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Safety and treatment compliance of subcutaneous immunotherapy: A 30-year retrospective study

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ABSTRACT

Background: Safety and treatment compliance are still considered important shortcomings of subcutaneous immunotherapy (SCIT).
Objective: To assess the rate of side effects (SE) to SCIT and treatment compliance at a hospital medically supervised facility.
Methods: A retrospective review of patients with allergic rhino-conjunctivitis (ARC) with or without asthma, who received SCIT to mites and pollens from 1988 to 2018, was performed. The information was collected from patient's allergen immunotherapy forms that had been prospectically filled in by expert physicians.
Results: Two thousand two hundred patients (50.2% males; mean age 29.4 ± 11.7 years) received 3037 SCIT courses. A total of 91,187 injections were given, with a mean SCIT duration of 2.5 ± 1.9 years. Nine hundred fifty-seven patients (43.5%) were compliant as they completed the minimally required treatment duration of 3 years. A total of 1087 SE (1.2% of all injections; 76.8% local reactions) were reported in 513 patients (23.3%). There were 42 anaphylactic reactions (in 29 patients) during the study period; two of these were severe. Adrenalin was administered only once. No anaphylactic shock was reported. Only 39 patients (1.8%) discontinued SCIT because of SE, the majority of whom (24; 61.5%) because of systemic reactions (urticaria, asthma, anaphylaxis). *Parietaria* vaccines were the most frequently associated to SE. Female gender, number of vaccines administered (2 vaccine *vs.* 1 vaccine) and year of SCIT inception (1996–2018 vs. 1988–1995) were independently associated to SE.
Conclusion: SCIT, although not absolutely free of risk, is safe and well tolerated. There is still room for improvement of treatment compliance.

1. Introduction

Allergen immunotherapy (AIT), administered either by the subcutaneous route (subcutaneous immunotherapy, SCIT) or the sublingual route (sublingual immunotherapy, SLIT), is effective in reducing symptoms and drug use, in subjects with allergic rhino-conjunctivitis (ARC) with or without allergic asthma [1–4]. According to the guidelines released by the European Academy of Allergy and Clinical Immunology's (EAACI) taskforce, SLIT should be regarded as a safe and well-tolerated treatment. Actually, SLIT was approved for self-administration at home because systemic reactions on SLIT are unusual. SCIT could also be considered safe and well-tolerated only when injections are given in a medical setting by experienced personnel, trained in the early recognition of systemic reactions and their management [5]. This different evaluation is based on the appreciation that systemic reactions to SCIT are more likely, compared to SLIT (approximately 2.1% *vs.* 1.1% of patients, respectively), although the overall rate of any side effects (both systemic and local) is similar in both treatments [5]. However, for SCIT administration, the location of care seems to influence safety profile, which appears increased in medical-supervised

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facilities compared to medical-unsupervised settings [6]. Both systemic and local side effects (SE) are one of the causes of cessation of treatment. Data on treatment compliance (*i.e.* rate of completion of the minimally required treatment duration of 3 years) vary widely, ranging from 18% to more than 90%, depending on the study type (lower in real-life observational studies, higher in RCT) [7,8]. A Dutch study, based on the analysis of a community pharmacy database, assessed SCIT compliance as being around 23% [9]. Other studies based on pharmaceutical company sale databases, reported higher rate of compliance, about 40% [7,8]. Besides SE, inconvenience and lack of efficacy appear to be the main causes of SCIT discontinuation [9]. Asthma has also been considered a negative predictor for treatment compliance [7–9].

Here, we report data on SE and treatment compliance collected from 2200 adult patients with respiratory allergies (moderate-to-severe ARC with/without mild-to-moderate allergic asthma), treated with SCIT for house dust mites (HDM) or pollens, over a 30-year period (from 1988 to 2018), at our hospital medically supervised facility.

