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TITLE PAGE

The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a paediatric assessment.

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Running title : Systemic reactions to AIT in children

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ABSTRACT PAGE

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Abstract:

Background: Safety data on “real-life” allergen immunotherapy (AIT) in children and adolescents is usually extrapolated from studies in adults.

Methods: Patients aged 18 or under initiating aeroallergen AIT were evaluated in a prospective European survey. Patient profiles and systemic reactions (SRs) were recorded. Descriptive, univariate and multivariate analyses were used to identify risk factors for SRs.

Results: A total of 1,563 patients (mean±SD age: 11.7±3.9 years; rhinitis: 93.7%; asthma: 61.5%; polysensitization: 62.5%) and 1,578 courses of AIT were assessed. Single-allergen AIT was administered in 89.5% of cases (n=1,412; mites: 49%; grass pollen: 25.8%; tree pollen: 8.7%; *Alternaria*: 4.6%; dander: 0.8%; weed pollen: 0.6%). Subcutaneous AIT (SCIT) was used in 71.4% (n=1,127) of the treatments, including 574 (50.9%) with natural extracts. Sublingual AIT (SLIT) was used for the remaining 451 treatments (drops: 73.8%; tablets: 26.2%). The mean±SD follow-up period was 12.9±3.3 months. The estimated total number of doses was 19,669 for SCIT and 131,550 for SLIT. Twenty-four patients (1.53%) experienced 29 SRs. Respiratory (55.7%) and skin symptoms (37.9%) were most frequent. Anaphylaxis was diagnosed in 3 SRs (10.3%), and adrenaline was administered in 2 of these cases. In a univariate analysis, the risk of SRs was lower in mite-sensitized patients and higher in cases of pollen polysensitization (>3), grass pollen extracts and the use of natural extracts (vs. allergoids).

Conclusions: In a real-life paediatric setting, AIT is safe. SRs are infrequent and generally not severe. Pollen polysensitization, grass pollen extracts and natural extracts (vs. allergoids) were risk factors for AIT-associated SRs.

Keywords : allergen immunotherapy, children, subcutaneous, sublingual, systemic reaction, risk factor, anaphylaxis, adrenaline, MedDRA.

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Introduction

Safety of AIT is still one of its weaknesses (1) and in some relevant guidelines is regarded as a severe limitation for its use (2). Data on systemic reactions (SRs) in children receiving allergen immunotherapy (AIT) in real-life settings are scarce (3) and are usually extrapolated from studies of adults. Clinical trials provide information on prevalence (4,5) but do not assess risk factors or correspond to routine clinical practice. Although large-scale surveys of AIT have attempted to identify risk factors for SRs (3), little information has been obtained in children.

To address this need, we analysed data on paediatric patients in the European Academy of Allergy and Clinical Immunology's prospective European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI) (6) (7).

Methods

Study design

The survey's methods have been extensively described elsewhere (6). Physicians in France, Germany and Spain took part. All reported SRs in patients receiving AIT were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology recommended by the European Medicines Agency (EMA) (8).

Inclusion criteria

Patients aged 18 or under (9,10) with IgE-mediated respiratory allergies induced by pollens, mites, *Alternaria* and/or animal dander and initiating subcutaneous or sublingual AIT (SCIT or SLIT, respectively) in a real-life clinical setting were included in the analysis. In line with drug registry procedures (11,12), two age groups were studied (3-11 years, children; 12-18 years, adolescents) (13).

Statistical analysis

Potential risks factors for SRs were evaluated using univariate analyses, Fisher's exact test and Student's t-test. A predictive multivariate analysis was performed by using logistic regression with stepwise selection (independent variable: SRs). Since some of the patients were receiving several concomitant AIT courses, the chosen study unit was a "patient-treatment" (constituted by one person and one treatment).

Results

One hundred and twelve physicians (France: 30.4%; Germany: 21.4%; Spain: 48.2%) agreed to participate in the survey and collect the data. Most doctors (94.6%) identified themselves as “allergists” with 19.9 ± 8.4 years of clinical experience in allergy.

Population characteristics. 1563 patients (762 children and 801 adolescents; males: 59.1%; Spain: 65.4%; France: 21.4%; Germany: 13.2%) and 1578 treatments were included. Thirteen patients were receiving two concomitant courses and one was receiving three. The mean $\pm$ standard deviation (SD) age was 11.7 ± 3.9 , 51.2% (n=801) were 12-18y.o. Patients had allergic rhinitis in 93.7% (n=1,464), allergic rhinitis and asthma in 56.1% (n=880), asthma alone in 5.2% (n=82) patients (**Table 1**).

Sensitization profile. The most frequent sensitizing allergens (detected in both skin prick tests and serum specific IgE assays) were pollens (45%), mites (36.8%) and dander (10.2%) (**Table E1**). Grass pollen was the most prevalent sensitizing pollen (Table E2). Polysensitization was observed in 62.5% of the patients, and was associated with the presence of asthma (in 65.6% of polysensitized patients vs. 60% of monosensitized patients; $p < 0.004$).

