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Efficacy of sublingual specific immunotherapy on allergic asthma and rhinitis in children's real life

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Abstract. – BACKGROUND: Sublingual-specific immunotherapy (SLIT) is considered as a valid treatment of respiratory allergies.

AIM: We performed a case-control study to evaluate the effect of SLIT in children with allergic asthma and rhinitis.

PATIENTS AND METHODS: The study plan included 140 patients (age 6-14 yr, 43% girls and 57% boys) presenting allergic rhinitis and/or asthma, 70 treated with SLIT actively for three years and 70 controls never treated with specific immunotherapy (only symptomatic drugs). Rhinitis Symptom Score (RSS), Asthma Symptom Score (ASS) and Medication Score (MS) were evaluated at beginning and during the 3 years of immunotherapy.

RESULTS: There was a significant improvement of RSS (mean ± SD) in the SLIT group: baseline 5.31 ± 2.01, third year 1.38 ± 1.06 ($p < 0.0001$ vs baseline). Control group: baseline 5.00 ± 1.08, third year 4.68 ± 1.152 (P ¼ NS). ASS (mean ± SD) in the SLIT group: baseline 4.09 ± 2.21, third year 1.23 ± 1.4 ($p < 0.0001$ vs baseline). Control group: baseline 4.04 ± 2.46, third year 3.62 ± 2.26 (p ¼ NS). MS (mean ± SD) in the SLIT group: baseline 3.30 ± 1.4, third year 0.88 ± 1.26 ($p < 0.0001$ vs baseline). Control group: baseline 3.19 ± 1.23, third year 3.39 ± 1.12 (p ¼ NS). There are no statistically significant differences among monosensitized/polysensitized patients and at different age ranges. None of the patients included reported severe systemic reactions or anaphylaxis.

CONCLUSIONS: During the treatment, the active group showed sustained reductions in mean asthma and rhinitis symptom scores when compared with controls to confirm the efficacy and safety of sublingual immunotherapy.

Key Words:

Sublingual immunotherapy, Allergic asthma, Allergic rhinitis, Symptom score, Medication score.

Abbreviations

SLIT = Sublingual immunotherapy; SCIT = Subcutaneous immunotherapy; RSS = Rhinitis Symptom Score; ASS = Asthma Symptom Score; MS = Medication Score.

Introduction

Allergic rhinitis is an increasingly prevalent condition affecting about a quarter of the population in the developed world limiting the social life, school learning and work productivity[1]. Rhinitis often coexists with asthma and is regarded as one of its major risk factors. Allergy caused by pollens or mites is a chronic condition that may require lifelong symptomatic treatment but the best way to prevent symptoms is to treat the allergic condition. Subjects with allergic asthma and rhinitis resistant to usual pharmacotherapy can be treated by allergen-specific immunotherapy, which has been recognized by the World Health Organization as the only causal treatment for allergic diseases. The most recent official document, the ARIA guideline, validated the clinical use of SLIT also in paediatric patients[2]. Traditionally, allergen-specific immunotherapy has been administered as subcutaneous injections. The sublingual approach has gained considerable interest as an alternative, and now several European countries use sublingual immunotherapy (SLIT) for the treatment of allergic respiratory diseases in preference to subcutaneous immunotherapy (SCIT) because of improved safety, easy administration and reduction of severe adverse reactions. Specific immunotherapy consists of a repeated administration of allergen products to allergic subjects to activate immunomodulatory mechanisms and provide sustained relief of symptoms during subsequent natural allergen exposure[3]. Polysensitization is a common feature in allergic patients and may cause some doubts in choosing the allergen extract for SLIT In this regard, the evaluation of SLIT efficacy in polysensitized pediatric patients still represents an unanswered question.

This article sustains the efficacy of sublingual immunotherapy in children during and at the end of 3 years of treatment, thereby confirming dis-

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ease modification, in terms of reduction in symptom scores of both allergic asthma and rhinitis.

