

COMPARISON OF EFFICACY, SAFETY AND IMMUNOLOGIC EFFECTS OF SUBCUTANEOUS AND SUBLINGUAL IMMUNOTHERAPY IN BIRCH POLLINOSIS: A RANDOMIZED STUDY

M. Mauroa (1), M. Russelloa (1), C. Incorvaia^b (2),
G.-B. Gazzolaa (1), G. Di Carac (3), F. Frati (3)

Sublingual immunotherapy (SLIT) is currently considered a valid option to subcutaneous immunotherapy (SCIT), but only a few studies made a direct comparison of their effectiveness. The aim of this study was to compare the clinical and immunological effects of SCIT and SLIT in pollinosis induced by *Betulaceae*.

Forty-seven adult patients were randomized to receive SCIT or SLIT, performed by *Betulaceae* (alder, birch, and hazel) extracts from Stallergenes (Antony, France) standardized in index of reactivity (IR) with the treatment schedules proposed by the producer. The clinical effects were established by symptom-medication scores recorded during the month of March. Side effects were reported directly by the physicians for SCIT and were registered in diary cards by the patients for SLIT. Immunologic evaluation was done by measuring specific IgE and IgG4 to Bet v 1.

Thirty-four patients (19 for SCIT and 15 for SLIT) completed the registration of symptoms and drug consumption during pollen period of *Betulaceae*. Mean cumulative doses of respectively 50.65 IR by SCIT and 4653.1 IR by SLIT were administered, with a SLIT/SCIT ratio of 92.

There was no significant difference in mean symptom-medication score between SCIT and SLIT. Systemic reactions occurred in 16% of SCIT treated but in none of SLIT treated. As to immunologic evaluation, Bet v 1 specific IgE did not rise after the pollen season in SCIT treated, while increased non significantly in SLIT treated. Bet v 1 specific IgG4 increased in both treatment, but only the increase with SCIT was significant ($p = 0.001$).

SLIT and SCIT with a ratio of about 100 are equally effective in controlling rhinoconjunctivitis caused by tree pollen allergy. SLIT is safer than SCIT, but does not show the same immunologic effects on serum specific IgE and IgG4 antibodies.

Pollinosis - Birch, Alder, Hazel - Subcutaneous immunotherapy - Sublingual immunotherapy.

INTRODUCTION

Specific immunotherapy with inhalant allergens is an effective treatment in respiratory allergy caused by sensitization to pollens, house dust mites, moulds, and animal epithelia (1). Besides the traditional, subcutaneous route of administration, also sublingual immunotherapy (SLIT) demonstrated a sound effectiveness by a meta-analysis study (2), with the advantage of a very good safety (3). Among the allergens tested by both subcutaneous immunotherapy (SCIT) and SLIT, tree pollens, namely birch, alder, and hazelnut pollen, were investigated in a number of studies, conducted by SCIT [4-8] and SLIT (9-11). However, only one trial compared the clinical effects of the two forms of treatment, which showed no significant differences in terms of efficacy and a better safety profile for SLIT (12).

The present study sought to evaluate the efficacy on allergic symptoms and drug consumption during the specific pollen season in patients with rhinitis caused by sensitization to tree pollens and randomized to receive SCIT or SLIT. Safety was assessed by registration of any adverse effect to the two treatments, and immunologic effects were studied by measuring the changes in pollen-specific IgE and IgG4 to the major birch allergen Bet v 1.

PATIENTS AND METHODS

■ **Patients:** From patients referring for seasonal rhinitis to the Allergy Unit of the Sant'Anna Hospital in Como (Italy), 47 subjects were included in the study. The inclusion criteria were: age higher than 18 years and lower than 60 years, presence of symptoms during the seasonal period of tree pollens (from February to April), symptom score indicating moderate to severe rhinitis in the previous season, duration from at least two consecutive years. The exclusion criteria were: sensitization to other allergens interfering with clinical symptoms (such as cypress pollen,

(1) Allergy Unit, Sant'Anna Hospital, Como (Italy).

(2) Allergy/Pulmonary rehabilitation, ICP Hospital, Milan (Italy).

(3) Department of Obstetric, Gynaecologic and Pediatric Sciences, University of Perugia (Italy).

house dust mites, and animal epithelia), previous immunotherapy treatment in any form, and occurrence of common contraindication to allergen immunotherapy (1).

