ORIGINAL ARTICLE Upper airways

Safety and effect on reported symptoms of depigmented polymerized allergen immunotherapy: a retrospective study of 2927 paediatric patients

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Abstract

Background: Allergen immunotherapy (AIT) is effective treatment for allergic diseases, and subcutaneous use of depigmented polymerized extracts may allow rapid up-dosing and safe therapy. To date, there is little information on their safety and clinical effects for children and adolescents with allergic disease.
Methods: We performed a retrospective survey of patient notes of 2927 children and adolescents across 136 centres who had received subcutaneous AIT (SCIT) with depigmented polymerized extracts to pollen or mite allergens for at least 1 yr to collect documentation on safety and clinical symptoms.
Results: 16.3% percent of patients had local reactions, of these 148 were larger than 12 cm in diameter. Systemic reactions were documented in 1.6% of children and in 0.8% of adolescents. There were no documented cases of anaphylactic shock. There were significant reductions in the frequency of patients with recorded nasal symptoms over time of treatment. Moreover, the prescribing rate of rescue medication was reduced over the course of SCIT.
Conclusion: These 'real-life' data from a large retrospective analysis including 2927 children and adolescents with pollen- and/or mite-induced allergic rhinoconjunctivitis with/or without allergic asthma indicate that AIT with depigmented polymerized extracts is well tolerated, and they are compatible with clinical response.

Prevalence of allergic rhinitis, conjunctivitis and/or allergic asthma has increased in the last decades (1,2). Allergen immunotherapy (AIT), in clinical use for more than 100 yr (3), is accepted on the basis of high-grade evidence as disease modifying treatment for these diseases (4–8). In Northern Europe, most of allergic patients are treated with extracts of grass or birch pollens, or house dust mites.

However, the use of subcutaneous AIT (SCIT) is limited to some extent by potential side effects which include anaphylaxis (9). An attempt to reduce this risk of SCIT was polymerization of natural (native) allergen extracts with chemicals such as glutaraldehyde, with the aim to reduce IgE binding yet to retain T-cell reactivity (10,11). This principle was later modified by treating the extracts with acid ('depigmentation') prior to polymerization (12,13). As shown in numerous DBPC trials, these depigmented polymerized extracts were well tolerated and efficacious in treating allergic adults and adolescents (14–18). However, there is little data for children. In addition, these

controlled trials are performed in accordance with strict study protocols on carefully selected allergic patients and therefore should be supported with data from large-scale, post-marketing analysis of physician's routine clinical practice (19–21). Data from two prospective, post-marketing, multicentre surveys on safety and clinical effects of depigmented polymerized allergen extracts in adult and paediatric allergic patients have been previously published (19,20).

Here, our aim was to analyse the safety and clinical effects of depigmented polymerized allergen extracts in a large cohort of children and adolescents with pollen- and/or mite-induced allergic rhinoconjunctivitis with/or without allergic asthma.

Methods

Patients and clinical study design

This was a non-interventional, retrospective study including paediatric patients (children 5–11 yr old and adolescents 12–18 yr old) with allergic symptoms to pollen and mite allergens who received SCIT for at least 1 yr within the last 5 yr. The allergy was confirmed by medical history together with positive skin prick test or RAST class ≥2 (ImmunoCAP, ThermoFisher, Schwerte, Germany). Data were collected from patient's medical records by participating physicians in a total of 136 centres in Germany between October 2008 and April 2009, using a standardized data collection form. This included demographic characteristics, information on indications, types and amounts of SCIT given, and the course of the allergic condition in terms of symptoms and rescue treatment.

The study was approved by local ethics committee and notified to the relevant regulatory bodies. Only data were collected which had been recorded in the patient files during routine therapy.

