Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: A randomized controlled trial

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Background: Asthma control is now recognized as the main goal of asthma therapy. Guidelines recommend finding the lowest effective dose of inhaled corticosteroids in children with persistent asthma.

Objective: The aim of this study was to investigate the efficacy of an allergen-specific immunotherapy with a high-dose hypoallergenic mite preparation (allergoid) as steroid-sparing agent in children with allergic asthma.

Methods: Sixty-five children with asthma (Global Initiative for Asthma treatment levels II and III; 6-17 years old), after reaching asthma control with inhaled steroids during a 5-month baseline period, were randomized for subcutaneous mite allergoid immunotherapy (SCIT) plus fluticasone propionate (FP) or FP therapy alone for 2 years. During 2 subsequent 5-month winter periods, steroid therapy was adjusted according to predefined dose steps, determining and comparing the changes in FP dosages and the lowest FP dose sufficient to maintain asthma control. Immunologic and functional investigations were also carried out.

Results: Children treated with house dust mite SCIT plus FP were able to significantly reduce the FP dose by more steps ($P < .05$), compared with the control group on FP alone. The mean daily dose in the immunotherapy group decreased from 330.3 μg in the baseline period to 151.5 μg after 2 treatment years, whereas in the control group the dose decreased from 290.6 μg to 206.3 μg. Compared with the control group, significant improvement was also observed in morning peak expiratory flow ($P = .0315$). Significantly increased levels of specific IgG_1 ($P = .0001$) and IgG_4 ($P < .0001$) were also observed.

Conclusion: Adding a mite allergoid SCIT to pharmacologic treatment is an effective and safe strategy to reduce corticosteroid doses while maintaining disease control in children with mite-induced allergic asthma. (J Allergy Clin Immunol 2010;126:942-9.)

Key words: *Subcutaneous immunotherapy, allergoid, house dust mite, asthma control, children, hypoallergenic preparation, controlled trial, efficacy, safety,* Dermatophagoides pteronyssinus

In recent years, the concept of disease control has emerged as the main goal in asthma therapy,[1] and guidelines now recommend that treatment be aimed at controlling the clinical and functional features of the disease.[2] Asthma guidelines also agree that in patients requiring regular controller therapy,[2] inhaled corticosteroids (ICSs) are the most effective anti-inflammatory medications and the drug of first choice in both adults and children.[2,3]

Although there is general agreement about the safety of low-to-moderate doses of ICS in adults, some concern has been raised about possible adverse effects of long-term treatment with ICS in children.[4,5] Systemic effects of inhaled agents such as decreased growth and effect on bone metabolism are important considerations. Accordingly, guidelines recommend using the lowest dose of inhaled steroids sufficient for maintaining disease control. Therefore, different strategies have been proposed to obtain a steroid-sparing effect. The most widely suggested is a different pharmacologic approach.[2]

There is now a growing body of evidence regarding the clinical efficacy of allergen-specific immunotherapy (SIT) in allergic asthma. Despite some initial debate,[6-9] in 2003 members of a Cochrane Systematic Review panel concluded that subcutaneous immunotherapy (SCIT) "reduces asthma symptoms and use of asthma medications and improves bronchial hyperreactivity."[10] The most recent updates of Global Initiative for Asthma (GINA) and National Asthma Education and Prevention Program (NAEPP) guidelines on the management of asthma both include SIT as an additional option in asthma therapy.[2,3]

Very few studies have investigated the efficacy of SIT as an add-on therapy to pharmacologic treatment in asthma. Regarding the disease control and the reduction of ICS requirement, 1 study found that SCIT in adults was effective,[11] whereas a study in children gave negative results.[12] Two publications on children with house dust mite–induced asthma who used sublingual immunotherapy (SLIT) also yielded conflicting results.[13,14]

A new, high-dose hypoallergenic preparation of *Dermatophagoides pteronyssinus* has already proved to be effective and safe in adults with allergic rhinitis with or without asthma.[15,16] The aim of this study was to assess the efficacy of this preparation as an add-on therapy for controlling allergic asthma in children

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Abbreviations used
FP: Fluticasone propionate
GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
PEF: Peak expiratory flow
SCIT: Subcutaneous immunotherapy
SIT: Allergen-specific immunotherapy
SLIT: Sublingual immunotherapy
SPT: Skin prick test
TU: Therapeutic unit

requiring ICSs. Because the lowest possible steroid dose is recommended for children on long-term ICS, we investigated the effect of reducing steroid dose while maintaining disease control in children with asthma and allergy to house dust mite.

