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Brief report

Effectiveness of high dose sublingual immunotherapy to induce a stepdown of seasonal asthma: a pilot study

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Abstract

Background:
There is ample evidence to support the efficacy of sublingual immunotherapy (SLIT) on allergic rhinitis, while there is less solid data regarding asthma. We evaluated the effects of a high dose birch SLIT on birch-induced rhinitis and asthma in a controlled study.

Methods:
This double-blind, placebo-controlled, randomised, single centre trial on SLIT with birch pollen allergen extract (Stallergenes, Antony, France) included 24 patients presenting severe rhinitis and slight to moderate asthma, 14 actively and 10 placebo treated. SLIT was performed by a pre-coseasonal protocol, and was repeated for 2 years. The study plan included a selection visit, a visit at the start of the first and the second treatment cycle, a follow-up visit after 1–3 months from the start of each cycle, and a final visit at the end of each yearly cycle.

Results:
A significant decrease ($p < 0.05$) in rhinorrhoea and nasal obstruction occurred in actively treated patients. The median number of days with asthma at visit 3 was 10 (0–27) in the active (SLIT) group and 13 (0–29) in the placebo group. The median number of days with asthma at visit 6 was 2 (0–6) in the SLIT group and 7 (0–15) in the placebo group ($p < 0.05$ between groups). A stepdown of asthma occurred in 77% of actively treated vs. none of placebo treated patients ($p = 0.05$). No severe adverse events were observed.

Conclusions:
This pilot study suggests that SLIT with high dose birch extract may be able to step down seasonal pollen-induced asthma after prolonged treatment.

Introduction

Sublingual immunotherapy (SLIT) was introduced with the aim of improving the safety of allergen immunotherapy, which in its traditional, subcutaneous injection route faced the problem of systemic reactions[1]. A number of meta-analyses on SLIT are available, demonstrating sound evidence of efficacy regarding allergic rhinitis[2,3], while contrasting data were obtained in allergic asthma. In fact, a meta-analysis in children and adolescents detected a good efficacy[4], while in a global meta-analysis the difference between actively and placebo treated patients was less significant[5].

Generally, randomised controlled trials on SLIT in allergic asthma have as their primary objective symptom and medication scores, while the severity assessment of asthma suggested in the Global INitiative on Asthma (GINA)

international guidelines[6], based on the frequency of asthmatic symptoms, is not used as a parameter to measure the clinical efficacy of the treatment. In the present double-blind, placebo-controlled, randomised, pilot study, we evaluated the effects of SLIT on birch-induced rhinitis and asthma, using for the latter the standards by GINA and EPR-3[7].

Methods

The trial was conducted in the Allergy Unit of the San Martino Hospital in Genoa, Italy, and included 24 patients, 14 actively (7 males, 7 females, mean age 43.8 ± 9.4 years) and 10 (3 males, 7 females, mean age 39.9 ± 6.6 years) placebo treated. All patients were monosensitised to *Betulaceae* pollen and had moderate/severe persistent rhinitis according to ARIA criteria[8] and slight intermittent to moderate persistent asthma (level I to III) according to GINA criteria[6] during the previous birch pollen season, as evaluated by diary cards registered from February to April. SLIT was performed using an allergen extract of birch at 10 Index of Reactivity (IR)/ml and 300 IR/ml (Stallergenes, Antony, France), with a build-up phase over 11 days started with 10 IR and culminating at 300 IR. It was then used in the maintenance phase by daily administration for 4 months. Patients were divided into active or placebo treatment groups using a computer-generated randomisation list. Placebo vials matched the active treatment in colour and flavour in order to ensure the double-blindness but contained no pollen allergens or other active ingredients. Active or placebo doses were taken sublingually in the morning before breakfast. The SLIT treatment was repeated over 2 consecutive years. The study plan included 6 visits, at selection (visit 1), at the start of treatment (visit 2), during the pollen season (visit 3), at the start of second year of treatment (visit 4), during maintenance treatment (visit 5), and at the end of treatment during the pollen season (visit 6). For the full duration of the trial patients recorded on diary cards the occurrence of symptoms (graded by a scale from 0 = no symptoms to 3 = very bothering symptoms) of rhinitis (sneezing, rhinorrhoea, nasal obstruction) and asthma (dyspnoea, chest constriction, wheezing). Days in which a 0 score was registered for lung symptoms were considered days without asthma. The consumption of drugs, including antihistamines (loratadine, desloratadine, cetirizine), topical nasal (fluticasone propionate) and bronchial (fluticasone propionate) corticosteroids, and inhaled bronchodilators (formoterol), used as needed, was registered on the same diary cards. Concerning asthma, the drug use defined the treatment step according to GINA criteria, that is, using only the bronchodilator defined step 1, using low dose bronchial corticosteroid defined step 2, using low dose bronchial corticosteroid plus the bronchodilator defined step 3, and using high dose bronchial corticosteroid plus the bronchodilator defined step 4[6].