Allergen immunotherapy

Previous AIT. 11.5% (n=181) patients had previously received AIT (SLIT: 59.1%; SCIT: 37.6%; both routes: 3.3%). In the present survey, 57.8% of these patients (89.7% in SCIT and 37.4% in SLIT) had repeated the previously used administration route and 74.6% were receiving the previously administered allergens either solely or along with other allergens. The prior tolerance of AIT was reportedly good or very good.

Current AIT composition. Single-allergen AIT accounted for 89.5% (n=1,412) of all prescriptions (mites: 49%; grass pollen: 25.8%, tree pollen: 8.7%; *Alternaria*: 4.6%; dander: 0.8%; weed pollen: 0.6%). Only 10.5% of the AIT courses were mixtures; 9.3%, 1.1% and 0.1% of these contained respectively two, three or more non-homologous allergens. Physicians with less than 10 years of practice were more likely than more experienced physicians to prescribe mixtures (21.9% vs. 8.5% of the prescriptions, respectively; $p < 0.0001$).

Current AIT route/formulation. SCIT accounted for 71.4% (n=1,127) of the treatments; this proportion varied significantly from one country to another (92.6% in Spain, 56% in Germany and 16.3% in France; $p < 0.0001$). For SCIT treatments, 50.9% (n=574) involved natural extracts and 49.1% (n=553) involved allergoids (**Table E3 and E4**). Patients receiving allergoids vs. natural extracts did not differ in terms of demographic or clinical parameters (**Table 2**).

SLIT accounted for 28.6% (n=451) of the treatments (drops: n=333, 73.8%; tablets: n=118, 26.2%). Drops were most prevalent in France (n=258, 91.2%), followed by Spain (n=53, 69.7%) and Germany (n=22, 23.9%) ($p < 0.0001$). Tablets were prescribed more frequently in adolescents (35.8%) than in children (20.6%) ($p = 0.001$) (**Table 2**).

AIT regimens and premedication. Conventional (42.8%), cluster (38.8%) and rush (18.4%) schedules were used for SCIT up dosing, (**Table 2 and Table E3**). The most frequent schedule was a rush procedure for allergoids (92.8%) and a conventional procedure for natural extracts (72.3%; $p < 0.0001$). Most of the SCIT maintenance regimens (94.4%) were year-round (**Table 2 and Table E4**). For SLIT, up dosing was generally not required or took only a few days. Most of the maintenance

regimens were year-round (72.7%) (**Table 2**). 20.3% of the patients premedicated before the administration of AIT (antihistamines for 95.9% and corticosteroids for 4.1%).

Survey follow-up and the estimated number of doses. A total of 1,371 (86.9%) patients were followed up for a year or more (mean $\pm$ SD: 12.9 $\pm$ 3.3 months). For SCIT, the patients received a mean $\pm$ SD of 6.4 $\pm$ 3.6 doses during up dosing and 11 $\pm$ 4 doses in the maintenance phase. An estimated 19,669 SCIT doses were given during the survey period (n=7,211 during up dosing and n=12,458 during maintenance). For SLIT, a mean $\pm$ SD of 291 $\pm$ 127.6 doses were administered in the maintenance phase. An estimated total of 131,550 SLIT doses were given.

Systemic reactions during AIT

Description of SRs. A total of 29 SRs were recorded in 24 patient-treatments. Twenty (68.9%) of these reactions occurred in boys (p=0.041 vs. girls). The mean $\pm$ SD age was 11.1 $\pm$ 3.7 years; 51.7% of the SRs occurred in children (i.e. under-12s). There were no intercountry differences in the SR distribution. Given the estimated number of doses received during the study period, the incidence of SRs was 0.017 per patient-year (Table 3).

SCIT was caused 23 (79.3%) SRs; 21 (91.3%) were related to natural extracts. Most SRs occurred during up dosing (n=21, 91.3%). The system organ classes (SOCs) most frequently affected by SCIT-associated SRs were respiratory (n=12, 60.9%), skin (n=11, 47.8%) general (n=2, 8.7%), nervous system (n=1, 4.3%) and vascular disorders (n=1, 4.3%). Urticaria was the most frequently reported symptom (n=10, 30.3%).

SLIT triggered 6 (20.7%) SRs (5 (83.3%) with SLIT drops and 1 (17.7%) with SLIT tablets). The most frequently affected SOC was gastrointestinal (n=3, 50%), respiratory (n=2, 33.3%), and eye and general disorders (n=1 each, 17.7%). No cases of SLIT-related anaphylaxis were recorded. (**Table 3, Figure E5**). Vomiting (n=3, 37.5%) was the most frequent symptom in SLIT-associated SRs.

Overall, the most frequently affected SOC was respiratory (55.2%), skin (37.9%), gastrointestinal (10.3%) and general disorders (10.3%). Most SRs involved a single SOC (75.9%) (**Table 4**).

Severity of SRs. Most SRs were mild (72.4%); only one SR was graded as severe. Three (10.3%) SRs were classified as anaphylaxis, and all were related to SCIT. The estimated incidence of anaphylaxis per patient-year was 0.00176. Most reactions occurred during up dosing (n=23, 79.3%, p=0.002) but were generally mild. Maintenance-phase SRs were significantly more severe than up dosing-phase SRs (p=0.023). Severity was not significantly influenced by the patient's age or gender (**Table E6**).

