

Specific immunotherapy: beyond the clinical scores

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Objective: The efficacy of specific immunotherapy always has been evaluated by clinical scores (symptoms or medication intake). Nonetheless, specific immunotherapy possesses some special or “additional” effects, including the carryover effect and the preventive actions, which are unique. Those effects are the consequence of the complex mechanism of action, which induces profound and persistent modifications in the immune response to allergens. The literature is reviewed to evaluate the available experimental data on this.

Data Sources: The main databases (EmBase, Medline, Scopus) were searched.

Study Selection: Clinical trials of immunotherapy, either randomized or not, including placebo-controlled trials, were selected.

Results: Currently, the carryover effect (persistence of the benefit after stopping the treatment) is well ascertained for injection immunotherapy, whereas fewer data are available for the sublingual route. On the contrary, the demonstration of the prevention of asthma onset relies on 2 randomized studies for sublingual immunotherapy, and 1 single study for subcutaneous immunotherapy.

Conclusion: Although additional confirmatory data are needed, possibly obtained with a rigorous methodology, the long-lasting and preventive effects of specific immunotherapy always should be taken into account when the efficacy is evaluated. The additional effects also may have relevant socioeconomic implications.

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INTRODUCTION

Since the middle 1960s, when the first randomized controlled trials of specific immunotherapy (SIT) were published, the efficacy of this treatment has been invariably assessed by symptom scores or medication intake scores, alone or in combination. This is because the evaluation of the efficacy is essentially clinical, and no reliable surrogate marker is available to replace the subjective assessment of symptoms, especially in allergic rhinitis. Also, the available systematic reviews and guidelines^{1–4} rely on the clinical assessment. Nonetheless, SIT is not a receptor antagonist or a mediator inhibitor, but rather an immune-modulator treatment, with profound effects on the immune response to allergens. The mechanism of action of SIT is complex and involves the Th2/Th1 balance, the emergence of allergen-specific immunoglobulin (Ig) G4 antibodies (which interfere with the immunoglobulin E-facilitated antigen presentation), and the activation of subsets of T regulatory cells.^{5–7} Consequently, SIT produces disease-modifying effects, which go beyond the symptoms’ reduction during the natural allergen exposure. The disease-modifying effect, not shared by traditional drugs, includes the persistence of the clinical benefit after discontinuation of SIT, the prevention of the onset of new sensi-

tizations, and the effect on the progression of allergic disease. The capacity of SIT for altering the natural course of respiratory allergy was first reported more than 40 years ago by Johnstone and Dutton,⁸ who observed in a 14-year follow-up that children receiving SIT developed asthma to a lesser extent compared with children treated with medications only. The study by Johnstone and Dutton suffered from important methodological limitations (open design, not randomized, poorly defined outcomes) and, therefore, the disease-modifying effects were not more considered until the middle 1980s, when the prevention of new sensitizations and the carryover effect were evaluated more in detail.

Nowadays we have available several trials, with both sublingual (SLIT) and subcutaneous (SCIT) immunotherapy confirming the “additional” effects of this treatment.^{3,9} Despite the need for more studies conducted with a rigorous experimental design, the results of the trials so far available suggest that SIT has an enormous potential as a curative and preventive therapy and that the disease-modifying effect also has economic implications.

Effects on Natural History

Respiratory allergy (allergic rhinitis/asthma) is not a static entity but changes its clinical presentation over time, according to a quite reproducible “natural history.” In fact, allergic rhinitis is well known to be an independent risk factor for developing asthma, and allergic rhinitis usually precedes asthma. Approximately 16% to 40% of subjects with rhinitis develop asthma later in life,^{10–13} and the relative risk for rhinitis patients to develop asthma varies from 2.2 to 5.4.¹⁴ In addition, prospective studies have

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suggested that allergic rhinitis may precede the development of bronchial hyperresponsiveness.^{15,16}

