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Treating allergic rhinitis by sublingual immunotherapy: a review

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Abstract. *Objective.* Allergic rhinitis (AR) is a disease with high and increasing prevalence. The management of AR includes allergen avoidance, anti-allergic drugs, and allergen specific immunotherapy (AIT), but only the latter works on the causes of allergy and, due to its mechanisms of action, modifies the natural history of the disease. Sublingual immunotherapy (SLIT) was proposed in the 1990s as an option to traditional, subcutaneous immunotherapy. *Material and methods.* We reviewed all the available controlled trials on the efficacy and safety of SLIT. *Results and conclusion.* Thus far, more than 60 trials, globally evaluated in 6 meta-analyses, showed that SLIT is an effective and safe treatment for AR. However, it must be noted that to expect clinical efficacy in the current practice SLIT has to be performed following the indications from controlled trials, that is, sufficiently high doses to be regularly administered for at least 3 consecutive years.

Key words: allergic rhinitis, sublingual immunotherapy, efficacy, safety, compliance, meta-analysis.

Riassunto *(Il trattamento della rinite allergica con l'immunoterapia sublinguale: revisione della letteratura). Obiettivo.* La rinite allergica è una malattia a prevalenza elevata e crescente. La gestione della rinite allergica consiste nell'allontanamento dell'allergene, nell'utilizzo di terapie anti-allergiche, e nell'immunoterapia specifica (AIT). Solo quest'ultima agisce sulle cause dell'allergia in quanto grazie al suo meccanismo d'azione modifica la storia naturale della malattia. L'immunoterapia sublinguale (SLIT) è stata proposta negli anni novanta come alternativa alla tradizionale immunoterapia sottocutanea. *Materiali e metodi.* Sono stati analizzati tutti gli studi controllati attualmente disponibili sull'efficacia e sulla sicurezza della SLIT. *Risultati e conclusioni.* Finora, più di 60 studi clinici controllati, analizzati globalmente in sei meta-analisi, hanno dimostrato la sicurezza e l'efficacia della SLIT nella terapia della rinite allergica. Tuttavia, per avere una buona risposta clinica, la SLIT deve essere eseguita seguendo le indicazioni degli studi controllati, che raccomandano l'utilizzo di dosi sufficientemente elevate per almeno tre anni consecutivi.

Parole chiave: rinite allergica, immunoterapia sublinguale, efficacia, sicurezza, compliance, meta-analisi.

INTRODUCTION

Epidemiologic data shows a high and increasing prevalence of allergic rhinitis (AR) worldwide [1]. AR is particularly frequent in children [2], in whom the atopic disease usually starts with atopic dermatitis and then develops into AR and asthma by the picture of the so-called "allergic march" [3].

AR is generally managed by allergen avoidance, which in reality is rarely feasible, drug treatment, which is mainly based on antihistamines and topical corticosteroids, and allergen-specific immunotherapy (AIT) [4]. AIT was introduced 100 years ago in the form of subcutaneous administration of gradually increasing doses of the specific causative allergen in order to decrease the clinical reactivity of allergic subjects [5]. The most important characteristic of AIT is the capacity to modify the natural course of the allergic disease, which ensures the persistence of its effectiveness even after the treatment is stopped, provided that sufficiently high doses are administered for an adequate period of time [4]. The availability of biologically potent allergen extracts in the 1980s disclosed the problem of the injective route, that is, the possible occurrence of adverse systemic reactions. Hence, when adequate measures are warranted, the safety profile of injective AIT is good [6]. However, if the reactions are of the anaphylactic type, they may be severe and, though very rarely, even fatal [7]. In 1987, the sublingual route was proposed for AIT [8], and in the ensuing years it emerged as the best option for immunotherapy, by demonstrating a comparable efficacy and better

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safety when compared to the classical subcutaneous route of administration [9].

Today, a high number of studies showing the efficacy of sublingual immunotherapy (SLIT) have made the use of this treatment more frequent than subcutaneous IT (SCIT) in several European countries, and recent studies are paving the way for the introduction of SLIT also in the USA [10, 11].

The goal of this review is to analyze up to date the role of SLIT in the treatment of AR through the evidence which demonstrates its efficacy and safety, while highlighting the pharmacoeconomic issue.

EFFICACY OF SUBLINGUAL IMMUNOTHERAPY

The clinical efficacy of SLIT in AR, similarly to AIT in general, is evaluated by the decrease in symptom scores of rhinitis and in the consumption of symptomatic anti-allergic drugs. Currently, more than 60 double-blind, placebo-controlled studies are available, and provided the material for numerous meta-analyses on SLIT.

The first meta-analysis was published in 2005, when 22 controlled trials were available, showing a significantly higher efficacy of SLIT *versus* placebo, with a standardized mean difference (SMD) corresponding to -0.42 for symptom scores ($p = 0.002$) and to -0.43 for medication scores ($p = 0.00003$) [12]. In 2011, the same group updated the meta-analysis: 60 controlled trials were retrieved from the literature and 49 were suitable for pooling in meta-analysis. Hence, a significant reduction was found in symptoms (SMD -0.49, $p < 0.00001$) and in medication use (SMD -0.32, $p < 0.00001$) compared to the placebo. Therefore, the authors concluded that the updated review reinforced the statement of the previous meta-analysis that SLIT is effective for AR [13].

