



For reprint orders, please contact: reprints@futuremedicine.com

One century of allergen-specific immunotherapy for respiratory allergy

Among the treatments available for respiratory allergy, which include allergen avoidance and pharmacotherapy, specific immunotherapy (SIT) is the only treatment able to not only act on the symptoms of allergy but also act on the causes. SIT is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects and was introduced one century ago. SIT remained an empirical treatment for more than 40 years, but the first controlled trial in 1954 paved the way for the scientific era. At present, SIT may be administered in two forms: subcutaneous (SCIT) and sublingual immunotherapy (SLIT). A large number of trials, globally analyzed in several meta-analyses, evaluated the efficacy and safety of SCIT and SLIT in allergic rhinitis and asthma. Current available data give solid evidence to the clinical efficacy of both SCIT and SLIT in allergic rhinitis and asthma. Providing the recommended doses and administration schedules are adhered to, the safety and tolerability are very good; however, adverse systemic reactions remain a drawback for SCIT. After one century of use, accumulating evidence surrounds SIT and the central role in the management of respiratory allergy.

KEYWORDS: allergy ■ asthma ■ efficacy ■ rhinitis ■ safety ■ specific immunotherapy

Sensitization to environmental inhalant allergens, such as pollens, house dust mites, animal epithelia and moulds, is clinically expressed by rhinitis, conjunctivitis and asthma [1]. The treatment of respiratory allergy is based on allergen avoidance (which is only rarely feasible), drug therapy and allergen-specific immunotherapy (SIT), but only the latter is able to act on the causes as well as the symptoms of allergy [2,3]. Moreover, SIT has a preventative role against new sensitizations and development of asthma in allergic rhinitis patients [2,3]. SIT is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects. It was introduced one century ago [4], but remained a merely empirical treatment until 1954, when the first controlled trial was published [5]. Until the 1980s, the only way to administer SIT was by the injective, subcutaneous route, but the introduction in the market of new, highly biologically potent allergen extracts raised the issue of safety because of a series of fatal systemic reactions [6]. To improve the safety, other routes of administration were investigated, such as oral immunotherapy and local nasal immunotherapy. However, the former was found to be ineffective despite administering very high allergen doses, while the latter showed clinical efficacy but had a poor tolerability, with nasal reactions to each administration of the

extract [2]. In 1986, the sublingual route was proposed for the first time as an alternative route of administration [7] and in the following years after it proved to be an effective and safe treatment for respiratory allergy and thus is the true alternative to the injection route [8]. To date, a very large number of trials provided a solid evidence for efficacy of both subcutaneous immunotherapy (SCIT), and sublingual immunotherapy (SLIT), which was accurately examined by a meta-analysis.

This article aims to provide the reader a comprehensive view on the characteristics of SCIT and SLIT, with a particular focus on their respective advantages and limitations.

Efficacy & safety of SCIT

■ Efficacy of SCIT in asthma

The first meta-analysis on SCIT was performed in 1995, when 20 randomized, placebo-controlled, double-blind trials of allergen immunotherapy for patients with allergic asthma were available [9]. Significant differences in favor of active treatment over placebo were found for symptomatic improvement (odds ratio [OR]: 3.2; 95% CI: 2.2–4.9), for reduction in medication (OR: 4.2; 95% CI: 2.2–7.9), and reduction in bronchial hyper-reactivity (BHR; OR: 6.8; 95% CI: 3.8–12). The authors argued that, although the benefits of SCIT could be overestimated because

**Cristoforo Incorvaia[†]
& Franco Frati^{1,2}**

[†]Institute of Pediatrics, University
Department of Medical & Surgical
Specialties & Public Health,
Perugia, Italy

²Medical & Scientific Department,
Stallergenes, Milan, Italy

[†]Author for correspondence:
Allergy/Pulmonary rehabilitation,
ICP Hospital Via Bignami 1,
20126 Milan, Italy
Tel.: +39 0257 993 289
Fax: +39 0257 993 315
cristoforo.incorvaia@gmail.com

future
medicine part of fsg

of unpublished negative studies, to overturn the positive results, an additional 33 negative studies would be necessary.

The same authors repeated the meta-analysis in 2003, when 75 randomized clinical trials (RCTs) had been published [10]. At that time, the analysis parameter had become the standardized mean difference (SMD). There was a significant improvement in asthma symptom scores in actively treated patients compared with placebo-treated patients (SMD: -0.72; 95% CI: -0.99 to -0.33), a significant reduction of allergen-specific BHR, and a reduction in nonspecific BHR as well. The results of the previous meta-analysis were confirmed using a much higher number of RCTs. The latest meta-analysis update was carried out in 2010, which include 88 RCTs [11].

