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European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a Real-Life Clinical Assessment.

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Short title: European Survey on Systemic Adverse Reactions in Allergen Immunotherapy

ABSTRACT

Background. Outside clinical trials, data on systemic reactions (SRs) due to allergen immunotherapy (AIT) are scarce.

Methods. A prospective, longitudinal, web-based survey of “real-life” respiratory allergen immunotherapy (AIT) clinical practice was conducted in France, Germany and Spain. SRs were recorded and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and risk factors associated with SRs were identified.

Results. A total of 4,316 patients (corresponding to 4,363 ongoing courses of AIT) were included. 109 SRs were recorded, and 90 patients (2.1%) presented at least one SR. Most of the SRs occurred in subcutaneous allergen immunotherapy (SCIT) (89%, n=97). The most frequently reported symptoms were urticaria, rhinitis, dyspnoea and cough. Respiratory symptoms appeared before skin symptoms. Most SRs occurred during the up-dosing phase (75.8%) and were mild in severity (71.6%). Intramuscular adrenaline was administered in 17 SRs but only 65% of these were subsequently classified as anaphylaxis. Independent risk factors for SRs during SCIT were: the use of natural extracts (odds ratio (OR) [95% confidence interval (CI)]=2.74 [1.61-4.87]; p=0.001), the absence of symptomatic allergy medications (1.707 [1.008-2.892], p=0.047), asthma diagnosis (1.74 [1.05-2.88], p=0.03), sensitization to animal dander (1.93 [1.21-3.09]; p=0.006) or pollen (1.16 [1.03-1.30]; p=0.012), and cluster regimens (vs. rush) (4.18 [1.21-14.37]; p=0.023). A previous episode of anaphylaxis increased the risk for anaphylaxis in SCIT (OR [95%CI]=17.35 [1.91-157.28]; p=0.01).

Conclusion. AIT for respiratory allergy is safe, with a low number of SRs observed in real-life clinical practice. A personalized analysis of risk factors could be used to minimize SRs.

Key words: allergen immunotherapy; allergoid; asthma; risk factor; systemic reaction.

INTRODUCTION

The safety profile of allergen immunotherapy (AIT) has been thoroughly documented in well-designed clinical studies (1-3). However, data on systemic reactions (SRs) due to respiratory AIT in “real-life” clinical practice are scarce (4-8).

Several retrospective, cross-sectional surveys on SRs due to subcutaneous allergen immunotherapy (SCIT) have been conducted in the USA. In a four-year survey (9, 10) of 23.3 million injection visits, the SR rate was 0.1% of visits. 97% of these SRs were classified as mild or moderate in severity. In line with the results of previous surveys in the USA (11), the incidence of severe SRs was approximately 1 in a million injections.

Reliable interstudy comparisons are prevented by marked methodological heterogeneity with regard to terminologies, survey design (prospective vs. retrospective), collection bias and diversity in clinical practice parameters (9-13).

In view of these various factors, the European Academy of Allergy and Clinical Immunology (EAACI)'s Immunotherapy Interest Group initiated a pilot, prospective, web-based survey of a group of patients receiving either SCIT or sublingual allergen immunotherapy (SLIT). The survey was designed to determine (i) the proportion of patients experiencing at least one SR, (ii) the incidence of SRs and, (iii) possible risk factors for SRs (14). To harmonise reporting and analysis, SRs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (15).

METHODS

Survey Design. This was a prospective, longitudinal, web-based survey conducted from September 1st, 2012, to February 28th, 2014, in three European countries (France, Germany and Spain.) Extensive details of the study's design and procedures have been published elsewhere (14).

The patient inclusion criteria were as follows: adults or children with IgE-mediated respiratory allergy to pollen, house dust mites, *Alternaria* and/or animal dander, about to initiate AIT. Patients were recruited on the day that they received their first dose of either SCIT or SLIT, in accordance with real-life clinical practice. Patients undergoing AIT for allergies to venom, moulds other than *Alternaria* or food components were not included in the survey.

In order to harmonize the reporting of SRs in the survey, a list of 31 symptom terms was extracted from the MedDRA dictionary (15). Three questionnaires were built: (i) the physician questionnaire, (ii) the patient questionnaire and (iii) the SR questionnaire (14). Participating physicians used the SurveyMonkey® online instrument to submit information directly to an anonymized central database (16). In each country, a designated national coordinator was responsible for recruiting at least 30 physicians.

Ethics. The survey complied with national and European ethical and regulatory requirements (including data protection). Each national coordinator was responsible for obtaining study approval from the appropriate national or local independent ethics committee.

Statistical analysis. The odd ratio (OR) [95% confidence interval (CI)] was calculated in univariate and multivariate analyses. Intergroup comparisons were performed with Fisher's exact test or Student's T test. A multivariate predictive analysis was performed using logistic regression with stepwise selection. The occurrence of an

SR was considered as independent variable. P values below 0.05 were considered to be statistically significant. All statistical analyses were performed with SPSS software (version 22, IBM Corporation, Armonk, NY, USA).

