Sublingual immunotherapy with natural grass pollen extracts: an appraisal of the evidence

Many clinical studies have demonstrated that sublingual immunotherapy is effective against allergic symptoms, but caution must be exercised with these conclusions because of the wide variation among different studies in, for example, allergen dose used, type of treatment, patient selection and type of outcome measures. In order to overcome the inconsistency between the results of different studies and to assess the magnitude of the treatment effect, we performed a systematic review of double-blind, placebo-controlled, randomized clinical trials of grass pollen-specific immunotherapy for the treatment of seasonal allergic rhinoconjunctivitis in adults and children. Our conclusions were that sublingual immunotherapy (SLIT) with grass allergens improves rhinosinusitis symptoms and that it reduces the need for medications compared with placebo in adults. Further studies are needed to define the role of SLIT with grass allergens in children.

KEYWORDS: allergic rhinitis ■ grass ■ meta-analysis ■ sublingual immunotherapy

Danilo Di Bona[1,2], Maria Stefania Leto-Barone[3], Simona La Piana[1] & Gabriele Di Lorenzo[†3]

[1]Dipartimento di Biopatologia e Metodologie Biomediche, Università degli Studi di Palermo, Italy
[2]Unità Operativa di Immunoematologia e Medicina Trasfusionale, Azienda Ospedaliera, Universitaria Policlinico di Palermo, Italy
[3]Dipartimento di Medicina Interna e Specialistica (DIMIS), Università degli Studi di Palermo, Italy
[†]Author for correspondence: dilo601@unipa.it

Allergic diseases including rhinitis, conjunctivitis, atopic dermatitis, urticaria, asthma and food allergies are frequent health problems in the developed world. Allergic rhinitis (AR) affects approximately one quarter of adults in Europe [1], and has a considerable effect on the quality of life of patients.

Since most allergic syndromes are not life-threatening diseases, they are often perceived as a nuisance by patients and clinicians alike, and perhaps less worthy of directed and aggressive diagnosis and treatment when compared with other chronic illnesses, such as diabetes and hypertension [2]. This paradigm ignores the fact that early diagnosis and treatment of more 'minor' allergic diseases, such as rhinitis, may prevent progression and long-term complications, such as the development of sinusitis and asthma, and that rhinitis and asthma are associated with significant impairments in quality of life in terms of work productivity, school performance, activities of daily life, overall wellbeing and enjoyment of leisure time [2–5].

Evidence-based guidelines conclude that the management of allergic rhinitis encompasses patient education, pharmacotherapy and allergen-specific immunotherapy [6,7]. Patient compliance is important for effective therapy, and education probably improves compliance [7]. With regard to pharmacotherapy, H1-antihistamines, medications blocking histamine at the H1-receptor level, are effective against symptoms mediated by histamine (e.g., rhinorrhoea, sneezing, nasal itching and eye symptoms), but less on nasal congestion [8].

Intranasal glucocorticosteroids are the most effective medications available for the treatment of AR [9]. These drugs are effective in improving all symptoms of allergic rhinitis as well as ocular symptoms [10]. If nasal congestion is present or symptoms are frequent, an intranasal glucocorticosteroid is the most appropriate first-line treatment, as it is more effective than any other treatment [11].

Finally, immunotherapy is the only allergen-specific therapy [7]. Since the early 1900s, allergen-specific immunotherapy has been recognized as an effective treatment for inhalant allergies. Injection immunotherapy is accepted as a practical and effective means of reducing sensitivity to allergens [12]. In 1986, the British Committee for the Safety of Medicines reported several deaths caused by subcutaneous immunotherapy (SCIT), and raised serious concerns about the safety and the risk:benefit ratio of specific immunotherapy (SIT), the benefit was also questioned owing to cheaper and effective drugs (e.g., oral H1-antihistamines and topical corticosteroids) had become available for the treatment of respiratory allergy [13].

For this reason, the idea of administering the allergenic extracts via noninjection routes has been evaluated. The first clinical attempts were through the 'oral' route, but in several clinical trials performed during the 1980s, the clinical results were inconsistent, and in some cases adverse gastrointestinal events were reported [14,15]. Subsequently, other routes of administration were proposed, such as local

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bronchial [16] and local nasal [17]. The oral route, after a revision, has been administered for the sublingual route [7].

Sublingual immunotherapy (SLIT) has been the subject of considerable skepticism over the past century, being commonly dismissed as the extreme of a spectrum of anecdotal treatments for allergy that belonged more to the realm of homoeopathy than to evidence-based medicine. Today there is a significant body of literature documenting the efficacy and safety of SLIT in Europe [18]. However, in the USA, SLIT has not been approved by the FDA.