METHODS

Participants

Patients included in the study were 6 to 17 years old, with mild-to-moderate house dust mite allergic asthma (GINA treatment levels II and III).[2] Inclusion criteria were a positive skin prick test (SPT; >5 mm in diameter and at least as large as histamine control reaction), a positive conjunctival provocation, and a significant RAST/CAP response (≥0.7 kU/L, class 2) to *D pteronyssinus*; requirement of ICS treatment with at least 100 μg fluticasone or at least 200 μg budesonide per day; and mite allergen in house dust samples.

Exclusion criteria were FEV_1 <80% of predicted normal values, a previous course of SIT against house dust mites or any unknown allergen, ongoing SIT with any other allergen, symptoms related to or skin test positivity to allergens that interfered with the annual diary phases, a positive SPT reaction against any other allergen that was greater than or equal to the *D pteronyssinus* reaction, severe persistent asthma (GINA treatment level IV), and the usual contraindications for SCIT.[17]

Visits

Patients were screened from May to September 2005 and then entered a 5-month baseline diary phase, September 15, 2005, to February 15, 2006.

Patients meeting GINA criteria for asthma control (well controlled and controlled) in the baseline period were randomized to receive SCIT and ICS therapy or ICS alone. Because the pharmacotherapy plus subcutaneous placebo-control group in children was not approved by the authorities, the pharmacotherapy group was introduced for comparison. Block randomization was carried out within trial centers. Therefore, the clinical trial was performed as a multinational, multicenter, randomized controlled trial.

Subcutaneous immunotherapy was then administered for 2 years. Because the use of a diary card over a 2-year period was unrealistic, asthma control was verified monthly during the same periods of highest mite exposure (September 15 to February 15 in 2007 and 2008) according to predefined asthma control criteria set forth in the GOAL study, which is the cornerstone of studies adjusting the doses according to asthma control criteria.[18] ICS dose was adjusted by using the same predefined criteria for dosing steps and ICS preparation. The local investigator was blind to the diary evaluation of asthma control and the assessment of the next dose step, which were made in real time by a remote Clinical Research Organization using fax. Patients recorded daily values of morning peak expiratory flow (PEF). A methacholine test was performed under the minimal asthma control ICS dose at baseline and at the end of the study to determine the degree of bronchial hyperreactivity.

Asthma control

Good asthma control, according to GOAL criteria,[18] was achieved if all the following criteria were met in the last 2 weeks of every 4-week diary phase: no nighttime awakenings, no exacerbations, and no emergency visits/asthma-related unscheduled visits; or at least 2 of the following criteria were met: daytime symptom score >1 on ≤2 days per week, use of salbutamol rescue medication ≤2 days per week, with a maximum of 4 occasions (8 puffs) per week; and morning PEF on each day ≥80% of predicted normal value.

Immunotherapy

The house dust mite allergoid (Acaroid) for SCIT was manufactured by Allergopharma Joachim Ganzer KG, Reinbek, Germany, according to the revised Good Manufacturing Practice Guidelines of the World Health Organization. House dust mite allergens were extracted from purified mite bodies (*D pteronyssinus*), characterized, chemically modified, and adsorbed onto aluminum hydroxide. The preparation is standardized in therapeutic units (TU) with 2 strengths: strength A (1000 TU/mL; a 1:10 dilution of strength B) and strength B (10,000 TU/mL). The peak dose of 0.6 mL strength B contains 7 μg Der p 1 and 6 μg Der p 2. Initial therapy consisted of weekly injections with increasing doses of strength A (0.1, 0.2, 0.4, and 0.6 mL) followed by strength B (0.1, 0.2, 0.4, and 0.6 mL). After the maximum individually tolerated dose had been reached, the intervals of the injections were gradually extended to 6 weeks (±2 weeks). PEF was measured before and after every injection.

ICSs

All patients were treated with fluticasone propionate (FP) dry powder via inhalation from a disk (accuhaler) device at doses ranging from 50 to 500 μg twice daily.

For adjusting fluticasone therapy, predefined steps in daily doses were as follows: step one, 0 μg twice daily; step two, 50 μg twice daily; step three, 100 μg twice daily; step four, 250 μg twice daily; and step five, 500 μg twice daily. For inclusion, at least a minimal asthma control dose of 50 μg twice daily was required.

Breakthrough symptoms of lower airways were treated with salbutamol metered-dose inhaler (100 μg per dose), used only as required. Other asthma medications (including long-acting ß-agonists, ICSs in the form of combination products, leukotriene antagonists, theophylline, and so forth) were not permitted during the study.