RESULTS

Characteristics of the participating physicians

One hundred and twelve physicians (48.2% from Spain, 30.4% from France and 21.4% from Germany) voluntarily took part in the survey. All 112 filled out the physician's questionnaire but only 95 (84%) recruited at least one patient. 94.6% of the 112 physicians identified themselves as "allergists" and reported a mean $\pm$ standard deviation of 19.9 ± 8.4 years of clinical experience in allergy. The physicians estimated that they saw an average of 450 new patients with respiratory allergy per year, and that approximately 35% of these were candidates for AIT. There was no correlation between the physicians' years of experience and their tendency to prescribe AIT. A preference to prescribe SCIT (62.2%) over SLIT (37.8%) was noted in Spain and Germany, although SLIT was more frequently prescribed in France. 49.1% of the physicians worked exclusively in public-sector hospitals (Spain: 68%; Germany: 37.5%; France: 26.5%), 24.1% worked exclusively in private-sector clinics, and 26.8% worked in both.

Characteristics of the participating patients

A total of 4,363 different courses of AIT (AIT-treatments) were initiated and monitored in 4,316 patients (663 in France, 756 in Germany and 2,897 in Spain), with a mean follow-up period of 12.7 ± 3.37 months. 4,270 patients had received a single course of AIT; 45 had two courses and 1 patient had received three courses with different allergen compositions. The number of AIT-treatments included was 2,917 in Spain (1.3% of which involved patients receiving more than one treatment), 759 in Germany (more than one treatment: 0.8%) and 687 in France (more than one treatment: 7.0%).

Demographic and clinical data. The survey populations in each country had a similar gender distribution. The mean age was 26.4 ± 14.3 years (**Table 1**). France reported the highest percentage of patients below the age of 18. Although the majority of patients had no relevant medical history, 143 patients (3.3%) were being treated for concomitant non-allergic conditions. Twelve patients (0.3%) had taken beta blockers while receiving AIT. Patients had allergic asthma and rhinitis with or without (w/wo) conjunctivitis (49.5%), rhinitis w/wo conjunctivitis but not asthma (47.3%), asthma only (3%) and conjunctivitis only (0.3%). The mean age at the onset of allergic disease was 18.7 ± 12.8 . The mean time interval between disease onset and initiation of AIT was 7.9 ± 7.9 years.

At inclusion, 2,067 patients (47.9%) were taking one or more types of symptomatic allergy medication: 90.3% of these patients were taking a symptomatic medication for rhinitis (antihistamines: 82.4%; nasal corticosteroids: 68.5%) and 57.3% of these patients were taking a symptomatic medication for asthma (inhaled corticosteroids: 36.9% of patients; long-acting beta agonists (LABAs) 23.8%; short-acting beta agonists: 33%; oral leukotriene receptor antagonists: 13.9%). Asthmatic patients receiving AIT for perennial allergens were stratified as having very mild, untreated asthma (7.3%), intermittent asthma treated with inhaled corticosteroids (56.6%), and persistent asthma treated with inhaled corticosteroids (plus LABAs, in some cases) (36.1%).

Sensitization patterns. Skin prick tests were the most frequently applied tests of sensitization status (in 99.5% of patients). Serum specific IgE assays were used in 73.4% of patients. Pollen was the most prevalent allergen in terms of both sensitizations *per se* and clinically relevant sensitizations. Polysensitization was reported in 45.7% of the patients; 32.7% of the survey population were sensitized to two allergens and 13.4% were sensitized to three or more allergens. Sensitization to both pollen and house dust mites was the most frequently reported polysensitized profile (reported in 8.6% of the survey population).

Sensitization to two or more types of pollen was observed in 62.7% of the pollen-sensitized patients. Sensitization to three or more different pollen species in 20.3% patients; of the latter, 81.2% were sensitized to grass pollen, 32.4% were sensitized to olive pollen and 24.6% were sensitized to birch pollen. Olive sensitization was most frequent in Spain (92.1% of all pollen-sensitized patients) and birch pollen sensitization was most frequent in France and Germany (84.2% of all pollen-sensitized patients). Sensitization to other tree pollens such as cypress, hazel and plane were detected in 17.2%, 11.3% and 10.2% of the surveyed patients, respectively. With regard to weeds, 10.2% of the surveyed patients were sensitized to plantain pollen was 10%, and fewer than 10% were sensitized to pellitory-of-the-wall, mugwort or lambsquarter pollen.

Allergen Immunotherapy

Previous AIT. In the survey population as a whole, 755 (17.5%) patients had previously received AIT as SCIT (66%), SLIT (30%) or both (4%). In general, patients reported good or very good tolerance of previous AIT. Among patients having previously undergone SCIT, 84% chose the same administration route while only 40% of those with previous SLIT chose the same administration route. The most frequently prescribed previous AIT was for grass pollen (51.3%) and mites (33.6%). Just over half the patients (53.3%) started on a course of AIT with the same allergen source as before, 24.6% received both the previously used allergen and another allergen, and 21.9% of patients were treated with a different allergen source.