After the aforementioned pioneering study by Johnstone and Dutton,⁸ the preventive effect of SCIT was specifically addressed in 2002 in the Preventative Allergy Treatment study.¹⁷ This was a randomized multicenter, controlled but not double-blind, study of SCIT versus pharmacotherapy alone, conducted in 205 children (aged 6–15 years), 163 of whom had only rhinitis attributable to grass or birch. Grass pollen SCIT reduced the risk of the onset of asthma in the SCIT group, with an overall odds ratio of 2.52 at 3 years. More in detail, of the 151 children without asthma at enrollment, 19 of 79 in the SCIT group and 32 of 72 in the control group had developed asthma after 3 years (Fig 1). This preventive effect was observed to persist in the same patients up to 7 years after the termination of SCIT.¹⁸ A significant decrease in the severity of nonspecific bronchial responsiveness also was documented in the children receiving SLIT. This study, although fascinating, suffers from important limitations, such as the open design, the presence of children with asthma at enrollment, and the variability of the results among the 6 participating centers. In fact, 2 of 6 centers failed to demonstrate any preventive effect.

No other clinical evidence has been seen of the preventive effects of SCIT, whereas 2 trials are available for SLIT. The first study was published in 2004¹⁹ and involved 113 children aged 5 to 14 years with seasonal rhinitis attributable to grass pollen. They received either SLIT or pharmacotherapy alone. After 3 years, 8 of 45 of the SLIT subjects and 18 of 44 controls had developed asthma, with a significant difference and a relative risk of 3.8 for untreated patients (Fig 1). Another randomized open controlled trial²⁰ involved 216 children (aged 5–17 years) suffering from allergic rhinitis with or without mild intermittent asthma who were allocated to SLIT or drugs only. One hundred ninety-six patients could be evaluated after 3 years (Fig 1). Persistent asthma appeared in 1.5% of the patients receiving SLIT versus 30% of the controls (odds ratio 0.04). In this study, 4 patients needed to

be treated with SLIT to prevent the onset of persistent asthma in 1. Also, the 2 SLIT studies have the limitation of an open design, although in the second study,²⁰ a sensitivity analysis (ie, evaluation of the “worst case”) reinforced the conclusions. Of note, none of the available medications, including antihistamines and inhaled steroids, display a preventive effect.^{21–23}

Apart from the Preventative Allergy Treatment study, Pajno et al,²⁴ in a double-blind placebo-controlled trial involving 30 children with *Parietaria*-induced asthma, showed that SLIT prevented the appearance of bronchial hyperresponsiveness to methacholine during the *Parietaria* pollen season. In the actively treated children, in fact, the degree of bronchial hyperreactivity remained similar to that measured out of the pollen season.

Long-Lasting Effect

All the drugs currently available for the treatment of respiratory allergy terminate their effect within few days after discontinuation, and this is expected with mediator or receptor antagonists. Conversely, SIT produces changes in the immune response to allergens so profound that its clinical effect may persist long after discontinuation. A summary of the long-lasting effects of SIT in clinical trials is reported in Table 1. This fact was repeatedly described, starting in the 1980s with the follow-up of some small studies,^{25,26} then in new double-blind trials with cats or dogs²⁷ and mites.²⁸ In those studies, the effects were reported to persist for 3 to 5 years after discontinuation. Subsequently, an open controlled study compared the clinical effect of SCIT and inhaled steroids after the treatment was discontinued.²⁹ Clearly SCIT had a delayed onset of clinical effects; however, after termination this effect was maintained for weeks, at variance with inhaled steroids, the effects of which vanished immediately. The most rigorous trial on the long-lasting effect of SCIT is probably that described by Durham et al.³⁰ In this double-blind randomized study, 1 group of grass-allergic patients received placebo for 1 year and SCIT in the subsequent 3 years. Another group received SCIT for 4 years. Afterwards, 1 group stopped the treatment, and the other continued for 3 further years. An open control group was also followed. At the 3-year follow-up, no difference was seen between the 2 SCIT groups; both maintained a significant improvement in symptom and medication scores versus baseline, and both did better than the control group. The long-lasting effect of SCIT was confirmed in another pediatric trial, with grass.³¹ Of note, in this trial, the beneficial effect of SCIT persisted for 10 years after the treatment had been stopped.³² Finally, a recent open controlled trial in 60 *Parietaria*-allergic patients confirmed a 5-year long-lasting effect also with a monophosphoril lipid-adjuvanted immunotherapy.³³