Treatment of allergic rhinitis/rhinoconjunctivitis and other concomitant diseases was left to the discretion of the investigators. If required, oral corticosteroids were permitted for the treatment of asthma exacerbations. However, the duration of oral steroid courses was kept to a minimum and their use precisely documented.

Skin test

At enrollment, a SPT was performed with a standard set of pollen, animal, house dust mite (*D pteronyssinus* and *Dermatophagoides farinae*), and mold allergens.

Conjunctival provocation tests

A conjunctival provocation test was performed before the start of therapy using a lyophilized allergen extract of *D pteronyssinus*. A concentration of 5 biological units/mL was the initial concentration, titration was done in half logarithmic steps (ie, using a factor of 3.2), and the highest concentration was 5000 biological units/mL.

Methacholine provocation test

The methacholine test was performed twice, at the end of the 5-month baseline period and at the end of the second year. The test was carried out according to a standardized and published short provocation protocol[19] under the achieved minimal asthma control dose.

Patients' diaries

During the baseline and assessment periods (September 15 to February 15) of each study year and at 3-month intervals during the rest of the year, the patients

recorded their asthmatic symptoms, intake of rescue medication (salbutamol), morning PEF values, and all the other control parameters in a diary.

Dust samples

At screening and 3 times during the second year of treatment, patients were asked to collect house dust samples from their beds and upholstered furniture by means of a vacuum cleaner. House dust mite allergens in the samples were biochemically (Acarex test , Davimed Pharma+HealthCare GmbH, Germany) and microscopically analyzed.

Ethical conduct of the study

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, consistent with Good Clinical Practice and the applicable regulatory requirements. Parents had to sign the consent form. Children and adolescents could also sign the consent form on the basis of the investigator's decision. The study was approved by the responsible ethics committees and the national authorities.

Primary and secondary outcomes

The primary endpoint of this study was the change in the ICS dose steps required to achieve asthma control (according to GINA) in children treated for 2 years with SCIT compared with children on ICS alone.

Secondary endpoints were the following:

- Change in prebronchodilator morning PEF before versus after treatment
- Immunologic changes, specifically IgE, IgG_1, IgG_4 levels
- Nonspecific bronchial hyperreactivity: changes of PD_{20} FEV_1

Statistical methods

Statistical study design. After a placebo-controlled study in children was rejected by the ethics committee, the overall trial was separated into 2 groups: children (randomized study of ICS + SCIT vs ICS alone) and adults (randomized double-blind study of ICS + SCIT vs ICS + placebo). Both study populations were planned to be evaluated in a meta-analysis on the basis of proportional odds models for changes in fluticasone dose steps or on the basis of an age-stratified Wilcoxon-Mann-Whitney test, respectively. Accordingly, the comparison of trial procedures within age groups was done in a proportional odds model or with the Wilcoxon-Mann-Whitney *U* test.

Determination of sample size. The odds ratio in the proportional odds model of changes in fluticasone dose can be estimated by rates of dose reduction by at least 1 dose step with immunotherapy. Therefore, the determination of sample size was based on results from previous studies in asthma control after treatment with ICSs and anti-IgE. These studies showed a reduction in the consumption of corticosteroids in 75% of actively treated and 50% of placebo-treated patients.

On the basis of the following parameters, the number of patients per group needed to show statistical significance was N = 77:

- A level of significance $\alpha = 0.05$ (type I-error; 2-tailed)
- Test power $1\text{-}\beta = 0.90$ (type II-error $\beta = 0.10$)
- A reduction rate of corticosteroids = 75% in actively treated patients (SIT)
- A reduction rate of corticosteroids = 50% in placebo-treated/untreated patients (no SIT)
- Active and placebo/untreated randomization of 1:1

Therefore, N = 78 patients were planned for each study group of children (randomized 39 active:39 only usual care) and adults (randomized 39 active:39 placebo).

Efficacy analysis

The primary endpoint variable was the change in the dose of ICS needed to ensure asthma control according to GINA recommendations. The dose could be selected among available dose steps from the accuhaler, and changes in these steps were quantified as –3, –2, –1 (steps of improvement), 0 (unchanged), +1, +2, and +3 (steps of deterioration). The multinomial distribution of the primary endpoint was analyzed in a proportional odds model. The primary analysis was completed by the Wilcoxon-Mann-Whitney test. Secondary endpoints were also analyzed with the Wilcoxon-Mann-Whitney test. In this publication, we report the study of children.