Specific immunotherapy products are sold as either unregistered, named patient preparations or nationally registered formulations. Recently, *Gramincae* grass pollen extract SLIT tablets have been registered in many European countries as pharmaceutical specialties [19]. However, the randomized controlled trials (RCTs) performed for the registration of the grass-pollen pharmaceutical preparations, showed conflicting results in regard to the magnitude of benefit of SLIT for AR.

We performed a systematic, review of double-blind, placebo-controlled randomized clinical trials of commercially available grass pollen SIT modalities for the treatment of seasonal allergic rhinoconjunctivitis in adults and children [20].

History of oral–mucosal route

The oral–mucosal route can be classified under four different headings:

- Oral SIT with gastric absorption, in which the 'vaccine ' is prepared as drops, capsules or tablets and is immediately swallowed [21,22];
- Oral SIT with enteric absorption in which the vaccine is modified to allow the delivery of antigen only to the small intestine, thereby avoiding degradation in the stomach [23];
- Sublingual swallow (dissolving) in which the vaccine is held sublingually for 2–3 min and then swallowed with subsequent gastric absorption [24];
- Sublingual spit, in which the vaccine is held in the mouth for 2 min and then spat out [25].

The oral route was first studied in the treatment of rhinoconjunctivitis [21]. However, only two studies showed a clinical benefit with significant improvement of symptoms, and decrease of drug consumption [22,23]. During the oral immunotherapy, significant adverse events have been reported: asthma, rhinitis and gastrointestinal symptoms such as vomiting, diarrhea and/or abdominal pain. Finally, the oral vaccine was very expensive owing to the large allergen amounts administered. These considerations led to the replacement of the oral SIT with gastric absorption and SIT with enteric absorption by the sublingual route [7]. Two forms of sublingual immunotherapy have been used: sublingual aqueous extracts and sublingual tablets. The majority of studies on sublingual oral and tablet immunotherapy have been performed in patients with allergic rhinitis with sensitization to pollen or house dust mites. Of the two treatment approaches, the best results have been obtained with sublingual tablet immunotherapy for grass pollen allergy. The studies on sublingual aqueous extracts and sublingual tablets were performed using the following oral constructs: sublingual aqueous grass immunotherapy (ALK-Abelló [Denmark], Stallergenes SA, [France], Leti SA [Spain], Allergopharma [Germany]); sublingual tablet grass immunotherapy (ALK-Abelló, Stallergenes SA).

The effectiveness of SLIT for grass pollen: an appraisal of evidence

We analyzed RCTs to evaluate the clinical effectiveness of SLIT for grass pollens by the assessment of symptom severity and rescue medication use during the exposure period to pollens. However, the results of these studies have been inconsistent leading to a difficult assessment of the treatment effectiveness. The explanation for the inconsistency in the results among the different studies is the heterogeneity of all available clinical studies of SLIT, with regard to different patient inclusion criteria, allergen used, doses, duration of treatment and length of preseasonal treatment, when present. In addition, the sample size and power of the RCTs are not always adequate and, moreover, in some studies methodological problems have been observed, hampering the reliability of the results.

Randomized double-blind placebo controlled trials of SLIT with grass allergens for seasonal allergic rhinitis

The measures of effectiveness of SLIT were symptom and medication scores. The interpretation of effectiveness was examined evaluating the 95% confidence interval (CI) for the difference between means for any active treatment versus placebo, both for the symptoms and the rescue medications.

For the analysis we used the mean ± standard deviation of the groups treated with SLIT and with placebo, present in each study selected. Using the statistical program, StatsDirect, we

performed an unpaired t-test, and calculated 95% CI for the difference between means. If the differences between the active group and placebo group for the symptom scores and the rescue medications were both in favor of active treatment, SLIT was considered 'effective'; if the differences between the active group and placebo group were both in favor of placebo for the symptom and the rescue medication scores SLIT was considered 'ineffective'; finally if the differences between the active and placebo groups for the symptom and the rescue medication scores were discordant SLIT was considered 'possibly effective'.

All of the RCTs compared grass pollen SLIT with placebo, included patients of any age with at least a 2-year history of AR to grass pollen with or without mild allergic asthma and/or conjunctivitis with a positive grass allergen-specific skin prick test and increased serum grass allergen-specific IgE, and assessed symptom and medication scores as outcome measures of the treatment effect.