Chronology and follow-up of SRs. Regarding the time interval between AIT administration and the SR onset, 27.6% occurred in the first 30 min, with 6.9% from 30 min to 2 hrs afterwards, 27.6% from 2 hr to 24 hrs afterwards and 37.9% more than 24 hrs afterwards (**Table 3**). There was no association between early/late SR onset (less/more than 30 minutes afterwards) on one hand and the reaction's severity or the use of premedication on the other. The time required for total resolution was <1 hr in 20.7% of the SRs, 1 to 3 hrs in 24.1%, 3 to 24 hrs in 24.1% and >24 hrs in 31.1%.

After resolution, 5 SRs (17.2%) induced AIT discontinuation, after 11 (37.9%) SRs AIT was continued as before and 13 (44.9%) SRs were followed by modification of the regimen (same dose repeated: 46.1%; dose reduction by at least half: 38.5%; restart from the first dose: 15.4%). AIT discontinuation was associated with SR severity (p=0.043) (**Table 5**). There were no associations between the continuation modality and the affected SOC.

Treatment of SRs. Antihistamines (58.6%), corticosteroids (27.6%) and short-acting beta 2 agonists (27.6%) were administered. Adrenaline was used in 2 cases (6.6%). Five SRs (17.2%) did not require any anti-allergic medication, and a single medication was administered in 55.2% of SRs (**Figure 1, Table E7**).

Risk factors for SRs. In a univariate analysis of patient-related factors, sensitization to more than three pollens was associated with a significant risk of SRs (odds ratio (OR) [95% confidence interval (CI)]: 3.793 [1.60-8.98]; $p=0.001$). Sensitization to mites was associated with a lower risk of SRs (OR: 0.407 [0.18-0.94], $p=0.036$). Regarding treatments, AIT with grass extracts was a risk factor for SRs (OR [95%CI]: 2.474 [1.1-5.56]; $p=0.033$). Mite AIT formulations were associated with a lower risk of SRs (OR: 0.269 [0.1-0.72]; $p=0.036$).

A univariate analysis of the occurrence of SRs during SCIT yielded an OR of 8.41 [1.93-36.57] ($p=0.001$) for patients using natural extracts (vs. allergoids) (**Table 5**). For SLIT, the incidence of SRs was similar for drops and tablets.

A multivariate regression model was used to identify independent risk factors for SRs in SCIT users. The risk was lower for allergoids than for natural extract treatments (OR: 0.125 [0.029-0.55]; $p=0.006$) but was higher for patients sensitized to four or more pollens (OR: 1.347 [1.069-1.699]; $p=0.012$).

Discussion

This study is one of the few prospective, non-interventional, multinational surveys to have evaluated the safety of AIT in children and adolescents. We analysed AIT-associated SRs and risk factors under “real-life” conditions.

Asthma and atopic dermatitis were more frequent in children, whereas conjunctivitis and rhinitis were more common in adolescents - mirroring the well-known “atopic march” (14). The incidence and severity of SRs were similar in the two age groups.

Interestingly, AIT was initiated significantly sooner after the onset of allergy in children (4.3 years) than in adolescents (5.4 years) (**Table 1**), which is even earlier than in adults (7.8 years) (7). Earlier treatment initiation in younger populations might be related to the concept of immune system immaturity/plasticity (15) and AIT’s potentially preventive effect on neosensitization (16,17) and asthma onset (18–20).

Single-allergen AIT was more frequent (89.5%) than multi-allergen AIT, even though 62% of the population were polysensitized; this probably reflects the European concept of treating patients solely with the most clinically relevant allergen (21). This contrasts with the American approach in which polysensitized patients receive multi-allergen mixtures (22). The question of whether allergen mixtures are less safe has long been debated (23). Here, the risk of an SR was not greater in patients receiving mixtures.

One of our survey’s strengths was its use of the EMA-recommended MedDRA terminology to code SRs (21). Although the MedDRA terminology is being used more frequently (24,25), the most common way of gathering safety data - even in clinical trials – involves a pre-established grading

system (26). Use of the single-term MedDRA terminology to record SRs minimizes observer and centre reporting bias and circumvents the previously reported difficulty of comparing safety data from different reporting systems (27).

The overall incidence of SRs was similar to that observed in other surveys of AIT in children (26). SRs were most frequently related to respiratory SOC (and bronchospasm in particular). Severe SRs were very uncommon (4.3%), which confirms AIT's good safety profile in children and adolescents.

As expected (28), SLIT was well tolerated, and 66.6% of the SLIT-associated SRs resolved in the absence of anti-allergic medication. Severe or anaphylactic SRs did not occur in SLIT-treated patients. The three cases of anaphylaxis occurred in patients on SCIT. These anaphylactic SRs only affected two SOC. Only one SR (4.3%) was considered to be severe. Thus, SCIT also displayed a good safety profile. Despite that SLIT is known to be safer than SCIT (29), we did not find statistically significant differences in the SR rate with regard to the administration route. However, a clear trend was observed towards more reactions in SCIT than in SLIT (79.3% vs 20.7%); moreover, qualitatively, SLIT SRs were milder than SCIT SRs. In conclusion, SLIT in the present survey showed a trend towards a safer profile than SCIT.

