

Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy

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Keywords

allergen immunotherapy; asthma; children; long-term effect; rhinitis

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Abstract

Background: Subcutaneous immunotherapy (SCIT) discontinuation data in children remain scarce.

Objective: We sought for differences in the clinical efficacy of 3 vs. 5 yr of SCIT in children with dust mite respiratory allergy.

Methods: We performed a 5-yr, phase IV prospective study. After the first year, the patients were randomized to 3 (IT3) or 5 yr of treatment (IT5). Efficacy was assessed at 3rd and 5th year by symptom and medication scores and visual analog scales (VAS). Skin tests with common allergens and *in vitro* assessments were also performed.

Results: Eighty-one children (mean age: 9 yr) were randomly assigned to 3 (IT3: 41) or 5 yr (IT5: 40) of immunotherapy. After 3 years, rhinitis global scores decreased in IT3 (44%; $p = 0.002$) and in IT5 (50%; $p = 0.001$). Asthma global, symptom and medication scores decreased by 100% in IT3 ($p = 0.001$) and IT5 ($p = 0.001$). VAS scores also diminished significantly (IT3: 70%, $p = 0.001$; IT5: 62.5%; $p = 0.001$). At 5th year, global rhinitis scores were reduced an additional 30% in IT5 children. Comparisons between both groups did not show differences in rhinitis ($p = 0.055$), asthma global scores ($p = 0.948$) or VAS scores at 5th year. Twenty percent of IT5 ($p = 0.002$) and 7% of IT3 children ($p = 0.705$) developed new sensitizations. At 5th year, sIgG4 determinations decreased in IT3 without significant variations in IT5.

Conclusions: Three years of SCIT induced significant improvement in children with dust mite respiratory allergy, but a 5-yr course added clinical improvement in rhinitis.

Background

Allergen avoidance, pharmacologic treatment and specific immunotherapy are the cornerstones when treating respiratory allergy.

Despite the increasing knowledge regarding immunotherapy mechanisms (1), efficacy (2), long-lasting effect, or preventive potential (3), its optimal duration remains unsolved. Treatment discontinuation is based on individual clinical decisions (4) and usually lasts for 3–5 years (5, 6). Some studies (3) suggest that 3 yr could induce prolonged symptom remission. Authors specifically addressing this issue have reported early high relapse rates (7, 8).

Abbreviations

SCIT, subcutaneous immunotherapy; EAACI, European Academy of Allergy and Clinical Immunology; HDM, house dust mite; LR, local reaction; VAS, visual analogue scale; WAO, World Allergy Organization.

Our group reported the first prospective study specifically seeking for differences in clinical efficacy between a 3-yr and a 5-yr course of house dust mite (HDM) subcutaneous immunotherapy (SCIT) (9). A 3-yr course induced significant improvement in patients with rhinitis and asthma, but 5 years improved rhinitis severity.

Clinical research in children presents specific questions. Diseases may pose different characteristics; drugs may have different pharmacodynamics and pharmacokinetics leading to possible differences in clinical efficacy or safety (10).

The pathophysiological events involving type I allergies are assumed to be identical in patients of all ages (11). There are no differences in the indications, duration, or the management of adverse reactions related to patients' age (12). Despite the limitations of pediatric data (12), the most recent studies support its efficacy (13). Unfortunately, most of the SCIT extracts do not have specific pediatric clinical data demonstrating their quality, efficacy, and safety (12, 14).

Decisions on immunotherapy discontinuation should also be based on specific pediatric data. Therefore, we analyzed children data separately, seeking for differences in SCIT efficacy between a 3-yr and a 5-yr course in children aged 5–15 with HDM-induced rhinitis and asthma.

Methods

Study design

We performed a 5-yr, phase IV, prospective study, in which the initial up-dosing schedule was blinded (15). After 1 year of treatment, half of the patients were randomized (16) to a 3-yr course (IT3) and the other half to a 5-yr course (IT5). At 3rd year (T3), a control group receiving pharmacological treatment exclusively was also included (15) (Fig. 1). Now we analyzed children data separately.