Populations evaluated

Clinical symptoms over the course of treatment and safety were evaluated for the total group (all evaluable patients), children (patients 5–11 yr of age) and adolescents (patients 12–18 yr of age). Each age group was divided into subgroups ('treatment groups') according to the type of allergen. Treatment groups were Depigoid®-Bäume ('Trees'; mixture of pollen from early-blooming trees, e.g. birch, alder, hazel), Depigoid®-Gräser ('Grasses'; mixture of grass pollen, rye and cereal pollens, e.g. wheat, oat, barley, rye, timothy), Depigoid®-Bäume/Gräser ('Trees/Grasses'; mixtures of pollen from the categories grasses and trees), Depigoid®-Kräuter ('Weeds'; mixture of weeds, e.g. mugwort, plantain, wall pellitory, lambs quarter), Depigoid®-Milben ('Mites'; mixture of *Dermatophagoides pteronyssinus* and *D. farinae*, *D. pteronssinus*, *D. farinae*, *Euroglyphus maynei*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, *Acarus siro*, *D. microceras*) and 'multiple SCIT' (application of different allergen classes other than 'Trees/Grasses', e.g. any pollen/mite, grass pollen/weed pollen SCITs). All extracts were manufactured by Laboratorios Leti, SL, Tres Cantos, Spain. Patients' demographics sensitization and extracts used are given in Table 1.

Table 1 Demographic and clinical details of children and adolescents

	Children (aged 5–11) Total 1678	Adolescents (aged 12–18) 1237
Gender	1018 male	728 male
Sensitization		
Grass pollen	1070	837
Tree pollen	783	608
Mites	698	562
Weeds	172	170
Disease		
Rhinoconjunctivitis	1385	1055
Asthma	958	586
Other	202	112
Allergen extract used for SCIT		
Grass pollen	488	374
Tree pollen	489	340
Tree/grass mix	174	127
Mites	470	332
Multi-allergen	56	61

Data are absolute numbers for each variable as recorded in case records. Allergic disease is that recorded, some were multiple. Multiple SCIT refers to patients treated with mixed extracts for three pollens, or mites plus pollens. Four additional patients have received SCIT with weed-extracts, but have not been displayed and considered for further discussion due to the limited group size.

Table 2 Adverse reactions to immunotherapy

Recording
Local reactions
Grade 1 (L1): local swelling or nodules <12 cm in diameter
Grade 2 (L2): local reaction ≥12 cm in diameter
Systemic reactions
Grade 1 (S1): exacerbation of patient-specific symptoms (mild allergy: itchy eyes, sneezing, cough, atopic eczema)
Grade 2 (S2): moderate allergic reaction (wheezing, breathlessness, angioedema, generalized urticaria)
Grade 3 (S3): anaphylactic shock

	Children				Adolescents			
Allergen	L1	L2	S1	S2	L1	L2	S1	S2
Grass pollen	(488) 228	28	22	4	(374) 104	19	5	0
Tree pollen	(489) 196	17	12	1	(340) 75	18	2	0
Tree/grass	(174) 89	11	0	0	(127) 26	5	0	0
Mites	(470) 153	12	7	1	(332) 114	20	0	8
Mixed	(56) 48	11	4	1	(61) 31	7	0	0

Numbers of recorded local or systemic reactions for each allergen extract (total number of patients treated with each extract shown in brackets). There were no recorded cases of anaphylactic shock. Dose reduction occurred 153 times in children and 67 times in adolescents following LR<10 cm, 31 times in children and 10 times in adolescents following large local reactions, eight times in children following mild systemic symptoms and two times in children following moderate systemic symptoms.

Evaluation of safety

The safety of the treatment was assessed by the number and frequency of local and systemic adverse drug reactions (ADRs), serious adverse drug reactions (sADRs) and the related measures. A standardized assessment was used for reactions considered related to immunotherapy (Table 2). If adrenaline was given, detailed description of the adverse event was required.

Evaluation of clinical symptoms over the course of treatment

The presence of eye, nose, lung and skin symptoms was recorded at different time points, and the prescription of symptomatic medication with time was used to assess clinical effects of SCIT.

Statistics

Data were analysed by descriptive statistics using SAS software (SAS Institute Inc., Cary, NC, USA; version 9.2). Continuous numeric values or values scaled on intervals were expressed as number of evaluable values, mean, standard deviation, median, minimum and maximum. Ordinal or categorical values were expressed in absolute and relative frequencies. Patients for which the respective parameters were missing were excluded from the evaluation of relative frequencies. Frequencies of patients reporting symptoms for each year of treatment were compared by chi-square test, comparing year one with baseline, year two with year one and year three with year two.

Results

Demographic data are shown in Table 1.

In the up-dosing phase of the SCIT, a mean of 4.7 injections was given in the total group which is in accordance with the recommended up-dosing regimen for these products. Patients receiving multiple SCIT required 1.5–2 times the number of injections to reach the maintenance dose.

The mean treatment duration for the study populations of the SCIT was 2.9 yr (SD 0.89 yr).