Significant differences were found among countries regarding the route of administration, with France the country prescribing SLIT more frequently (91.2%). Although there is no clear scientific rationale for this difference, it was expected and previously reported (30), and could be due to the fact that SLIT was first developed in this country in the 80s and 90s. These country-differences in the route did not have a significant impact in the rate of SRs.

The classic risk factors for AIT-related SRs are severe/uncontrolled asthma, administration errors and previous SRs during AIT (31,32). In the present survey, we did not observe the previously reported association with baseline asthma (31–33). This might have been because most of the asthmatic patients (61.5%) probably had well-controlled, mild-to-moderate asthma, given that only around 20% and 10% were taking inhaled corticosteroids and long-acting beta 2 agonists, respectively.

We identified some novel risk factors (such as pollen polysensitization) for SRs in a univariate analysis, and then confirmed this factor (for SCIT) in a multivariate analysis. Pollen polysensitization is reportedly a marker of more advanced/severe allergic disease (34), and thus might explain the higher risk observed in these patients.

The AIT composition also influenced the occurrence of SRs; the use of grass extracts was associated with a higher risk of SRs, whereas mite extracts were associated with a lower risk. This contrasts with literature reports in which perennial allergens were determinants of a higher risk for AIT. Moreno et al. (35) prospectively monitored 428 patients and found that mite AIT was associated with a greater SR rate than pollen AIT (0.40% vs. 0.15%, respectively; $p < 0.01$). One could argue that the greater incidence of SRs in patients receiving grass pollen AIT was due to overexposure to the disease-inducing allergen during the pollen season, as has been previously described (36). However, none of the SRs associated with grass extracts occurred during the pollen season (data not shown). The lower incidence of SRs in patients receiving mite AIT might be due to the shorter time since allergic disease onset and thus milder, less chronic disease, as has been suggested in the literature for children on AIT (37). In addition, the good safety profile showed in our population should encourage the use of mites-AIT early in life, considering that mites' sensitization is associated with loss of lung function and wheeze development (38).

In line with the theoretically lower degree of IgE stimulation by allergoids (39), patients receiving AIT with natural extracts had a higher risk of SRs. The robustness of this result was confirmed in the multivariate analysis.

Worryingly, 72.4% of the SRs were late-phase reactions (i.e. occurring more than 30 min after AIT administration). Severity was not related to the time of onset, and all episodes of anaphylaxis occurred more than 2 hours after AIT administration. These findings highlight a dilemma with regard to the current guidelines (which recommend a 30-minute surveillance period) (40) and reinforce the need for adequate patient education and the prescription of an emergency personalized action plan; so that the patient must be able to promptly recognize SRs that occur away from the physician's office and can thus seek rapid medical assistance. Upon our results, it can be suggested that the prescription of adrenaline autoinjectors should be routinely done in all SCIT patients (41).

Our study was hampered by the inherent limitations of non-interventional, observational protocols. First, each patient was not continuously monitored throughout the survey - in contrast to clinical trials- what could have a negative impact in the reporting of SRs and the awareness of lack of adherence to the treatment. However, the participating physicians were experienced in this field, and the survey's objective was to collect data on real-life practice. Secondly, the fact that doctors volunteered for the survey might have biased our sample towards more interested and expert doctors in the field of AIT. Thirdly, we decided not to ask the participating physicians to record the identity of the specific AIT products, although we are aware of the poor comparability in allergen content of marketed products and its potential impact on safety. However, this choice was appropriate for a non-commercially biased survey.

In conclusion, AIT proved to be safe in a paediatric population and was associated with a low incidence of generally non-severe SRs. Pollen polysensitization, grass pollen sensitization and (for SCIT) the use of natural extracts (vs. allergoids) were risk factors for AIT-associated SRs.

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Demoly P: Is a consultant and a speaker for Stallergenes-Greer, Circassia, ALK, Thermofisher Scientific and Chiesi, and was a speaker for Merck, Astra Zeneca, Pierre Fabre Médicaments, Menarini, Allergopharma and GlaxoSmithKline

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Table 1. Demographics, baseline allergic disease and symptomatic medication in the surveyed children and adolescents.