TABLE I. Demographic data and clinical characteristics

	SCIT + ICS	ICS only
No. of patients	33	32
Age (y), range (median)	6-17 (9)	6-16 (11)
Age groups, n		
6-9 y	18	12
10-13 y	9	14
14-17 y	6	6
Sex, male/female, n	22/11	22/10
Asthma level, n (%)		
GINA II	26 (78.8)	26 (81.3)
GINA III	7 (21.2)	6 (18.8)
Duration of asthma (y), median	3	2
Mean ICS baseline daily dose (μg)	330.3	290.6
Patients with specific IgE (%)		
≥0.7 kU/L, <3.5 kU/L	15.2	3.1
≥3.5 kU/L, <17.5 kU/L	36.4	53.1
≥17.5 kU/L, <50 kU/L	33.3	28.1
≥50 kU/L	15.2	15.6
FEV_1 in relation to predicted value, mean ± SD	90.4 ± 7.6%	90.4 ± 8.1%

RESULTS

Patients

In total, 111 children were screened for the study. Overall demographic and clinical characteristics are shown in Table I.

The randomization resulted in comparable treatment groups: overall, 84 exploratory tests for homogeneity of baseline characteristics were performed, and 7 (8.3%) yielded *P* values below .15.

Fig 1 shows that 45 patients could not be randomized and includes the reasons for the missed randomization. Eleven patients were excluded from the trial because they were weaned off ICS treatment, and their asthma remained well controlled.

House dust mite samples

The pre-treatment concentrations of the house dust mite samples were not significantly different between the 2 groups both at baseline ($P = .2270$) and during the second treatment year ($P = .9482$), showing that allergen exposure was comparable between the 2 groups throughout the study.

Asthma control

Because of the study design, no significant difference between the 2 groups regarding parameters of asthma control was detected during asthma control phases in the first and second treatment years (Table II).

Fluticasone reduction

A significant advantage in favor of the house dust mite allergoid was obtained. Children treated with SCIT were able to reduce the FP dose by significantly more steps ($P < .05$) compared