The primary source of the reviewed studies was MEDLINE with the following medical subject headings: rhin* (which covers rhinitis, rhinopathy, rhinosinusitis and rhinoconjunctivitis), SLIT, grass, sublingual and immunotherapy. The computer search was supplemented with manual searches of reference lists for all available review articles, primary studies, and abstracts from conferences. The search, limited only to English language literature published up to August 2010, identified 119 abstracts, of which 88 were considered unsuitable for inclusion (i.e., review articles, observational studies, RCTs that were not double-blind and analysis of other outcomes such as costs and IgE profile). Among the studies reviewed, 31 RCTs [26–56] met the inclusion criteria; however, only 19 RTCs [27,28,30,32,34–39,42–45,47,49,50–52] were included in the review. Six studies were excluded because they were duplicate studies [40,41,46,53,55,56], one because a mixture with nongrass allergens was used for SLIT [48], one because the outcome was the asthma symptom score [55], and finally, four because of insufficient data [26,29,31,33]. Indeed, Dahl's study [38] was also performed in asthmatic patients with rhinoconjuntivatis. We included this study because the secondary end points were rhinoconjunctivitis symptom and medication scores during the grass pollen season, as well as all the other studies analyzed.

For studies not reporting all of the values required for the analysis, data were provided by the authors of the original studies or by the pharmaceutical companies [35,44,49–52].

We used the items of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) for systematic reviews and meta-analyses both in this paper and in our previous publication [20,57].

Since different scoring systems and scales were used by the authors of the different individual studies, to compare the results of the studies, we used the standardized mean difference (SMD), expressing the differences in means between SLIT and placebo in units of the pooled standard deviation. A SMD of approximately 0.20 means little difference between the two groups, approximately 0.50 is a modest difference and approximately 0.80 represents a considerable difference between two groups.

SLIT (drops)

We identified 12 trials (from 1994 to 2009). Population sizes ranged from 18 to 121 SLIT-treated subjects [27,28,30,32,34–36,42,44,45,47,50]. Three studies were performed both with SLIT administered as drops and as tablets [30,35,44]. In five studies SLIT was only in adults [28,32,42,44,47], in three it was only in children [34,36,45], in four it was in both adults and children [27,30,42,50]. The treatment duration ranged from 2 weeks of preseasonal administration and 3 months of seasonal administration [27] to year-long treatment [36]. The monthly dose of major allergen varied greatly from one study to another, from 6 µg of major allergen group 5 to 1200 µg of *Phleum pratense* (Phl p5) [34,47]. These variations may have contributed to the heterogeneity of the trial outcomes.

Interpretation of effectiveness: effective

The interpretation of effectiveness was 'effective' in three RCTs [27,44,46].

Feliziani *et al.* [27] included 34 older children and adults suffering from grass pollen rhinitis (asthma not excluded) treated for 3 months with a monthly dose of 120 µg of five allergens (*Dactylis glomerata*, *Lolium perenne* [Lol p5], *Festuca pratensis*), Phl p5 and *Poa pratensis*), administered as drops. The length of preseasonal treatment was >4 weeks. Interpretation of effectiveness was effective. Symptoms: 95% CI for difference between means was 33.9–178.44. Drugs for relief of symptoms: 95% CI for difference between means was 7.4–98.2.

Mösges *et al.* [44] included 101 adults (asthma was not reported) treated for 9 months with a monthly dose of Phl p5 600 µg. The

maintenance treatment was administered as tablets. The length of preseasonal treatment was 16 weeks. Interpretation of effectiveness was effective. Symptoms: 95% CI for difference between means was 3.6–31.1. Drugs for relief of symptoms: 95% CI for difference between means was 0.4–19.7.

Pfaar *et al.* [47] included 90 adults (asthma not excluded) treated for 24 months with a monthly dose of Lol p5 1200 µg, administered as drops. The length of preseasonal treatment was 16 weeks. The data have been reported as the symptom score for the consumption of rescue medication in a composite outcome. Interpretation of effectiveness was effective. Symptoms and drugs to relief of symptoms: 95% CI for difference between means was 35.9–144.0.

Interpretation of effectiveness: possibly effective

The interpretation of effectiveness was 'possibly effective' in one RCT [45].

Röder [45] *et al.* included 168 children (asthma not excluded) treated for 24 months with a monthly dose of Lol p5 168 µg, administered as drops. The length of preseasonal treatment was up to 24 weeks. Interpretation of effectiveness was possibly effective. Symptoms: 95% CI for difference between means was -0.2 to 0.8. Drugs to relief of symptoms: 95% CI for difference between means was 3.8–5.9.

Interpretation of effectiveness: not effective

The interpretation of effectiveness was 'not effective' in eight RCTs [28,30,32,34,35,36,42,50].

Hordijk *et al.* [28] included 57 grass pollen allergic adult rhinitic patients treated for 10 months with a monthly dose of Lol p5 168 µg administered as drops. The length of preseasonal treatment was of 12 weeks. Interpretation of effectiveness was not effective. Symptoms: 95% CI for difference between means was -0.02 to 3.8. Drugs for relief of symptoms: 95% CI for difference between means was -0.07 to 0.3.