Other meta-analyses examined the results according to the type of patient or to the allergen used. Olaguibel *et al.* focused the interest on children and analyzed 7 controlled studies; the results showed that SLIT was significantly effective on asthma symptoms (SMD -1.42) and on drug consumption (SMD -1.01), but no significant improvement was found with respect to nasal and eye symptoms [14]. However, a subsequent meta-analysis on SLIT in children, concerning only the efficacy on AR, showed positive outcomes, with a significant reduction of symptoms (SMD -0.56, $p = 0.02$) and medication scores (SMD -0.76, $p = 0.03$) [15].

Concerning the allergen used, Compalati *et al.* considered 8 controlled studies for house dust mite-induced AR, including 194 adults and children, and found a significant reduction in symptoms of AR (SMD -0.95; $p = 0.02$) and in anti-allergic medication use (SMD -1.88; $p = 0.04$) in SLIT treated patients when compared to the placebo [16]. Furthermore, Di Bona *et al.* analyzed the randomized controlled studies performed with grass pollen extracts: a significant decrease of both symptoms (SMD -0.32) and medication use (SMD -0.33) was found for SLIT when compared to placebo. Of note, when using an amount of 275 mcg/month of major allergen as a cut-off separating low doses from high doses, the clinical benefit was much better (SMD -0.47) in patients receiving higher doses as compared to those receiving low doses (SMD -0.16). Other observations concerned higher efficacy in adults rather than children, and when preseasonal treatment was continued for more than 12 weeks [17]. The main features of the meta-analyses on SLIT are summarized in *Table 1*.

It must be noted that meta-analysis is not the perfect method, for it is affected by the problem of the heterogeneity of the included studies, due to the different dosages, standardization methods, treatment schedules, and patient populations. When the meta-analyses are dissected, it is possible to draw different conclusions. In fact, Nieto *et al.* 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 [18]. Conversely, the overall evaluation of all meta-analyses (5 on SLIT and 2 on SCIT) by Compalati *et al*, in spite of a significant heterogeneity of studies and one negative analysis, allowed the authors to conclude that "AIT can be recommended for the treatment of respiratory allergy because of its efficacy in reducing asthma and rhinitis symptoms" [19].

A possible solution to the problem of heterogeneity is offered by single studies conducted on large num-

Table 1 | *Results from meta-analyses on SLIT in allergic rhinitis*

Author (year)	Population	Number of patients	Allergen used	SMD*
Wilson *et al.* (2005) [12]	Adults and children	979 (503 active, 476 placebo)	Various	- 0.42
Olaguibel *et al.* (2005) [14]	Children	256 (129 active, 127 placebo)	Various	- 0.44
Penagos *et al.* (2006) [15]	Children	484 (245 active, 239 placebo)	Various	- 0.56
Compalati *et al.* (2009) [16]	Adults and children	382 (194 active, 188 placebo)	House dust mite	- 0.95
Di Bona *et al.* (2010) [17]	Adults and children	2971 (1518 active, 1453 placebo)	Grass pollen	- 0.32
Radulovic *et al.* (2011) [13]	Adults and children	4589 (2333 active, 2256 placebo)	Various	- 0.49

**SMD: standardized mean difference.*

bers of patients that allow adequate statistical power. The development of SLIT preparations has led to the introduction of grass pollen tablets, that were evaluated on large populations of patients, namely 855 adults treated by a Timothy grass extract [20], 628 adults treated by a 5-grass pollen extract [21], and 278 children treated by the same 5-grass preparation [22]. The results of these studies confirmed that SLIT induces a highly significant improvement during the grass pollen season in symptoms and medications scores in actively treated patients when compared to the placebo-treated patients. In addition, valuable observations on the dose dependence of clinical efficacy were done: only high doses, corresponding to 75 000 standard quality (SQ) units in the trial with the Timothy grass pollen [19] and to 300 Index of reactivity (IR) units in the trial with the 5-grass extract [20] were efficacious. Such doses are equivalent to 15 mcg and 20 mcg of the major grass allergen Phl p 5, respectively. Based on this information, the World Allergy Organization Position Paper on SLIT suggested as optimal a monthly cumulative dose of 600 mcg of the major allergen Phl p 5 [23].

Furthermore, a central issue of SLIT efficacy is the identification of patients who are more prone to respond to the treatment. By a *post-hoc* analysis of data from the studies performed for the registration of the new grass pollen tablets for SLIT cited above [21, 22], the magnitude of efficacy was found to be higher in patients with more severe symptoms during the pollen season. In particular, in the study on adults the differences of the symptom-medication score in the active *versus* placebo were 15%, 26%, and 37% for the low, moderate and high severity tertiles, respectively. In the study on children, these values corresponded to 10%, 33% and 34%, respectively [24].

