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REVIEW

The current role of sublingual immunotherapy in the treatment of allergic rhinitis in adults and children

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Abstract: Allergic rhinitis is a very common disease affecting about 20% of people. It may be treated by allergen avoidance when possible, by antiallergic drugs such as antihistamines and topical corticosteroids, and by allergen-specific immunotherapy. The latter is the only treatment able to act on the causes and not only on the symptoms of respiratory allergy and is able to maintain its efficacy even after stopping, provided an adequate duration of treatment of 3–5 years is ensured. Sublingual immunotherapy (SLIT) was introduced in the 1990s as a possible solution to the problem of adverse systemic reactions to subcutaneous immunotherapy and has been demonstrated by more than 50 trials and globally evaluated thus far by five meta-analyses as an effective and safe treatment for allergic rhinitis. Life-threatening reactions are extremely rare. However, it is important to note that clinical efficacy occurs only if SLIT meets its needs, ie, sufficiently high doses are regularly administered for at least 3 consecutive years. This is often overlooked in the current practice and may prevent the same success reported by trials from being achieved.

Keywords: allergic rhinitis, sublingual immunotherapy, efficacy, safety, compliance, meta-analysis

Introduction

Allergic rhinitis (AR) is a very common disease with a high and still increasing world prevalence.[1] AR causes an important medical and social burden,[2] which further increases when the disease is associated with allergic asthma.[3] In fact, the concurrence of AR and asthma requires more doctor visits and more drugs and worsens patients' quality of life.[4]

The management of respiratory allergy relies on, when possible, allergen avoidance, drug treatment, and allergen-specific immunotherapy (SIT).[3] SIT is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects. This treatment has pivotal importance because of its ability to modify the natural history of the disease and to extend its effectiveness after treatment withdrawal, provided it is administered with sufficiently hgh doses and for an adequate duration.[5] Subcutaneous immunotherapy (SCIT) has for decades been the traditional technique of administration, but it is flawed by the problem of adverse systemic reactions, which, when they are of an anaphylactic type, may be severe and, though very rarely, even fatal.[6] In recent years, sublingual immunotherapy (SLIT) has emerged as an actual treatment option because of its clinical efficacy and safety.[7]

The first studies on SLIT used low allergen dosages,[8,9] but it soon became apparent that doses much higher than those administered by SCIT were needed to expect clinical

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efficacy. In consensus documents, an optimal dose as high as at least 50 times the dose administered by injection was suggested.[3] The high number of trials on SLIT conducted in recent years allows an accurate evidence-based assessment of its efficacy based on several meta-analyses, and the most recent data also give an indication on optimal doses to be used.

This review aims to analyze the current role of SLIT in the treatment of AR using evidence-based demonstrations of its efficacy and safety.

Search strategy and study selection

The medical literature was searched by means of the MedLine database for the years 1990–2010 using the following key words: "sublingual immunotherapy", "efficacy", "safety", "tolerability", "compliance", "meta-analysis", and "systematic review". The search was augmented by scanning the references cited in the articles identified. Only full-length articles in English that had been published in referenced journals were considered. Full copies of the articles were retrieved for analysis and the relevant data were extracted.

Analysis of efficacy of SLIT

The clinical efficacy of SLIT in AR, as for SIT in general, can be evaluated by a decrease in symptom scores of rhinitis and in the use of symptomatic drugs. Most of the placebo-controlled studies usually include small patient populations and thus are exposed to the issue of not having fully reliable statistical significance. An adequate statistical method to achieve statistical reliability is meta-analysis that estimates more powerfully the effect size of a medical treatment by combining the results of several trials and expresses the results as standardized mean difference (SMD), comparing the effect of active and placebo treatment on patients. The results from the meta-analyses on SLIT in AR are summarized in Table 1.

In 2005, when 22 randomized controlled trials (RCTs) were available, Wilson et al published the first meta-analysis on SLIT,[10] which demonstrated a significantly higher efficacy

of SLIT versus placebo, with an SMD corresponding to −0.42 for symptom scores ($P = 0.002$) and to −0.43 for medication scores ($P = 0.00003$). In the same year, another meta-analysis dealt with seven RCTs conducted on children aged up to 14 years and found that SLIT was significantly effective on asthma symptoms (SMD −1.42; $P = 0.01$) and on drug consumption (SMD −1.01; $P = 0.06$), but the improvement did not reach significance for nasal and eye symptoms.[11]

However, a further meta-analysis on SLIT in children, concerning only efficacy on AR, showed positive results.[12] Ten RCTs with an overall number of 484 patients (245 actively treated and 239 placebo treated) were included, and a significant reduction of both symptoms (SMD −0.56, $P = 0.02$) and medication scores (SMD −0.76, $P = 0.03$) was found. Of note, the subanalysis addressing the length of treatment and the kind of allergen administered demonstrated a higher efficacy for durations longer than 18 months and for pollen allergens compared with house dust mites.