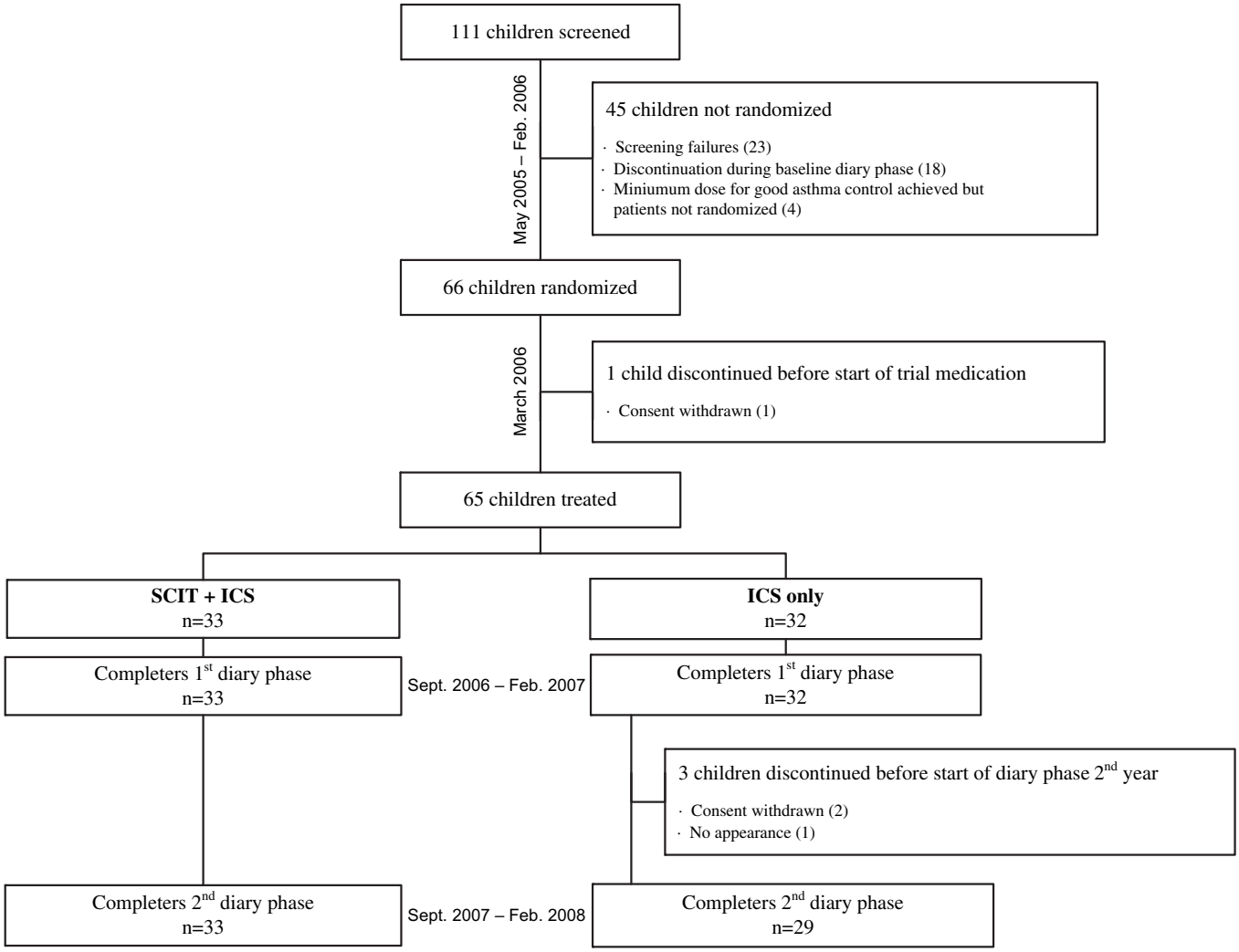

FIG 1. Consort flow.

with the control group on FP alone. After 2 years, 48.5% of children treated with SCIT improved in at least 2 FP dose steps, compared with 18.7% in the control group (Fig 2). A nonparametric analysis of differences in steps of change of ICS at 1 and 2 years is shown in Table III. After 2 treatment years, the mean daily dose of fluticasone in the SCIT group decreased from 330.3 μg in the baseline period to 151.5 μg after 2 years, whereas the FP group dose changed from 290.6 μg to 206.3 μg.

Asthma exacerbations

According to one of the most common asthma exacerbation definitions, "requirement of oral steroids"[20], we observed 2 episodes in 2 patients within the SIT group and 1 in 1 patient in the ICS only group. Episodes lasted a few days and did not interfere with immunotherapy schedules.

Functional parameters

PEF. After 2 years of treatment, morning PEF significantly increased more in the SCIT group (median, +50.7 L/min; SD, 49.19) compared with the control group (median, +23.55; SD, 44.45; $P < .05$ between the 2 groups; Table IV).

Methacholine provocation test. No significant differences were observed in bronchial hyperreactivity after 2 years, despite a larger ICS reduction in the SCIT group. In 15 cases, the test result was negative at baseline and at year 2. In 26 patients treated with SCIT + ICS, 7 subjects decreased, 1 unchanged, and 18 increased threshold PC_{20} FEV_1 doses. On ICS alone, the corresponding incidences were 7, 1, and 11, respectively.

Immunologic profile. 'A decrease in specific IgE levels was detected for the SCIT + ICS group, both at the end of the first year (–10.9% vs +15.3% for the control group) and at the end of the treatment (–22.9% vs +2% for the control group; $P = .0217$ vs control group after the second year). Specific IgG_1 and Specific IgG_4 levels significantly increased during treatment in the SCIT group compared with the control group ($P = .0001$ and $P < .0001$, respectively) (Table IV).

Safety. Adverse events in the treatment period occurred in 32 of 33 (97.0%) in the allergoid group and in 31 of 32 (96.9%) in the control care group. The presence of at least 1 possible relationship with the study procedure was suspected in 12 of 33 (36.4%) children in the SCIT group and none in the control group. Table V shows the assessment of adverse events according to Medical Dictionary for Regulatory Activities (MEDRA): the systemic

TABLE II. Asthma control (2-week control phases)