Characteristic	Total	3-11 yo	12-18 yo
Patients, n (%)	1563	762 (48.8%)	801 (51.2%)
Age (mean $\pm$ SD), years	11.7 $\pm$ 3.9	8.29 $\pm$ 2	15 $\pm$ 2
Gender* (M) n (%)	923 (59.1%)	480 (63%)	443 (55.3%)
Mean time interval between allergy onset and initiation of AIT*	4.3 $\pm$ 3.3	3.3 $\pm$ 2	5.4 $\pm$ 4
Baseline allergic diseases			
rhinitis *	1464 (93.7%)	689 (90.4%)	775 (96.8)
conjunctivitis*	1079 (68.9%)	493 (64.7%)	586 (73.2%)
asthma*	962 (61.5%)	499 (65.5%)	463 (57.8%)
atopic dermatitis*	216 (13.8%)	123 (16.1%)	93 (11.6%)
food allergy	150 (9.6%)	71 (9.3%)	79 (9.9%)
drug allergy	12 (0.8%)	5 (0.7%)	7 (0.9%)
chronic urticaria	10 (0.6%)	2 (0.3%)	8 (1%)
hymenoptera venom allergy	2 (0.1%)	0 (0%)	2 (0.2%)
Symptomatic medications at baseline	798 (51.1%)	369 (48.4%)	429 (53.6%)
inhaled corticosteroids	302 (19.2%)	149 (19.4%)	153 (19%)
long-acting beta agonists	166 (10.6%)	73 (9.5%)	93 (11.6%)
short-acting beta agonists	308 (19.5%)	153 (19.9%)	155 (19.1%)
antileukotrienes*	196 (12.4%)	117 (15.3%)	79 (9.7%)
nasal corticosteroids*	506 (32.3%)	203 (26.5%)	303 (37.8%)
antihistamines*	634 (40.2%)	267 (34.8%)	364 (45.3%)

* indicates significant differences between children and adolescents ($p < 0.05$). SD: standard deviation; M: male; AIT: allergen immunotherapy; yo: years old.

TABLE 2. Characteristics of AIT for the survey population as a whole and for the 2 age groups (children and adolescents).

		SCIT					
		Whole population n=1127		Children (3-11 yo) n=481		Adolescents (12-18 yo) n=646	
		natural n= 574	allergoid n=553	natural n=242	allergoid n=239	natural n=322	allergoid n=314
Allergen	mites	275 (24.4%)	302 (26.8%)	122 (25.4%)	132 (27.4%)	153 (23.7%)	170 (26.3%)
	grass	135 (12%)	116 (10.3%)	56 (11.6%)	40 (8.3%)	79 (12.2%)	76 (11.8%)
	mixture*	60 (5.3%)	90 (8%)	16 (3.3%)	51 (10.6%)	44 (6.8%)	39 (6%)
	tree	34 (3%)	39 (3.5%)	13 (2.7%)	14 (2.9%)	21 (3.3%)	25 (3.9%)
	<i>Alternaria</i>	59 (5.2%)	1 (0.1%)	33 (6.9%)	1 (0.2%)	26 (4%)	0 (0%)
	epithelia	9 (0.8%)	0 (0%)	2 (0.4%)	0 (0%)	7 (1.1%)	0 (0%)
	weed	2 (0.2%)	5 (0.4%)	0 (0%)	1 (0.2%)	2 (0.3%)	4 (0.6%)
Baseline disease	rhinitis and asthma	348 (30.9%)	303 (26.9%)	141 (29.3%)	144 (29.9%)	207 (32%)	159 (24.6%)
	rhinitis alone	190 (16.9%)	237 (21%)	74 (15.4%)	85 (17.7%)	116 (18%)	152 (23.5%)
	asthma alone	34 (3%)	10 (0.9%)	26 (5.4%)	7 (1.5%)	8 (1.2%)	3 (0.5%)
	conjunctivitis alone	2 (0.2%)	3 (0.3%)	1 (0.2%)	3 (0.6%)	1 (0.2%)	0 (0%)
Updosin g scheme	conventional	349 (30.9%)	134 (11.9%)	168 (34.9%)	67 (13.9%)	181 (28 %)	67 (10.4%)
	cluster	210 (18.6%)	227 (20.1%)	67 (13.9%)	91 (18.9%)	143 (22.1%)	136 (21.1%)
	rush	15 (1.3%)	192 (17%)	7 (1.5%)	81 (16.8%)	8 (1.2%)	111 (17.2%)
Mainten ance	perennial	571 (50.7%)	499 (44.3%)	242 (50.3%)	229 (47.6%)	329 (50.9%)	270 (41.8%)
	pre/coseasonal	1 (0.1%)	29 (2.6%)	0 (0%)	7 (1.5%)	1 (0.2%)	22 (3.4%)
	preseasonal	1 (0.1%)	25 (2.2%)	0 (0%)	3 (0.6%)	1 (0.2%)	22 (3.4%)
	coseasonal	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)
		SLIT					
		Whole population n= 451		Children (3-11 yo) n= 286		Adolescents (12-18 yo) n=165	
		Drops n=333	Tablets n=118	Drops n=227	Tablets n=59	Drops n=101	Tablets n=59
Allergen	mites	168 (37.3%)	28 (6.2%)	115 (40.2%)	18 (6.3%)	53 (32.1%)	10 (6.1%)
	grass	70 (15.5%)	86 (19.1%)	41 (14.3%)	39 (13.6%)	29 (17.6%)	47 (28.5%)
	tree	60 (13.3%)	4 (0.9%)	42 (14.7%)	2 (0.7%)	18 (10.9%)	2 (1.2%)
	mixture	16 (3.5%)	0 (0%)	15 (5.2%)	0 (0%)	1 (0.6%)	0 (0%)
	<i>Alternaria</i>	12 (2.7%)	0 (0%)	10 (3.5%)	0 (0%)	2 (1.2%)	0 (0%)
	epithelia	4 (0.9%)	0 (0%)	1 (0.3%)	0 (0%)	3 (1.8%)	0 (0%)
	weed	3 (0.7%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)	0 (0%)
Baseline disease	rhinitis and asthma	191 (42.4%)	44 (9.8%)	132 (46.2%)	23 (8%)	59 (35.8%)	21 (12.7%)
	rhinitis alone*	128 (28.4%)	49 (10.9%)	83 (29%)	19 (6.6%)	45 (27.3%)	30 (18.2%)
	asthma alone	14 (3.1%)	24 (5.3%)	12 (4.2%)	16 (5.6%)	2 (1.2%)	8 (4.8%)
	conjunctivitis alone	0 (0%)	1 (0.2%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)
Mainten	perennial*	246 (54.5%)	82 (18.2%)	167 (58.4%)	41 (14.3%)	79 (47.9%)	41 (24.8%)