Current AIT composition. The majority of AIT preparations (89.4%, 3902 out of 4363) included a single allergen source. The percentage of patients undergoing AIT with two or more allergen sources was significantly higher in Spain than in France and Germany ($p<0.001$). AIT was primarily prescribed for allergy to pollen ($n=1810$, 41.5%) or mites ($n=1772$, 40.6%). Physicians with less than 10 years of experience in the field of allergy were significantly more likely to prescribe AIT with two or more allergen sources ($p<0.001$). Physicians working in both private and public institutions were less likely ($p<0.05$) to prescribe AIT mixtures than those working exclusively in private or public institutions.

Current AIT route and type of extract used. Overall, SCIT was more frequently prescribed than SLIT (3398 treatments, 77.9%, vs. 965, 22.1%, respectively). SCIT was preferred in Spain (93.7%) and Germany (73.3%), whereas SLIT was preferred in France (84.3%) ($p<0.0001$).

For SCIT, 50.2% of treatments were based on natural allergen extracts and 49.8% were based on allergoids. The latter were used significantly more frequently in Germany than in Spain or France. There were no significant differences in the use of natural allergens vs. allergoids as a function of the patient's age.

For SLIT, drops (72.5%) were more commonly used than tablets (27.5%). Drops were preferred in 88.9% of patients in France, 28.6% of patients in Germany and 69.4% in Spain. Tablets were less frequently prescribed in patients aged under 12 ($p<0.01$).

AIT administration, schedules and follow-up time. SCIT was administered by a physician (19.9%) or by a nurse under a physician's supervision (79.8%), while SLIT was mostly (self-)administered by the patient or legal guardian (87.4%). The first dose of SLIT was administered under the supervision of a physician or a nurse in 12.6% of cases. Premedication was used in 16% of the survey population (with antihistamines, in 93.7% of cases). The proportion of premedicated patients did not differ when comparing SCIT with SLIT.

Conventional (46.8%), cluster (36.8%) and rush (16.4%) schedules were used for SCIT up-dosing. Cluster schedules were more common in Spain (53.4%), and conventional schedules were more common in France and Germany (in 98% and 75.8% of cases, respectively). Rush up-dosing schedules were more frequently used for SCIT with allergoids, whereas conventional and cluster regimens were more frequently preferred for SCIT with natural allergens.

When considering SLIT regimens, 63% were perennial while 32.6% were pre- and co-seasonal, 2.6% were pre-seasonal and 1.8% were co-seasonal. For SLIT drops, 67.7% of the patients followed a continuous regimen and 29% followed a pre- and co-seasonal regimen. These figures were respectively 50.6% and 42.3% for SLIT

tablets. SLIT drops were administered daily in 60.7% of cases and every other day in 39.3%. These figures were respectively 98.9% and 1.1% for SLIT tablets.

We estimate that a total of 57,463 SCIT doses and 259,800 SLIT doses were administered during the survey period.

Systemic adverse reactions during AIT

Descriptive analysis of SRs. When considering a total of 4363 patient-treatments (PT), 90 (2.1%) presented at least one SR. We observed 109 SRs, of which 88% (97/109) were SCIT-related and 11% (12/109) were SLIT-related. The frequency of SRs did not differ greatly from one country to another: 1.7% in France (13 SRs and 12 PTs), 2.4% in Germany (25 SRs and 18 PTs) and 2.1% in Spain (71 SRs and 60 PTs). SRs were less frequent when AIT was prescribed by physicians with 21 to 30 years of experience. The frequency of SRs did not vary significantly by gender. SRs were more frequent in children (under-18s) than in adults. However, German patients having experienced SRs were significantly older (36.7 ± 17.8 years) than their Spanish or French counterparts (26.5 ± 11.9 and 25.6 ± 13.9 years, respectively) ($p=0.017$). After taking into account the length of follow-up of the surveyed patients, the frequency of SRs was estimated at 0.023 per patient and per year.

With regard to the time of AIT administration, 41.3% (45/109) SRs appeared within 30 minutes, 8.3% (9/109) appeared between 30 to 60 minutes later, 14.7% (16/109) appeared between 60 to 120 minutes later and 35.8% (39/109) appeared more than 120 minutes later.

According to the MedDRA classification, urticaria was the most frequent symptom (followed closely by rhinitis and dyspnoea) (**Table 2 and Figure 1**). The most frequently reported SRs occurring within 30 minutes of AIT administration were bronchospasm, general disorders, vascular disorders, flushing and foreign body sensation in the throat. Skin disorders in general and urticaria in particular were frequently observed after 60 and even 120 minutes. The frequencies of isolated symptoms and SOCs as a function of the time to onset are described in detail in Table 2. The duration of the SR was widely distributed: 19% of the SRs lasted for less than an hour, 29% lasted up to 3 hours, 24% lasted up to 24 hours and 28% lasted for more than 24 hrs.

The physicians mainly used antihistamines and corticosteroids to treat SRs (**Figure 2**). Although intramuscular adrenaline was administered in 17 SRs, only 65% of these reactions were subsequently classified as anaphylaxis.