	SCIT + ICS (N = 33)				ICS only (N = 32)				
Control parameter	**Baseline**	**Year 1**	**Year 2**	**Outcome**	**Baseline**	**Year 1**	**Year 2**	**Outcome**	***P* value (*U* test)**
Nighttime awakenings	—	3 (9.1)	1 (3.0)	3 (9.1)	—	3 (9.4)	2 (6.3)	5 (15.6)	.4227*
No. of days with PEF <80%	2.2 ± 4.4	1.4 ± 3.6	1.8 ± 4.0	−0.4 ± 5.3	1.3 ± 3.1	2.3 ± 4.6	1.7 ± 4.3	0.5 ± 4.1	.5901
Score of cough/dry cough	4.6 ± 5.7	3.9 ± 6.2	5.3 ± 6.9	0.7 ± 6.5	4.2 ± 6.1	3.3 ± 5.1	3.7 ± 5.1	−0.5 ± 7.5	.4443
Score of chest tightness	0.7 ± 2.8	0.4 ± 1.5	0.2 ± 0.6	−0.5 ± 2.7	0.2 ± 0.8	0.6 ± 2.5	0.4 ± 1.7	0.2 ± 1.9	.6851
Score of wheeze	1.7 ± 4.3	0.5 ± 1.1	0.8 ± 2.9	−1.0 ± 3.3	0.3 ± 0.7	0.4 ± 0.9	0.2 ± 0.6	−0.0 ± 0.9	.2559
Score of dyspnea	0.8 ± 2.9	0.8 ± 2.6	0.5 ± 1.4	−0.3 ± 2.8	0.7 ± 1.9	0.4 ± 1.2	0.6 ± 1.3	−0.1 ± 2.0	.8961
Score of daytime asthma symptoms	7.8 ± 12.3	5.6 ± 8.4	6.8 ± 8.3	−1.1 ± 13.1	5.3 ± 6.2	4.7 ± 6.7	4.9 ± 6.6	−0.5 ± 8.9	.4106
No. of days with asthma symptom score >1	1.2 ± 3.4	1.3 ± 2.8	1.7 ± 3.2	0.4 ± 4.4	1.3 ± 2.2	0.9 ± 1.6	0.7 ± 1.8	−0.5 ± 3.0	.2247
No. of salbutamol administrations	1.5 ± 5.0	1.0 ± 1.9	0.8 ± 2.9	−0.7 ± 5.6	1.2 ± 3.8	2.3 ± 5.9	1.1 ± 2.5	−0.1 ± 4.5	.2298
Changes in other asthma medication	—	—	—	—	—	1 (3.1)	—	1 (3.1)	.3061*
Investigator contact in the last 2 wk	—	—	—	—	—	—	—	—	NA

N, Number of children (3 cases completed in year 2 by LOCF [Last Observation Carried Forward] in the FP group); *NA*, not applicable.
Results are presented as means ± SDs or n (%). Outcome values are means ± SDs of differences year 2 – baseline or n (%) for both years.
*χ^2 Test instead of Wilcoxon-Mann-Whitney *U* test.

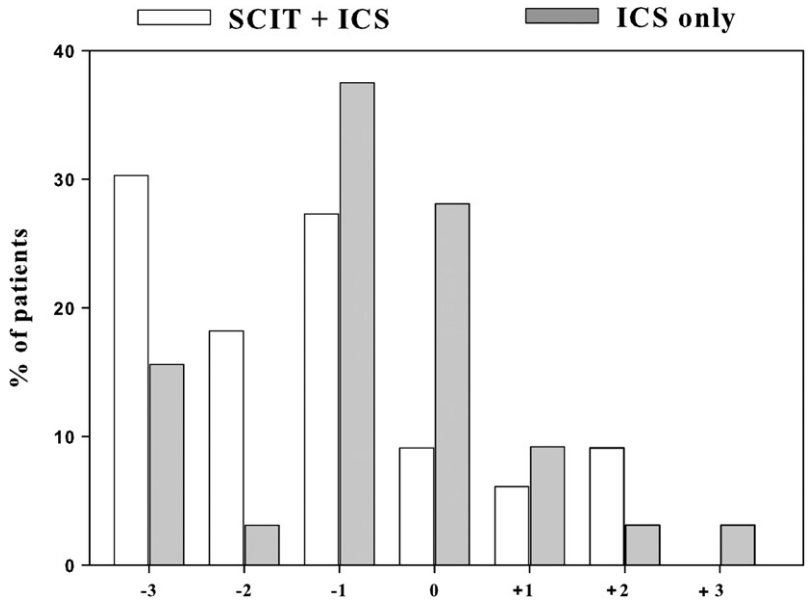

FIG 2. Percentage of patients with changes in fluticasone dose steps after 2 years of therapy by comparison with baseline ($P < .05$).

organ classes and the preferred terms with at least possible relationship to the study medication. In 3 children of the SIT group, we observed 4 general reactions like rhinitis, conjunctivitis, or urticaria. These events were mild to moderate, were treated with antihistamines, and did not interfere with the SIT schedule. No serious adverse events with a possible relationship occurred in either group. Serious adverse events requiring hospitalization, unrelated to the study medication, occurred in 3 children: 1 child in the SIT group underwent tonsillectomy, 1 child in the control group had 2 events (asthma exacerbation and recurrent abdominal pain), and the third child in the control group had appendicitis. These events were classified as not relevant (3 events) or unlikely (1 event). No relevant changes from baseline were observed in laboratory parameters and vital signs.