Patients

All the patients aged between 5 and 15 years attended at our department over a period of 1 yr (April 1998 to April 1999) with HDM-induced moderate-severe rhinitis and/or asthma were offered to take part in the study (Fig. 1). Subcutaneous immunotherapy indication was based on the European Academy of Allergy and Clinical Immunology (EAACI) recommendations (6). Diagnosis and pharmacological treatment of rhinitis and asthma were based on The International Consensus Report on the Diagnosis and Management of Rhinitis (17) and National Institutes of Health, National Heart, Lung and Blood Institute (18), respectively. All patients showed positive skin tests and specific IgE results. In non-monosensitized patients, HDM had to be the eliciting allergen of most symptoms. Patients sensitized to epithelia with coexisting animals were excluded. The initial sample included 81 children with a median of 2 years of respiratory symptoms. SCIT duration was randomly (16) assigned. The control group did

not yield enough children for statistical analysis. Ten children were discarded at 3rd year for non-adherence (Fig. 2).

Subcutaneous immunotherapy efficacy was assessed by a clinical assessment. New sensitizations were documented by skin tests with a panel of allergens detailed below. Lung function was determined by a spirometry. Patients' perceived severity was measured by a visual analog scale (VAS). Assessments were made at baseline, 3rd and 5th year. The patients' parents signed an informed consent specific for minors. The study followed the principles established in the World Medical Association Declaration of Helsinki (19) and was approved by the Hospital Clinical Research Ethics Committee and by the Spanish Drug Agency.

Allergen extract

A biologically standardized *D. pteronyssinus* extract quantified in micrograms of *Der p1* and *Der p2* (Pangramin Depot UM (ALK-Abelló, Madrid, Spain) was used for treatment. Two up-dosing schedules were performed: a cluster and a conventional schedule, as previously published (15). Maintenance doses were monthly administered, each containing 3.6 µg of *Der p1*. Patients were monitored for 30 min after each dose. All the doses were recorded in the Immunotherapy Unit Management software INMUNOWIN® (ALK-Abelló, Madrid, Spain).

Assessments

Safety and compliance

INMUNOWIN® program records were checked for adverse effect and compliance evaluations. Adverse effects were graded according to the EAACI guidelines (6) Irregular compliance was defined as frequent delays (≥ 3 consecutive doses) or at least one administration delay in the maintenance phase longer than 16 wk.

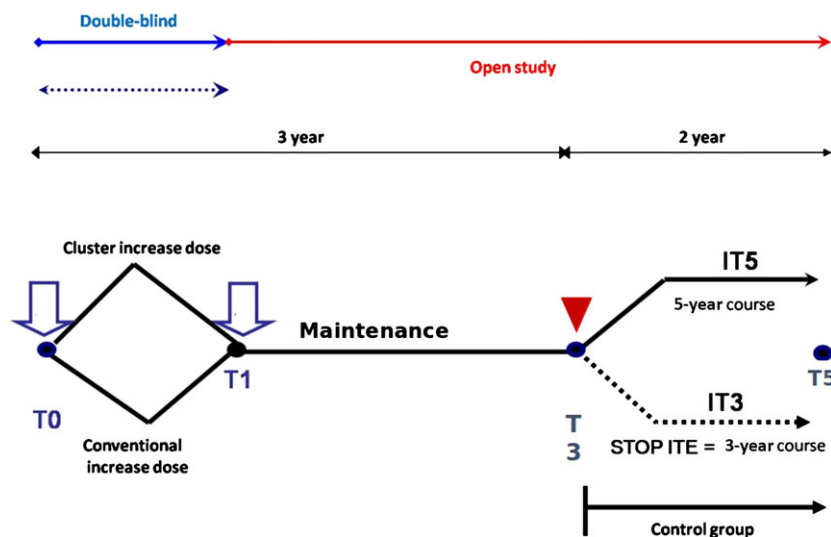


Figure 1 Study design. Dotted line. Results published in J Allergy Clin Immunol. 2005 Jul; 116(1):109-18. Arrows: Randomization. Red triangle: STOP SIT. Evaluation timelines: T0: baseline evaluation; T1: 1-yr follow-up; T3: 3-yr follow up; T5: 5-yr follow-up. Patients: IT5: Patients receiving SIT for 5 yr; IT3: Patients receiving SIT for 3 yr; Controls.