ance	pre/coseasonal*	82 (18.2%)	34 (7.5%)	58 (20.3%)	16 (5.6%)	24 (14.5%)	18 (10.9%)
	preseasonal	2 (0.4%)	2 (0.4%)	1 (0.3%)	2 (0.7%)	1 (0.6%)	0 (0%)
	coseasonal	3 (0.7%)	0 (0%)	1 (03%)	0 (0%)	2 (1.2%)	0 (0%)

* indicates significant differences ($p < 0.05$) between children and adolescents (in Fisher's exact test) for the direct comparison of the same type of extract. When SCIT with a mixture of allergens was used, allergoids were more frequently administered in children than in adolescents. For SLIT, adolescent patients with rhinitis but not asthma were more frequently prescribed tablets than drops. For continuous and pre/coseasonal regimens, tablets were prescribed more frequently in adolescents than in children.

Table 3. Description of all SRs having occurred in the study population

Age, gender, country	Respiratory allergy	Type of AIT	Phase of AIT	Severity & symptoms	Time to onset	Time to resolution	Treatment	Change in AIT schedule
5, M, GR	C+R	SCIT, natural, Mites	Updosing (Conventional)	Mild: Rhinitis	1 hour	2 days	Oral anti-H1	No
			Maintenance	Severe: Bronchospasm*	20 min	4 hours	Oral anti-H1+ Anti-H1 iv + Corticosteroids iv + Saline iv	AIT discontinued
5, M, SP	A+R	SCIT, natural, Mites	Updosing (Conventional)	Mild: Asthma	6 hours	2 hours	Beta 2 agonists	Same dose repeated
6, M, SP	C+R	SCIT, allergoid, Tree	Updosing (Conventional)	Mild: Urticaria	12 hours	6 hours	Oral anti-H1	Same dose repeated
7, M, FR	A+C+R	SLIT, drops, Grass	Maintenance	Moderate: Vomiting+Ethmoiditis	45 days	8 days	Antibiotics, no anti-allergics+	No
7, M, SP	A+R	SCIT, natural, <i>Alternaria</i>	Updosing (Conventional)	Mild: Asthma+Rhinitis	2 hours	2 days	Oral anti-H1+Beta 2 agonists	No
7, M, SP	A+ C+R	SCIT, natural, Tree	Updosing (cluster)	Mild: Headache+Fever	2 hours	6 hours	No anti-allergics + paracetamol	AIT discontinued
9, M, GR	R	SCIT, natural, Grass	Updosing (rush)	Mild: Flushing+Urticaria	30 min	2 hours	Oral anti-H1	Same dose repeated
9, F, SP	A+R	SCIT, natural, Grass	Updosing (cluster)	Mild: Asthma	6 hours	1 day	Beta 2 agonists	Started again
10, M, SP	C+R	SCIT, natural, Grass	Updosing (Conventional)	Mild: Cough	90 min	15 min	Oral anti H1+oral corticosteroids +Beta 2 agonists	No
10, M, SP	A+C+ R	SCIT, natural, Grass	Updosing (Conventional)	Moderate**: Asthma+ Bronchospasm+ Urticaria	3 hours	24 hours	Adrenaline im+ Anti-H1 im+Corticosteroids im	Next dose ≤50%
11, M, FR	C+R	SLIT, drops, Tree	Updosing (Conventional)	Mild: Vomiting	1 min	1 hour	None	No
			Updosing (Conventional)	Mild: Vomiting	1 min	1 hour	None	No
11, M, GR	C+R	SLIT, tablets, Grass	Maintenance	Moderate: Chest tightness	15 min	15 min	Oral anti-H1	AIT discontinued