Pradalier *et al.* [30] included 63 adults suffering from grass pollen rhinitis (asthma not excluded) treated for 5 months with a monthly dose of 255 µg of Phl p5, administered as drops and as tablets. The length of preseasonal treatment was 8 weeks. Interpretation of effectiveness was not effective. Symptoms: 95% CI for difference between means was -0.3 to 0.9.

Torres Lima *et al.* [32] included 49 adult patients with grass pollen-induced rhinitis (asthma not excluded), treated for 18 months with a monthly dose of Phl p5 900 µg, administered as drops. The length of preseasonal treatment was between 8 and 30 weeks. Interpretation of effectiveness was not effective. Symptoms: 95% CI for difference between means was -1046.4 to 1104.4. Drugs for relief of symptoms: 95% CI for difference between means was -861.0–1867.0.

Rolinck-Werninghaus *et al.* [34] included 77 children (asthma not excluded) treated for 32 months with a monthly dose of 6 µg of major allergen of *Dactylis glomerata*, *Poa pratensis*, Lol p5, *Anthoxanthum odoratum* and Phl p5, administered as drops. The length of preseasonal treatment was 4 weeks. Interpretation of effectiveness was not effective. Symptoms: 95% CI for difference between means was -9.1 to 11.2. Drugs for relief of symptoms: 95% CI for difference between means was -1.3 to 1.9.

Smith *et al.* [35] included 96 adult patients with grass pollen induced rhinitis (asthma not excluded), treated for 10 months with a monthly dose of Lol p1 867 µg and 504 µg of dactylis glomerata g5, administered as drops and as tables. The length of preseasonal treatment was 12 weeks. Interpretation of effectiveness was not effective. Symptoms: 95% CI for difference between means was -0.1 to 1.1. The drugs used as needed to relief of the symptoms not reported.

Bufe *et al.* [36] included 132 children (asthma not excluded) treated for 36 months with a monthly dose of Phl p5 273 µg, administered as drops. The length of preseasonal treatment was 20 weeks. Interpretation effectiveness was not effective. Symptoms: 95% CI for difference between means was -0.2 to 0.3. Drugs for relief of symptoms: 95% CI for difference between means was -0.005 to 0.1.

de Blay *et al.* [42] included 104 adults (asthma not excluded) treated for 10 months with a monthly dose of 275 µg of major allergen of group 5 of *Dactylis glomerata*, Phl p5 and Lol p5, administered as drops. The length of preseasonal treatment was 32 weeks. Interpretation of effectiveness was not effective. Symptoms: 95% CI for difference between means was -5.6 to 7.6. Drugs for relief of symptoms: 5% confidence interval for difference between means was -2.3 to 6.3.

Ott *et al.* [50] included 145 subjects (11 children) treated for for 3 months per year for 3 consecutive years, with a monthly dose of Lol p5 600 µg, administered as drops. The length of preseasonal treatment was not reported. We obtained crude data (mean ± stardard deviation of symptoms and medication score) by Stallergenes (Anthony, France). Interpretation

of effectiveness was not effective. Symptoms: 95% CI for difference between means was -0.3 to 1.1. Drugs for relief of symptoms: 95% CI for difference between means was -1.4 to 2.6. An important flaw of the Ott study must be noted: the significant difference between placebo and SLIT already at study entry during the baseline season, which represents an important limitation of this study, hampering the reliability of the results.

SLIT (tablets)

We identified seven trials (from 2006 to 2009). Population sizes ranged from 61 to 282 SLIT-treated subjects [37–39,43,49,51,52].

Of the seven trials identified, five studies only involved SLIT-treated adults [37,38,39,43,52] and two only involved SLIT-treated children [49,51].

In the study the preseasonal phase was 112.1 ± 10.1 days and the coseasonal period 38.6 ± 16.2 days [49].

The monthly dose of major allergen varied from one study to another: in four RTCs 450 µg of Phl p5 [37,38,39,51], in two studies 600 µg of Phl p5 [49,52] and in one RTC 750 µg of major allergen group 5 [43].

Interpretation of effectiveness: effective

The interpretation of effectiveness was 'effective' in five RTCs [37,38,43,49,52].

Dahl *et al.* [37] included 586 adults (asthma was not reported) treated for 6 months with a monthly dose of Phl p5 450 µg, administered as tablets. The length of preseasonal treatment was 16 weeks. Interpretation of effectiveness was effective. Symptoms: 95% CI for difference between means was 0.6 to 1.3. Drugs for relief of symptoms: 95% CI for difference between means was 0.5–1.2.