As noted above, the major advantage of AIT over drug treatment is that the efficacy on allergic symptoms persists after its discontinuation [5]. This was recently demonstrated also concerning SLIT. In a study on SLIT performed by a dust mite extract, 137 patients were divided in 2 groups, 67 receiving the treatment for 2 years and 70 receiving the treatment for 3 years; all patients were followed-up for 3 years after stopping SLIT, and a greater improvement of symptoms was found in patients treated for 3 years [25]. In a prospective open controlled study, patients monosensitized to mites were divided in 4 groups, 1 receiving only drug treatment and the other 3 receiving SLIT for 3, 4, or 5 years. The observation period was extended to 15 years, and the clinical scores showed that the clinical benefit continued for 7 years in patients treated for 3 years, while it continued for 8 years in those treated for 4-5 years [26].

SAFETY AND TOLERABILITY OF SUBLINGUAL IMMUNOTHERAPY

The first observations on safety and tolerability of SLIT were reported in the meta-analyses on efficacy, and showed that the most common adverse events were local reactions in the mouth followed by gastrointestinal reactions (including vomiting and diarrhea), that systemic reactions such as asthma, rhinitis, or urticaria were quite rare, and that no anaphylactic reaction was described in controlled trials [12-15].

However, reviews specifically addressing SLIT safety are also available, concerning only children [27, 28] or patients of any age [29, 30]. Of interest, differently from SCIT, a dose-dependence of safety was not apparent, since the rate of systemic reactions was comparable in studies using low doses and in studies using high doses [29]. The local reactions are generally estimated to affect 20-40% of patients, but they can be easily managed and generally do not require to withdraw the treatment [31]. Still, single reports of anaphylactic reactions are available. In most cases, the reaction was associated with mistakes, such as the use of incorrect mix of allergens or the consumption of very high allergen doses [32]. Notwithstanding, an increased risk is apparent in subjects undergoing SLIT because of previous systemic reactions to SCIT [33, 34], in particular when no updosing regimens are used, and this warrants reconsideration of systemic reactions to SCIT as an admission criteria to SLIT [35]. Indeed, starting the SLIT treatment with the maintenance dose is generally not recommended, regardless of previous reactions to SCIT, because a phase 1 study comparing different doses and different regimens showed that only the group of patients treated with the highest dose with no updosing had severe local reactions, including swelling of the throat [36].

PHARMACOECONOMIC ASPECTS

The significant reduction in the use of symptomatic drugs showed by all meta-analyses on SLIT highlights the cost-effectiveness of this treatment. In fact, a number of studies addressed the pharmacoeconomics of AIT. The review of such studies in 2008 led to the conclusion that there was clear data that substantiated the capacity of both SCIT and SLIT to be very beneficial to the healthcare system. The major advantage of AIT takes place when the treatment, usually after 3 years, is stopped, because the effectiveness of AIT persists over time [37]. Such persistence is related to the immunologic changes induced by AIT, especially regarding the T lymphocytes and their cytokine profile and the production of IgG blocking antibodies [38] and the consequent modification of the natural history of respiratory allergy [39]. Recent studies expanded the concept of economic advantage of AIT even before its termination. In a study performed in US, children with AR treated with AIT had significantly lower 18-month median total health care costs ($ 3247 *vs* $ 4872), outpatients costs of AIT-related care ($1107 *vs* $ 2626), and pharmacy costs ($1108 *vs* $ 1316) compared with matched controls ($p < 0.001$ for all comparisons). This data has led the authors to conclude that "This study demonstrates the potential

for early and significant cost savings in children with AR treated with immunotherapy. Greater use of this treatment in children could significantly reduce AR-related morbidity and its economic burden" [40]. Of interest, the direct comparison of costs between SCIT and SLIT was in favour of the latter, as expected because of the lack of the necessity for hospital visits for the injections. In France, the reported savings compared with drug treatment over a 6-year period were € 393 for dust mite and € 1327 for pollen allergy with SCIT, but they were € 3158 for dust mite and € 1708 for pollen allergy with SLIT [41]. In the Czech Republic, the sum of direct and indirect costs recorded, over a 3-year treatment, € 684 for SLIT and € 1004 for SCIT [42].

CONCLUDING REMARKS

SLIT has achieved sound evidence of efficacy and safety and currently in some European countries is more frequently used than the classical SCIT, due to better safety. Other advantages over SCIT concern the cost [37] as well as the compliance [43], because SLIT does not need to be administered in a medical setting. Still, it is important to note that such outcomes take place only if SLIT meets its needs, that is, the administration of high doses is continued on a regular basis for at least 3 consecutive years. In fact, SLIT efficacy is dose-dependent and a sufficient duration is crucial to elicit the immunologic changes underlying its clinical effectiveness.

Conflict of interest statement

Cristoforo Incorvaia is a scientific consultant for Stallergenes Italy. Franco Frati is the Medical Director of Stallergenes Italy. Alessia Di Rienzo, Camilla Celani and Eleni Makrì have no competing interest.

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