The most recent meta-analyses highlighted the results according to the allergen used for SLIT. Compalati et al examined eight RCTs for AR (including 194 adults and children).[13] A significant reduction in symptoms of AR (SMD −0.95; $P = 0.02$) and a significant decrease in antiallergic medication use (SMD −1.88; $P = 0.04$) in SLIT-treated patients compared with placebo was found. Di Bona et al performed a meta-analysis on RCTs conducted with grass pollen extracts, concluding that SLIT significantly reduces both symptoms (SMD −0.32) and medication use (SMD −0.33) compared with placebo, that it is more efficacious in adults than in children, and that prolonging the duration of preseasonal treatment for more than 12 weeks improves treatment efficacy.[14]

A recognized limit of meta-analysis is the usually relevant heterogeneity of the included studies, due to the different dosages, standardization methods, treatment schedules, and patient populations. Recent evaluations considered the available meta-analyses altogether but reached contrasting conclusions. Nieto et al checked the data reported in the

Table 1 Summary results from meta-analyses on sublingual immunotherapy in allergic rhinitis

Study	Population	Number of patients	Allergen used	Standardized mean difference
Wilson et al[10]	Adults and children	979 (503 active, 476 placebo)	Various	−0.42
Olaguibel et al[11]	Children	256 (129 active, 127 placebo)	Various	−0.44
Penagos et al[12]	Children	484 (245 active, 239 placebo)	Various	−0.56
Compalati et al[13]	Adults and children	382 (194 active, 188 placebo)	House dust mite	−0.95
Di Bona et al[14]	Adults and children	2971 (1518 active, 1453 placebo)	Grass pollen	−0.32

original studies and concluded that the meta-analyses show "discrepancies, inconsistencies, and lack of robustness" and "do not provide enough evidence" for the current routine use of SLIT in patients with allergic asthma or rhinoconjunctivitis.[15] By contrast, the overall evaluation of all meta-analyses (five on SLIT and two on SCIT) by Compalati et al, despite a significant heterogeneity of studies and one negative meta-analysis, led 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".[16]

The limit of heterogeneity can be overcome by analyzing single studies conducted on large numbers of patients that allow adequate statistical power. The recent preparations for SLIT in tablets of grass pollen extract were evaluated on large populations, including 855 adults treated by a Timothy grass extract,[17] 628 adults treated using a five-grass pollen extract,[18] and 278 children treated using the same five-grass preparation.[19] These studies showed a highly significant improvement in symptoms and rescue medication scores in actively treated compared with placebo-treated patients during the grass pollen season.

Important observations from such studies concern the dose dependence of clinical efficacy: only high doses, corresponding to 75,000 SQ in the trial with the Timothy grass pollen[17] and to 300 IR in the trial with the five-grass extract,[18] were effective. These doses correspond to 15 mcg and 20 mcg of the major allergens Phl p 5, respectively. Calculating the monthly cumulative dose, the World Allergy Organization Position Paper on SLIT suggested the monthly dose of 600 mcg of the grass pollen major allergen Phl p 5 as being optimal.[20] This is confirmed by the meta-analysis on grass pollen SLIT by Di Bona et al, showing clearly better results (SMD −0.47) in patients receiving monthly doses of 275–600 mcg than in patients receiving monthly doses lower than 275 mcg (SMD −0.16).[14]

Another important aspect of SLIT efficacy is the identification of patients more prone to respond to the treatment. Devillier et al[21] performed a post hoc analysis of data from the registrative studies with the new grass pollen tablets for SLIT.[18,19] From such analysis it was apparent that the magnitude of efficacy was higher in patients with more severe symptoms during the grass pollen season. In fact, for the adult trial, the differences of the symptom–medication score in the active versus placebo groups were 15%, 26%, and 37% for the low-, moderate-, and high-severity tertiles, respectively; in the pediatric trial, these values were 10%, 33%, and 34%, respectively.[21]