The primary objective of the study was to assess the immunological reactivity by dosing birch-specific IgE and IgG, ECP and tryptase at the nasal mucosa level. This is analysed in another article (manuscript in preparation). The secondary objectives were to assess the rhinitis and asthma symptoms and the safety of SLIT. The trial was approved by the San Martino Hospital ethical committee and was performed in accordance with the declaration of Helsinki and Good Clinical Practice. All patients gave a written informed consent before entering the study.

Statistical method

Due to the small number of patients included in the pilot study, nonparametric tests were used. This choice of a nonparametric method gave us the possibility of a statistical analysis with fewer assumptions, as our data had a ranking but not completely clear numerical interpretation (part of the symptoms not objective).

The Mann–Whitney *U* test was used to compare the scores registered at the different visits, the univariate analysis was used to compare the number of days with asthma. The results were expressed as median values with 5–95 percentiles. The chi squared test was used to compare the number of subjects showing a stepdown of asthma in the two groups. A p value <0.05 was set as significant.

Results

There were two dropouts during the study, one actively and one placebo treated. Table 1 shows the characteristics of patients completing the study. The mean cumulative dose administered in each pre-coseasonal course was 13.800 IR, corresponding to 6.900 mcg of the major birch allergen Bet v 1. The efficacy of SLIT on rhinitis was demonstrated by a significant decrease ($p < 0.05$) in rhinorrhoea and nasal obstruction in actively treated patients during the pollen season at the first year of treatment (Table 2). The median number of days with asthma at visit 3 was 10 (0–27) in the actively treated group and

Table 1. Characteristics of patients at inclusion.

	Active group (13 pts)	Placebo group (9 pts)
Gender	7 males	6 males
Mean age (years)	43.8	39.3
Asthma level 1	4	2
Asthma level 2	5	5
Asthma level 3	4	2
Mean FEV_1 value (% predicted)	100.9%	101.2%

Table 2. Symptom scores (median with 5–95 percentiles in actively and placebo treated patients).

Symptom score (median with 5–95 percentiles)	Active group		Placebo group	
Rhinorrhoea	Before SLIT 2 (1–3)	After 1 yr SLIT 1 (0–2)	Before SLIT 2 (1–3)	After 1 yr SLIT 1.5 (0–2)
Nasal obstruction	Before SLIT 2 (1–3)	After 1 yr SLIT 1.5 (0–2)	Before SLIT 2 (2–3)	After 1 yr SLIT 2 (0–3)

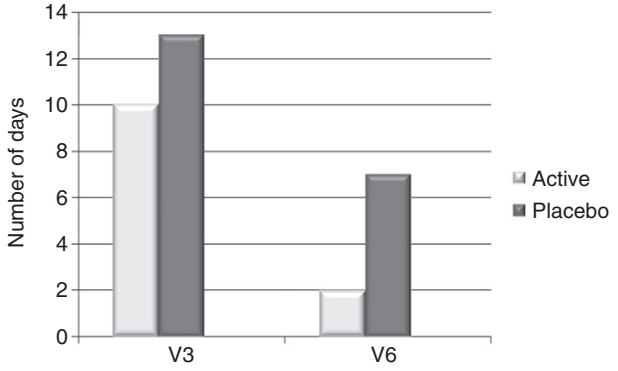

Figure 1. Number of days with asthma (median) at the first (visit 3) and the second (visit 6) year of treatment in 13 actively and 9 placebo treated patients.