Dahl *et al.* [38] included 93 adults (all with asthma) treated for 5 months with a monthly dose of Phl p5 450 µg, administered as tablets. The length of preseasonal treatment was between 10 and 14 weeks. Interpretation of effectiveness was effective. Symptoms: 95% CI for difference between means was 0.3–2.0. Drugs for relief of symptoms: 95% CI for difference between means was 0.07–3.5. In this study the primary end points were average asthma medication and symptom scores during the grass pollen season, and secondary variables were average rhinoconjunctivitis symptom and medication scores during the grass pollen season. This is the only study in which efficacy of SLIT for allergy rhinitis was the secondary end point. Even though this study does not completely fit the inclusion criteria, we chose to include it in the overall analysis since it was not responsible for the heterogeneity of the results among individual studies, and so we believe that the exclusion of this study could have led to a loss of information (and statistical power) without a clear improvement of the accuracy of the analysis.

Didier *et al.* [43] included 248 adults (asthma not excluded) treated for 6 months with a monthly dose of 750 µg of major allergen of group 5, administered as tablets. The length of preseasonal treatment was 20 weeks. Interpretation of effectiveness was effective. Symptoms: 95% CI for difference between means was 0.6–2.0. Drugs for relief of symptoms: 95% CI for difference between means was 0.05–0.2.

Wahn [49] included 266 children (asthma not excluded) treated for 8 months with a monthly dose of Lol p5 600 µg, administered as tablets. The length of preseasonal treatment was 16 weeks. Interpretation of effectiveness was effective. Symptoms: 95% CI for difference between means was 0.5–1.9. Drugs for relief of symptoms: 95% CI for difference between means was 0.03–0.3.

Horak *et al.* [52] included 99 adults (asthma was not reported) treated for 4 months with a monthly dose of Phl p5 600 µg, administered as tablets. The study was carried out in an artificial set-up (provocation chamber), thus no information about the clinical efficacy in daily life as in all other studies is available. Rescue medication was not given and thus could not be reported. Interpretation of effectiveness was effective in this condition. Symptoms: 95% CI for difference between means was 0.9–3.0.

Interception of effectiveness: possibly effective

The interpretation of effectiveness was 'possibly effective' in one RTC.

Durham *et al.* [39] included 260 adults (asthma was not reported) treated for 6 months with a monthly dose of Phl p5 450 µg, administered as tablets. The length of preseasonal treatment was 8 weeks. Interpretation of effectiveness was 'possibly effective'. Symptoms: 95% CI for difference between means was -0.03 to 0.9. Drugs for relief of symptoms: 95% CI for difference between means was 0.07–1.1.

Although this study is a Phase II, dose-finding RCT, it is appropriate to include it in the analysis, since we analyzed the results with the same dose used in the subsequent studies, and the characteristics of the included populations

are the same as those included in the other subsequent studies [37,38,51]. The results were indeed similar to the other subsequent studies using the same drug at the same dose, even with marginal statistical significance.

Interpretation of effectiveness: not effective

The interpretation of effectiveness was not effective in one RTC.

Bufe *et al.* [51] included 238 children (asthma not excluded) treated for 6 months with a monthly dose of Phl p5 450 µg, administered as tablets. length of preseasonal treatment was 8 weeks. Interpretation of effectiveness was not effective. Symptoms: 95% CI for difference between means was -0.07 to 1.0. Drugs for relief of symptoms: 95% CI for difference between means was -0.4 to 1.2.

Safety

Through the analysis of the double-blind RCTs available to date, a total of 4856 adverse events (AEs) were revealed, 3286 (2.6 AEs/patient) in the SLIT group and 1570 (1.34 AEs/patient) in the placebo group. The majority of AEs were modest in severity for both treatment and placebo groups. A total of 54 patients (3%) in the SLIT group and 12 patients (0.7%) in the placebo group were withdrawn from the studies for treatment-related AEs [20].

The effectiveness of SLIT with grass pollen extracts for AR

On the basis of the results of the available RCTs, summarized in our recent meta-analysis [20] it is possible to conclude that for seasonal allergic rhinoconjunctivitis, SLIT with grass allergens provides an improvement of symptoms and a reduction of anti-allergic medication use in comparison to placebo. These conclusions are based on a positive effect of SLIT compared with placebo observed on nine [27,28,37,38,43,44,47,49,52] out of 19 double-blind randomized controlled trials (DB-RCTs) [27,28,30,32,34–39,42–45,47,49–52] for symptom score and nine [27,37–39,43–45,47,49] out of 17 [27,28,30,32,34,36–39,42–45,47,49–51] studies for rescue medication score.