Fewer studies investigated the long-term effect of SLIT. Di Rienzo et al,³⁴ in a prospective controlled nonrandomized open study, followed 60 mite-allergic children for 10 years. They were subdivided into 2 matched groups, with 35 subjects undergoing 4 to 5 years of SLIT and 25 receiving only

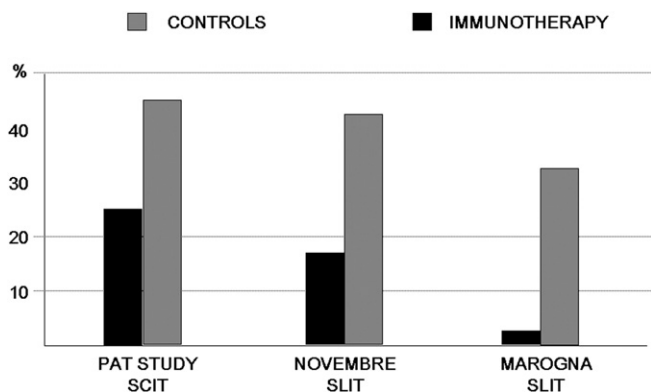


Figure 1. Percentage of children in the immunotherapy and control groups who developed asthma after 3 years, in the 3 available trials. In the study by Marogna et al,³⁷ the development of persistent asthma was assessed.

Table 1. Summary of the Studies Assessing the Long-Lasting Effect of SIT

Author, yr (ref)	Allergen	Patients enrolled	Sit	Design of original trial	Duration Sit	Patients reevaluated	Outcomes at follow-up	Main results at follow-up
Mosbech, 1988 ⁽²⁶⁾	Grass	39	SCIT	R-DB-C with 2 active arms. Open FU 6 yrs	2.5 yrs	32	Symptoms and drug intake in pollen season	The clinical benefit of SCIT was maintained at 6 yrs in both groups
Grammer, 1984 ⁽²⁵⁾	Ragweed	63	SCIT	R-DB-PC, 2 arms + untreated group Open FU 2 yrs	4 mo	63	Symptoms and drug intake in pollen season	Patients receiving placebo in the 2 nd season maintained a clinical benefit similar to those receiving SCIT. Both groups better than untreated
Hedlin, 1995 ⁽²⁷⁾	Cat/dog	32	SCIT	Open, prospective Open FU 5 yrs	3 yrs	30	Specific and nonspecific bronchial challenge; subjective evaluation	Persisting clinical benefit reported 5 yrs after stopping SCIT. Bronchial responsiveness returned almost to baseline values.
Des Roches, 1996 ⁽²⁸⁾	Mite	40	SCIT	Prospective controlled Open FU 3 yrs	1–8 yrs	40	Appearance of asthma symptoms	Most subjects remained asymptomatic after 3 yrs. The long-lasting effect is related to the duration of SCIT
Durham 1999 ⁽³⁰⁾	Grass	40	SCIT	R-DB-C 3 or 4 yrs SCIT. One group continued for 3 years more	3–4 yrs	32	Symptoms and medication scores	After 3 years, symptoms and medication scores remained low in the group who discontinued and in the group who continued to receive maintenance SCIT
Di Rienzo 2006 ⁽³⁴⁾	Mite	60	SLIT	Open, non R, control led. Open FU 5 yrs	5 yrs	60	Clinical evaluation of asthma symptoms	The effect of SLIT on asthma symptoms persisted up to 5 yrs after stopping.
Eng 2002 ⁽³¹⁾	Grass	28	SCIT	R-DB-PC Open FU 6 yrs	3 yrs	23	Symptom+drug score, individual symptoms, drug intake.	6 Years after discontinuation, the total score remained lower in the formerly SCIT group. No difference in drug intake between groups.
Tahamiler 2007 ⁽³⁵⁾	Mite	137	SLIT	R-DB-C 2 or 3 years SLIT. Open FU 3 yrs	2-3 yrs	137	Symptom + drug score, individual symptoms, nasal resistance	3 Years after discontinuation both groups maintained improvement in all parameters versus baseline, with better improvement in the 3-year SLIT group.
Durham 2010 ⁽³⁶⁾	Grass	308	SLIT	R-DB-PC. Open FU 1 yr	3 yrs	257	Rhinoconjunctivitis score; drug intake	1 Year after discontinuation, the difference remained in favour of the former SLIT group