Most of the SRs occurred during the up-dosing phase (75.8%, 72/109). In terms of severity, most of the SRs were mild (71.6%, 78/109), and only 3.7% (4/109) were classified as severe SRs. Four severe SRs were recorded (2 in the up-dosing phase and 2 in the maintenance). None of the severe SRs were classified as serious.

After resolution of the SRs, 80.7% of the patients continued to receive AIT. In the remaining 19.3% (including those affected by the four severe SRs), AIT was withdrawn. When considering patients who continued to receive AIT, 60.2% changed their schedule (52.9% used the same dose, 35.8% reduced the dose by less than 50%, 7.5% decided to start the up-dosing phase from the beginning, and 3.8% reduced the dose by more than 50%).

Analysis of risk factors for SRs.

In univariate analyses, two groups of risk factors were identified: those related to patient characteristics and those related to AIT modalities (**Table 3**).

In the first group, a diagnosis of asthma was associated with the occurrence of SRs. There were 59 SRs in asthmatics (2.6%) and 31 in non-asthmatics (1.5%) (OR [95%CI]=1.74 [1.12-2.70]; $p=0.015$). Furthermore, patients sensitized to animal dander (OR [95%CI]=1.93 [1.26-2.97]; $p=0.003$) or pollen (1.85 [1.08-3.15]; $p=0.02$) were significantly more likely to experience SRs. In contrast, patients sensitized to mites were significantly less likely to experience SRs (OR [95%CI]=0.55 [0.36-0.85]; $p=0.007$).

In the second group of factors, the AIT administration route was associated with the occurrence of SRs. 89% of the SRs occurred after SCIT (OR [95%CI]=2.06 [1.09-3.89], $p=0.02$) and 11% occurred after SLIT (0.48 [0.25-0.91], $p=0.02$). The AIT phase also appeared to have an influence: a significantly higher number of SRs were reported during SCIT up-dosing ($p<0.001$). In general, SRs were more likely to be associated with cluster and conventional SCIT up-dosing schedules than with rush schedules ($p=0.007$).

Furthermore, infections ($n=5$ SRs), natural exposure to allergens ($n=4$) and physical exercise ($n=1$) were identified as associated factors for 10 SRs.

Multivariate regression analyses revealed that the following variables (listed in the order in which they automatically entered the equation) were significantly associated with a greater risk of an SR during SCIT: (i) administration of natural extracts ($p=0.001$ vs. allergoids), (ii) the absence of symptomatic allergy medications ($p<0.001$), (iii) sensitization to two or more types of pollens ($p=0.01$), (iv) a cluster up-dosing schedule ($p=0.02$ vs. rush schedules), (v) sensitization against animal dander, irrespective of the AIT composition ($p=0.006$), and (vi) a diagnosis of asthma ($p=0.03$) (**Table 4**). According to the relative weight of each variable, we developed an equation to estimate the risk of an SR in a given patient on AIT (**Table S1**).

The multivariate regression model was also applied to anaphylaxis. The most relevant factors (with regard to increased risk) were found to be (i) a previous episode of anaphylaxis and (ii) the use of a cluster up-dosing schedule (**Table 4**). This multivariate regression model was not used to analyze SLIT, due to the low number of SRs in this treatment group. However, the application of decision trees enabled us to quantify the relative risk associated with some of the variables such as sensitization to two or more types of pollen..

DISCUSSION

In the present international survey, we collected information on SRs related to AIT (either SCIT or SLIT) and coded the reactions according to the harmonized, well-defined MedDRA-based terminology (15). Our approach differed from other previous surveys because (i) we used a prospective, observational, multicentre, web-based questionnaire to assess real-life settings, (ii) all participating physicians were instructed to report symptoms or SRs using the same terminology in English, and (iii) we sought to identify risk factors for SRs.

We have collected data on a total of 109 AIT-related SRs in 90 patients out of a total of 4,363 PTs (2.1% overall; 2.4% for SCIT and 1.1% for SLIT) for a mean period of 12.7 ± 3.3 months. Our findings are in agreement with previous reports on the frequency of SRs (ranging from 1.9% (17) to 4.7% (18) for SCIT and from 0.1% to 0.84% (19) for SLIT).

According to published reports from well-powered clinical trials of SCIT (20) and SLIT (19, 21-23), SRs most frequently reported within 30 minutes were bronchospasm, general disorders, vascular disorders, flushing and foreign body sensation in the throat. Skin disorders, particularly urticaria, were more frequently observed after 60 minutes. The fact that 59% of the SRs appeared more than 30 min after AIT administration underpins the emphasis placed on this topic by the current practice parameters, which have suggested extending the observation period in some cases (24). It is important to note that the SRs were predominantly mild (71.6%). As expected, most of the SRs (75.8%) occurred during the up-dosing phase (9, 24).

Anaphylaxis occurred in 20 SRs (18.3%) but even though intramuscular adrenaline was administered in 17 SRs, only 65% of them were considered anaphylaxis. This use of adrenaline as the first-choice, real-life treatment for anaphylaxis raises concerns about the dissemination and implementation of the various anaphylaxis guidelines published by the World Health Organization and national bodies (25-27).