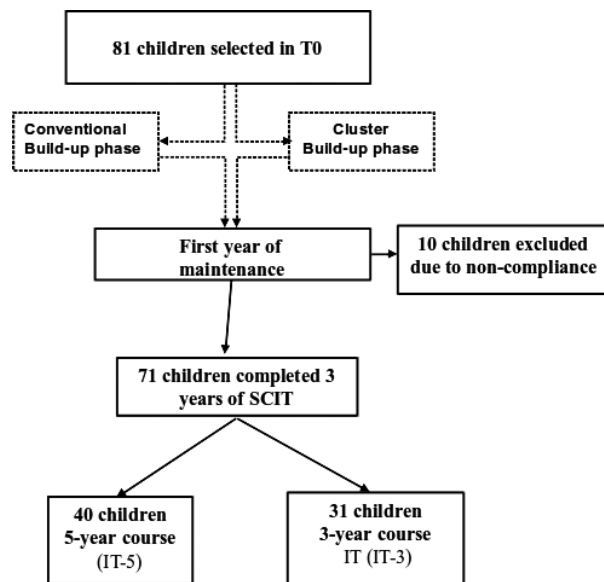


Figure 2 Patient's flowchart throughout the study.

Efficacy assessment

Primary outcomes were symptoms and rescue medication use, assessed by objective scales previously used by our group (9, 15, 20–22). We used combined Meltzer's (23) scales for symptoms (0–12 points) and medication (0–2 points) for rhinitis severity. Asthma was evaluated by an asthma symptom scale modified from Aas (24) assessing symptoms (0–5 points), medication (0–5 points), and lung function tests (0–2). For rhinitis, rescue medication included topical corticosteroids and/or oral antihistamines. For asthma, reliever medication included short-acting β_2 agonists and the most frequent controller medication were inhaled corticosteroids.

Patient-perceived severity was measured by a VAS, fulfilled by parents exploring the week prior to the visit. Its values ranged from 0 (very good) to 10 (very bad) (25).

Pulmonary function tests

Patients with asthma underwent forced spirometry with bronchodilation test according to the American Thoracic Society guidelines (26). We used a Jaeger spirometer (Master-Scope, Jaeger Toennies; Erich Jaeger GMBH, Hoechberg, Germany).

Asthma-free patients

Patients asymptomatic with normal lung function and without any pharmacological treatment for at least the three previous months to the assessments were considered asthma-free patients (7, 9).

Assessment of new sensitizations

Skin prick tests

Skin prick tests were performed with the following allergens according to the recommendations of the EAACI Subcommittee

on Skin Tests (27): egg, cow milk, peanut, cod, wheat grain, shrimp, peach, *D. pteronyssinus*, *Phleum pratense*, *Salsola kali*, *Plantago lanceolata*, *Alternaria tenuis*, cat and dog epithelium, latex, saline, and histamine.

In vitro testing

Serum levels of *D. pteronyssinus*-specific IgG, IgG4, and IgE were determined by enzyme immunoassay following the CAP System RAST FEIA method (ThermoFisher, Uppsala, Sweden). Measurements were made at the end of the study using the same assay for each evaluated parameter.

Statistical and computing methodology

The statistical software SPSS 17.0 for Windows, BMDP Statistical Software release 7, and Star Xact (Cytel Software Corp 675 Massachusetts Ave., Cambridge, MA 02139–3309) were used for analysis. Clinical efficacy variables such as VAS, asthma- and rhinitis- combined scores, and *in vitro* parameters were assessed by Mann–Whitney *U*-test for between-group comparisons and by Wilcoxon test for within-group comparisons, respectively. Patients' characteristics were analyzed by the following: sex, baseline diagnosis, asthma severity, mono-sensitized and asthma-free patients' rates by a chi-square test; skin tests by Mann–Whitney *U*-test, chi-square test, and Fisher's exact *t*-test, age by *t*-test, and rhinitis severity by a test of trend in proportions (detailed in Table 1).