The patients were randomized to receive SCIT or SLIT according to randomization tables, resulting in 24 SCIT and 23 SLIT treatments.

■ **Immunotherapy:** SCIT and SLIT were performed by tree pollen (alder, birch, and hazel) extracts from Stallerg enes (Antony, France) standardized in index of reactivity (IR). For SCIT a calcium phosphate extract (PhostalTM), and for SLIT a glycerinated extract (StaloralTM) was used. The treatment schedules were those proposed by the producer: for SCIT, the build-up phase was in 12 weeks with a top dose of 8 IR and the subsequent maintenance phase was done by administration of the same dose with a three week interval; for SLIT, the build-up phase was in 11 days with a top dose of 100 IR and the maintenance phase was done by administration of the same dose each day. The clinical effects of the treatment were established by symptom-medication scores recorded during the month of March in diary cards. The scoring method was as previously reported (13), grading for each nasal symptom (sneezing, runny nose, and nasal blockage) and for conjunctivitis from 0 to 3, and consisting drug consumption of 0 = no drug, 1 = nedocromil eye drops, 2 = antihistamine tablet, and 3 = fluticasone nasal spray.

Side effects were reported directly by the physicians for SCIT and were registered in diary cards by the patients for SLIT.

■ **Immunologic evaluation:** Blood samples were obtained in all patients by venipuncture at baseline and at the end of the pollen season. Specific IgE and IgG4 to Bet v 1 were measured by the CAP/RAST method (Pharmacia, Uppsala, Sweden) using the immunoenzymatic method.

■ **Statistical analysis:** Non parametric tests, particularly the Wilcoxon test for inter-group analysis and the Mann-Whitney U test for intra-group analysis, were used, considering significant a p value lower than 0.05.

RESULTS

Of the 47 patients randomized for SCIT or SLIT, only 40 started immunotherapy (20 for each treatment), and 34 (19 for SCIT and 15 for SLIT) completed the registration of symptoms and drug consumption during the month of March. Their characteristics are shown in table 1.

Mean cumulative doses of respectively 50.65 IR by SCIT and 4653.1 IR by SLIT were administered, with a SLIT/SCIT ratio of 92.

The mean symptom-medication score during March was 4.77 ± 1.41 for SCIT and 3.63 ± 1.08 for SLIT. Figure 1 shows the mean daily symptom-medication score from 1 to 31 March with the two treatment and the daily counts of birch pollen. There was no significant difference between SCIT and SLIT.

All adverse reactions were during the build-up phase, consisting for SCIT of three large local reactions and

Treatment	No of patients	Male/female	Mean age in years (range)	Pts completing the registration of symptom/medication scores
SCIT	20	9/11	39.8 (20 to 59)	19
SLIT	20	12/8	39.1 (18 to 57)	15

Table 1: Characteristics of patients.

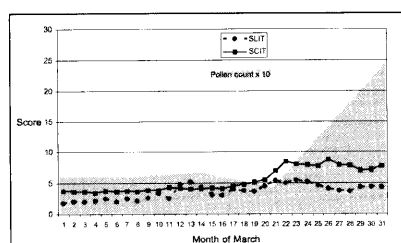


Figure 1: Symptom-medication scores and pollen counts during the month of March in SLIT and SCIT treated patients.

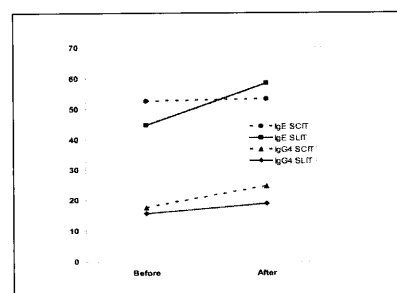


Figure 2: Changes in Bet v 1 specific IgE and IgG4 antibodies in SLIT and SCIT treated patients.

three systemic reactions (one generalized itching, one rhinitis, and one slight laryngeal oedema), and for SLIT of four local reactions with oral itching. Reactions to SCIT were treated by oral antihistamines and, for laryngeal oedema, by intravenous corticosteroids. Dose adjustments were done, resuming the treatment from the last tolerated dose, and SCIT was continued up to the maintenance dose in all patients. Reactions to SLIT were short-lasting and self-remitting, requiring no drug treatment.