Even after having suffered a SR, 80.7% of the affected continued receiving AIT. This high proportion might reflect the patients' and physicians' interest in AIT and their understanding of AIT's efficacy (28).

Factors that might alert the physician to an increased risk of SRs before he/she initiates AIT in a given patient were identified:

(i) Type of extract. We found that natural (non-modified or native) extracts increased the risk by a factor of three with respect to chemically modified allergen extracts (allergoids). This finding correlates with data from the Paul-Ehrlich Institute (collected between 1991 and 2000) from which the incidence of SRs was calculated to be higher for natural allergen extracts than for allergoids (29, 30).

(ii) Absence of symptomatic medications (for either the allergic condition or a non-allergic disease). This could be related to the disease severity and the need for proper symptom control prior to initiation of AIT (31, 32)

(iii) Up-dosing schedule. Rush schedules were less strongly associated with SRs. Although contradictory data have been published (33-35), these differences could be due to the type of extract associated preferentially with each protocol.

(iv) Sensitization to animal dander or pollen, regardless of whether or not these allergens were present in the AIT formulation used. These findings emphasized the importance of correct patient selection. The physicians should consider the patient's polysensitization status, allergic profile, the intensity of exposure to aero-allergens and the severity of allergic disease prior to initiation of AIT. These aspects should be evaluated in detail in well-powered clinical studies.

(v) Asthma. In our survey population, asthmatic patients had a two-fold greater risk of SRs and a three-fold greater risk of anaphylaxis (compared with non-asthmatics). Most of the asthmatic patients included in the survey had intermittent or mild asthma, and were supposed to have had their asthma well under control while receiving AIT. However, given that 52.5% of the surveyed population was asthmatic and there was no pharmacological intervention, a certain level of "not well-controlled asthma" could be expected in real-life settings. Furthermore, the presence of asthma *per se* (as a more severe medical condition than rhinitis) might explain the higher incidence of SRs (7, 36, 37).

Although the present survey was not sufficiently powered to determine the relevance of AIT mixtures, we did not identify these preparations as risk factors for SRs (38-40). Moreover, the great majority of patients (90%) received AIT with one allergen source in accordance with current European guidelines.

The mean time interval between symptom onset and AIT initiation was eight years. This long period of time should be put into context with regard to national differences in social security systems, patient referral processes, levels of awareness of AIT as a therapeutic intervention and the false beliefs about AIT (28).

The inclusion of only three countries, the unmatched SCIT-SLIT population, and the short follow-up period could be considered as study limitations. These aspects were due to practical, ethical and logistic obstacles in other countries invited to participate in the survey. We are aware of inter-country differences and the difficulties in interpreting results in patients with different allergen extracts, AIT routes and regimens; however, these limitations can be set against the high number of patients included in the present survey. The large number of included patients/profiles also enabled us to determine the main risk factors for the occurrence of SRs. Web-based survey questionnaires are known to reduce clinician-centre biases (14,41).

Our present results show that it is possible to use the harmonised MedDRA terminology to collect data in multicentre, multinational surveys of real-life clinical practice. The survey constitutes a major step forward in the collection of data for a safety registry that would enable academics, health authorities and industry to exchange and analyse AIT data from clinical settings (6, 14).

In conclusion, AIT for respiratory allergy seems to be safe (in trained hands), with a low incidence of SRs - even during SCIT. We suggest that the personalized, early identification of risk factors, proper patient selection, and appropriate AIT allergen sources and schedules will minimize the occurrence of SRs. Lastly, we hope this initiative will encourage and facilitate the design of Europe-wide safety data registries for AIT in real-life clinical settings.

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Moisés Calderón (MC), Carmen Vidal (CV), Pablo Rodríguez del Río (PRR), Pascal Demoly (PD), Jocelyne Just (JJ) and Oliver Pfaar (OP) all made substantial contributions to the conception and design of the survey. CV, OP, Ana Tabar (AT), Inmaculada Sanchez-Machín (ISM), Petra Bubel (PB), Jesus Borja (JB), Peter Eberle (PE), Rainer Reiber (RR), Michel Bouvier (MB), Alain Lepelliez (AL) and Ludger Klimek (LK) contributed by recruiting at least 90 patients per centre and by collecting data. MC, CV, PRR and PD analyzed and interpreted data and drafted the article. All co-authors provided their final approval of the version to be published.