An important open question relates to the appraisal of the magnitude of SLIT effectiveness. The scoring systems and scales used by the authors of different studies as measures of effectiveness are mostly represented by symptom and medication scores. The benefit is expressed as the differences between SLIT and placebo at the end of treatment. This mean represents a measure expressing the average reduction of symptoms or medication use in the entire population. Unfortunately, in most of RTCs the percentage of subjects who actually benefit from therapy is not reported. Consequently, an important limitation of the studies is that it is not possible to infer which patients would most likely benefit from treatment, and no predictors of response are available yet.

With this important limitation in mind, the results of our meta-analysis showed a statistically significant benefit 'on average' of SLIT compared with placebo, but the general effect was modest both for symptom (SMD: -0.32; 95% CI: -0.44 to -0.21; $p < 0.0001$) and medication (SMD: -0.16; 95% CI: -0.50 to -0.16; $p < 0.0001$) scores [20]. However, these estimates were drawn by studies with very different results, also including the ten negative or insignificant studies [20]. Subgroup analyses allowed us to explain the diversity between the results of the different studies. One of the sources of the between-study heterogeneity is the different effect of SLIT observed in relation to the allergen dose used in different studies. The monthly and cumulative dose of major antigen was largely variable from trial to trial, ranging from 6 to 1200 µg/month. Analyzing studies by monthly dose administered we found that a monthly dose <276 µg of the major allergen Phl p5 was not effective either in symptom reduction or in rescue medication reduction. The best results in terms of effectiveness were obtained in the RCTs using an antigen dose ranging from 276 to 600 µg, with no substantial difference within this range (median SMD: -0.47). Thus, 276–600 µg of the major allergen Phl p5 seems to be the best cost-effective antigen dose [20], in accordance with the statement of the World Allergen Organization (WAO) recent position paper 2009, suggesting 600 µg of the major allergen Phl p5 as the optimal dose [58]. However, it is important to note that the differences in major allergen content reported for different commercially available pharmaceutical preparations is also due in part to the underlying method for major allergen determination. This means that the 'optimal dose' must still be more precisely defined. In any case, keeping these limitations in mind, a clear dose-response effect was demonstrated by a few dose-finding studies, in particular by Durham *et al.* [39] and Didier *et al.* [43]. The Durham study compared three different doses of pharmaceutical preparation administered by tablets, identifying the 75,000 SQ-T,

corresponding to 450 µg/month of the major allergen Phl p5, as the most effective [39]; the Didier study compared three different doses of a different pharmaceutical preparation, also administered by tablets, showing that the 300 IR, corresponding to 600 µg/month of the major allergen Phl p5, was the optimal dose [43]. Other reliable dose-finding studies are lacking, and additional data on the optimal allergen dose were thus obtained by the comparison of different RCTs by meta-analyses, which, however, confirmed data from the aforementioned studies.

Regarding children, the data are not sufficient to conclude that SLIT is effective [20]. However, even in this case the difference with adults could be, at least in part, related to allergen dose, since the only positive study, Wahn's study [49], the only one using high dose of allergen (Phl 1 p5 600 µg) showed a statistically significant benefit. Another two studies, from Rolinck-Werninghaus *et al.* [34] and from Bufe *et al.* [36], using doses ranging from 6 to 273 µg of the same antigen (Phl 1 p5), did not show any difference between SLIT and placebo, while a later study from Bufe [51], even using a high dose of Phl p5, although lower than the one used in the Wahn [49] study (450 µg), showed a positive result with marginal statistical significance (SMD: -0.22; 95% CI: -0.48; 0.03), suggesting a possible dose-related effect. The remaining study, from Röder *et al.* [45], using Lol p5 168 µg as major antigen, did not show any benefit of SLIT compared with placebo.

Another issue that is worth noting is that the Wahn study [49] included a low percentage of patients with asthma (21.4%), compared with the other four studies [34,36,45,51], including 40–58.3% of children with asthma, leaving the doubt that the different population in this study could at least in part influence the final result [20].

Another controversial issue is related both to the duration of treatment and to the correct timing of starting therapy. Our analysis showed that a course of treatment <12 months is more effective than a longer treatment (≥12 months) [20]. Long-term studies confirm the results of this analysis. The study by Smith *et al.* [35] showed that subjects treated with SLIT during the first year and placebo during the second year had a bigger reduction in symptom score compared with placebo than subjects treated with SLIT for two consecutive years. The studies by Dahl *et al.* [46] and Durham *et al.* [59] (representing the extension of the first study by Dahl *et al.* [37]), showed similar differences between SLIT and placebo for symptom score over 3 years of treatment and the first year of follow-up. These studies also show that the benefit of SLIT is maintained over time after cessation of treatment.

