Treating allergic rhinitis by sublingual immunotherapy: a review

Cristoforo Incorvaia(1), Alessia Di Rienzo(2), Camilla Celani(3), Eleni Makri(1) and Franco Frati(4)

(1) Pneumologia Riabilitativa, AO Istituti Clinici di Perfezionamento, Milan, Italy
(2) Allergologia, ASL di Frosinone, Frosinone, Italy
(3) Dipartimento di Pediatria, Sapienza Università di Roma, Rome, Italy
(4) Dipartimento Medico-Scientifico, Stallergenes, Milan, Italy

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

Address for correspondence: Cristoforo Incorvaia, Pneumologia Riabilitativa, AO Istituti Clinici di Perfezionamento, Via Bignami 1, 20126 Milan, Italy. E-mail: cristoforo.incorvaia@gmail.com.
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 = 0.00003) 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 pre-seasonal 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>
<thead>
<tr>
<th>Author (year)</th>
<th>Population</th>
<th>Number of patients</th>
<th>Allergen used</th>
<th>SMD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al. (2005) [12]</td>
<td>Adults and children</td>
<td>979 (503 active, 476 placebo)</td>
<td>Various</td>
<td>-0.42</td>
</tr>
<tr>
<td>Olaguibel et al. (2005) [14]</td>
<td>Children</td>
<td>256 (129 active, 127 placebo)</td>
<td>Various</td>
<td>-0.44</td>
</tr>
<tr>
<td>Penagos et al. (2006) [15]</td>
<td>Children</td>
<td>484 (245 active, 239 placebo)</td>
<td>Various</td>
<td>-0.56</td>
</tr>
<tr>
<td>Compalati et al. (2009) [16]</td>
<td>Adults and children</td>
<td>382 (194 active, 188 placebo)</td>
<td>House dust mite</td>
<td>-0.95</td>
</tr>
<tr>
<td>Di Bona et al. (2010) [17]</td>
<td>Adults and children</td>
<td>2971 (1518 active, 1453 placebo)</td>
<td>Grass pollen</td>
<td>-0.32</td>
</tr>
<tr>
<td>Radulovic et al. (2011) [13]</td>
<td>Adults and children</td>
<td>4589 (2333 active, 2256 placebo)</td>
<td>Various</td>
<td>-0.49</td>
</tr>
</tbody>
</table>

*SMD: standardized mean difference.
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), outpatient 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, i.e., 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 Makri have no competing interest.

References