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LEGENDS OF FIGURES

Figure 1: Frequency of individual symptoms in SRs (according to the MedDRA classification) by AIT administration route (SCIT or SLIT)

Figure 2: Pharmacological medications used to treat SRs due to AIT

SUPPORTING INFORMATION

Supporting Information may be found in the online version of this article:

Table S1: An equation for assessing the individual risk of SRs prior to the initiation of AIT

Table 1

	FRANCE n=663	GERMANY n=756	SPAIN n=2,897	TOTAL n=4,316
Age, years	22.8 ± 14.4	30.1 ± 15.4	26.3 ± 13.8	26.4 ± 14.3
Age < 18	330 (49.8%)	209 (27.6%)	1024 (35.4%)	1563 (36.2%)
Gender (male)	343 (51.7%)	365 (48.3%)	1416 (48.9%)	2124 (49.2%)
Time between allergy diagnosis	7.87 ± 7.9	7.85 ± 8.7	7.96 ± 7.6	7.93 ± 7.9

and initiation of AIT (years)				
Baseline allergic disease symptoms				
Asthma (yes)	346 (52.2%)	253 (33.5%)	1667 (57.5%)	2266 (52.5%)
Rhinitis (yes)	634 (95.6%)	709 (93.8%)	2810 (97.0%)	4153 (96.2%)
Conjunctivitis (yes)	463 (69.8%)	617 (81.6%)	2112 (72.9%)	3192 (74.0%)

Demographic and clinical characteristics of the survey population by country and as a whole. Significant differences between the three countries were found with respect to patient age and the baseline disease symptoms ($p < 0.001$). Data are quoted as the mean $\pm$ standard deviation or the number (percentage).

Table 2

TIME INTERVAL BETWEEN AIT ADMINISTRATION AND THE ONSET OF A SYSTEMIC REACTION									
	<30 min (n=45)		30-60 min (n=9)		60-120 min (n=16)		>120 min (n=39)		TOTAL (n=109)
	SCIT (%)	SLIT (%)	SCIT (%)	SLIT (%)	SCIT (%)	SLIT (%)	SCIT (%)	SLIT (%)	
SYMPTOM									
Urticaria	4 (15.4)	0	3 (11.3)	0	10 (38.5)	0	9 (34.6)	0	26
Allergic rhinitis	9 (42.9)	0	1 (4.8)	1 (4.8)	1 (4.8)	0	10 (47.6)	1 (4.8)	23
Dyspnoea	10 (58.8)	0	2 (11.8)	0	2 (11.8)	0	3 (17.6)	0	17
Cough	8 (57.1)	0	2 (14.8)	0	2 (14.8)	0	2 (14.8)	1	15
Asthma	5 (35.7)	1 (100)	0	0	1 (6.3)	0	8 (20.5)	0	15
Bronchospasm	11 (84.6)	0	1 (7.7)	0	0	0	1 (7.7)	1 (100)	14
Generalized pruritus	4 (30.8)	0	2 (15.4)	0	2 (15.4)	0	5 (38.5)	0	13
Conjunctivitis	7 (77.8)	0	0	1 (50.0)	0	0	2 (22.2)	1 (50.0)	11
Sensation of foreign body	8 (72.7)	0	2 (18.2)	0	0	0	1 (9.1)	0	11
Erythema	4 (40.0)	0	1 (10.0)	0	2 (20.0)	0	3 (30.0)	0	10
Angioedema	3 (40.2)	1 (50)	2 (28.6)	0	1 (14.3)	0	1 (14.3)	1 (50.0)	9
Chest discomfort	6 (66.7)	0	0	0	1 (11.1)	0	2 (22.2)	0	9
Generalized erythema	1 (14.3)	0	2 (28.6)	0	0	0	4 (57.1)	0	7
Chest tightness	4 (80.0)	1 (100)	0	0	0	0	1 (20.0)	0	6
Wheezing	5 (83.3)	0	0	0	0	0	1 (16.7)	0	6
Flushing	2 (50.0)	0	2 (50.0)	0	0	0	0	0	4
Headache	0	0	0	0	1 (25.0)	0	3 (75.0)	0	4
Dysphagia	1 (50.0)	0	0	0	0	0	1 (50.0)	1 (100)	3
Dizziness	3 (100)	0	0	0	0	0	0	0	3
Vomiting	0	2 (66.7)	0	0	0	0	0	1 (33.3)	3
Abdominal pain	1 (50.0)	0	0	0	0	0	1 (50.0)	0	2
Fatigue	1 (100)	0	0	0	0	0	0	1 (100)	2
Dysphonia	0	1 (100)	0	0	0	0	0	0	1

Drop in blood pressure*	1 (100)	0	0	0	0	0	0	0	1
Diarrhea	0	0	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	0	0	0
Laryngeal edema	0	0	0	0	0	0	0	0	0
Loss of consciousness	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	0	0	0	0	0
Syncope	0	0	0	0	0	0	0	0	0
Tachycardia	0	0	0	0	0	0	0	0	0
SYSTEM ORGAN CLASS									
Respiratory	29(50.0)	2 (33.3)	4 (6.9)	1 (16.1)	5 (8.6)	0	20(34.5)	3 (50.0)	64
Skin	14(30.4)	1 (50.0)	5 (10.9)	0	12 (26.1)	0	15(32.6)	1 (50.0)	48
General	15(71.4)	1 (50.0)	2 (9.5)	0	1 (4.8)	0	3 (14.3)	1 (50.0)	23
Eye disorders	7 (77.8)	0	0	1 (50.0)	0	0	2 (22.2)	1 (50.0)	11
Gastrointestinal	2 (50.0)	2 (50.0)	0	0	0	0	2 (50.0)	2 (50.0)	8
Nervous system	3 (42.9)	0	0	0	1 (14.3)	0	3 (42.9)	0	7
Vascular	2 (50.0)	0	2 (50.0)	0	0	0	0	0	4
Cardiac	0	0	0	0	0	0	0	0	0

Frequency of SRs (coded using the MedDRA classification) according to the time of onset and the administration route (SCIT or SLIT). SRs are presented as individual symptoms and by System Organ Class. (*) Subjective drop in blood pressure.