Patients and Methods

Participants and recruitment

A total of 140 children with allergic rhinitis and/or asthma, 43.6% monosensitised and 56.4% polisensitised to grass pollen or house dust mite, were enrolled consecutively in a case-control study. Recruitment took place in November 2006 to June 2012. 70 cases were actively treated (6-14 yr; mean age 10.67 ± 3 yr, 61.4% male) while 70 controls (mean age: 10.71 ± 3 yr, 53% male), during selection matched to the active subjects for sex- age- and type of allergen, were never treated with specific immunotherapy. The main inclusion criteria were age > 6 yr, clinical history of allergic rhinitis and/or controlled asthma, a skin prick test (Lofarma S.p.A., Italy; wheal diameter 3 mm) and specific immunoglobulin E (IgE CAP class 3) positive to grass pollen or house dust mite and never received immunotherapy previously. The 41.4% of cases were treated with specific house dust mite sublingual immunotherapy while 58.6% with specific grass pollen sublingual immunotherapy.

Specific IT and pharmacological treatment

SLIT was prescribed only for the clinically relevant allergen, based on clinical history and skin positivity. The SLIT (Lofarma S.p.A., Milan, Italy) was prepared as monomeric allergoid tablets, administered as sublingual in the morning, after the patient had fasted. The patients were carefully instructed by the physician about the self-administration, and detailed written instructions were provided. The build-up phase, of about 4 days, involved the administration of the extract at progressively increasing concentrations (300, 600, 900, 1.000 UA). In the maintenance phase, from two to five 1.000 UA tablets were weekly given. The SLIT was administered continuously for approximately of 3 years.

The following medications were allowed: oral antihistamines (loratadine or cetirizine 10 mg, 1 tablet/day), intranasal corticosteroid (beclometasone dipropionate 1 puff b.i.d.), inhaled salbutamol (100 mcg three to four puff on demand), inhaled corticosteroid (budesonide 125 mcg, two puff/day), oral corticosteroid (betamethasone 1 mg on demand) and antileukotrienes (montelukast 5 mg, 1 tablet/day).

Study design

Parents of cases provided written informed consent and then children were treated for 3 years with specific SLIT with the related allergen extracts most responsible for disease.

The study plan included 4 visits, skin prick test, lung function test and dosage of total and specific IgE: at beginning (T0) and after one (T1), two (T2) and three (T3) years of treatment. During the trial patients recorded on diary cards the occurrence of symptoms of rhinitis and asthma and other complaints.

Study outcomes

The clinical evaluation provides for the use of numerical scores: 4-items of "Rhinitis Symptom Score" (RSS) (sneezing, rhinorrea, nasal itch, obstruction) and "Asthma Symptom Score" (ASS) (wheezing, dyspnea, cough and exercise-induced asthma) were evaluated with a ranging scale from 0 (=no symptoms) to 3 (=severe symptoms) (max score=12), according to ARIA and GINA guidelines, at T0, T1, T2 and T3. Concerning rhinitis and asthma, a "Medication Score" (MS) defined the severity of disease. It was calculated according to the following criteria: use of topic drug (antihistamine, nasal corticosteroid, inhaled corticosteroid, inhaled B2 stimulant) – 1 point; oral drug (corticosteroid and antilekotrienes) – 2 points (score max=8)[4].

Statistical analysis

Statistical analyses were performed using SPSS (SPSS, Chicago, IL, USA) software version 19. Descriptive statistics were performed expressing continuous data as means with SDs, or as medians with interquartile ranges while categorical data were expressed by frequency and percentage. Comparisons were evaluated using a *t*-test, a chi-square test, or a Mann-Whitney U-test. Correlations were calculated with Pearson's correlation test. The General Linear Model (GLM) for repeated measures was used in order to assess the effect of age and sensitizations as random factors on symptom scores and their variations over time. Statistical analyses were performed using SPSS (SPSS, Chicago, IL, USA) software version 19. A *p*-value less than 0.05 was considered statistically significant.

Assessment of safety, tolerability and compliance

Adverse effects will be assessed by patients and parents reporting effects in the diary, or

calling the research assistant with complaints. All adverse events reported during the study will be recorded. Compliance will be measured by self-report of SLIT administration in the diary and determined by weighing the returned study medication.

Results

One hundred and fourty patients completed the baseline assessment (1-year observation) and were consecutively enrolled to receive SLIT (70 patients) or drug therapy alone (70 patients). The two populations were comparable according to a matched case-control study design. Age, sex distribution, type of asthma and/or rhinitis and polysensitized patients were equally distributed in the two groups. The clinical and demographic characteristics of the patients are summarized in Table I. Each patient received SLIT only for one allergen as follows: 29 mites (41.4%) and 41 grasses (58.6%).