2. Methods

A retrospective review of patients with moderate-to-severe ARC with/without mild-to-moderate asthma due to HDM or pollens who received SCIT at our institution (University Hospital of Bari, Italy) from 1988 to 2018 was performed. The allergic condition was defined by a typical clinical history, positive skin prick tests and/or specific serum IgE. The information was collected from the *ad hoc* AIT administration forms (including, among other features, allergen, manufacturer, dose, date of injection, extract concentration, doses administered and annotations from physicians, such as including side of injections, type and severity of reactions) that had been prospectically filled in by the physicians at vaccine administration sessions. This administration form has been used for more than 30 years, for data collection and monitoring the patients (S-Figure).

Several allergen extracts by different manufacturers were administered throughout the 30-year study period. The administration schedule of the various vaccines, usually including a build-up phase and a maintenance phase, was according the specific manufacturer's instructions. The build-up phase consisted in injections administered on a weekly basis; no cluster or rush schedules were used during the up-dosing phase. In the maintenance phase the injections were given on a monthly basis. In the case of pollen vaccines, a 50%-reduction of the maintenance dosage was implemented throughout the high pollen season. In patients with overt asthma symptoms, severe rhino-conjunctivitis or infection episodes the injection was postponed. Patients with asthma were not commonly advised to use bronchodilator medication prior to the scheduled injection. Dose reductions were also done owing to previous systemic or large local side effects (redness and/or swelling >5 cm in diameter), if they did not subside after halving the dose and administering it on the two arms or after administration of local steroids, or intervals between two consecutive administrations exceeding 6 weeks. The observation time after the injections was 30 min.

Any signs or symptoms that were judged as potentially related to SCIT injections were considered as SE. Types of local and systemic SE were registered in the administration form. Redness, itching, or swelling represented local reactions at the injection site. In our series, we defined large local reactions those with diameter >5 cm. We chose this cut-of point (instead of 10 cm, the classic cut-off point to define large local reactions) since the mean local reaction size observed in our series was 5 cm (±3 cm). Patients were instructed to record and measure late cutaneous reactions at home. Systemic reactions were represented by cutaneous symptoms (generalized pruritus, urticaria, flushing, angioedema), rhino-conjunctivitis, asthma, cardiovascular symptoms. The size of local reactions, such as wheals or deep itching erythema, was measured and reported in the patient's form.

Severe SE were considered those responsible for treatment discontinuation. Anaphylaxis was defined according to the EAACI Taskforce on Anaphylaxis position paper [10].

Antihistamine pretreatment, recommended in many centers in order to increase safety of SCIT, was not used in our Center.

The study was conducted according to Good Clinical Practice and in observance of the Declaration of Helsinki with successive modifications. The study was approved by the Ethical Committee of our Institution.

2.1. Statistical analysis

Data description was primarily based on means and standard deviations (SD), or frequencies for categorical endpoints. Comparisons between means were made using the Student's t-test. Crude comparisons of frequencies were made using 2×2 contingency tables, analyzed by the chi-square test. A logistic regression model was also considered in analyzing the data, to derive a reduced and easily interpretable model for predicting the risk of SE. The binary outcome variable was the presence/absence of SEs (regardless of their actual number). In order to make the logistic regression estimates more easily interpretable, continuous variable such as age and year of inception were discretized into binary variables, using an optimal cut-point search algorithm [11]. The algorithm used determines the number and the location of the cut-points using the area under the curve (AUC) of the logistic model, suitably correcting the AUC obtained, which may be biased upward when the same data-set is used both to fit the logistic regression model (involved in the cut-point selection process) and compute the AUC [11]. The whole analysis was performed by R 3.5.1 (R Core Team, 2018) [12].

3. Results

Two thousand two hundred patients (1104 males, 50.2%; mean age, 29.4 ± 11.7) who received in total 3037 courses of SCIT from 1988 to 2018 were included in this study (see Table 1). Patients characteristics are reported in Table 1. Forty-nine percent of these had ARC without asthma; 38.7% had both ARC and asthma (Table 1). Sixty-two percent of our patients (n = 1363) received a single vaccine. The remaining 38% of patients (n = 837) were treated with 2 vaccines, 90.4% of which were administered simultaneously. Three thousand thirty-seven vaccine courses were administered, accounting for 91,187 injections.