All statistical tests had a significance level of 0.05.

Results

Eighty-one children were initially included. At T3, 71 children (rhinitis: 7; asthma: 17; both rhinitis and asthma: 47) were still on treatment with good compliance. Forty patients continued immunotherapy for 2 more years (IT5 group) and 31 ceased the treatment (IT3 group; Figs 1 and 2).

Patients' baseline characteristics are detailed in Table 1. We observed significant differences in baseline values in sex distribution and rate of patients sensitized to *P. pratense*, without relevance in SCIT indication or clinical efficacy.

Safety

During the study, 5694 doses were administered including the placebo doses for the up-dosing phase. Two patients with asthma in IT5 group developed an asthma episode within the first 30 min after a maintenance dose at 2nd year, resolved with bronchodilators (Type II systemic reaction according to EAACI-grading). The following dose was adjusted in both patients. Three patients (two in IT5 group and one in IT3 group) presented isolated local reactions (LR) larger than 10 cm, resolved with oral antihistamines. One patient in IT3 group developed nodules. Long-term tolerance was confirmed in every patient. SCIT duration did not influence on the timing of onset of adverse events. The incidence of systemic adverse effects was 0.03% of the administered doses, corresponding to 2.46% of the children.

Table 1 Patients' characteristics

		IT5 (40)	IT3 (31)	p
Mean age ($\pm$ SD)		8.9 ($\pm$ 2.88)	9.26 ($\pm$ 3.19)	0.622*
Sex (M/F)		32 (80%)/8 (20%)	18 (58.1%)/(13 (41.9%))	0.045†
Diagnosis At Baseline	Rhinitis	4	4	0.436†
	Asthma	8	9	
	Rhinitis and Asthma	28	18	
Severity	Rhinitis (Mi, Mo, S)	(1,7,24)	(2,20,0)	0.392‡
	Asthma (Mi, Mo, S)	(21,15,0)	(17,11,0)	0.847†
Patients without other sensitizations	T0	20 (50%)	19 (61.2%)	0.343†
	T3	16 (40%)	16 (54.8%)	0.357†
	T5	9 (30%)	15 (54.8%)	0.016†
Median of other sensitizations	T0	0.5 (0–4)	0 (0–1)	0.125¶
	T3	1 (0–5)	0 (0–4)	0.123¶
	T5	2 (0–5)	0.5 (0–4)	0.011¶
Food allergens	T0	2 (5%)	3 (6.4%)	0.445†
<i>Phleum pretense</i>		11 (27.5%)	3 (9.7%)	0.070†
<i>Salsola kali</i>		2 (5%)	0	0.503§
<i>Plantago lanceolata</i>		3 (7.5%)	1 (3.2%)	0.630§
<i>Alternaria tenuis</i>		1 (2.5%)	1 (3.2%)	1.000§
Dog epithelium		2 (5%)	2 (6.5%)	1.000§
Cat epithelium		6 (15%)	4 (12.9%)	1.000§
Latex		1 (2.5%)	0	1.000§
Food allergens	T3	5 (12.5%)	3 (10%)	0.709†
<i>Phleum pretense</i>		12 (30%)	6 (19.3%)	0.452†
<i>Salsola kali</i>		4 (10%)	0	0.124§
<i>Plantago lanceolata</i>		8 (20%)	2 (6.4%)	0.167§
<i>Alternaria tenuis</i>		3 (7.5%)	1 (3.2%)	0.624§
Dog epithelium		9 (22.5%)	5 (16.1%)	0.477†
Cat epithelium		9 (20%)	7 (22.6%)	0.925†
Latex		0	0	–
Food allergens	T5	(30%)	5 (16.1%)	0.174†
<i>Phleum pretense</i>		15 (37.5%)	6 (19.3%)	0.103†
<i>Salsola kali</i>		4 (10%)	0	0.128§
<i>Plantago lanceolata</i>		9 (22.5%)	3 (6.4%)	0.161†
<i>Alternaria tenuis</i>		4 (10%)	1 (3.2%)	0.380§
Dog epithelium		8 (20%)	4 (16.1%)	0.450†
Cat epithelium		12 (30%)	7 (22.6%)	0.514†
Latex		2 (5%)	0	0.502§
<i>D. pteronyssinus</i>	IgE (T0)	55 (1.38–100)	79.1 (0.55–100)	0.838¶
Specific immunoglobulins determinations	IgE (T3)	64.2 (0.78–100)	60 (1.09–100)	0.656¶
	IgE (T5)	50 (0.35–100)	53.35 (0.5–100)	0.669¶
	IgG T0	13.3 (2.0–53.6)	10.7 (2.0–46.5)	0.806¶
	IgG(T3)	21.6 (10.2–64.1)	21.85 (12.6–66)	0.872¶
	IgG (T5)	25.85 (8.83–45.8)	12.25 (7.25–49.1)	0.04¶
	IgG4 (T0)	501.5 (150–1795)	374 (150–1842)	0.920¶
	IgG4 (T3)	2710 (990–11520)	3275 (920–12800)	0.501¶
	IgG4 (T5)	3010 (10–20810)	1930 (10–6500)	0.042¶
Asthma-free patients		37 patients are analyzable	27 patients are analyzable	
	T0	0	0	
	T3	18 (64.37%)	18 (75.01%)	0.404†
	T5	23 (69.7%)	15 (60.0%)	0.442†