Table 1. (Continued) Summary of the Studies Assessing the Long-Lasting Effect of SIT

Author, yr (ref)	Allergen	Patients enrolled	Sit	Design of original trial	Duration Sit	Patients reevaluated	Outcomes at follow-up	Main results at follow-up
Marogna 2010 ⁽³⁷⁾	Mite	78	SLIT	Open, controlled, non R. Open FU up to 15 yrs	3 yrs 4 yrs 5 yrs	59	Symptoms, drug intake, nasal eosinophils, bronchial challenge	The 3 groups receiving SLIT improved significantly vs controls. Clinical benefit maintained for 7 years in groups treated for 4 or 5 years and for 5 years in group treated for 3 years
Musarra 2010 ⁽³³⁾	parietaria	57	SCIT	Open, controlled, nonrandomized. Open FU 5 yrs	3 yrs	57	Visual analog scale for symptoms. Severity of asthma/rhinitis	The clinical improvement persisted for 5 years after stopping SIT in the active group, according to VAS and severity of asthma/rhinitis

Abbreviations: R, randomised; DB, double blind; PC, placebo controlled; FU, follow-up.

drugs. They were reevaluated at the end of SLIT (5 years) and 5 years after discontinuation. In the SLIT group, a significant difference was seen compared with baseline for the presence of asthma, and this difference persisted 5 years after the SLIT discontinuation. Tahamiler et al,³⁵ in a 6-year randomized prospective trial, evaluated 2 groups of patients up to 3 years after SLIT discontinuation. One group of 67 patients received SLIT for 2 years and placebo in the subsequent year. The other group (70 patients) received SLIT for 3 years. Symptoms and specific nasal reactivity improved in both groups during treatment, and the improvement was maintained 3 years after stopping SLIT. More recently, the existence of a carry-over effect of SLIT was confirmed in the 1-year follow-up of a large and methodologically rigorous trial conducted with grass allergen tablets.³⁶ A 15-year follow-up of mite-allergic patients treated with SLIT for 3, 4, or 5 years has suggested that a 4-year course represents the best combination of clinical efficacy and long-term effect.³⁷ Patients who received SLIT for 4 or 5 years had significantly better monthly symptom scores up to 7 years after discontinuation, as compared with the groups that were treated with SLIT for 3 years or received medications only (Fig 2).

Looking at the literature, clearly the long-lasting effect of SIT, both SLIT and SCIT, was demonstrated in studies of low methodological quality. In particular, all studies report the results of an open follow-up of small samples after stopping the treatment, with variable outcomes considered, and most studies suffer from a high rate of dropout. In this regard, we should take into account the practical and ethical problems in keeping trials double blind for many years. Despite all those methodological problems, the long-lasting persistence of a clinical benefit from SIT appears to be reproducible and consistent across the trials.

Effects on Allergic Sensitizations

Another well-recognized aspect of the natural history of respiratory allergy in both adults and children is the tendency

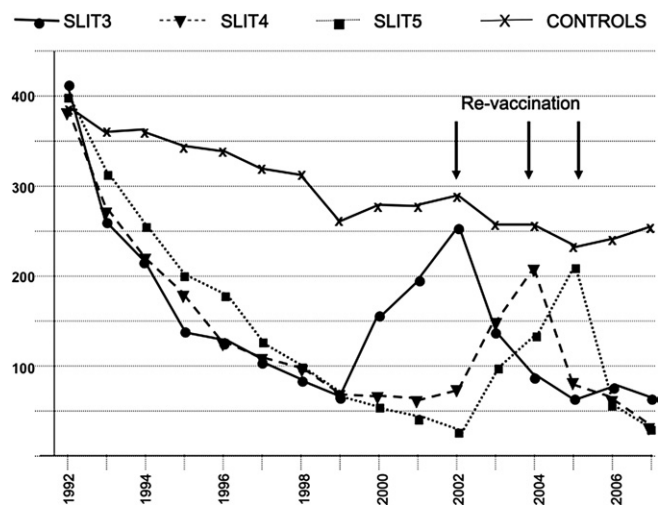


Figure 2. Symptom + medication scores year by year in 4 groups receiving mite SLIT for 3, 4, or 5 years or medications only. The arrows indicate the start of the new course of SLIT when the clinical benefit had vanished (from Marogna et al³⁷).