Many authors suggested that starting SLIT before the onset of the pollen season could increase the effectiveness of treatment [20]. Indeed our analysis confirms this suggestion, demonstrating that a preseasonal treatment ≥12 weeks is associated with a better response rate both for symptom reduction and anti-allergic medication [20]. Thus, starting the treatment before the beginning of the pollen season could be more important than the duration of the treatment itself for a better clinical response [20].

Regarding the different pharmaceutical preparations, our analysis showed that tablets are more effective than drops for reducing symptoms. This difference is mainly due to the results of child studies. However, in child studies using drops for SLIT, a low monthly dose of antigen was administered, again suggesting that the low effectiveness of drops compared with tablets could be related to the low allergen dose used [20]. It is worth noting that in the group of tablets there are products with very different characteristics and properties. For example, the tablets available so far are actually one fast dissolving lyophilized tablet (1.5 s melting time) and one long-lasting tablet which melts in 2 min. We could not compare studies using fast dissolving tablets to those using long-lasting tablets, because the subgroups would have been too small to gain reliable results. However, when we compared tablets with drops, the subgroup including the studies with tablets showed a very low degree of heterogeneity between the results of individual studies (I^2 = 0 for drug score and 0.33 for symptom score), suggesting that the differences in the tablet pharmaceutical preparations seem not to be important in determining the effectiveness of the treatment. This indicates that the studies using tablets, despite different pharmaceutical preparations, are comparable.

Nonetheless, no definitive conclusion can be drawn from this preliminary analysis, without robust data.

It is worth noting that a high degree of heterogeneity was reported for studies using drops (I^2 =0.58), while a very low degree of heterogeneity was seen in the studies with tablets (I^2 = 0.23). One possible explanation could be that products used for drop studies are highly

heterogeneous. In contrast the very low degree of heterogeneity showed when we analyzed the studies with tablets (I^2 = 0.23), seems to suggest that the different pharmaceutical products have similar effectiveness [20,60].

As mentioned above, a significant source of inconsistency between study results might be the diversity of the populations enrolled in different RCTs, such as patients with different comorbidities (e.g., asthma) [20]. Indeed, the RTCs that showed the largest benefit both for reduction of rhinitis symptoms and anti-allergic medications compared with placebo are those including the lowest percentage of children with asthma [49]. Another hypothesis is that in many patients with nasal symptoms, positive skin tests or serum specific IgE could not be related to nasal symptoms [61]. In other words, researchers should consider including only patients with an accurate diagnosis of an allergic disease, and in whom the allergen sensitization is correlated with symptoms in RCTs. For example, patients enrolled in SLIT studies should have a minimal level of symptoms during exposure (possibly historical for pollen trials or at baseline). Therefore, many patients would be considered for SLIT without there being a true indication.

Concerning this, it must be noted that the selection of patients for SLIT RCTs doesn't necessarily reflect the current suggestions (e.g., patients with long-lasting symptoms and/or those who did not benefit from the best pharmacotherapy and/or those who had side effects from pharmacotherapy and/or those who do not wish pharmacotherapy) [58]. Since these patient characteristics are not included in the published RCTs, we cannot know for certain the precise effectiveness in the general population.

In our previous study, we reported the clinical results of 279 patients who received 4 years of ASI in a clinical setting administered either by means of SCIT or SLIT [62]. We retrospectively examined the relationship of the following parameters determined at the time of diagnosis: diameter of wheal induced by the allergen, serum t-IgE levels, serum s-IgE levels, b-eos counts and clinical response to ASI. We used receiver operating characteristic curves to determine the sensitivity, specificity, and predicted values for wheal diameter, serum s-IgE level, serum t-IgE level, serum s-IgE:t-IgE ratio and b-eos count, all obtained at the time of diagnosis, in predicting one's response to ASI. We found that the serum s-IgE:t-IgE ratio is the best predictor of clinical response to allergen-specific immunotherapy [62].

Although SCIT is still considered the gold standard of immunotherapy, the relative efficacy of SCIT and SLIT has not yet been determined. The comparative efficacy of the two administration routes in grass pollen allergic patients have been evaluated in only one small RCT [62], which was far too small to give reliable results. In any case, it seems that the two routes have the same efficacy if we consider the clinical response, but SCIT seems more effective when we consider the laboratory parameter improvements. In addition, on the basis of the results of the meta-analyses, it seems likely that SLIT has 60–100% of the efficacy of SCIT, analyzing all the antigens tested for immunotherapy, while it is more difficult with the available data to make any inference for grass pollen [63]. Hence, it is difficult to make valid comparisons.

