

Review

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Sublingual immunotherapy for treating respiratory allergy: a review on its effectiveness and suitability

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Abstract

Sublingual immunotherapy (SLIT) was introduced in the treatment of respiratory allergy as an option to subcutaneous immunotherapy (SCIT), which is clinically effective but has the problem of adverse systemic reactions, quite rare but sometimes life-threatening. A large number of trials, globally evaluated in several meta-analyses, demonstrated that SLIT is an efficacious treatment for allergic rhinitis and allergic asthma and has a satisfactory safety profile, severe reactions being extremely rare, though an increased risk is apparent in subjects undergoing SLIT because of previous systemic reactions to SCIT.

The suitability of SLIT is ensured by a good compliance, higher than reported for SCIT, the injections being a major factor for noncompliance with the latter, and by its cost-effectiveness performances. In fact, a number of studies showed that SLIT may be very beneficial to the healthcare system, especially after its stopping, when there is no more the cost of the treatment but its efficacy on symptoms persists. *Clin Ter 2010; 161(6):543-547*

Key words: compliance, cost-effectiveness, efficacy, respiratory allergy, sublingual immunotherapy

Introduction

Respiratory allergy is caused by sensitization to environmental aeroallergens such as pollens, house dust mites, moulds, and animal epithelia, and is clinically expressed as rhinitis and asthma.

The management of respiratory allergy relies upon, when possible, allergen avoidance, drug treatment, and allergen specific immunotherapy (IT) (1). IT is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects. IT has central importance because of its ability to modify the natural history of the disease and to extend its effectiveness also after treatment withdrawal, provided it is administered for adequate duration (2). The traditional route of administration of IT has been for decades, following the first demonstration of efficacy in a controlled study (3), subcutaneous, but in recent years the sublingual route emerged as an actual treatment option (4). The main

reason to introduce sublingual immunotherapy (SLIT) was the safety problems with the injective route, which may include systemic reactions, sometimes severe and, though very rarely, even fatal (5).

The first studies on SLIT used low allergen dosages (6, 7) but it was soon apparent that doses much higher than those administered by subcutaneous route were needed to ensure clinical efficacy, and in consensus documents an optimal dosage as higher as at least 50 times the dose administered by injection was suggested (1).

The high number of trials on SLIT conducted in recent years allowed an accurate evidence based assessment of its effectiveness by several meta-analyses on the whole patient population as well as on subgroups defined by clinical expression (rhinitis, asthma) or age (adults, children) parameters (8-14). At the same time, other studies evaluated important aspects defining the suitability of SLIT, such as the compliance and the cost-effectiveness.

This review will consider the whole matter with the aim to provide to the reader a comprehensive view of this treatment that concerns very common diseases.

Effectiveness and safety of SLIT

The clinically efficacy of SLIT, as of SIT in general, is evaluated by the decrease in symptom scores of rhinitis and asthma and in consumption of symptomatic drugs. Many placebo-controlled studies are conducted on small patient populations and cannot achieve a reliable statistical significance, but their combined evaluation by the tool of meta-analysis is considered an adequate method to obtain more solid data. The results are expressed as standardized mean difference (SMD) and allow to compare the effect of SLIT on actively and placebo treated patients.

The first meta-analysis on SLIT was published in 2005, including 22 randomized controlled studies (8). Such analysis demonstrated a significantly higher efficacy of SLIT versus placebo, with a SMD corresponding to - 0.42 for symptom scores ($p = 0.002$) and to - 0.43 for medication scores ($p = 0.00003$). The authors did not succeed in

detecting differences concerning subgroups such as the kind of allergen and patients age because of the relatively low numbers.

The meta-analysis by Olaguibel et al. dealt with seven randomized controlled studies conducted on children aged up to 14 years (9) and found that SLIT was significantly effective on asthma symptoms (SMD -1.42, $p = 0.01$) and on drug consumption (SMD -1.01, $p = 0.06$), while the improvement did not reach the significance for nasal and conjunctival symptoms.

A further meta-analysis on SLIT in children was published in 2006 (10): in this case the evaluation concerned the efficacy on allergic rhinitis including 10 randomized controlled studies, with an overall number of 484 patients (245 actively and 239 placebo treated). A significant reduction of both symptoms (SMD -0.56, $p = 0.02$) and medication (-0.76, $p = 0.03$) was observed. A remarkable aspect was provided from the sub-analysis addressing the length of treatment and the kind of allergen administered, which demonstrated a higher efficacy for durations longer than 18 months and for pollen allergens compared to house dust mites.