Regarding the immunologic evaluation, Bet v 1 specific IgE did not rise after the pollen season in SCIT treated (from 52.8 ± 23.1 to 53.1 ± 23.4), while increased from 44.6 ± 21.7 to 58.4 ± 26.5 kU/L in SLIT treated. Bet v 1 specific IgG4 increased in both treatment, from 17.6 ± 5.8 to 24.5 ± 6.1 kU/L in SCIT treated and from 15.6 ± 7.1 to 18.8 ± 6.8 kU/L in SLIT treated, respectively, as depicted in figure 2. Only the increase with SCIT was significant ($p = 0.001$).

DISCUSSION

The efficacy of SLIT in seasonal allergic rhinitis caused by grass, ragweed, and tree pollens is clearly demonstrated by meta-analysis studies both in adults (2) and children (14), but the range of effective dosage remained until recently a debated issue. According to expert's opinion, to expect a clinical effectiveness SLIT should be administered in cumulative dosage 50-100 times higher than SCIT considering allergen extracts from the same producer (15). This statement received a stronger evidence by a number of recent studies clearly demonstrating for SLIT a dose-dependence similar to that well known for SCIT (16).

Moreover, in a double-blind, double-dummy, placebo-controlled study directly comparing the efficacy of SCIT and SLIT with a birch pollen extract no significant difference was observed using for SLIT a cumulative dose 175 times higher than SCIT (12). On the other hand, the safety of SCIT was clearly lower, with systemic reactions in 29% of patients - two reactions requiring adrenaline - comparing to no systemic reactions in SLIT.

The allergen extracts we used were from the same producer as in Kinchi's study but contained a mixture of birch, alder and hazel and not only birch pollen, because our patients were sensitised and symptomatic also to the other two *Betulaceae*. The SLIT/SCIT ratio was about 100 and the efficacy was comparable, patients reporting scores not significantly different - indicating slight/moderate symptoms - for both treatments. This offers a further confirmation to the range of 50-100 times the

dosage of SCIT needed to SLIT to provide a comparable efficacy (15).

The study was designed also to evaluate the immunologic response, in particular the effects on IgE and IgG4 antibodies specific for Bet v 1, the major allergen of birch. Some studies assessed allergen specific IgE and IgG4 response to SLIT, reporting significant changes to grass pollen (17) and ragweed (18) but negligible changes to olive pollen (19), grass pollen (20, 21) and house dust mites (22, 23). In the latest study, conducted on children with mite-induced asthma, SLIT induced a decrease of specific IgE but no change on IgG4 [23]. In our patients, only SCIT blunted the seasonal rise of pollen-specific IgE, a well known immunologic effect of allergen immunotherapy (1), while specific IgG4 increased with both treatments but the change was not significant with SLIT.

However, the recent advances on the mechanism of action of SLIT suggest that the particular role of dendritic cells of the oral mucosa in capturing and presenting the allergen molecules to T cells, and particularly to Treg cells, may induce a different kind of tolerance compared to SCIT (24). In fact, in a study assessing in patients with grass pollen rhinitis treated with SLIT the immunologic response in the target organ - by using as a material the nasal secretions - the seasonal rise of specific IgE was actually blunted by high dose treatment (25). Therefore, it is likely that evaluating the antibody changes in serum may be an inappropriate model in analyzing the immunologic effectiveness of SLIT. On the other hand, the increase of specific IgG4 in serum seems mostly influenced by gastrointestinal absorption of the allergen extract, but we know from studies on oral immunotherapy that the oral route bypassing the sublingual mucosa was poorly effective - and is no more suggested as a feasible form of immunotherapy (15, 26) - thus the IgG4 induced by such stimulus should represent an epiphenomenon devoid of immunologic significance. For SLIT, a model assessing the antibody response at local level should provide more reliable data. In this view, studies comparing the immunologic effects of SLIT with allergen swallowing or spitting, the latter indicating the pure effect of the interaction with dendritic cells, should further elucidate the mechanism of action of this kind of immunotherapy.

In conclusion, the results of this randomized study confirm that SLIT with adequate dosage is as effective as SCIT but better tolerated in patients with seasonal rhinitis caused by sensitisation to *Betulaceae* pollen. The data on immunologic response suggest that different models of assessment should be used for the two treatments.

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