Safety

Numbers of recorded treatment-related local and systemic ADRs for each allergen extract are shown in Table 2.

In ten times adolescents received subcutaneous adrenaline for large local reactions without systemic reactions. Six of these were during up-dosing (four receiving mite extract, one grass pollen and one tree pollen), three were in year two of treatment (two receiving mite extract and one tree pollen), and one was in year three of treatment with grass pollen extract. One of these patients elected to discontinue treatment, and the rest continued after dose reduction for the next visit. Most systemic reactions occurred during up-dosing or the first year of treatment. None of the systemic reactions were treated with adrenaline. In seven times in children and in two times in adolescents intravenous antihistamines were given for systemic reactions, and in six times in children and in two times in adolescents intravenous steroids were given for systemic reactions. All of these patients continued treatment after dose reduction. The frequency of patients affected by ADR was twice as high in the 'multiple SCIT' group as in the other treatment groups. Most ADRs were observed at the beginning of the SCIT and reached a minimum by the end of the treatment. Seven per cent of patients discontinued treatment (5.3% of children and 9.3% of adolescents). In no case was SCIT discontinued by the doctor because of serious ADR. Most discontinuations were due to the patient's/parent's wishes or other reasons, which included change of the doctor, relocation, concomitant symptoms/diseases, poor success of the treatment and non-compliance. In seven children and four adolescents the treatment was discontinued due to ADRs.

Clinical assessment

Before treatment, most patients' allergic symptoms were nasal (90.0%), followed by eyes (76.3%) and lungs (61.0%). In fewer patients (14.1%), the skin was affected by allergic symptoms. More children than adolescents suffered from lung symptoms (65.9% vs. 54.1%). Data for changes in the recorded frequency of nasal symptoms over the course of treatment are presented in Table 3. Numbers of patients reporting nasal symptoms were significantly reduced over the course of treatment (using chi-square test; Table 3). Data on eye, lung and skin symtoms are not shown.

The prescription of anti-allergic co-medication decreased for all allergen groups (see Fig. 1). This was seen for oral and topical antihistamines, topical (nasal and inhaled) corticosteroids and for topical cromoglycate.

Discussion

In this study, we present a retrospective survey of safety and clinical effects of subcutaneous AIT with depigmented polymerized preparations containing pollen and/or mite allergens in a large cohort of nearly 3000 children and adolescents. The data suggest this treatment was well tolerated and show a significant reduction in the proportion of patients with symptoms over the years of treatment.

In a previous analysis of data collected prospectively 766 patients (including 17% children and 24% adolescents), the safety profile of AIT using depigmented polymerized extracts of pollen or mite allergens was excellent with 54 local reactions and 16 systemic reactions (15 grade 2 and 1 grade 3) (19). In a subsequent prospective survey of 768 patients (210 children and adolescents) with allergic rhinoconjunctivitis and asthma receiving AIT with these preparations under daily practice conditions, our group found both a good safety profile and a reduction of symptoms and need of concomitant anti-allergic medication (20). In that survey, there were 14 local reactions and 27 systemic reactions (20 grade 1, seven grade 2 and no grade 3 or 4 reactions). In a study comparing rush (two injections to reach maintenance dose at visit one) vs. conventional up-dosing of AIT with depigmented polymerized extracts, the rates of systemic reactions were 5.8% for rush AIT and 2% for conventional up-dosing (all grade 2 or less) with rates of local reactions of 24% and 11%, respectively (14). However, to date, clinical data on AIT with depigmented

