion, we showed that a prospective observational trial in a real-life setting is not only feasible but adds highly valuable information about patients' overall health during SCIT. Due to the small numbers of participants per group, we observed no statistically significant differences between the six SCIT products in terms of efficacy in our pilot study. Considerable variability was observed in symptoms and medication use during the study period. Taken together, SCIT was safe and well tolerated for all tested products. There were no severe adverse events during the study period. Our study protocol is a new and valuable tool to collect further data about safety, tolerability, and efficacy of SCIT in children and adolescents.

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Statement of Ethics

Informed consent was obtained from all patients and their legal guardians. The study was approved by the local Ethics Committee of the University of Lübeck.

Disclosure Statement

M.V.K. has received a speaker honorarium or consultant fees from ALK-Abello, Allergopharma, Chiesi, Infectopharm, Meda, Novartis Pharma, Vertex and has received a speaker honorarium or consultant fees from Abbvie, ALK-Abello, Allergopharma, Chiesi, Infectopharm, Meda, Novartis Pharma, and Nutricia. F.F. and B.N. have received a speaker honorarium or consultant fees from the companies: Allergopharma and Infectopharm. I.R.K., H.U.U. and M.M.-U. declare that they have no conflict of interest.

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