Table 3

Variable	No SRs (n=4,273)	SRs (n=90)	P value	Odds ratio [95%CI]
Patient-related factors				
Age, years (mean±SD)	26.38±14.3	28.42±14.0	0.179	NA
Age 18 years or more at enrolment	2717 (63.5%)	66 (73.3%)	0.6	1.57 [0.98-2.52]
Gender (male)	2112 (49.4%)	38 (42.2%)	0.201	0.74 [0.49-1.14]
Clinically relevant history of non-allergic disease	84 (1.9%)	4 (4.5%)	0.107	0.43 [0.15-1.2]
Previous cardiovascular disease	47 (1.0%)	3 (3.3%)	0.083	3.10 [0.94-10.15]
Previous mastocytosis	4 (0.1%)	0 (0.0%)	1.000	NA
Previous anaphylaxis	34 (0.7%)	1 (1.1%)	0.519	1.4 [0.19-10.34]
Atopic dermatitis	370 (8.6%)	6 (6.6%)	0.703	0.75 [0.32-1.73]
Chronic urticaria	42 (0.9%)	1 (1.1%)	0.594	1.13 [0.15-8.31]
Allergic rhinitis	4111 (96.2%)	88 (97.7%)	0.775	1.73 [0.42-7.1]
Allergic conjunctivitis	3155 (73.8%)	68 (75.5%)	0.809	1.09 [0.67-1.78]
Allergic asthma	2228 (52.1%)	59 (65.5%)	0.014	1.74 [1.12-2.70]
Food allergy	377 (8.8%)	10 (11.1%)	0.451	1.29 [0.66-2.51]
Drug allergy	61 (1.4%)	3 (3.3%)	0.145	2.38 [0.73-7.73]
Hymenoptera venom allergy	10 (0.2%)	0 (0.0%)	1.000	NA
Taking a symptomatic medication	2169 (50.7%)	41 (45.5%)	0.340	0.81 [0.53-1.23]
Sensitization to pollen	2986 (69.8%)	73 (81.1%)	0.020	1.85 [1.08-3.15]
Sensitization to mites	2330 (54.5%)	36 (40.0%)	0.007	0.55 [0.36-0.85]
Sensitization to dander	1094 (25.6%)	36 (40.0%)	0.003	1.93 [1.26-2.97]
Sensitization to moulds	347 (8.1%)	12 (13.3%)	0.081	1.74 [0.93-3.22]
Sensitization to food	265 (6.2%)	8 (8.8%)	0.271	1.47 [0.7-3.08]
Sensitization to Hymenoptera venom	8 (0.1%)	0 (0.0%)	1.000	NA
Sensitization to latex	27 (0.6%)	0 (0.0%)	1.000	NA
Previous course of AIT	735 (17.2%)	20 (22.2%)	0.207	1.37 [0.83-2.27]
AIT-related factors				
Mite AIT (n=1772)	1749 (98.7%)	23 (1.3%)	0.003	0.49 [0.30-0.79]
Grass pollen AIT (n=1252)	1216 (97.1%)	36(2.9%)	0.025	1.67 [1.09-2.56]
Tree pollen AIT (n=558)	545 (97.7%)	13 (2.3)	0.632	1.15 [0.63-2.09]
Mixture of allergens (n=461)	452 (10.5%)	9 (10.0%)	1.000	NA

<i>Alternaria</i> AIT (n=127)	122 (96.1%)	5 (3.9%)	0.188	2.00 [0.79-5.02]
Weed pollen AIT (n=106)	105 (99.1%)	1 (0.9%)	0.726	0.45 [0.06-3.23]
Dander AIT (n=87)	84 (96.6%)	3 (3.4%)	0.427	1.72 [0.53-5.54]
SCIT	3318 (77.6%)	79 (87.7%)	0.021	2.06 [1.09-3.89]
SLIT	965 (22.4%)	11 (13.3%)	0.021	0.48 [0.25-0.91]
Natural extract vs allergoid (out of 3,318 courses of SCIT)	1644 (49.5%)	62 (78.4%)	<0.001	3.71 (2.16-6.38]

Univariate analysis comparing patients with SRs and those without SRs as a function of patient-related and AIT-related factors. The odds ratio (OR) [95% confidence interval (CI)] was calculated for the different populations defined in terms of every variable for each option.

Table 4.