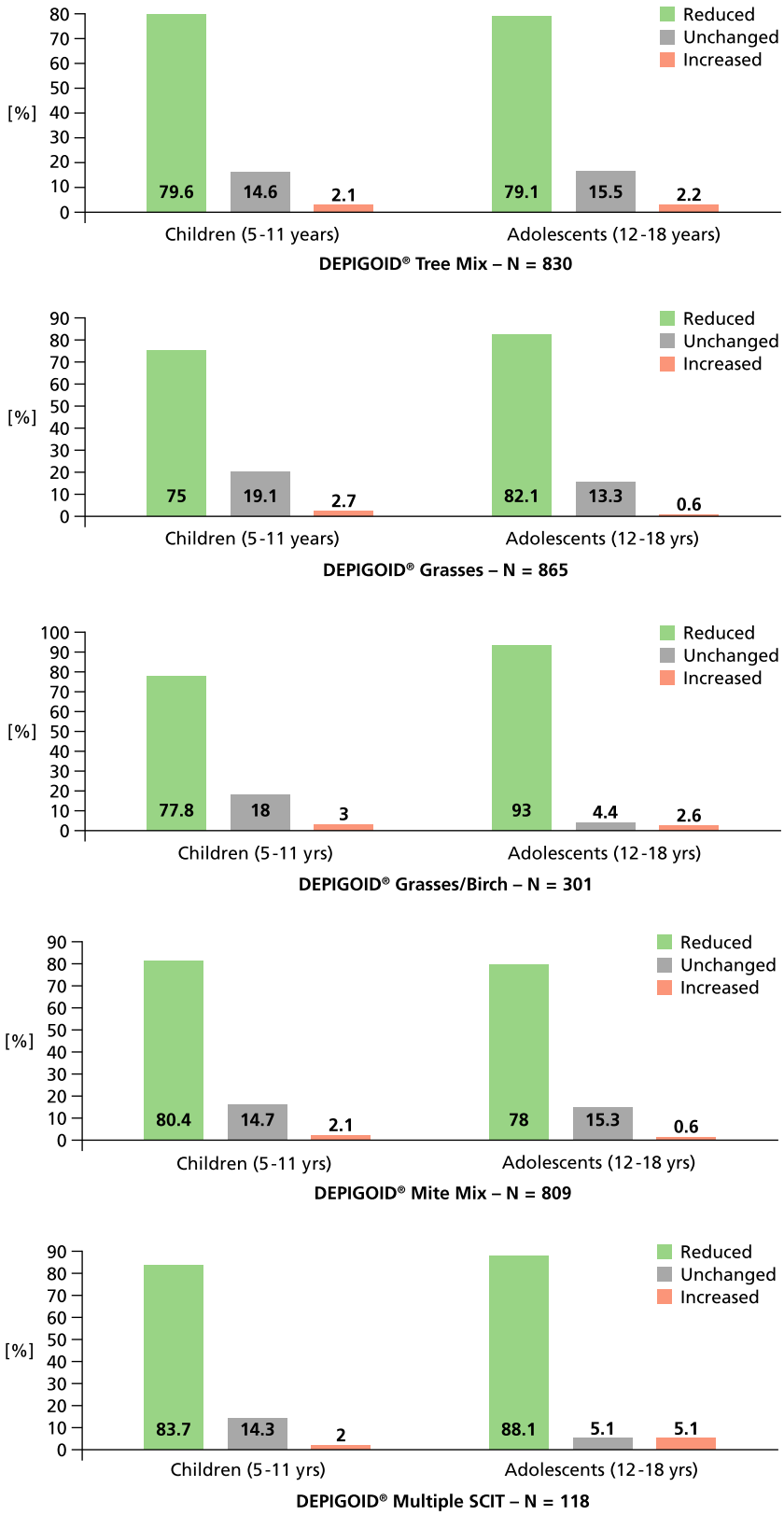

Figure 1 Percentage of patients with reduction of anti-allergic co-medication (and completion of a treatment course of at least 1 year of AIT).

Table 3 Numbers of patients reporting nasal symptoms over the course of immunotherapy

	Nasal symptoms					
	Children			Adolescents		
		Symptoms			Symptoms	
Treatment	Year	Yes	No	Year	Yes	No
Grass pollen	0	458	30	0	348	25
	1	436	41	1	318	50***
	2	313	69****	2	210	75****
	3	172	72****	3	115	73***
Tree pollen	0	470	19	0	321	19
	1	428	52****	1	295	41***
	2	306	65**	2	203	69****
	3	169	53	3	104	68***
Tree/Grass	0	158	16	0	119	8
	1	145	24	1	111	9
	2	101	39***	2	82	20**
	3	67	29	3	40	30***
Mites	0	361	107	0	273	59
	1	304	154****	1	242	81*
	2	230	197****	2	205	107*
	3	137	164*	3	126	101*
Mixed	0	53	3	0	58	3
	1	49	6	1	53	8
	2	40	9	2	46	12
	3	26	11	3	35	9

Statistical comparison by chi-square test of distribution for each year with preceding year (*$p < 0.05$, **$p < 0.01$, ***$p < 0.005$, ****$p < 0.001$).

polymerized extracts in children and adolescents are still limited.