Analysis of safety and tolerability of SLIT

The meta-analyses including, along with efficacy, the safety and tolerability aspects of SLIT found that the most common adverse events were local reactions in the oropharynx followed by gastrointestinal reactions (such as vomiting and diarrhea) and that systemic reactions such as asthma, rhinitis, or urticaria were quite rare.[10,13]

Specific reviews on safety are also available that address only children[22,23] or patients of any age.[24,25] Of note, differently from SCIT, there was not a dose dependence of safety, as the rate of systemic reactions was similar in studies using low doses and in studies using high doses.[24] In a subsequent trial evaluating seven groups of patients treated with increasing doses, the treatment-related adverse events, including irritation of the throat, and itching sensations in the mouth and ears, increased with dose.[26] In fact, local reactions are generally estimated to concern 20%–40% of patients, but they can be easily managed and usually do not result in treatment withdrawal.[27] Anaphylactic reactions are extremely rare; a review of published reports showed that in most cases the reaction is associated with mistakes, such as the use of an improper mix of allergens or the consumption of very high allergen doses.[28] However, an increased risk is apparent in subjects undergoing SLIT because of previous systemic reactions to SCIT,[29,30] especially when no updosing regimens are used. This warrants reconsideration of systemic reactions to SCIT as an admission criterion to SLIT.[31] In any case, starting directly with the maintenance dose is not recommended in any patient, regardless of previous reactions to IT. In fact, a Phase I study comparing different doses and different updosing or no updosing regimens showed that only the group of patients treated with the highest dose with no updosing had severe local reactions with swelling of throat.[32]

Analysis of compliance with SLIT

Based on the available studies, the major cause of noncompliance with SLIT is inconvenience due to visits to allergists' offices for the injections.[33] SLIT has different compliance issues from SCIT, because it is administered at home by patients themselves, and thus should have compliance problems similar to drug treatment. However, the findings from studies specifically designed for compliance and adherence indicate quite satisfactory results, with values between 75% and 95% of treated subjects.[33] In a survey on allergists' opinions on the factors positively influencing adherence to SLIT, the issues judged to be most important were the patient's perception of efficacy, reimbursability,

and tolerability and the patient's education.[34] Concerning perception of efficacy, as previously noted in SCIT 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 longer needed.[35] However, this aspect also belongs to the field of patient education, which has pivotal importance, as shown in a recent study that found a clear difference in compliance between patients receiving a complete educational course on SLIT and those receiving only standard instructions.[36]

Analysis of the carryover effect of SLIT

A major advantage of SCIT over drug treatment is that efficacy on allergic symptoms persists after its discontinuation.[5] Recent studies showed that SLIT also has such a carryover effect. In a survey on SLIT using a dust mite extract, 137 patients were divided into two groups, 67 receiving SLIT for 2 years and 70 receiving SLIT for 3 years. All patients were followed up for 3 years after stopping the treatment. A greater improvement of symptoms was found in the patients treated for 3 years.[37] In a prospective open controlled study, patients monosensitized to mites were divided into four groups, one receiving only drug treatment and the other three receiving SLIT for 3, 4, or 5 years. The observation period reached 15 years, and the clinical scores showed that the benefit persisted for 7 years in patients treated for 3 years, whereas the benefit persisted for 8 years in those treated for 4–5 years.[38] Moreover, new allergen sensitizations occurred in all patients treated only with drugs and in less than 25% of patients receiving SLIT.

Conclusion

SLIT has gained ample evidence of efficacy and safety and in some European countries is currently used more frequently than SCIT. Apart from its better safety profile, the advantages of SLIT over SCIT are with regard to compliance, which is higher because SLIT does not need to be administered in a medical setting, and cost-effectiveness, because the cost of the injections is not involved.[39] However, it is important to note that such favorable outcomes exist only if SLIT meets its needs, ie, the administration of high doses is continued regularly for at least 3 consecutive years. In fact, SLIT efficacy is dose dependent, and a sufficient duration of treatment is necessary to induce the immunologic changes underlying clinical effectiveness. Recent studies showed that the mechanism of action of SLIT is similar to that demonstrated for SCIT,[40] and that when high doses are administered, immunoglobulin

G-blocking antibodies, which were not found in SLIT studies employing low doses, are produced in significant amounts and persist after the discontinuation of treatment.[41]

Disclosure

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