Drop-outs and safety

During the 3 years of the controlled study 13 patients dropped-out: 6 patients (8.6%) in the SLIT group and 7 patients (10%) in the control group. The overall difference between the two groups was not significant. Noteworthy, all control patients vs four of 6 SLIT patients dropped out because of intolerable worsening of symptoms requiring more aggressive treatment including systemic corticosteroids. The two dropouts because of economic reasons and lack of compliance. Thus, 64 patients of the SLIT group and 63 patients of the control group could be analysed at the end of the 3-year period of observation.

Types of asthma and rhinitis

At baseline the percentage of persistent rhinitis was 44.3% vs 34.3% in the active group and control-group respectively. The 41.4% of the case group compared to the 57.1% of the control group presented intermittent rhinitis. Asthma was defined intermittent in the 41.4% vs 44.3%, mild persistent in the 24.3% vs 22.9% of the case and control groups respectively and moderate persistent in the 2.9% of the case group compared to the 1.4% of the control group.

At the end of the observation period the percentage of persistent rhinitis was 20% vs 37.1% in the active group and control-group respectively. The 45.7% of the case group compared to the 57.1% of the control group presented intermittent rhinitis. Asthma was defined intermittent in the 37.1% vs 44.3%, mild persistent in the 4.3% vs 25.7% of the case and control groups respectively and moderate persistent in none of the case group compared to the 1.4% of the control group.

At T0 cases affected by rhinitis and asthma have an higher ASS (mean ± SD) than cases affected by asthma only (4.18± 2.13 vs 3.63± 2.72). At T3 they have similar ASS (1.31± 1.49 vs 1.13 ±1.39) ($p < 0.0001$ vs baseline) (Figure 1).

At T3 SLIT patients with intermittent and mild persistent asthma reach the same ASS. Controls with different kind of asthma don't have any symptoms' improvement ($p < 0.0001$ vs baseline) (Figure 2).

Clinical scores

RSS (mean ± SD) significantly improved only in the SLIT group, where they approximately halved since the first year (baseline 5.31 ± 2.01, first year 3.88 ± 1.86, second year 2.43 ± 1.45, third year 1.38 ± 1.06 ($p < 0.0001$ vs baseline). No change was seen in the control group (base-

Table I. Demographic and clinical data at baseline (randomization).

	SLIT	Control	Test	d.f.	p
Patients	70	70			
Mean age	10.46	10.67	U=2420.500		0.902
Sex ratio (M/F)	43/27	37/33	$\chi 2$= 1.050	1	0.306
Rhinitis alone	20 (28.6%)	22 (31.4%)	$\chi 2$=1.144	2	0.624
Rhinitis and asthma	40 (57.1%)	42 (60.0%)		2	0.624
Asthma alone	10 (14.3%)	6 (8.6%)		2	0.624
Monosensitized to HDM	16 (22.9%)	17 (24.3%)	$\chi 2$=0.287	2	0.866
Monosensitized to grasses	13 (18.6%)	15 (21.4%)		2	0.866
Polysensitized	41 (58.6%)	38 (54.3%)		2	0.866