SLIT has gained considerable interest as an alternative approach to SCIT because of its improved safety and easy administration [58]. Only a minority of adverse events leading to withdrawal were reported in RCTs, indicating SLIT as a safe procedure with limited, mostly mild side effects. Nevertheless, in some case reports, significant systemic side effects were reported after SLIT both in patients previously treated with SCIT and in patients previously untreated with SCIT at the first dose of SLIT [20,64–67]. So, both for SLIT and SCIT, a careful evaluation of the patient before starting treatment is recommended. SLIT can be considered a safe treatment. In RCTs, side effects were limited, mostly mild, and only a minority of serious side effects leading to withdrawal were reported. The most common side effects, reported in approximately half the patients, were represented by some local irritation with the first dose. However, such irritation was minor and generally did not require a dose reduction. Initial side effects disappeared in approximately half the patients during the first days of treatment. The risk of anaphylaxis appears to be extremely low. Nevertheless, in a very limited number of patients, significant systemic side effects were reported after SLIT both in patients previously treated with SCIT and in patients previously untreated with SCIT at the first dose of SLIT [65–68]. Therefore, we recommend that the first dose of SLIT should be administered in a doctor's office.

A 'large placebo effect' is another open problem with allergic rhinitis found both in study with drugs and SLIT. The reasons for the large placebo effect may be due to several factors; for example, selection of the patients without sufficient symptoms [69]. For these reasons it has

been suggested that the magnitude of improvement induced by active treatment should be calculated as the percentage reduction of disease severity compared with placebo [70]. In combination with the statistical evaluation of the difference between active and placebo treatment, this gives useful information on the degree of efficacy. This concept represents a very conservative estimate of efficacy, as only the additional effect, compared with the possible beneficial effect of placebo treatment (optimal care and adjustment of drugs) is taken into consideration.

The magnitude of efficacy should be established as the percentage reduction of the global clinical scores in the active versus placebo group. Additional efficacy inferior to the one obtained by antihistamines is not considered acceptable, and consequently the minimal clinically relevant efficacy should be at least 20% higher than placebo [68,71].

Conclusion

In conclusion, the available evidence is sufficient to conclude the following: SLIT with grass allergens improves rhinosinusitis symptoms and reduces the use of antiallergic medications compared with placebo, the overall effect is clinically modest, prolonged preseasonal treatment significantly increases the response rate [20], and a course of treatment no longer than 12 months

Executive summary

Indications for sublingual immunotherapy

- Patients who have long-lasting symptoms during the year.
- Patients who did not respond well to the best pharmacotherapy (e.g., severe chronic upper airway disease).
- Patients who have had side effects from pharmacotherapy and/or do not desire pharmacotherapy.
- Criticisms: patients with these characteristics are not included in the published randomized controlled trials (RCTs).

Effectiveness of sublingual immunotherapy

- Cumulative
  - Symptom score (SS): standardized mean difference (SMD) of -0.32 (95% CI: -0.44 to -0.21; $p < 0.0001$);
  - Medication score (MS): SMD of -0.33 (95% CI: -0.50 to -0.16; $p = 0.0003$).
- Adults
  - SS: median SMD of -0.47
  - MS: median SMD of -0.35
- Children
  - SS median SMD of -0.16
  - MS median SMD of -0.12
- Criticisms:
  - A generalization of the results is not possible;
  - An average benefit for the whole population included in RCTs is reported, but the rate of the patients who actually respond to therapy is unknown;
  - No definite conclusions for children.

Safety

- Good: low rate of adverse events; very low rate of serious adverse events.
- Criticisms: not completely safe. One death has been reported.

Best treatment option

- Long preseasonal treatment (at least 12 weeks).
- Duration of treatment not longer than 1 year.
- Monthly dose between 450 and 600 µg.
- Criticisms:
  - Data drawn from highly heterogeneous RCTs, in terms of dose of allergens and protocols;
  - Many RCTs also had methodological problems.

Future perspective

- Future RCTs must take into account suggestions from previous RCTs and meta-analyses:
  - Homogeneous populations;
  - Adequate duration of preseasonal treatment and treatment;
  - Optimal suggested dose;
  - Sound methodology.
- Defining the role of SLIT in children.

with a monthly allergen dose of 450 µg appears to be the best treatment option [20]. Further studies are needed to clearly define the role of SLIT with grass allergens in children.

Future perspective

The current challenge is to identify those patients who are most likely to benefit from the administration of immunotherapy, subcutaneous immunotherapy or SLIT, and answer the questions: what are the steps necessary to identify likely candidates? And what investigations are needed to validate that choice? Therefore, we suggest that responder analysis should be included in all future immunotherapy studies.

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