A total of 1087 SE were reported in 513 out of the 2200 patients (23.3%) (Table 2). The vast majority of these reactions were local (76.8%). The mean size of the local reactions was 5 ± 3 cm.

Overall, 223 systemic SE (20.5% of total SE) were recorded, with a rate of 2.4/1000 injections. Urticaria asthma and rhino-conjunctivitis were the most frequent systemic reactions (Table 2).

The episodes of anaphylaxis were 42 (in 29 patients; 1.3%); two episodes were severe (both occurring in the same patient), but adrenaline was used once, because of severe dyspnea and urticaria. Anaphylactic shock was never observed. In 14 out of 29 patients (48.3%), anaphylaxis was the first SE. In the remaining 15 one patient had a previous asthmatic reaction, whereas the other 14 had only local SE previously.

Table 1
Characteristics of the study population.

	Patients n = 2200
Mean age ±SD, years	29.4 ± 11.7
Male, n (%)	1104 (50.2)
Disease, n (%)	
- ARC	1077 (48.9)
- ARC and asthma	825 (37.5)
- Missing data	298 (13.6)
Patients undergoing SCIT, n (%)	
1 Vaccine	1363 (62)
2 Vaccines	837 (38)

n, number; SD, standard deviation; ARC, allergic rhino-conjunctivitis; SCIT, subcutaneous immunotherapy.

Table 2
SE to SCIT (2200 patients receiving 3037 SCIT courses).

	Patients with SE 513/2200 (23.3)	Total number of SE 1087/3037 (35.8)
Males, n (%)	157 (30.6)	384 (35.3)
- Local	390 (76.1)	835 (76.8)
- Systemic	109 (21.2)	223 (20.5)
o Urticaria	54	104
o Angioedema	3	4
o Asthma	33	66
o Rhino-conjunctivitis	22	47
o Non-specific symptoms	22	42
o Anaphylaxis	28	40
o Severe anaphylaxis	1	2
- Local and systemic	14 (2.7)	29 (2.7)
Time of SE occurrence, n (%)		
- Build-up	340 (66.3)	760 (70)
- Maintenance	173 (33.7)	327 (30)
o Co-seasonal	17 (9.8)	36 (11)
o Non co-seasonal	102 (59)	182 (55.7)
o Perennial	54 (31.2)	109 (33.3)
o Full dose	103 (59.5)	218 (66.7)
o Reduced dose	70 (40.5)	109 (33.3)

SE, side effects; n, number; SCIT, subcutaneous immunotherapy.

The majority of SE occurred during the build-up phase (70%). The percentage of systemic reactions in pollen AIT patients was lower during the pollen season, in the reduced-dosage phase (co-seasonal), than during the maintenance full-dosage phase, outside the pollen season (Table 2).

The mean treatment period was 2.5 ± 1.9 years per patient (Table 3). Nine hundred fifty-seven patients (43.5%) completed the minimally required treatment duration of 3 years (603 patients ≥3–5 years plus 354 patients ≥5 years) (Table 3). Only 39 patients (1.8%) discontinued SCIT because of SE. The majority of these patients discontinued AIT during the first year of treatment (53.8%). Female patients had a higher discontinuation rate following SE (67% of patients).

Treatment related discontinuation because of systemic SE was due to anaphylaxis (7 out of 24 cases), urticaria (6 out of 24 cases), asthma (4 out of 24 cases), rhicoconjunctivitis (4 out of 24 cases) and aspecific symptoms such as malaise, tiredness, etc. (3 out of 24 cases).

Table 3
Duration, discontinuation and completion (2200 patients receiving 3037 SCIT courses).