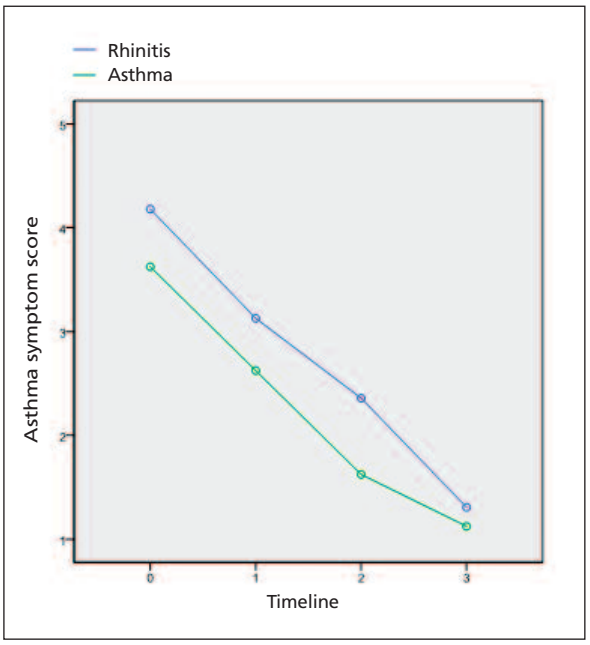

Figure 1. At T0 cases affected by rinhitis and asthma have an higher ASS (mean ± SD) than cases affected by asthma only (4.18 ± 2.13 vs 3.63 ± 2.72). At T3 they have similar ASS (1.31 ± 1.49 vs 1.13 ± 1.39) ($p < 0.0001$ vs baseline).

line 5.00 ± 1.08, first year 4.69 ± 1.09, second year 4.65 ± 1.01, third year 4.68 ± 1.152; p ¼ NS at all times). Also the inter-group comparisons showed a significant difference at the all time points. No difference in clinical efficacy among allergens could be detected.

There was a significant improvement of ASS (mean ± SD) in the SLIT group: baseline 4.09 ± 2.21, first year, 2.98 ± 1.88, second year 2.19 ± 1.71, third year 1.23 ± 1.4 ($p < 0.0001$ vs baseline). Control group: baseline 4.04 ± 2.46, first year 3.83 ± 2.45, second year 3.62 ± 2.28, third year 3.62 ± 2.26 (p ¼ NS). MS (mean ± SD) in the SLIT group was significantly reduced all over the years: baseline 3.30 ± 1.4, first year 2.81 ± 1.56, second year 1.98 ± 1.7, third year 0.88 ± 1.26 ($p < 0.0001$ vs baseline). Control group: baseline 3.19 ± 1.23, first year 3.44 ± 1.34, second year 3.49 ± 1.15, third year 3.39 ± 1.12 (p ¼ NS) (Figure 3).

Pulmonary Function Tests

At baseline the mean FEV_1 values of the SLIT and control groups were 91.92 ± 13.40 SD and 93.54 ± 5.44 SD respectively. The mean FEV_1 values after the 3-year immunotherapy period were 100.02 ± 12.6 SD in the SLIT group and 95.21 ± 4.59 SD in the control