to develop new skin sensitization over time. This fact may have relevant clinical implications, because the severity of the disease partially correlated with the number and size of positive skin tests.^{38,39}

The first description of a preventive effect of SCIT on the onset of new sensitizations to skin test was published in 1997.⁴⁰ The authors followed up for 3 years 22 monosensitized children receiving SCIT for house dust mite and 22 controls. None of the SCIT-treated children developed new sensitizations, versus 10 of 22 in the control group. An effect on the magnitude of skin positivity was reported in 82 subjects, 8 to 16 years after participating in a randomized double-blind trial with various allergens.⁴¹ A large retrospective study⁴² confirmed that SCIT can prevent the onset of new

atopic sensitizations, as determined by skin prick testing. This study involved approximately 8,000 patients and found that after 4 years of follow-up, 24% of the SCIT-treated patients had developed new skin sensitizations versus 60% of the controls. Another prospective study in children, 75 receiving SCIT and 63 treated with drugs only, reported a rate of new sensitizations of 33% and 75%, respectively.⁴³

Some randomized controlled open trials have suggested such an effect also for SLIT. One study⁴⁴ assessed the onset of new allergy skin test sensitizations after 3 years in 511 patients randomly allocated to SLIT (319 subjects) or drugs only (192 subjects). At the end of the study, 64 of 170 (38%) of controls and 16 of 271 (5.9%) of SLIT patients ($P < .001$) had developed new skin sensitizations. In the aforementioned study conducted in children,²⁰ at the 3rd year of follow-up, the rate of onset of new sensitizations was 4 of 130 in the SLIT group and 23 of 66 in the control group. Also, in the prospective 15-year trial by Marogna et al.,³⁷ all the patients of the control group developed at least 1 new sensitization, versus 20% of the SLIT-treated patients.

Clearly almost all the studies specifically assessing the onset of new sensitizations suffer from methodological biases (eg, open design and questionable randomization). In addition, the clinical significance of the appearance of new sensitizations is not clear, although some studies suggested that the severity of disease could be related to the number of skin positivities.^{38,39}

CONCLUSIONS

The effect of SIT on symptoms and medication intake is considered the most relevant outcome to judge the efficacy of the treatment and, in fact, the combined symptom + medication score is recommended as the primary outcome to be used in randomized clinical trials.⁴⁵ Nonetheless, the “additional” effects, namely the carry-over and the preventive effects, are of great importance because they are not possessed by pharmacological treatments. In addition, the long-term effect and the capacity of preventing the onset of asthma also may have economic implications.^{46,47} For instance, Berto et al.,⁴⁵ using a pharmaco-economy model, under the hypothesis that SLIT prevents the onset of asthma in 40% of patients, demonstrated that SLIT would save approximately 2,100 Euros per year over a period of 6 years. Conversely, the pharmaco-economic aspects of the carry-over effect have not been formally assessed, but one could reasonably suppose that a long-lasting reduction in symptoms and need for medications would result.

We have available some experimental data consistently confirming the capacity of both SLIT and SCIT to prevent asthma onset and to maintain clinical efficacy over years. Nonetheless, the quality of the data is moderate or low, because many trials, especially the preventive studies, were conducted in an open fashion (although controlled and randomized), and the number of patients was small. With long-term trials of SCIT and SLIT come further methodological problems: the open follow-up, the heterogeneity of outcomes,

and the variability of study designs. In most studies, the outcomes were measured only at the end of the follow-up period, without intermediate measurements. Conversely, ethical and feasibility issues strongly limit the design of long-term trials, in which giving a placebo treatment for many years would be not acceptable. Thus, confirmatory trials are needed in which patients are rigorously selected, and objective parameters are included.^{48,49}

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