There were 42 RCTs of SCIT for house mite allergy, 27 for pollen allergy, ten for animal dander allergy, two for *Cladosporium* mould allergy, two for latex and six RCTs looking at multiple allergens. There was a significant improvement in asthma symptom scores (SMD: -0.59; 95% CI: -0.83 to -0.35) and it would have been necessary to treat three patients (95% CI: 3–5) with SCIT to avoid one deterioration in asthma symptoms and to treat four patients (95% CI: 3–6) to avoid one requiring increased medication. SCIT significantly reduced allergen-specific BHR and reduced nonspecific BHR. The authors concluded that SCIT reduces asthma symptoms and use of asthma medications and improves BHR, and that one RCT found that the size of the benefit is possibly comparable with inhaled steroids [11].

■ Efficacy of SCIT in rhinitis

The only meta-analysis available to date was reported by Calderon *et al.* in 2007, who included 51 RCTs [12]. Symptom score data from 15 trials were suitable for the analysis and showed an overall reduction in the SCIT group (SMD: -0.73; 95% CI: -0.97 to -0.50; $p < 0.00001$). Suitable medication score data from 13 RCTs showed an overall reduction in the SCIT group (SMD: -0.57; 95% CI: -0.82 to -0.33; $p < 0.00001$). The authors concluded that SCIT in properly selected patients with seasonal allergic rhinitis results in a significant reduction in symptom scores and medication use. A particular aspect was considered by Nelson, who reviewed studies simultaneously using two or more distinct allergen extracts [13]. A total of 11 studies using SCIT were identified; administration of two extracts was effective, and in studies

using multiple allergens, three studies showed clear efficacy, whereas in the other two studies, a lack of efficacy might have been due to inadequate doses of extract or omission of clinically relevant allergens in the treatment regimen. The authors argued that simultaneous administration of more than one allergen extract is clinically effective, and this is relevant considering that most patients selected for immunotherapy are sensitized to multiple allergens [14].

■ Safety of SCIT

The reports in the 1980s of fatal anaphylactic reactions to SCIT [6,15] raised the important issue of safety, which has actually lead to a decreasing use of such forms of immunotherapy, particularly after SLIT was introduced. Safety was also taken into account in the meta-analyses; in the conclusion of the latest meta-analysis by Abramson *et al.* on SCIT in asthma, it was stated that the possibility of local or systemic adverse effects (such as anaphylaxis) must be considered [11]. In the meta-analysis by Calderon *et al.* on rhinitis, SCIT showed a relatively low risk of severe adverse events. Adrenaline was administered in 0.13% (19 out of 14,085 injections) of those on active treatment and in 0.01% (one out of 8278 injections) of the placebo group for treatment of adverse events, and there were no fatalities [12].

In addition, studies specifically on SCIT safety are available. In 2000, Møllerup *et al.* evaluated the safety of three different induction regimens of clustered immunotherapy (several injections administered during each visit) with both aqueous and aluminum depot extracts in 657 patients (10,369 injections). An overall number of 454 systemic (immediate and late) reactions were observed in 257 patients corresponding to 4.4% of the injections and 39.1% of the patients. Most of the systemic reactions were of little clinical importance and less than 1% were anaphylactic reactions. The 8-week induction regimen using exclusively alum depot extracts showed a statistically significant lower frequency and severity of systemic side effects. Immunotherapy with cat and mite allergen extracts showed the highest frequency of severe side effects, probably because these extracts were used predominantly in asthmatic patients [16].

In a recent survey conducted in 11 Italian allergy departments using only standardized depot extracts, 1738 patients received SCIT from eight different manufacturers, for a total of 2038 courses (300 patients received two extracts). A total of 60,785 injections were administered over a mean SCIT duration of

3 years [17]. Overall, 95 reactions were observed in 57 patients (3.28%), corresponding to 4.7% of the courses and 1.56 of 1000 injections. A total of 25 patients had more than one adverse event. There were 34 grade 2, 60 grade 3 and one grade 4 reactions (classified according to the recommendation of the European Academy of Allergy and Clinical Immunology) [18] and no fatalities. Systemic reactions occurred more frequently in patients with asthma than in patients with rhinitis alone (4.1 vs 1.1%), and were equally distributed between the build-up and the maintenance phase. Ragweed and grass extracts caused significantly more side effects than other allergens.