In the same year appeared a meta-analysis on the efficacy of SLIT in asthma, which included 25 studies with an overall number of 1706 patients (11). Calculating the SMD, the reduction of asthmatic symptoms did not reach the statistical significance, but using the intention-to-treat method for outcome measures significant decreases of asthma symptoms and drug consumption and significant improvement of lung function and bronchial hyperreactivity were detected. The NNT was 3.7, that is in the range of those reported for injective SIT in asthmatic and rhinitic patients. Better results were obtained analyzing 9 studies on pediatric patients, the total number of patients was 441, 232 actively treated and 209 placebo-treated (12). A significant reduction was found in both symptoms scores (SMD -1.14, $p = 0.02$) and drug use (SMD -1.63, $p = 0.007$).

A limit of meta-analysis is the relevant heterogeneity of the included studies, mainly due to different scoring systems. Recent evaluations considered altogether the meta-analyses but reached contrasting conclusions. According to Nieto et al., the meta-analyses, by checking the data reported in the original studies, show "discrepancies, inconsistencies, and lack of robustness" and "do not provide enough evidence" for current routine use of SLIT in patients with allergic asthma or rhinoconjunctivitis (13). By contrast, the overall evaluation of all meta-analyses (5 on SLIT and 2 on subcutaneous SIT) by Compalati et al., despite a significant heterogeneity of studies and one negative meta-analysis, leads the authors to conclude that "SIT can be recommended for the treatment of respiratory allergy because of its efficacy in reducing asthma and rhinitis symptoms" (14). However, the major effects on asthma were achieved with the subcutaneous route.

A data source alternative to meta-analysis are studies conducted on large numbers of patients that allow adequate statistical power. The recent preparations for SLIT in tablet of grass pollen extract were evaluated on large populations, including 855 adults treated by a one grass (*Phleum pratense*) extract (15), 628 adults treated with a 5-grass pollen extract (16), and 278 children treated with the same

preparation (17). These studies showed a highly significant improvement in symptom and rescue medications scores in actively treated compared with placebo treated patients during the grass pollen season. Nevertheless, there is yet criticism on the therapeutic role of SLIT, especially regarding the efficacy in children, in asthmatic patients and in house dust mite sensitization (18). A balanced and updated review by Larenas-Linnemann concluded that there is yet room for investigations on long-term effects and preventive action of SLIT, as well as on optimal dosing for dust mites (19). Concerning pollen allergy, the appropriate dosing was accurately evaluated, as well as the administration regimens, which include pre-seasonal, co-seasonal, and pre-co-seasonal protocols (20).

Focusing SLIT safety and tolerability, all systematic revisions and meta-analysis found that the most common adverse events are local reactions in the oropharynx, and that systemic reactions such as asthma, rhinitis, or urticaria, are quite rare (21). In the study by Calamita et al (11) was calculated the number needed to harm, that is the number of patients to treat to have one adverse reaction, which corresponded to 14.3. Anaphylactic reactions are extremely rare, but an increased risk is apparent in subjects undergoing SLIT because of previous systemic reactions to injection SIT (22, 23), especially when no up dosing regimens are used (22).

Compliance with SLIT

The first studies on compliance with SIT were conducted when only the subcutaneous route was available and reported a low compliance, ranging from 45% to 60%, but the demanding schedules used, with very frequent injections, accounted for this outcome, as shown by patients' recognizing of inconvenience as the major cause of noncompliance. More recent studies using less aggressive schedules reported a better compliance, estimated in 75% to 90%, inconvenience remaining the major cause of noncompliance, followed by cost of the treatment (24).

SLIT has different compliance issues than injective SIT, because it is administered at home by patients themselves and thus it is not affected by most causes reported for non-compliance to allergen injections, having instead compliance problems similar to drug treatment. Some studies not specifically designed for compliance (for instance safety and tolerability analyses) reported that treatment withdrawal is frequently caused by repeated local reactions in the mouth or at gastrointestinal level (8, 25). Moreover, as previously noted in injection SIT studies, it was observed that a lack of compliance to SLIT may be caused by the erroneous perception that once allergic symptoms are improved, SLIT is no more needed (26).

Concerning specific compliance and adherence studies, the available data indicate quite satisfactory results. In a study on 319 patients mainly addressing the efficacy of SLIT, the adherence to treatment (assessed by measuring the consumed allergen extracts) was estimated to be good - i.e. > 80% - in 72% of patients, and fair - i.e. > 60% - in 18% of patients (27).