RISK FACTOR	Odds ratio with 95%CI	P value
FOR SRs DURING SCIT		
Type of extract (natural vs. allergoid)	2.739 (1.612-4.878)	0.001
Baseline treatment: No treatment vs. symptomatic medication for allergy Other treatment vs. symptomatic medication for allergy	1.707 (1.008-2.892) 9.204 (3.962-21.385)	0.047 <0.001
Sensitization to pollen (yes vs. no)	1.162 (1.033-1.307)	0.012*
Up-dosing schedule: cluster vs. conventional rush vs. conventional cluster vs. rush	1.577 (0.980-2.540) 0.377 (0.110-1.298) 4.185 (1.218-14.375)	0.061 0.122 0.023
Sensitization to animal dander (yes vs. no)	1.935 (1.209-3.096)	0.006
Asthma (yes vs. no)	1.743 (1.055-2881)	0.030
FOR ANAPHYLAXIS DURING SCIT		
Up-dosing schedule (cluster vs. conventional)	4.756 (1.524-14.839)	0.007
Previous episode of anaphylaxis (yes vs. no)	17.375 (1.919-157.281)	0.011
Sensitization to mites (yes vs. no)	0.279 (0.105-0.741)	0.010
Previous course of AIT (yes vs. no)	2.708 (1.099-6.674)	0.030
Asthma (yes vs. no)	2.961 (0.977-8.970)	0.055

Evaluation of risk factors (using a multivariate regression analysis model) for SRs and anaphylaxis during SCIT. (*) Each additional sensitization to pollen exponentially increases the risk.

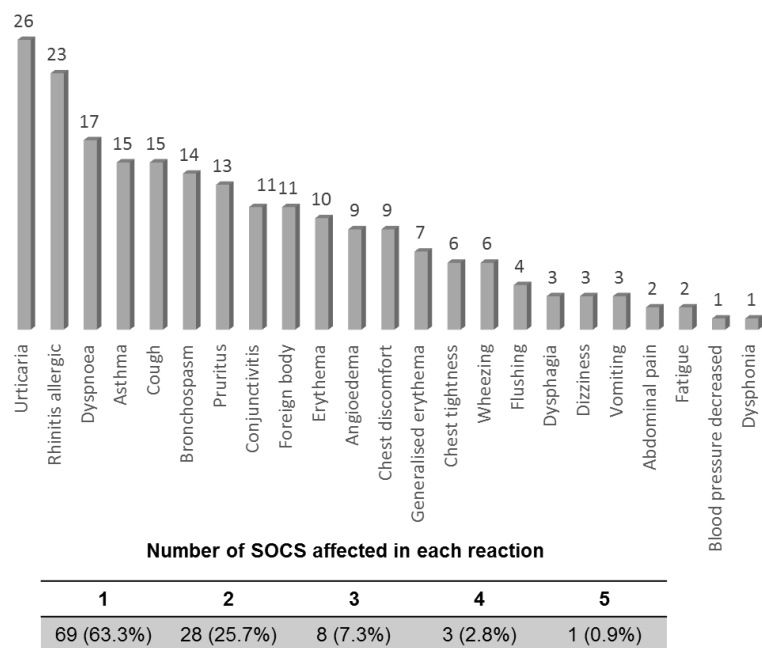


Figure 1

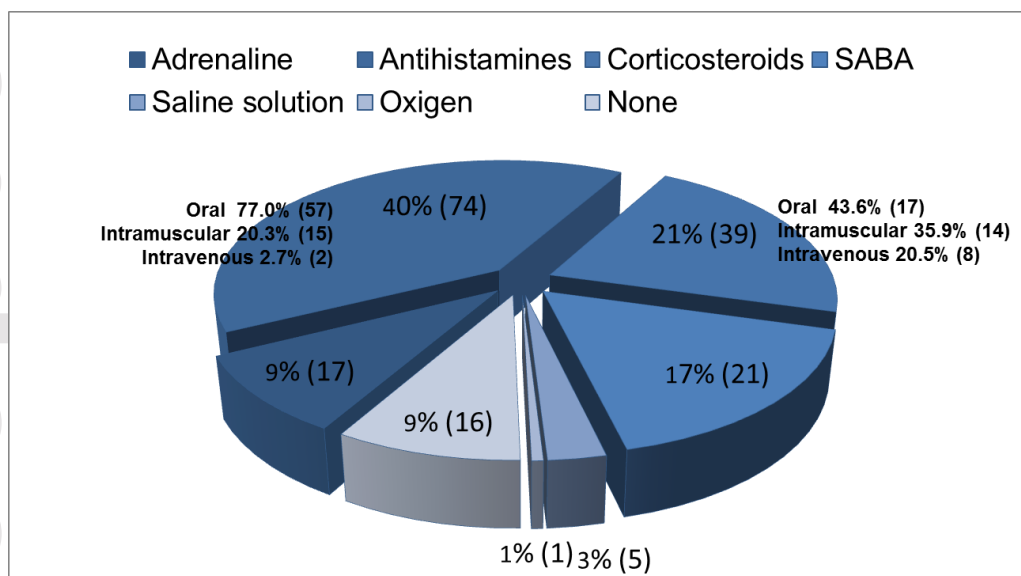


Figure 2