In our study, 79 large local reactions (≥ 12 cm in diameter) and 714 smaller reactions (< 12 cm) were recorded in a total number of 1677 children treated with similar figures for 1234 adolescents treated (69 large local reactions, 350 smaller local reactions) which is higher than the two prospective series referenced above. However, these numbers are in line with rates of local reactions seen in double-blind placebo-controlled studies of depigmented polymerized extracts (15–18). In the present study, 7.4% of all local reactions were treated with oral antihistamines and/or topical corticosteroids and 23.2% of all local reactions lead to a dose reduction in children and 18.4% in adolescents, but treatment was continued. Surprisingly, subcutaneous adrenaline was given 10 times in adolescents with large local reactions, but no recorded systemic reaction. Most of these were during up-dosing and most were being treated for mite allergy. Systemic reactions were recorded in 27 children (1.6%) and 10 adolescents (0.8%) and were mostly mild. There was a higher rate of local and systemic reactions in children compared with adolescents. The higher frequency of patients affected with ADR in the 'multiple SCIT' group may be explained by the higher numbers of injections, due to the parallel administration of two preparations, one on each arm, and not by a lower tolerability of the therapy. Further data are required on whether local reactions are more troublesome in children treated with AIT, but overall, the safety profile here is reassuring.

Data in this report were collected retrospectively from patient notes rather than from a placebo-controlled study. One cannot therefore firmly ascribe any documented reduction in the presence of symptoms to the medication given, and the descriptive data are less rigorous than a standardized daily symptom and medication diary as used in prospective placebo-controlled trials (22). Nonetheless, the significant reductions seen here in proportions of children and adolescents with recorded nasal symptoms over the course of treatment are compatible with an improvement due to immunotherapy and are in accordance with data from randomized, double-blind placebo-controlled trials of depigmented polymerized extracts for AIT performed in adolescents and adults (15–18). Overall, there was a reduction in those reporting symptoms, and a reduction in use of rescue medication, which was seen for each of the allergen treatment groups in both children and adolescents. Strengths of the data presented here are that they present real-life clinical practice, and a very large group of patients.

When the trend for reduced proportion with recorded symptoms was analysed for treatment year, the data suggested that there might be a year-on-year improvement with continuing SCIT with depigmented polymerized extracts. Such a finding would be in accord with data from other studies of both SCIT and SLIT (4–6). Further research is required to determine the optimal dose and duration of SCIT in paediatric patients. Of note, some caution should be applied to this interpretation as the same patients were not studied over a 3-yr time course. Controlled, prospective long-term studies are warranted.

The group treated with multiple allergen SCIT appeared to respond equally well to treatment as those treated with a single allergen, although it is of note that more adverse events were reported in this group. This finding is at variance with previous reports and reviews, suggesting that mixed multi-allergen SCIT might be less effective than single allergen dosing as dose reductions are required for each allergen in the mixture (18, 23). Here, most multi-allergen regimens were of two allergens given one in each arm without dose reduction rather than mixtures of multiple allergens used in other studies, and this might explain the apparent difference. The data here need to be confirmed by prospective controlled trials. A recent pilot study suggests it may be safe to mix depigmented polymerized extracts without dose reduction (data on file, Laboratorios Leti, Madrid, Spain).

For our analysis, we selected children and adolescents who had completed at least 1 yr of AIT. It is possible that such selection may have introduced bias as any children not responding to AIT might discontinue earlier than 1 yr. Prescribing data (data on file, Leti Pharma GmbH, Witten, Germany) emphasize that the dropout rate during the first year of AIT with depigmented polymerized extracts during the study period was around 10%. We therefore suggest that this bias was unlikely to have an important effect on the study conclusion, although prospective controlled data are required.

Similarly, it is possible that the study design did not detect delayed adverse events treated at other medical centres, although, as adverse events were always asked about before giving the next dose, these should have been detected and recorded.

In summary, this large retrospective survey analysing 'real-life' data of almost 3000 children and adolescents with rhinoconjunctivitis with/or without asthma suggests that AIT with depigmented polymerized pollen or mite extracts is well tolerated as well as reducing symptoms.

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Authors contribution

OP and DSR have substantially contributed to the manuscript from the first draft stage. AS was the sponsor's project manager of the trial and sponsor's medical director and was involved in the study design and conduct of the analysis. She furthermore contributed to the manuscript by reviewing and commenting as well as critically revising where applicable.

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