	Patients N = 2200	SCIT courses N = 3037
Mean duration of treatment, years ±SD	2.5 ± 1.9	2.5 ± 1.9
- 0–1 years, n (%)	678 (30.8)	919 (30.3)
- ≥1, <3 years, n (%)	565 (25.7)	756 (24.9)
- ≥3, <5 years, n (%)	603 (27.4)	796 (26.2)
- ≥5 years, n (%)	354 (16.1)	566 (18.6)
Treatment-related discontinuations, n (%)	39 (1.8)	60 (2)
- Due to systemic reactions	24 (61.5)	40 (66.7)
Anaphylaxis	*7*	*9*
Urticaria	*6*	*13*
Asthma	*4*	*7*
Rhino-conjunctivitis	*4*	*8*
Other (aspecific)	*3*	*3*
- 0–1 years, n (%)	21 (53.8)	37 (61.7)
- >1–3 years, n (%)	11 (28.2)	14 (23.3)
- >3 years, n (%)	7 (18)	9 (15)
Treatment completion (≥3 years) by disease*		
- ARC	515/1077 (47.8)	683/1470 (46.5)
- ARC and asthma	400/825 (48.5)	542/1154 (47.0)

n, number; SD, standard deviation; ARC, allergic rhino-conjunctivitis; SCIT, subcutaneous immunotherapy. *Data missing in 298 patients receiving 413 SCIT courses.

The mean local reaction size of the 15 patients who discontinued because of local SE was 8.8 ± 4.3 cm, larger than the average size of all the patients with local SE (5 ± 3 cm in diameter).

We observed 42 anaphylactic reactions in 29 patients, 7 of these discontinuing the treatment (against our advice). Thus, 42 episodes of anaphylaxis led to 7 discontinuations (1 discontinuations out of 6 anaphylactic episodes). Only 2 out of the 35 patients who continued AIT did not reach the full maintenance dose.

During the period 1988–1995, 881 vaccines were administered. Of these only 15 were discontinued because of SE (1.7%). Forty-five vaccines out of 2156 administered from 1996 to 2018 were discontinued because of SE (2.1%; OR 0.8; p = *NS*). In contrast, we observed a lower discontinuation rate for any reason during the period 1988–1995 (554 out of 881; 62.8%) compared to the period 1996–2018 (1481 out of 2156; 68.7%; OR, 0.77; $p < 0.01$).

The most frequently administered extracts were: HDM (a mixed vaccine *Dermatophagoides pteronyssinus* and *farinae* in almost all patients) (26.7%) and *Parietaria* (26.1%), followed by grass (23.8%), olive (15.1%) and cypress (6.6%) (Table 4). *Parietaria* extracts were the most frequently associated with SE.

Altogether, 30.5% of SE were due to *Parietaria* (Table 4), followed by HDM and grass. Accordingly, we observed a statistically significant difference between the occurrence of SE due to *Parietaria* and that of all the other pollens (OR, 1.5; $p < 0.01$) and HDM (OR, 0.78; $p < 0.05$), respectively. In contrast, cypress vaccines were less likely to cause SE compared to other pollen vaccines (OR, 0.39; $p < 0.01$) (Table 4). We also calculated the compliance rate of each vaccine (Table 4), which does not correlate with SE.

We reported 223 systemic reactions, due to *Parietaria* (61 out of 223 [27.3%]), HDM, (60 out of 223 [27%]), *grass* (47 out of 223, 21%), *olive* (45 out of 223 [20.2%]), *cypress* (5 out of 223, [2.2%]).

By univariate analysis, female sex was associated with a higher risk of developing SE compared to male sex, with 32.5% of females experiencing SE of any kinds (males *vs.* females OR: 0.34; $p < 0.01$). No difference was observed when patient's age was analyzed (Table 5). Furthermore, patients with asthma had an increased risk of SE compared to patients affected by ARC (OR, 1.27; $p < 0.05$). Patients receiving two vaccines are at higher risk of SE compared to those receiving only one vaccine (OR, 1.41; $p < 0.01$) (Table 5). Finally, the year of SCIT inception was associated to a difference in risk of SE, being higher (OR, 5.6; $p < 0.01$) with vaccines administered from 1996 to 2018, compared to the vaccines administered from 1988 to 1995.

When we limited the analysis to systemic side effects, we confirmed asthma, gender and year of inception as risk factors, whereas double vaccine administration did not reach statistical significance (Table 5).