DISCUSSION

This study has shown that in children with persistent asthma, the addition of a SCIT with a high-dose hypoallergenic mite preparation allows significant reduction of the corticosteroid controller therapy while maintaining asthma control. The larger reduction of FP dose steps in the SCIT group, compared with the ICS monotherapy, was not only statistically significant ($P < .05$) but also clinically relevant and safe, considering the possible

TABLE III. Changes in FP dose steps after 1 and 2 years

Changes in dose steps		1 Year		2 Years	
		SCIT + ICS (N = 33)	ICS only (N = 32)	SCIT + ICS (N = 33)	ICS only (N = 32)
Improvement	−3	3 (9.1%)	2 (6.3%)	10 (30.3%)	5 (15.6%)
	−2	9 (27.3%)	—	6 (18.2%)	1 (3.1%)
	−1	11 (33.3%)	8 (25.0%)	9 (27.3%)	12 (37.5%)
No change	0	6 (18.2%)	11 (34.4%)	3 (9.1%)	9 (28.1%)
Deterioration	1	4 (12.1%)	8 (25.0%)	2 (6.1%)	3 (9.4%)
	2	—	2 (6.3%)	3 (9.1%)	1 (3.1%)
	3	—	1 (3.1%)	—	1 (3.1%)
Proportional odds model		Odds ratio	5.100	Odds ratio	2.506
		95% CI	1.966-13.233	95% CI	1.017-6.179
		P value	.0008	*P* value	.0459
Wilcoxon-Mann-Whitney		*P* value	.0006	*P* value	.0487

N, Number of children (3 cases completed in year 2 by LOCF [Last Observation Carried Forward] in the FP group).

TABLE IV. Changes from baseline in functional parameters

Functional parameter	SCIT + ICS					ICS only					Test (*P* value)
	Baseline	Year 1	Year 2	Outcome	No.	Baseline	Year 1	Year 2	Outcome	No.	
PEF (L/min)*	296 ± 101	326 ± 107	351 ± 116	55 ± 49	33	315 ± 91	325 ± 93	345 ± 95	30 ± 44	32	.0315
Specific IgE (kU/L)†	16.29	14.51		−10.9%	28	14.46	16.68		15.3%	27	.0186
	15.40		11.87	−22.9%	29	14.46		14.76	2.0%	27	.0397
Specific IgG_1 (μg/L)†	532.0	1250.4		135.1%	28	488.4	440.2		−9.9%	27	<.0001
	548.8		1016.3	85.2%	29	488.4		412.7	−15.5%	27	.0001
Specific IgG_4 (μg/L)†	105.9	835.2		689.0%	28	88.3	89.0		0.8%	27	<.0001
	104.7		1305.5	1146.9%	29	88.3		91.7	3.8%	27	<.0001

N, Number of children (3 cases completed in year 2 by LOCF in the FP group with respect to PEF, 1 case completed in year 2 by LOCF [Last Observation Carried Forward] in the FP group).

*Results are presented as means ± SDs; test = *U* test; outcome values are means ± SDs of differences year 2 – baseline.

†Results are presented as geometric means; test = *t* test of logarithmically transformed data; outcome values are proportional changes in geometric means.

side-effects of long-term therapy with inhaled steroids at pediatric ages.[4,21-24] Moreover, it has been shown that chronic use of ICS does not improve long-term outcomes in children with asthma.[25]

Unfortunately, the usual strategies proposed to achieve ICS reduction consider different pharmacologic agents, either in addition to or as a substitute for corticosteroids,[26-32] but the use of these agents is very often restricted in children—for example, long-acting β-agonists.[33,34] Thus, introducing SIT in children with mite allergic asthma may be critical for reducing potential adverse effects of steroid therapy during a period of rapid growth and development. According to GINA,[2] the daily average low dose reached by the SIT group in this study is not normally associated with any side effect in children.

Studies with SIT in asthma have usually focused on the reduction of symptoms and medication scores, and very few attempts have been made to verify the efficacy of SIT with respect to corticosteroid-sparing action while maintaining acknowledged criteria of asthma control.

In the current study, we decided to use the same ICS (FP) and the same device (accuhaler) for all patients, avoiding the need to calculate arbitrary equivalent doses for different ICS. The disadvantage of this was that for dose reduction, we had no choice but to use the commercially available (50, 100, 250, 500 μg FP) doses, which may not have been completely linear. However, the dose-effect relationship for ICS—particularly at high doses—is flat. Thus, we decided not to use ICS dose (in micrograms) as the primary outcome and used dose-step reduction instead. Moreover, it is important that the dose-step reduction be consistent with real life.