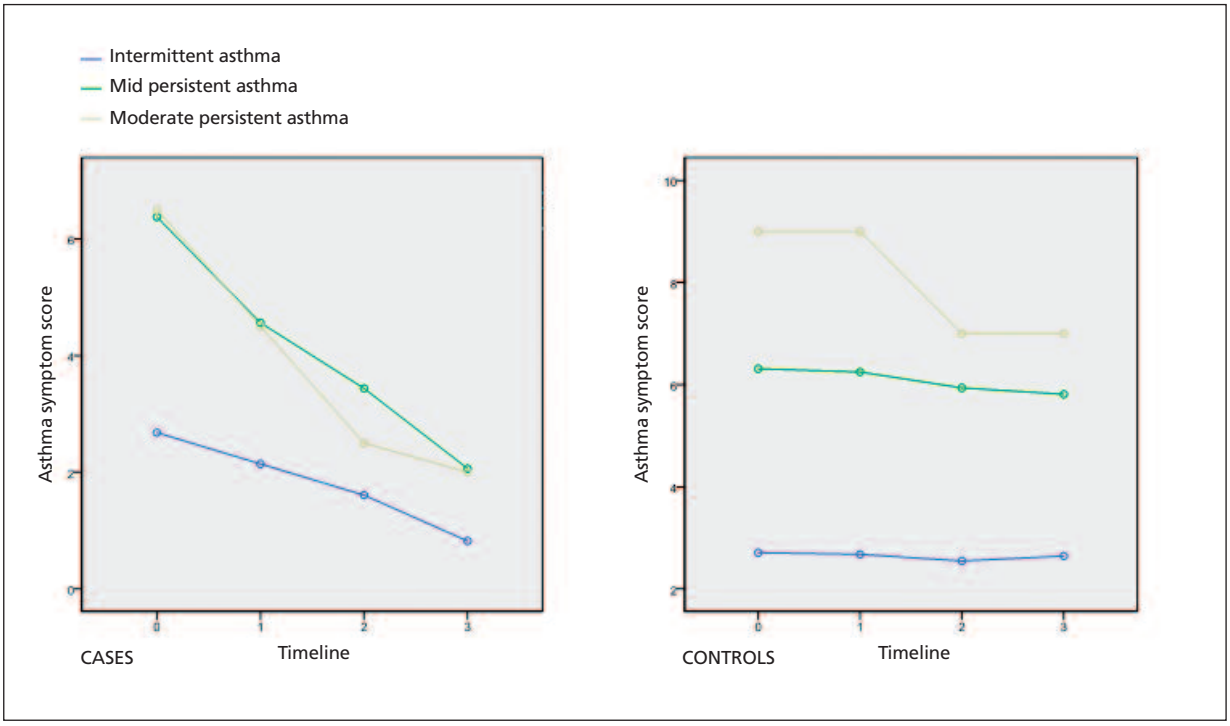

Figure 2. At T3 SLIT patients with intermittent and mild persistent asthma reach the same ASS. Controls with different kind of asthma don't have any symptoms'improvement ($p < 0.0001$ vs baseline).

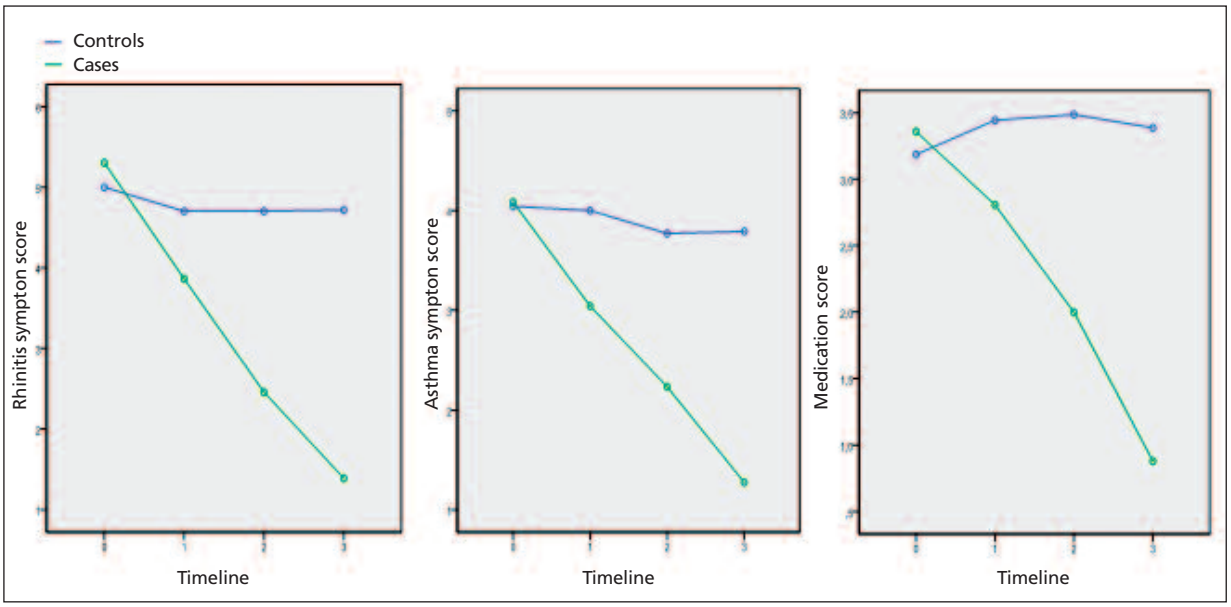

Figure 3. Trend of RSS, ASS and MS at T0, T1, T2 and T3.

group. When compared with the baseline year, FEV_1 values increased significantly with SLIT ($p < 0.0001$), but did not change significantly in the placebo group (P ¼ NS). In cases with asthma alone or asthma and rhinitis the improvement of respiratory parameters (FEV_1 and PEF) is statistically significant compared to controls ($p < 0.001$) (Figure 4).