11, M, SP	A+C+ R	SCIT, natural, Grass	Updosing (Conventional)	Moderate**: Dyspnoea+Urticaria	3 hours	6 hours	Adrenaline im+ Anti-H1 im + Corticosteroids im	Next dose <=50%
12, M, FR	C+R	SLIT, drops, Mites	Maintenance	Mild: Conjunctivitis +Rhinitis	1 hour	45 days	None	Started again
13, F, FR	R	SLIT, drops, <i>Alternaria</i>	Maintenance	Mild: Cough	1 day	1 day	Oral corticosteroids	AIT discontinued
13, F, SP	A+C+ R	SCIT, natural, Tree	Updosing (Conventional)	Moderate**: Rhinitis +Urticaria	5 hours	2 hours	Anti-H1 im+ Corticosteroids im	Same dose repeated
14, M, SP	A+R	SCIT, natural, Grass	Updosing (Conventional)	Mild: Chest discomfort+Urticaria	90 min	30 min	Corticosteroids im	Next dose <=50%
14, M, SP	C+R	SCIT, natural, Grass	Updosing (cluster)	Mild: Urticaria	90 min	10 hours	Oral anti-H1	No
			Updosing (cluster)	Mild: Urticaria	90 min	10 hours	Oral anti-H1	Same dose repeated
14, M, SP	A+C+ R	SCIT, natural, Grass	Updosing (rush)	Mild: Urticaria	90 min	12 hours	Oral anti-H1	No
			Updosing (rush)	Mild: Urticaria	90 min	12 min	Oral anti-H1	Next dose <=50%
15, F, GR	A+R	SCIT, natural, Tree	Updosing (cluster)	Mild: Cough+ Drop FEV1> 10%	1 day	11 days	Beta 2 agonists	No
15, F, SP	A+C+ R	SCIT, natural, Mites	Updosing (cluster)	Mild: Asthma+ Cough+ Bronchospasm+ Chest discomfort+ Wheezing	30 min	30 min	Oral anti-H1+Beta 2 agonists+Oxygen	No
16, M, SP	A+C+ R	SCIT, allergoid, Grass	Maintenance	Moderate: Angioedema	30 min	2 hours	Oral anti-H1	No
16, F, SP	A+C+ R	SCIT, natural, Mixture (Grass + Cupressus)	Updosing (Conventional)	Mild: Asthma	22 hours	1 hour	Beta 2 agonists	Next dose <=50%
			Updosing (Conventional)	Moderate: Asthma	24 hours	3 days	Anti-H1 + Oral corticosteroids	AIT discontinued
18, F, SP	A+C+ R	SCIT, natural, Mites	Updosing (Conventional)	Mild: Dyspnoea	15 min	15 min	Beta 2 agonists	Same dose repeated

Each line represents one patient-treatment. In the five patients having experienced two reactions, the latter are listed chronologically. SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; FR: France; GR: Germany; SP: Spain; R: rhinitis; C: conjunctivitis; A: asthma; Anti-H₁: H1 antihistamines, im: intramuscular; iv: intravenous.

* This reaction was classified by the physician as severe and serious. ** SRs classified as anaphylaxis.

Table 4: Frequency of SRs (coded using the MedDRA classification) by the time of onset and the administration route (SCIT vs. SLIT).

ONSET OF SYSTEMIC REACTIONS									
	< 30 min (n=8, 27.6%)		30-60 min (n=2, 6.9%)		60-120 min (n=8, 27.6%)		>120 min (n=11, 37.9%)		TOTAL (n=29)
	SCIT (%)	SLIT (%)	SCIT (%)	SLIT (%)	SCIT (%)	SLIT (%)	SCIT (%)	SLIT (%)	
Symptom									
Urticaria	1 (10%)	0	0	0	5 (50%)	0	4 (40%)	0	10
Asthma	1 (14.3 %)	0	0	0	1 (14.3%)	0	5 (71.4 %)	0	7
Allergic rhinitis	0	0	1 (33.3 %)	1 (100%)	1 (33.3%)	0	1 (33.3 %)	0	4
Cough	1 (33.3 %)	0	0	0	1 (33.3%)	0	1 (33.3 %)	1 (100%)	4
Bronchospasm	2 (66.7 %)	0	0	0	0	0	1 (33.3 %)	0	3
Vomiting	0	2 (66.7%)	0	0	0	0	0	1 (33.3%)	3
Dyspnoea	1 (50%)	0	0	0	0	0	1 (50%)	0	2
Chest discomfort	1 (50%)	0	0	0	1 (50%)	0	0	0	2
Conjunctivitis	0	0	0	1 (100%)	0	0	0	0	1
Angioedema	1 (100%)	0	0	0	0	0	0	0	1
Chest tightness	0	1 (100%)	0	0	0	0	0	0	1
Wheezing	1 (100%)	0	0	0	0	0	0	0	1
Flushing	1 (100%)	0	0	0	0	0	0	0	1
Headache	0	0	0	0	1 (100%)	0	0	0	1
System Organ Class (grouped disorders)									
Respiratory	3 (21.7 %)	0	31 (7.1%)	1 (50%)	2 (14.3%)	0	8 (57.1 %)	1 (50%)	16
Skin	2 (18.2 %)	0	0	0	5 (45.5%)	0	4 (36.4 %)	0	11
General	1 (50%)	1 (100%)	0	0	1 (50%)	0	0	0	3

		)				
Gastrointestinal	0	2 (66.7%)	0	0	0	1 (33.3%)
Eye disorders	0	0	0	1 (100%)	0	0
Nervous system	0	0	0	0	1 (100%)	0
Vascular	1 (100%)	0	0	0	0	0
Anaphylaxis						
Anaphylaxis	0	0	0	0	3 (100%)	0

The following symptoms were not reported and thus not included in the table: generalized pruritus, sensation of foreign body, erythema, generalized erythema, dysphagia, dizziness, abdominal pain, fatigue, dysphonia, drop in blood pressure, diarrhea, hypotension, laryngeal edema, loss of consciousness, nausea, syncope, tachycardia. Cardiac SOC's were not recorded.