There are only a few controlled studies that have investigated the influence of SIT on ICS intake. One study has been done with this aim by using SCIT in adults, and it showed a statistically significant difference between the treated and the placebo group for year 2.[11] Because the criteria for asthma control used in that study are different from ours, it was impossible to compare datasets. In our trial, asthma control criteria were defined according to the classic GOAL study.[18]

Previous similar studies performed in children with SLIT reached conflicting conclusions, probably because of the different treatment duration.. In the study by Ozdemir et al,[13] 3 years long, children in the SLIT + ICS group demonstrated significantly lower mean daily doses and annual duration of ICS compared with controls on ICS alone. In contrast, in the study by Pham-Thi et al,[14] which lasted only 18 months, ICSs and inhaled β_2-agonist use was reduced in the SLIT + ICS and ICS alone groups without significant differences between groups. The authors concluded that "when mild to moderate asthmatic children are optimally controlled by pharmacologic treatment and house-dust mite avoidance, SLIT does not provide additional benefit."

This conclusion appears to be in agreement also with the well known study by Adkinson et al,[12] who failed to find a significant benefit of SCIT in children with asthma under optimal pharmacologic therapy. This article received many criticisms both for study design (use of mixtures of allergenic extracts, up to 7 different

TABLE V. Incidence of adverse events per system organ class with possible relationships to study medication or comparator in the treatment period

	SCIT + ICS	ICS only
No. of patients	33	32
No. of patients with adverse events with at least possible relationship to the study procedure	12 (36.4%)	—
General disorders and administration site conditions	11 (33.3%)	—
Injection site pain	4	
Injection site pruritus	5	
Injection site swelling	9	
Respiratory, thoracic, and mediastinal disorders	2 (6.1%)	—
Cough	1	
Rhinitis allergica	2	
Skin and subcutaneous tissue disorders	2 (6.1%)	—
Rash	1	
Urticaria	2	
Injection site pain	4	
Injection site pruritus	5	
Injection site swelling	9	

allergens, tailored to the sensitivities of each patient, patient selection) and conclusions.[35-40] Despite these criticisms, this study is often cited to deny the efficacy of SCIT in asthma; since then, however, many clinical investigations and systematic reviews have demonstrated such efficacy in adults and children.[10,41-47]

In this study, children with mild to moderate persistent asthma,[2] well controlled by fluticasone inhalation therapy, were treated with SCIT mite allergoid and were able to reduce the FP dose significantly by more steps compared with the control group on FP alone. Some studies have demonstrated the possibility of steroid reduction in asthma[48,49]; in some investigations, however, the clinical benefits were not sustained for long periods.[50-53]

Although ICS reduction was quite high in the SCIT group, no worsening of the clinical features of the disease from baseline to the second year could be seen. Among the inclusion criteria to define asthma control, morning PEF had to be >80% of predicted normal on each day. Nevertheless, a significant improvement in morning PEF was still observed in the SCIT group (mean, +55.06 L/min, $P < .05$ compared with the control group). A bronchial hyperreactivity test, using methacholine under asthma control conditions at baseline and after 2 years of treatment, showed no worsening, despite the ICS reduction in the SIT group (difference pre-post was not significant), demonstrating no increase in airways inflammation despite the ICS reduction.

The clinical efficacy of the allergoid is supported by strong immunologic changes. In keeping with recent updates of the SCIT mechanisms,[54,55] a significant decrease in mite-specific IgE was observed in the allergoid-treated group, whereas mite-specific IgG_1 and IgG_4 significantly increased ($P = .0001$ and $P < .0001$, respectively). Significant changes for $sIgG_4$ were already observed at the end of the first year of treatment, followed by further increase at the end of second year. Immunologic changes observed in children were similar to those reported in a previous article with the same mite preparation in adults.[15]

There are many strengths of this study, including the rigorous criteria for asthma control before reducing ICS, the proof of allergen exposure compared with sensitization only, the homogenous treatment with FP without the need for arbitrary dose-equivalence, and avoiding long-acting β-agonists, which are not highly recommended for treating children.

We consider the inability to attain the calculated size and the lack of a placebo control as limitations of this study. Placebo treatment in children is always a problem for parents as well as authorities and ethics committees. On the other hand, we clearly demonstrated clinical efficacy and safety of SCIT in reducing fluticasone controller therapy while maintaining asthma control in children over a 2-year period. One of the most important features of SCIT was the proven long-lasting efficacy, up to 12 years after the discontinuation of treatment.[56-58] The ongoing third year of this trial will allow us to determine whether asthma control could be maintained for longer periods after discontinuation of SCIT.

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Clinical implications: Children with house dust mite-induced allergic asthma benefit from SCIT with a hypoallergenic mite extract that allowed a strong steroid-sparing effect while maintaining guideline-defined asthma control.

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