Such data show that SCIT is well tolerated in most patients and that anaphylactic reactions are rare; however, the risk of a fatal or near-fatal reaction, although very low, requires that the anticipated benefit attributed to the treatment must be weighed against such potential risk [19]. One may argue that this balance may be considered unfavorable in treating patients with respiratory allergy, and this was a major impulse for the development of SLIT.

Efficacy & safety of SLIT

■ Efficacy of SLIT in asthma

In the first meta-analysis on efficacy of SLIT there was an insufficient number of RCTs on asthmatic patients to allow a separate analysis [20]. Indeed, in the meta-analysis by Olaguibel *et al.* including seven RCTs conducted on children aged up to 14 years [21], SLIT was significantly effective on asthma symptoms (SMD: -1.42; $p = 0.01$). The significantly positive effect in children was later confirmed by a meta-analysis of nine studies, including a total number of 441 subjects, 232 actively treated and 209 placebo-treated patients [22]: a significant reduction was found in both symptoms scores (SMD: -1.14; $p = 0.02$) and drug use (SMD: -1.63; $p = 0.007$).

Instead, in meta-analysis including 25 studies on subjects of any age, with a total number of 1706 patients, the SMD of the reduction of asthmatic symptoms did not reach the statistical significance [23]. However, using the intention-to-treat method for outcome measures, significant decreases of asthma symptoms and drug consumption and significant increases of lung function and BHR were detected. The number needed to treat (NNT) to avoid leaving one patient with the same symptoms or worse was 3.7, which is in the range of those reported for injective SIT in asthmatic and rhinitic patients.

■ Efficacy of SLIT in rhinitis

The first meta-analysis was performed in 2005 when 22 RCTs were available [20], and 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 patient age and the type of allergen, because of the relatively low numbers. This was assessed in subsequent analyses. In 2006, a meta-analysis on the efficacy of SLIT in children with rhinitis was published, including ten RCTs with an overall number of 484 patients (245 actively treated and 239 placebo treated). A significant reduction of both symptoms (SMD: -0.56; $p = 0.02$) and medication (SMD: -0.76; $p = 0.03$) was observed [24]. 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 lasting longer than 18 months and for pollen allergens compared with house dust mites. In 2010, the global meta-analysis on rhinitis was updated, including 49 RCTs, 2333 patients treated with SLIT and 2256 treated with placebo [25]. Significant reductions were confirmed for symptoms (SMD: -0.49, 95%CI: -0.64 to -0.34; $p < 0.00001$) and medication scores (SMD: -0.32, 95% CI: -0.43 to -0.21; $p < 0.00001$) in favor of the active treatment.

Indeed, further recent meta-analyses addressed the allergen source issue. As for house dust mites, a meta-analysis limited to SLIT with mite extracts showed “promising evidence of efficacy” but suggested a need for “more data, derived from large population-based high-quality studies” [26]. Instead, the meta-analysis limited to studies on grass pollen allergy found that SLIT significantly reduces both symptoms (SMD: -0.32) and medication use (SMD: -0.33), compared with placebo, is more efficacious in adults than in children, and prolonging the duration of preseasonal treatment for more than 12 weeks improves the treatment efficacy [27].

■ Safety of SLIT

All meta-analyses found that the most common adverse events are local reactions in the oropharynx and in the GI tract after the extract is swallowed, and that systemic reactions such as asthma, rhinitis or urticaria are quite rare [20–25]. In the analysis by Calamita *et al.* [23], the number needed to harm (i.e., the number of patients

to treat to have one adverse reaction) was also calculated. The number calculated was equivalent to 14.3, therefore, more than 14 patients with asthma must be treated with SLIT to have one patient with an adverse reaction. Most local reactions are self-limiting and easy to manage. The safety of SLIT was confirmed by systematic reviews on patients of any age [28,29] as well as in children younger than 5 years [30,31]. Of note, in the review including the highest number of studies, no difference in rate of systemic reactions was found comparing trials using low allergen doses and high allergen doses, respectively [29]. Anaphylactic reactions are extremely rare; an analysis of a series of case reports showed that in most cases the reaction is caused by a mistake, such as the assumption of very high doses or the use of improper allergen mix [32]. However, an increased risk is apparent in subjects undergoing SLIT because of previous systemic reactions to SCIT [33,34], particularly when no up dosing regimens are used [33], and this suggests that the occurrence of systemic reactions to SCIT such as an admission criterion to SLIT should be considered [35]. In any case, SLIT should not be considered a completely safe method of SIT and needs to be applied following the correct indication, prescription and follow-up by specialists.