Severity of respiratory allergy: Mi: mild; Mo, moderate, S, severe.

Skin tests performed at T0, T3, and T5.

Evolution of specific IgE (kU/l), IgG (kU/l), and IgG4 (mcg/ml) levels against *D. pteronyssinus* during the study [median (interquartile)].

Asthma-free patients' analysis. Only performed in patients with a diagnosis of asthma, with or without rhinitis during the study. (Asthma-free patients: global asthma score = 0 (asthma symptoms + asthma medications) = 0.

Statistics: **t*-test, †chi-squared test, ‡test of trend in proportions, §Fisher's exact *t*-test, ¶Test of Mann–Whitney *U*-test.

Clinical efficacy

Rhinitis severity

At 3rd year, IT5 and IT3 patients presented significant decreases in symptom (IT3: 44%; $p = 0.001$) (IT5: 50%; $p = 0.012$) and global (combined symptom and medication) (IT3: 44%; $p = 0.002$) (IT5: 50%; $p = 0.001$) scores. Most of the patients did not use any rescue medication at baseline. At 5th year, IT5 children nose symptom scores had decreased an additional 30% compared to 3rd year scores ($p = 0.029$), while IT3 children symptom ($p = 0.714$) and global scores ($p = 0.812$) remained unchanged. Besides, final rhinitis symptom in IT5 group was almost significantly lower than IT3 children results ($p = 0.052$). Global score decreases differences between IT5 and IT3 and did not reach statistical significance (Fig. 3 and Table 2).

Asthma severity

At T3, all the asthma variables: asthma symptoms, medication, and global scores were diminished by 100% in both groups IT5 ($p = 0.001$; $p = 0.001$; $p = 0.001$) and IT3 ($p = 0.001$; $p = 0.001$; $p = 0.001$) and no changes were observed at 5th in both groups either. Lung function tests were within normal values. We observed no differences between both groups at 5th year (Asthma symptom score: $p = 0.632$; asthma medication score: $p = 0.926$; asthma global score: $p = 0.948$) (Fig. 4 and Table 2).

Asthma-free patients

At T0, all patients with asthma were symptomatic and/or required anti-asthmatic medication for control. At 3rd year, 64.37% of IT5 patients with asthma and 75.01% of IT3 were asthma free. At 5th year, 69.7% patients in T5 and 60% in IT3 group remained asthma free, without differences in within-group comparisons and/or in between-group comparisons (Table 1).