The approach of evaluating the adherence by measuring the consume of allergen extracts was used in other three

studies, which were facilitated by the fact that preparations in tablets or in liquid monodoses were employed. In the first of these, adult patients under SLIT treatment were asked by phone (without being warned in advance) to count the remaining tablets in the box; the phone interview was done during the first year in patients treated for dust mite allergy and during the first pollen season in patients treated for pollen allergy; the adherence value was comprised between 75% and 97% (28). The other two surveys were real-life studies investigating the compliance to SLIT in 443 adult and adolescent patients (29) and in 71 children (30) respectively. In the study on adults, data on compliance were obtained (by unscheduled phone calls) after 3 months in all patients, while after 6 months data were obtained on 266 patients because the remaining 217 had received a pre-seasonal SLIT of 3-4 months duration; 76.3% of patients after three months and 74.8% after six months had a compliance higher than 90%; in 4% of patients SLIT was discontinued for various reasons unrelated to treatment and in 1% for side effects possibly related to treatment (29).

Similarly, in the study on children with the same product in monodoses, parents were interviewed by unscheduled phone calls at the third and sixth month of SLIT and asked to count at once the remaining doses; a compliance rate higher than 75% was found in 85% of children at the third month and in 84% of children at the sixth month; the major cause of withdrawal (5.6% of cases) was the cost of treatment, while side effects accounted for 1.4% of stopping (30).

In a study comparing compliance to SLIT, injective and local nasal immunotherapy in children, data on SLIT concerned 806 patients, 173 of whom (21.4%) were noncompliant, with a highly significant difference ($p < 0.0001$) for a better compliance in hospital setting (90.5%) compared to private office setting (61.2%); the most common reason of withdrawal was the cost of treatment, reported globally in 36.4% of cases, followed by inconvenience, feeling of inefficacy, and side effects (31). In a recent survey on allergist's opinion about the factors positively influencing adherence to SLIT, the issue judged most important were the patient's perception of efficacy, reimbursability, tolerability, and patient's educations (32).

Cost effectiveness of SLIT

Currently, cost-effectiveness is an important matter in medicine. Some studies addressed this aspect in SLIT treatment. The first published study dealt with the evaluation of cost effectiveness of SLIT in children with allergic rhinitis and asthma, assessed by direct costs (drugs, specialists visits, and SLIT) and indirect costs (costs resulting from children school and parental work loss), indicating that high dose SLIT may be effective in reducing the global cost of allergic rhinitis and asthma (33).

An overall number of 135 patients were analyzed, 46 with perennial and 89 with seasonal allergy, with comparable gender and age distribution. A substantial reduction was found in all outcome measures during SLIT compared with the previous period. The average annual cost/patient was € 2672 before SLIT initiation and € 629/year during SLIT. Similar results were found for allergen subgroups.

The asthma analysis involved 41 children with SLIT and 35 controls, and also showed a substantial reduction in outcomes, though the direct cost per patient over the 4 years follow-up was € 1182 for SLIT-treated children and € 1100 for controls. These findings showed that high dose SLIT may be effective in reducing the global cost of allergic rhinitis and asthma and comparably expensive to conventional drug treatment in children with allergic asthma over a 4 year follow-up.

The second study was addressed on a cohort of adults with pollen allergy and was conducted using a decision tree developed and populated with epidemiologic and resource utilization data concerning about 2200 patients (34). Target population were young adults suffering from pollen-induced rhinitis with or without asthma. Time perspective was over 6 years in order to include long term effectiveness of SLIT, and patients' data were collected in 25 Italian centers.

Main assessment criteria for the two different strategies were: a) costs, including the direct medical costs assessed in the National Health Service (NHS) perspective (visits, diagnostic procedures, drugs, SLIT and hospitalizations) and the direct plus indirect costs (lost working days) and patient out-of-pocket expenses assessed in the societal perspective; b) effectiveness end-point, including: number of patients improved and number of asthma cases avoided; c) incremental cost per improved patient and incremental cost per asthma case avoided.

A mean cost per patient treated over a period of 6 years was calculated for each therapeutic strategy and for each of the two perspectives studied. SLIT strategy resulted in less expense in term of both direct and indirect costs. The break-even point of SLIT, that is the time in which the overall cost of treatment for SLIT patients becomes lower than for patients receiving only drugs for the societal perspective was reached at year 4.

The third study evaluated the economics of SLIT in patients with pollen allergy and suffering from allergic rhinitis alone or associated with asthma compared with standard case controls (35). This study was made by a longitudinal observational database operated by a network of Allergy centers. Patients were randomly assigned to SLIT (plus drugs as needed) or to treatment with drugs alone. The outcome measures included use of: drugs, SLIT, visits and tests. Costs were assessed in the perspective of the Italian NHS.