Logistic regression analysis confirmed the effect of sex (male *vs.* female Adj.–OR, 0.55; $p < 0.01$) and number of vaccines (2 *vs.* 1 Adj.–OR, 1.50; $p < 0.01$) on SE risk (Table 6). Also, the year of inception was independently associated with SE risk with subjects undergoing SCIT from 1996 to 2018 having approximately twice as much the risk of occurrence of SE compared to those treated from 1988 to 1995 (Adj.–OR, 1.98; $p < 0.01$) (Table 6). Conversely, age and disease type (ARC *vs.* asthma and ARC) did not show a statistically significant association with the risk of SE.

An analysis by extract type showed that native-conjugated extracts were associated with a higher rate of local and systemic SE than allergoids (OR, 1.55; $p < 0.001$) (Table 7). However, the difference did not attain statistically significance when we analyzed only the systemic reactions (OR, 1.34; p = *N.S.*).

4. Discussion

This retrospective observational study shows that, in patients with moderate-to-severe ARC with or without moderate asthma, SCIT is safe and well tolerated, with a rate of systemic reactions, from mild to severe,

Table 4
SE according to allergens.

	SCIT courses, n = 3037	Total number of SE, n = 1087	SE rate per allergen (%)	Comparison (rate of SE)	OR	*P*	Vaccine administered ≥3years, n (%) n = 3037
Allergens							
- HDM	812 (26.7)	291 (26.8)	35.8	*vs.* parietaria	0.78	<0.05	326 (40.1)[#]
- Parietaria	794 (26.1)	332 (30.5)	41.8	*vs.* other pollens	1.50	<0.01	354 (44.6)[°]
- Grass	723 (23.8)	260 (23.9)	35.9				329 (45.5)
- Olive	460 (15.1)	153 (14.1)	33.3				211 (45.9)
- Cypress	200 (6.6)	38 (3.5)	19	*vs.* other pollens	0.39	<0.01	91 (45.5)[§]
- Others*	48 (1.6)	13 (1.2)	27.1				12 (25)

SE, side effects; n, number; OR, odds ratio; SCIT, subcutaneous immunotherapy; HDM, house dust mites. *Cat (n = 3), dog (3), grass and olive mix (16), grass and *Parietaria* mix (2), *Alternaria* (2), *Parietaria* and olive mix (1), *Betulaceae* (1), *Compositae* (12), missing data (8). [#]Difference between HDM and *Parietaria* was not statistically significant. [°]Difference between *Parietaria* and other pollens was not statistically significant. [§]Difference between Cypress and other pollens was not statistically significant.

Table 5
Univariate analysis to predict SE occurrence.

Variable	Value/option	Patients with total SE n (%)	OR	*P*	Patients with systemic SE n (%)	OR	*P*
Gender	M	157/1104 (14.2)	0.34	<0.01	41/1104 (3.7)	0.48	<0.01
	F	356/1096 (32.5)			82/1096 (7.5)		
Disease	ARC and Asthma	215/825 (27.3)	1.27	<0.05	61/825 (7.4)	1.95	<0.05
	ARC	234/1077 (21.7)			42/1077 (3.9)		
N° of SCIT	2	226/830 (27.2)	1.41	<0.01	56/830 (6.7)	1.46	*NS*
	1	287/1370 (20.9)			67/1370 (4.9)		
Year of inception	From 1996 to 2018	974/2156 (45.2)	5.6	<0.01	101/2156 (4.7)	1.92	<0.01
	From 1988 to 1995	113/881 (12.8)			22/881 (2.5)		
		Mean ± SD		*P*	Mean ± SD		*P*
Age	Patients with SE	29.36 ± 13.8		*N.S.*	29.32 ± 11.7		*N.S.*
	Patients w/o SE	29.51 ± 14.4			29.51 ± 14.5		

SE, side effects; n, number; OR, odds ratio; ARC, allergic rhino-conjunctivitis; SCIT, subcutaneous immunotherapy.

Table 6
Logistic regression model to predict the risk of SE.