Monosensitized and Polysensitized

Children with monosensitization were 29 (41.4%): more specifically 16 (55.2%) to dust mites and 13 (44.8%) to grass pollens. Overall children with polysensitization were 41 (58.6%) and among them the most relevant allergens were grass pollens, giving positive skin-prick test in 55 (34.09%) followed by dust mites positive in 47

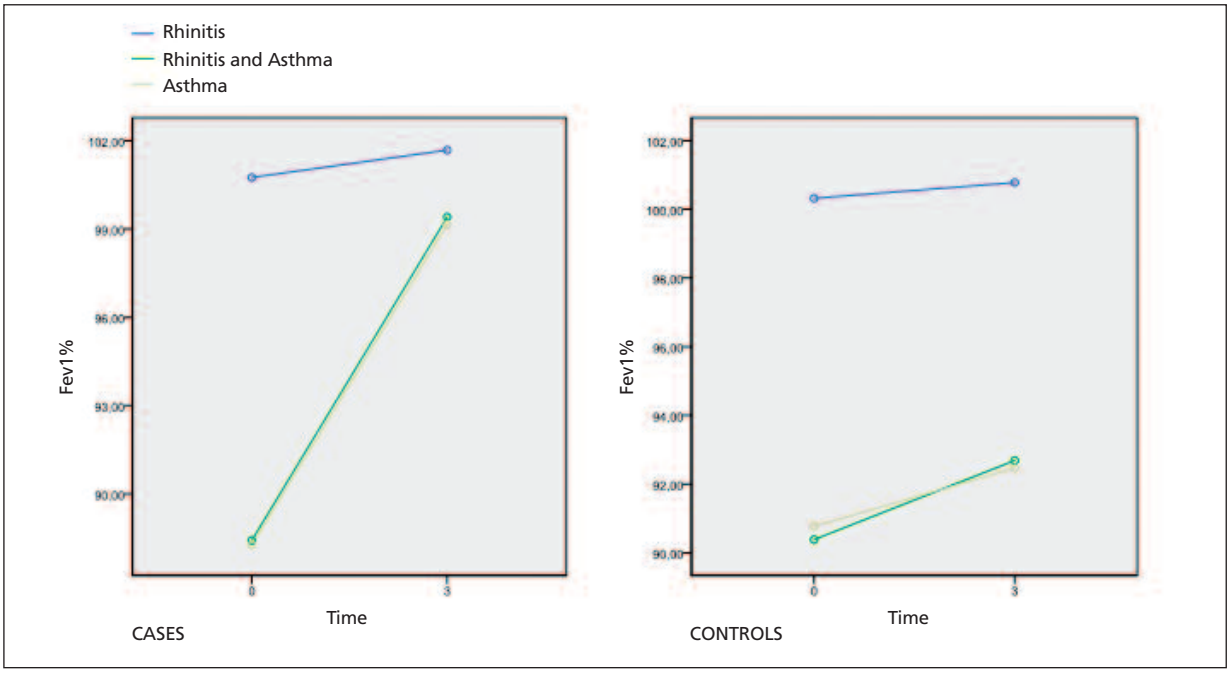

Figure 4. Changes in FEV_1 in cases and controls.

(26.7%) patients. Three (18.8%) monosentitized to dust mites were affected by rhinitis, 2 (12.5%) by asthma and 11 (68.8%) by asthma and rhinitis. On the other hand 3 (23.1%) monosensitized to grass were affected by rhinitis, 5 (38.5%) by asthma and 5 (38.5%) by asthma and rhinitis. Concerning polysensitized children: 14 (34.1%) had rhinitis, 3 (7.3%) asthma and 24 (58.5%) asthma and rhinitis. A progressive reduction in all the scores was found for all patients without any significant difference at the four time points among these groups of children. Furthermore the reduction of asthma, rhinitis and medication scores over time did not show any statistically significant difference among monosensitized to dust mite, monosensitized to grass pollens and polysensitized patients ($F = 0.72$, $p > 0.05$; $F = 1.59$, $p > 0.05$; $F = 3.63$, $p = 0.06$). Similar results were obtained when comparing the overall group of monosensitized with polysensitized patients ($F = 0.24$, $p > 0.05$; $F = 1.436$, $p > 0.05$; $F = 0.57$, $p > 0.05$).