The results showed that the overall per patient yearly cost of treatment was higher in SLIT patients, both in the whole sample (€ 311 vs 180/patient), in rhinitis (€ 288 vs 116) and rhinitis associated with asthma (€ 362 vs 230) sub-groups. Patients with rhinitis plus asthma generated more costs than rhinitis alone in both groups, but considerable savings were obtained in the cost of symptomatic drugs (-22% for rhinitis, -34% for rhinitis plus asthma) in SLIT patients, thus focusing the use of symptomatic drugs as an important indicator of effective allergy control.

A recent study evaluated for the first time the cost-effectiveness of SLIT in patients with house dust mite-induced asthma, reporting a higher mean annual cost in the first year in subjects treated with SLIT plus the needed symptomatic drugs compared with subjects only receiving drug treatment, while an economic advantage was apparent in the ensuing years and especially when SLIT was discontinued after

three years, due to the persistence of good clinical control in SLIT-treated patients (36).

Two other studies concerned the evaluation of economic aspects of SLIT performed with oral tablets for grass pollen allergen in Northern (37) and Southern Europe (38). Aim of the first study was the assessment of cost-effectiveness of grass allergen tablets compared with use of symptomatic drugs in seven Northern European countries. A societal perspective was adopted, and the analysis had a 9-year time horizon. Main outcome measure was Quality Adjusted Life Years (QALYs). QALYs measure patients' health-related Quality of Life on a scale from 0 (death) to 1 (perfect health), and is a multi-attribute utility scale that can generate a single numeric index of health-related QoL.

The findings of this study showed that SLIT produced statistically significant differences compared with drug treatment for all efficacy end-points, including the number of QALYs gained. There was a significantly higher usage of rescue medications (antihistamines and corticosteroids), and more hours missed from work (productivity losses) in the symptomatic group. The cost per QALY gained in the SLIT group was similar in the 7 countries (€ 12930 to 18263 for an annual cost of SLIT of € 1500). The analysis showed that SLIT was cost-effective for all countries for an annual cost below € 2200. This pharmacoeconomic analysis confirmed that SLIT is a cost-effective intervention for the prevention of grass pollen induced rhinoconjunctivitis in Northern European countries.

The second study (38) assessed the cost-effectiveness of SLIT in patients suffering from grass pollen induced rhinitis living in four Southern European countries (Spain, France, Italy, and Austria). A prospective pharmacoeconomic analysis was carried out alongside a multinational clinical trial measuring the efficacy of SLIT. Pooled data on resource use and health outcomes were collected. A societal perspective was adopted, and the analysis had a nine-year time horizon. SLIT was superior to standard care for all efficacy endpoints, including QALYs gained, and resulted in significantly less use of rescue medication and fewer hours missed from work. SLIT was cost-effective for all countries for an annual price in the range of €1500-1900.

Concerning the cost comparison between SCIT and SLIT, the first study was conducted in France in 2007: a cost/efficacy analysis was performed using a decision tree model by the perspective of the French Social Security, comparing IT and current symptomatic treatment in adults and children with dust mite and pollen allergy (39). In adults, the savings with subcutaneous IT were 393 € for dust mite and 1327 € for pollen allergy over a 6-year period. In children, the savings were 583 € for dust mite and 597 € for pollen allergy over a 7-year period. The data from SLIT showed – as expected because of no need of visits for injections – higher savings, corresponding to 3158 € for dust mite and 1708 € for pollen allergy in adults, and to 3938 € for dust mite and 824 € for pollen allergy in children.

A recent study was done in Czech Republic on patients with allergic rhinoconjunctivitis receiving SLIT, SCIT, or only drugs for 3 years (40). The total average direct cost per patient was 416 € for SLIT and 482 € for SCIT. A SLIT-treated patient paid less than a SCIT-treated patient for all out-of-pocket costs (176 € vs. 255 €), but paid more for

allergen extracts (72 € vs. 55 €). The sum of direct and indirect costs gave, over the 3-year treatment, 684 € for SLIT and 1004 € for SCIT.

In conclusion, there are clear data indicating that SLIT, and SCIT as well, may be very beneficial to the healthcare system, because it could bring more clinical effectiveness at a reduced cost versus standard drug treatment, or it could bring extra benefit at an acceptable extra cost, thus fully accomplishing the significance of the term cost effectiveness (41).

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