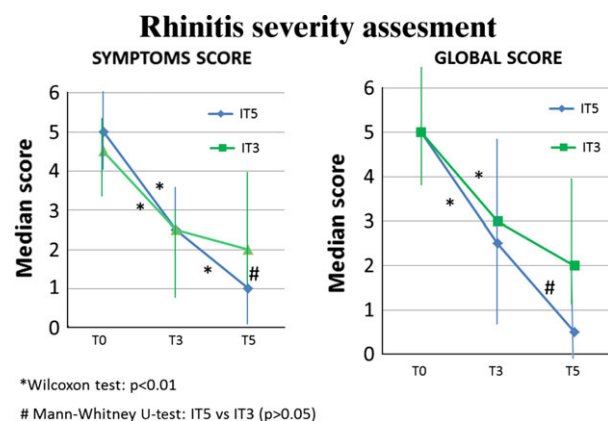


Figure 3 Clinical Assessment: rhinitis severity evolution (global scores). Median values (IQ) *Comparisons within groups (Wilcoxon's test): $p < 0.01$. #Comparisons between groups (Mann-Whitney U-test): $p > 0.05$.

Visual analog scale

Visual analog scale scores decreased at 3rd year in IT5 (62.5%; $p = 0.001$) and 70% in IT3 (70%; 0.003) in IT3 group. No differences were observed between T3 and T5 scores in within-group comparisons (IT5: $p = 0.302$; IT3: $p = 0.787$) or in between-group comparisons either ($p = 0.519$) (Table 2).

New sensitizations assessment

Along the study, 20% of IT5 (chi-square test: $p = 0.002$) and 7% of IT3 children (chi-square test: $p = 0.705$) developed new sensitizations rising the rate of polysensitized patients from 50 to 70% (IT5) and from 38.8% to 44.2% (IT3), respectively (Table 1).

Besides, IT5 group children presenting other sensitizations prior to SCIT administration developed additional sensitizations during the follow-up, rising from initial 0.5 (0–5) sensitizations to 2 (0–5) at 5th year, while the median values in IT3 children remained unchanged (Details in Table 1).

In vitro determinations

In vitro results showed sIgG4 level increases in both groups at T3. Two years later sIgG4 decreased in IT3 patients, although remaining higher than baseline values (Table 1).

Discussion

Optimal duration of SCIT should provide top clinical benefit, a good safety profile, and reasonable costs offering long-term clinical benefit and preventive effect (3). The most recent reviews suggest a period of at least 3 years to obtain long-lasting effects after cessation (5). A panel of experts addressed recently the limitations of current knowledge of SCIT in children (12). Treatment duration was identified as an unsolved question.

We had previously observed that 3 years of SCIT induced significant clinical improvement in patients aged 5–45 with moderate rhinitis and asthma, without significant relapses during first 2 years after discontinuation (11), so we sought for possible differences in efficacy in children.

We assessed the efficacy of SCIT comparing with baseline assessments. The follow-up period of 2 years should enable us to detect possible relapses in the IT3 group as published in the bibliography, appearing within the first 2–3 years after discontinuation (9, 10).

The lack of placebo injections in pediatric SCIT clinical trials has been addressed in several experts' committee meetings (12–14), and it is still in conflict as for some authors, the efficacy of SCIT in children is yet to be proved (28). We considered that giving placebo injections might condition compliance and could bring unnecessary burden to our patients. Besides, a 'real-life' approach would offer the benefit of assessing real effectiveness and chances of developing new hypothesis.