Age range

According to the age we divided children into 3 groups: 20 patients (28.6%) aged between 6 and 8 years (Group 1); 31 patients (44.3%) aged between 9 and 11 years (Group 2); 19 patients (27.1%) age > 12 years old (Group 3). At the baseline Asthma was diagnosed in 3 children (15%) of Group 1, 4 (12.9%) of Group 2, 3 (15.8%) children of Group 3. Rhinitis in 4 children (20%) of the first group, 10 (32.3%) of second group, 6 (31.6%) of the third group; while both asthma and rhinitis were diagnosed in 13 (65%) patients of Group 1, in 17 (54.8%) of group 2, 10 (52.6%) of group 3. A significant clinical improvement was observed since the first year of treatment, assessed by a decrease of Symptom Score in all 3 age ranges.The reduction of asthma, rhinitis and medication scores over time did not show any statistically significant difference among different age ranges ($F = 2.160$ $p > 0.05$; $F = 0.904$, $p > 0.05$; $F = 1.702$, $p > 0.05$) although the older children start from an higher SS and MS.

Adverse effects

SLIT were well tolerated. During the 3 years of SLIT treatment no systemic adverse effect have been reported. The large majority of the adverse events is mild (Table II). During the first year of immunotherapy the 7.2% of SLIT patients had a worsening of symptoms, the 5.7% oral burning or itching, the 2.9% and the 1.4% urticaria and gastrointestinal effects (stomachache, nausea) respectively, usually self-resolving in a few days without any intervention. The 2.9% reported one episode of urticaria within 30 min after taking the dose. Those patients were instructed to temporarily halve the dose, then to gradually increase it again. This intervention allowed tolerating the maximum dosage. During the second year of ITS the 1.4% of the cases only reported oral itching, who had never complained before. During the third year of treatment in the 1.4% of the cases persisted the worsening of symptoms.

Compliance

Compliance was good. Patients took a mean value of 88% of SLIT treatment doses per day and 91% per administration.

Discussion

Our trial have shown that SLIT is an effective treatment in pediatric patients suffering from allergic respiratory diseases such as allergic rhinitis and asthma with significantly improved clinical out-

Table II. Adverse reactions to SLIT.

Adverse effects	T0		T1		T2	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Worsening of asthma	3	4.3	0	0	1	1.4
Worsening of rhinitis	2	2.9	0	0	0	0
Gastrointestinal effects	1	1.4	0	0	0	0
Oral burning/itching	4	5.7	1	1.4	0	0
Urticaria	2	2.9	0	0	0	0
Total	12	17.1	1	1.4	1	1.4

comes (less symptoms and less medication intake) in comparison with children treated with symptomatic drugs only. In this study, large and statistically significant differences in symptom and medication scores were demonstrated in patients receiving SLIT compared to placebo. Despite the main clinical effects of SLIT are in general obtained in the long-term in our study the clinical scores showed an improvement of about 50% vs baseline values, since the first year of treatment, despite the scores were significantly higher in the SLIT group at baseline. So SLIT might offer a generally safe and potentially disease-modifying treatment option for children and adolescents. According to the literature[5,6] we demonstrated the improvement in lung function after three year of immunotherapy: FEV_1 values showed an average increase of 8% with SLIT and 1.7% in the control group.

An improvement in clinical outcome was observed in both monosensitized and polysensitized patients, demonstrating that polysensitization might not rappresent a counter-indication for prescribing sublingual immunotherapy.

Although the clinical features of allergic rhinoconjunctivitis are slightly different in young children and adolescents or adults[7], the efficacy of SLIT treatment was not influenced by the patients age. Adolescents rated their symptoms as more severe than younger children. This could be explained by underestimation of symptoms by parents or a higher awareness of symptoms with age.

Clinical improvement, simplicity of dosage (one tablet daily), good tolerability and high compliance[7] were probably responsible for this success.

More patients reported oral pruritus and mouth oedema in the SLIT group, but these local events usually resolved spontaneously over the following days. Only 7.8% of patients in the SLIT group withdrew from the study because of AEs.

As this is a pilot study, these results are to be tested for further case studies.

Conclusions

Sublingual immunotherapy is effective for allergic rhinitis and is generally advantageous because of the convenient administration and the favourable safety profile.

Conflict of Interest

The Authors declare no conflict of interest with any financial organization regarding the material discussed in the manuscript. All Authors contributed equally to the manuscript. Authors do not have sources of funding.

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