Variable	Code	Est. β	Std. Err	Adj. OR (95%CI)	*P*-value
		−0.60	0.11	0.55 (0.44, 0.69)	<0.01
Gender	male				
	female (← ref)				
		0.68	0.13	1.98 (1.54, 2.54)	<0.01
Year of inception	1996 to 2018				
	1988 to 1995 (← ref)				
		0.40	0.11	1.5 (1.2, 1.87)	<0.01
Number of vaccines	2				
	1 (← ref)				

Age and type of disease (ARC *vs.* asthma and ARC) are not reported, as their estimated coefficients were not significant ($p > 0.10$). SE, side effects; ARC, allergic rhino-conjuntivitis; CI, confidence interval; Adj. OR, adjusted odds ratio; Std. Err, standard error; Est. β, Estimated β; ref, reference level. The logistic regression model was estimated excluding those patients who had any data missing (complete case analysis, for a total of 1876 patients).

of 2.4/1000 injections and no anaphylactic shock case over 30-years. This study shows also that treatment compliance of SCIT is relatively high (compared to other reports) [9], since 43.5% of patients completed the minimally required treatment duration of 3 years.

Our data support the concept that the location of care, such as a hospital medically supervised facility, may increase the safety of SCIT and, indirectly, enhance treatment compliance, likely due to the patients' perception that a clinical setting with trained personnel, appropriate equipment and medications may prevent potential serious SE.

However, SEs represent only a minor cause of treatment discontinuation (only 39 discontinuations; 1,8% of patients who discontinued).

Table 7
Local and systemic SE according to SCIT brand and type of extract.

Brand	Vaccine (N = 3037) n (%)	Total number of SE (N = 1087) n (%)[a]	Type of extract	*OR* (Native-conjugated *vs.* allergoid)
Alk/Abellò/Neo-Abellò/Alk-Abellò	726 (23.9)	228 (31.4)	Native-conjugated	
Allergopharma/Bracco/Merk	393 (12.9)	182 (46.3)	Native-conjugated	
Allergy Therapeutics/Kallergen	330 (10.8)	152 (46.1)	Native-conjugated	
Bayer/Bayropharm	359 (11.8)	111 (30.9)	Native-conjugated	
Lofarma	49 (1.6)	19 (38.8)	Native-conjugated	
Stallergenes	392 (12.9)	137 (34.9)	Native-conjugated	
- Total	**2249 (74.0)**	**808 (35.9)**		
Anallergo	303 (10)	80 (26.4)	Allergoid	
Bial/Aristegui	36 (1.2)	8 (22.2)	Allergoid	
Hal Allergy	101 (3.3)	29 (28.7)	Allergoid	
- Total	**440 (14.5)**	**117 (26.6)**		1.55 (P < 0.001)
Others/Missing	348 (11.5)	139 (39.9)	Unknown	

[a] The percentage is calculated on the number of vaccines.

Thus, discontinuations appear to be mainly due to personal reasons, such as inconvenience of receiving a treatment requiring repeated visits for its administration and a not negligible investment of time and financial resources by the patients. One can also speculate that these

patients discontinued treatment because they have an improvement in their symptom after one or two years of treatment and do not feel the need to continue for 1 or 2 years. It is also possible that non-compliant patients had more often SE than compliant ones and were lost-to-follow up. As a consequence, the number of side effects may be underreported.

About 40% of SE leading to discontinuation were local ones. SE leading to discontinuation were more severe (or perceived as more severe by the patients) than those not leading to discontinuation. However, it is also possible that other factors contributed, such as a perceived lack of efficacy that made the patients not sufficiently motivated to continue a costly treatment in the presence of local side effects. So, large local reactions *per se* are unlikely to be a reason for discontinuation.