Table 5. Univariate analysis comparing the appearance of SR in the groups created by each variable

Risk comparison	Overall odds ratio [95%CI]	3 to 11 yo Odds ratio [95%CI]	12 to 18 yo Odds ratio [95%CI]
Age ≤11 yo vs. ≥12 yo	1.25 [0.56-2.82]	NA	NA
Gender: male vs. female	1.39 [0.59-3.27]	3.27 [0.72-14.85]	0.67 [0.20-2.22]
History of non-allergic disease	4.18 [0.53-32.8]	10.39 [1.16-93.06]	0% vs. 1.4%
Previous cardiovascular disease	67.5* [4.10-1112.8]	100% vs. 1.6%	NA: 0% vs. 1.4%
Previous mastocytosis	NA: 0% vs. 1.5%	NA: No mastocytosis	NA: 0% vs. 1.4%
Previous anaphylaxis	NA: 0% vs. 1.5%	NA: 0% vs. 1.7%	NA: 0% vs. 1.4%
Atopic dermatitis	0.563 [0.131-2.412]	0.951 [0.208-4.345]	NA: 0% vs. 1.5%
Chronic urticaria	7.464 [0.91-61.35]	NA: 0% vs. 1.7%	11.329 [1.273-100.834]
Allergic rhinitis	NA: 0% vs. 1.6%	NA: 0% vs. 1.9%	NA: 0% vs. 1.4%
Allergic conjunctivitis	1.099 [0.453-2.666]	1.234 [0.376-4.044]	0.993 [0.261-3.776]
Allergic asthma	1.051 [0.457-2.417]	0.614 [0.204-1.846]	1.981 [0.522-7.523]
Food allergy	1.347 [0.397-4.569]	1.777 [0.386-8.177]	0.913 [0.115-7.223]

Drug allergy	NA: 0% vs. 1.5%	NA: 0% vs. 1.4%	NA: 0% vs. 1.7%
Receiving any active treatment	0.685 [0.303-1.553]	0.923 [0.307-2.773]	0.492 [0.143-1.693]
Sensitization to pollen	2.153 [0.8-5.797]	3.904 [0.859-17.734]	1.205 [0.317-4.581]
Sensitization to mites	0.407* [0.18-0.94]	0.222* [0.61-0.815]	0.747 [0.226-2.469]
Sensitization to epithelia	1.233 [0.508-2.996]	1.449 [0.441-4.761]	1.040 [0.273-3.957]
Sensitization to moulds	1.179 [0.348-3.993]	0.607 [0.078-4.724]	2.087 [0.443-9.832]
Sensitization to food	1.647 [0.485-5.6]	3.076 [0.826-11.451]	NA: 0% vs. 1.5%
Previous course of AIT	1.104 [0.326-3.740]	NA: 0% vs. 1.8%	2.064 [0.540-7.888]
>3 vs. ≤ 3 pollen sensitizations	3.793* [1.601-8.987]	5.658* [1.805-17.737]	2.455 [0.641-9.4]
Current AIT: dander	NA: 0% vs. 1.5%	NA: 0% vs. 1.7%	NA: 0% vs. 1.4%
Current AIT: weed pollen	NA: 0% vs. 1.7%	NA: 0% vs. 1.4%	NA: 0% vs. 1.5%
Current AIT: <i>Alternaria</i>	1.927 [0.444-8.359]	1.378 [0.175-10.844]	2.863 [0.354-23.173]
Current AIT: grass pollen	2.474* [1.1-5.568]	4.038* [1.339-12.178]	1.442 [0.418-4.975]
Current AIT: mites	0.269* [0.1-0.725]	0.174* [0.038-0.792]	0.408 [0.108-1.55]
Current AIT: tree pollen	2.835 [1.042-7.715] P=0.051	3.026 [0.813-11.262]	2.556 [0.541-12.08]
Current AIT: mixture	0.366 [0.049-2.728]	NA: 0% vs. 1.9%	0.864 [0.109-6.833]
SCIT vs. SLIT	1.53 [0.57-4.12]	2.00 [0.55-7.34]	1.15 [0.25-5.38]
Natural extract vs. allergoid (for the 1127 SCIT treatments)	8.41* [1.93-36.57]	9.19* [1.16-73.14]	7.73** [0.96-62.15]
Any premedication	0.56 [0.17-1.88]	0.35 [0.05-2.74]	0.81 [0.17-3.76]

The odds ratio (OR) [95% confidence interval (CI)] for each variable was calculated for the different populations. If not specified, the comparison was made for the variable Yes vs. No. Statistically significant differences ($p < 0.05$) are indicated by *. **= in Natural Vs Allergoid for the 12-18 yo population $p = 0.038$, but the confidence interval crossed the non-effect line. NA= not applicable, since the OR could not be calculated if one of the SR rates was 0%. yo: years old; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; AIT: allergen immunotherapy; HDM: house dust mite.

Figure 1: Pharmacological treatments for AIT-associated SRs