13 (0–29) in the placebo group (nonsignificant difference), while the results were 2 (0–6) in the actively treated group and 7 (0–15) in the placebo group at visit 6 during the pollen season of the second year ($p<0.05$). This is shown in Figure 1. The asthma severity assessed by GINA criteria stepped down in 10 of 13 actively treated patients compared with 0 of 9 placebo treated patients ($p=0.05$). As regards safety and tolerability, at least one adverse event (AE) was reported by 75% of actively treated and 44.4% of placebo treated patients, most AEs being slight/moderate and consisting of local reaction in the mouth. There was no need to stop treatment in this case.

Discussion

The efficacy of subcutaneous immunotherapy (SCIT) in allergic asthma is established by a sound meta-analysis of 75 double-blind, placebo-controlled studies[9]. SLIT has demonstrated a substantial therapeutic equivalence to SCIT in allergic rhinitis, provided that high doses – i.e. corresponding to at least 50–100 times the doses administered with SCIT[8] – are used. This noninferiority to SCIT has also been demonstrated by a direct comparison between the two methods of immunotherapy in patients with birch allergic rhinitis[10,11]. However, the effectiveness of SLIT in asthma remains object to discussion, with good evidence of efficacy being obtained in paediatric populations[4] but not in adults[5]. The present study confirms once again that SLIT with high dose birch extract is able to significantly reduce the nasal symptoms to the specific allergen during the first year of treatment, including nasal obstruction, which is the most critical symptom and is related to the infiltration of inflammatory cells and their products in the nose. However, the object of the study was to investigate whether SLIT would be able to induce a stepdown of allergic asthma as assessed by GINA criteria. In the first season of treatment, the median number of days with asthma registered by actively treated patients was nonsignificantly lower compared with the placebo treated group. In the second year of treatment, the median number of days with asthma in the actively treated group was significantly lower than in placebo treated group (2 vs. 7 days) and reached statistical significance also regarding the number of patients showing a stepdown of the GINA level of asthma severity. These findings suggest that SLIT may be able to induce a stepdown of seasonal asthma. However, in order to arrive at this outcome requires more time compared with the clinical control of allergic rhinitis.

The present study has its main limitation in the low number of patients. The sample size calculation would have required 14 patients in each group, but due to the difficulty of finding monosensitised adult patients this number was not reached. Also, the possible non-normal distribution of data due to small sample size dictated the choice of using nonparametric tests, which gave us the possibility of a statistical analysis with fewer assumptions. This is why the trial must be considered a pilot study, and controlled trials on larger populations are required to confirm its findings and observations. Considering that most SLIT studies included in meta-analysis[2–5] are single year trials, future investigations on SLIT in asthma would need to be based on a longer (at least two-year) time period.

Transparency

Declaration of funding
The study was sponsored by Stallergénes, Antony, France.

Declaration of financial/other relationships
Cristoforo Incorvaia is a scientific consultant for Stallergénes. Franco Frati is Medical Director of Stallergenes Italy. The other authors have no financial/other relationships.

Some peer reviewers receive honoraria from CMRO for their review work. Peer reviewers 1 and 2 have disclosed that they have no relevant financial relationships. Peer reviewer 3 has disclosed that he/she has received research funding from Alk, Lofarma and Stallergenes, and that he/she has acted as an advisor to Alk, Schering-Plough, Lofarma, Stallergenes and Anallergo.

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