A very small number of patients discontinued AIT because of systemic reactions (about 1.1%). Although the risk of systemic reactions with SCIT is low and the fatalities are exceptional, safety is still considered a major concern, owing to the potential occurrence of serious/life-threatening reactions [13,14]. A review of fatal reactions to SCIT, conducted in the United Kingdom, identified 26 deaths from 1957 to 1986, all of which occurring in asthmatic patients [13]. In the USA there were 76 reports of deaths due to SCIT, occurring between 1973 and 2001, approximately 1 death every 2 million injections. Also in this review, uncontrolled asthma was reported in more than 60% of cases and diagnosis of asthma in almost all cases [14]. The most recent surveillance study in the USA, reporting data from 2008 to 2013 on 28.9 million injections, showed a dramatic decrease of deaths: only 4 in the observed period [15]. This decrease was attributed to the practice of never administering SCIT in uncontrolled asthma [15]. These data suggest that SCIT should not be considered free of risk. But, at the same time, a careful management of patients to be treated may dramatically reduce the risk of severe reactions and fatalities. Actually, according to the current guidelines [5], nowadays SCIT is contra-indicated in patients with uncontrolled asthma, in order to reduce the risk of severe SEs.

Apart from clinical trials data on systemic reactions due to AIT are scarce. A recently published prospective, longitudinal, web-based survey of "real-life" respiratory AIT in clinical practice, conducted in France, Spain and Germany (EASSI) [16] assessed the rate of systemic reactions over a mean observation period of 12.7 ± 3.4 months. The survey included data from 4363 patients receiving either SLIT or SCIT collected by 112 physicians, about 50% of whom working exclusively in public sector hospitals. The rate of patients undergoing systemic reactions estimated in the EASSI study was 2.1%, (89% of whom with SCIT).

We reported a higher rate of patients with systemic reactions (4.9%) compared to EASSI study [16]. However, our rate was consistent with a recent study, similar to ours, reporting data of AIT experience in a single paediatric clinic over 10 years (4.7%) [17]. The difference with the EASSI can be explained by the different observation period (30 years in our study and 10 years in the Nacaroglu study [17] *vs.* only 1 year in the EASSI study) [16]. An alternative possible explanation is that the SCIT studies that are published are always performed in centers that meet the requirements of international guidelines, are conducted under the supervision of experienced doctors and exclude patients with partial or uncontrolled asthma.

In our single center series, we did not report any fatalities. Only one patient experienced a serious anaphylactic reaction with respiratory tract involvement, requiring adrenaline administration. We confirm that asthma is a significant risk factor for SE, since patients with both asthma and ARC had a higher frequency of total SE, systemic side effects and SE leading to discontinuation, compared to patients with ARC alone. SCIT was not administered to patients with overt asthma symptoms at vaccination sessions. This clinical choice might explain the low rate of severe SE reported.

In our study epinephrine was significantly less often administered as compared to percentage that was published in the EASSI study (once *vs.* 17 times, respectively) [16]. However, the higher rate of adrenalin administration in the EASSI study may depend on specific clinical indications (e.g. administration in case of reactions milder than anaphylactic shock) or different patient population (e.g. high percentage of patients with asthma). Actually, current guidelines recommend treating anaphylaxis with adrenalin [10]. The rather infrequent use of adrenaline in our series may reflect our clinical practice in less recent years, favoring the use adrenaline only for the most severe reactions.

Regarding factors that may predict anaphylaxis, we could not show that systemic reactions, such as asthma, predict subsequent anaphylactic episodes.

Dose reduction during the pollen season decreased total SE occurrence.

Moreover, patients receiving only one vaccine had a low SE rate, compared to those receiving two vaccines.

The type of allergen extract appears to be another important factor associated to a differential risk of SE occurrence. We observed the highest frequency of SE in patients receiving *Parietaria* AIT, compared to either HDM or other pollens (grass pollens, olive pollens, cypress pollens). The lowest frequency of SE was observed with cypress extracts. Other studies showed a differential risk of SE depending on the extract type. However, this difference did not attain statistical significance [18–20].

Since vaccine composition and standardization has been changing over the years (native extracts *vs.* chemically modified extracts, allergoids, etc.), we sought to assess whether these changes might had influenced vaccine safety and discontinuation rate. Unexpectedly, we found an increased SE frequency and higher discontinuation rate with the vaccines administered from 1996 to 2018, compared to those administered from 1988 to 1995 (adj. OR, 1.98; $p < 0.01$).