Analyzing the clinical outcomes, there was moderate improvement in rhinitis scores at 3rd year compared to baseline. Most patients were untreated for allergic rhinitis symptoms before referred to an allergist. We observed an

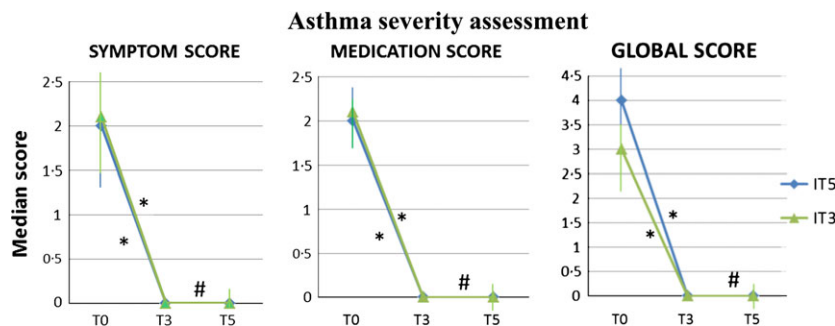
Table 2 Severity assessment. Rhinitis, asthma, and visual analog scores

			Median (P25–P75)			p (test Wilcoxon)		
			N	T0	T3	T5	T0 vs. T3	T3 vs. T5
Rhinitis								
IT5	Symptoms	24	5 (4–6)	2.5 (0.25–4)	1 (0–2.75)	0.000	0.029	
	Medication	24	0 (0–0.75)	0 (0–0)	0 (0–0)	0.340	0.739	
	Global score	24	5 (4–7)	2.5 (0.5–4.7)	0.5 (0–2)	0.001	0.012	
IT3	Symptoms	20	4.5 (2.25–8)	2.5 (1–4)	2 (1–4)	0.002	0.714	
	Medication	20	0.5 (0–2)	0 (0–0)	0 (0–0)	0.022	0.317	
	Global score	20	5 (3–9)	3 (1–4)	2 (1–4)	0.002	0.812	
Asthma								
IT5	Symptoms	23	2 (1–2)	0 (0–0)	0 (0–1)	0.000	0.916	
	Medication	23	2 (1–3)	0 (0–0)	0 (0–1)	0.000	0.521	
	Global score	23	4 (3–5)	0 (0–3)	0 (0–2)	0.000	0.309	
IT3	Symptoms	20	2 (1–2)	0 (0–0)	0 (0–0)	0.000	0.739	
	Medication	20	2 (1–2)	0 (0–0)	0 (0–0)	0.000	0.854	
	Global score	20	3 (2.25–4)	0 (0–1)	0 (0–1)	0.000	1.000	
Global score								
IT5		26	9 (6.75–10.25)	2 (0–5)	2 (0–4)	0.000	0.547	
IT3		22	8 (5.75–11.25)	2.5 (0–5)	2.5 (0.75–5)	0.000	0.614	
Visual analog scale score								
IT5		26	4 (2.75–6.25)	1.5 (0.75–2)	1 (0–2)	0.000	0.302	
IT3		20	5 (1–6.75)	1.5 (0.25–2)	1 (1–2)	0.003	0.787	

IT5, Patients receiving 5 years of SCIT; IT3, patients receiving 3 years of SCIT.

p values <0.05 highlighted in bold.

Figure 4 Clinical Assessment: asthma severity evolution. (global scores). Median values (IQ) *Comparisons within groups (Wilcoxon's test): $p < 0.01$. #Comparisons between groups (Mann–Whitney U -test): $p > 0.05$.



overall reduction of 85% in global scores at 5th year in IT5 group children. Two additional years provided significant additional benefit to these patients. However, comparisons between both groups' rhinitis score did not reach statistical significance ($p = 0.055$). Maybe a larger group might yield different results.

Asthma scores improvement was even better than rhinitis results, with 100% decreases in symptom, medication, and global scores at T3. More than 60% of our patients with asthma were asthma free. Two additional SCIT years did not improve the rate of asthma-free patients at 5th year, and those treated for 3 years did not relapse either.

Two additional findings stood out: Rhinitis residual symptoms may persist in children too after receiving immunotherapy for coexisting rhinitis and asthma, despite the patient becoming asthma free. Besides, SCIT efficacy in children might be better than in adults. This fact should be carefully considered as it was not a specific aim of the study but a

statistical finding. Analyzing children results alone, global asthma scores decreased by 100% in these patients and may be considered cured, while global analysis including both adults and children had shown decreases of 80% (9). There were no differences in patients' selection, immunotherapy extract, diagnosis, or allergen doses that may affect the results. So the age of the patients may have had an influence in SCIT efficacy. Many physicians delay the prescription of SCIT even in patients with rhinitis till symptom worsening or asthma development. If our observation was confirmed by further studies, it could reinforce the convenience of early SCIT indication to enable optimal clinical benefit.