However, it must be noted that 1992 was remembered in Italy as the year of the Great Crisis, with the unsustainable rising of fiscal deficits. The financial act of 1992 helped avoid the bail-out of public debt and the restoring of the public finance equilibrium was pursued through major cuts to public spending, including health expenditure. This might have caused a substitution effect, that is a change in consumption patterns of health care goods, in which subcutaneous immunotherapy (the entire cost of this treatment is borne by users) was perceived to be less important than others diagnostic procedures or pharmaceuticals and, thus, abandoned.

Regarding the increase of SE from 1996 to 2018, we speculate that the vaccine induction schedules in recent years, with a smaller number of injections required to reach the maintenance phase in order to increase compliance, might be associated with a higher risk of SE. Nonetheless, the number of discontinuations due to SE remained low also after 1996 (2.1% of all discontinuations compared to 1.7% before 1996; p, *NS*), while the number of discontinuations due to reasons other than SE increased (from 62.8% up to 1995 to 68.7% from 1996 to present; OR, 0.77; $p < 0.01$). This finding suggests that inconvenience related to repeated administrations and possibly the burden of costs are likely the main reasons for treatment discontinuation.

Female sex was strongly associated to the occurrence of SE (70% of patients with SE were females; $OR = 2.9$; $p < 0.001$). An association between female sex and the risk of SE was inconsistently reported. Furthermore, in small studies, this association did not reach statistical significance [18–20]. The large sample size of our series, along with the even gender distribution of patients undergoing SCIT, makes this observation reliable, suggesting a possible gender or hormonal influence [21–24].

Finally, we assessed whether different brands or vaccine types (native-conjugated extracts *vs.* allergoids) could influence the rate of SE occurrence. Similarly to other reports [16,25], native-conjugated extracts were associated to a higher risk of total SE (Table 7), but not systemic reactions. Furthermore, the analysis carried out did not show any difference in the risk of total SEs among the several brands (Table 7). Therefore, our results cannot be possibly referred as lacking in generalization.

Differently from other reports, we were unable to provide

information on the risk of SE with cluster or rush AIT, since these administration schedules have never been used at our Clinic [16].

This study has many strengths:

a) Treatment compliance: we showed that more that more than 44% of our patients complete the required minimum length treatment (3 years). This completion rate is sensitively higher than expected, compared to the sales figures of main pharmaceutical companies or community pharmacy databases.

b) Long-term follow-up: we report data on patients treated up to 5 years.

c) Differently from other multicenter studies or surveys, we report data collected in a single Center. We speculated that the clinical setting of an outpatient clinic might have played a role.

d) Compliance and SE rates changed over time. We believe that a 30-year series of a single Center with an established clinical routine that did not change sensitively over time is suitable to assess this issue. Data collected from different Centers may be biased by confounding limiting the validity of the conclusions (e.g. different protocols, patient selections, prophylactic use of medications or bronchodilators, dosage-changes, etc.).

e) Differently from many other Countries, Parietaria vaccine is one of the most frequently used in Italy. This vaccine is precisely associated with the higher rate of SE.

f) The big sample size of this study and its high statistical power make results reliable.

A limitation of this study is that we could analyze only the available variables, as in all retrospective studies. We could not clearly evaluate SE severity, since severity was not clearly graded in the patients' AIT forms. That prevented us from analyzing data in a predictive model. In fact, we considered as severe ones only SE leading to discontinuation, possibly causing underestimation.

Another limitation is the possible impact on our findings of missing data (which are expected in all retrospective analysis).

In some European countries, SLIT is currently preferred to SCIT, owing to ease of administration and supposed better safety [23]. However, our data highlight that SCIT, although not absolutely free of risk, has also an excellent safety profile, provided that AIT is accurately managed.

Author contributions

DDB and LM developed the concept of this study. SM, LM, AL and RL collected the data for the study. MB performed statistical analysis. The first draft of the manuscript was written by DDB and thoroughly revised by LM. MFC and MA provided critical revision of the manuscript. MFC provided also institutional and financial support.

Declaration of competing interest

We declare that we have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.105843.

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