Visual analog scales scores correlate with the severity of allergic rhinitis as assessed by ARIA guidelines (25). Our patients' scores decreased significantly at T3 and remained similar at 5th year in both groups. Moreover, VAS results matched the clinical scores, and so did physicians' and patients' perception regarding their health status.

Regarding the skin test results, almost half of our patients had associated sensitizations before SCIT and a significant number of IT5 patients developed new sensitizations and/or increased its number. This fact had no impact in the clinical efficacy, but a longer duration did not prevent further sensitizations.

In vitro results showed common modifications associated with successful immunotherapy: At 3rd year, sIgG4 levels increased in all patients, persisting high at 5th year in IT5 patients, decreasing in IT3 patients. This finding may have different significance. Immunoglobulin levels decrease after discontinuation despite the persistence of clinical benefit, and those allergen-specific antibodies maintain sIgE-blocking properties (29). However, sIgG decreases might precede a clinical relapse. Only a longer follow-up period would rule out this possibility.

Stelmach et al. (30) observed no differences in efficacy between a 3-yr and a 5-yr course of HDM SCIT in asthmatic children and the persistence of the clinical benefit for 3 years

after discontinuation. There are no current data about possible differences in rhinitis or the evolution of *in vitro* parameters.

We conclude that 3 years of HDM SCIT is an adequate duration to treat respiratory in children aged 5–15, inducing significant improvement in both rhinitis and asthma severity and clinical asthma remission in a significant number of children. This effect remains at least for 2 years after discontinuation. A 5-yr course adds clinical significant benefit in rhinitis severity.

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Conflict of interest

The authors have no conflict of interest to declare.

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Supporting Information

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

Table S1. Rhinitis severity. Symptoms and medication score.

Table S2. Asthma severity. Symptom, medication and lung function scores.

SYMPTOM AND MEDICATION SCORES

Symptoms	Sneezing AND/OR Nose itching	0	Absent
		1	Mild
		2	Moderate
		3	Severe
	Anterior rhinorrhea	0	Absent
		1	Mild
		2	Moderate
		3	Severe
	Nose obstruction	0	Absent
		1	Mild
		2	Moderate
		3	Severe
	Postnasal drip	0	Absent
		1	Mild
		2	Moderate
		3	Severe
Medication	0	No medication needed	
	1	Topical steroids OR oral antihistamines	

	2	Topical steroids AND oral antihistamines

Table . Rhinitis severity. Symptoms and medication score

Symptoms	0	No symptoms
	1	Less than 5 short episodes (<7 days long), without any symptoms between crisis
	2	5 a 10 short episodes (< 7 days long) without symptoms between crisis OR o airflow obstruction less than 12 weeks per year
	3	More than 10 short episdes, without symptoms between crisis OR o airflow obstruction less than 12 weeks per year
	4	Frequent symptoms and airflow limitation for more than 6 months in 1 year. Two or 3 Emergency Department attendances.
	5	Incapacitating and chronic asthma, with severe and frequent exacerbations despite optimal treatment. More tha 3 Emergency Department attendances.

Medication	0	No treatment
	1	Intermittent Short-acting β2 agonists
	2	Cromones
	3	Inhaled steroids

	4	Inhaled steroids plus sustained release theophylline OR 1-3 oral short glucocorticosteroids treatment
	5	Regular oral steroids treatment (lowest dose) OR more than 4 o oral steroids courses

Lung function	0	Normal base spirometry (FEV1 > 80%)
	1	Complete reversible airflow limitation after inhaled bronchodilator
	2	Partial reversible airflow limitation after inhaled bronchodilator

Asthma severity. Symptom, medication and lung function scores