Conclusion & future perspective

Specific immunotherapy in both its current routes of administration is an effective treatment for respiratory allergy, as shown by a series of meta-analyses, in particular, by the latest updates including a huge number of trials [11,25] that attribute to SCIT and SLIT the maximum level of evidence (the Ia level) [36]. In fact, the categories of evidence are classified from a minimum level of IV (evidence from an expert committee reports or opinions of clinical experience of respected authorities) to a maximum level of Ia (evidence from meta-analysis of randomised controlled trials) [37]. Yet, meta-analysis is still not the perfect method, since the heterogeneity of the included studies is a major limitation, which when statistically analyzed is generally highly significant. Such limitations can be obviated by single studies conducted on high 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 [38], 628 adults treated using a five-grass pollen extract [39] and 278 children treated using the same five-grass preparation [40]. These studies, known as 'big trials', showed a highly significant

improvement in symptoms and rescue-medication scores in actively treated patients compared with placebo-treated patients during the grass pollen season. In addition, the big trials provided important observations concerning the dose dependence of clinical efficacy: only high doses, corresponding to 75,000 standard quality in the Timothy grass pollen trial [38], and an index of reactivity of 300 in the five-grass extract trial [39], were effective. These new products in tablets were aimed at introducing formulations fulfilling the requirements of the European regulatory authorities to be registered for use in patient with an allergy to grass pollen, and thus to be considered (differently from the old named patient product preparations) comparable with drugs.

Calculating the monthly cumulative dose, the World Allergy Organization position paper on SLIT suggested a dose of 600 µg of the grass pollen major allergen Phl p 5 was optimal [41].

This compares SLIT, although provisionally limited to grass pollen extracts, with SCIT concerning the concept of dose dependence, which has long been recognized in the latter. In fact, for SCIT, the amounts in microgram of major allergens administered in the maintenance phase to expect clinical efficacy were identified for the most important allergens, including ragweed pollen, dust mites and cat epithelium [42]. Indeed, the search for optimal dose in SLIT should be based on the microgram of major allergens. Since one of the reasons for different results in different studies may obviously depend on difference as large as 50-times in major allergen contents in allergen extracts from different sources, only trials using extract with similar allergen content should be compared in future meta-analyses.

The future perspectives for SIT include introduction of new materials concerning active components such as recombinant allergens, modified allergens, hypoallergenic isoforms and tolerogenic peptides; as well as adjuvants to enhance the efficacy such as monophosphoryl lipid A or bacterial DNA, with the latter inducing tolerance to allergens through the stimulation of Toll-like receptors that control innate immunity [43,44].

As far as other allergic diseases are concerned, SCIT has a central role in hypersensitivity to hymenoptera venom; it is able to prevent fatal reactions in all treated subjects [45]. Meanwhile, there are initial data on the feasibility of further applications, such as SLIT in food allergy [46,47] and both SCIT and SLIT in atopic dermatitis [46,48].

In addition, new routes of administration were recently proposed based on intralymphatic and epicutaneous administration, with

both demonstrating encouraging results in first studies [49,50]. In particular, in a study of grass pollen allergy, 165 patients were randomized to receive either 54 injections with pollen extract over 3 years or three intralymphatic injections over 2 months; despite the huge difference in cumulative allergen doses, the intralymphatic administration was equally effective than standard SCIT, and was significantly better tolerated [49]. The study on epicutaneous immunotherapy was conducted on a small population, including 37 patients with grass pollen allergy, 21 of them being actively treated and 16 being placebo treated; active treatment achieved

significantly lower scores to specific nasal challenge and was well tolerated [50]. Further investigations are needed to add these new routes of SIT to current practice.

Financial & competing interests disclosure

Cristoforo Incorvaia has received fees as a scientific consultant to Stallergenes, Milan, Italy. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Efficacy of subcutaneous immunotherapy in asthma

- The updated global meta-analysis, including 88 randomized controlled trials, showed that subcutaneous immunotherapy (SCIT) reduces asthma symptoms and use of asthma medications.
- SCIT also improved bronchial hyper-responsiveness and, in one trial, demonstrated a sizable benefit in comparison with inhaled steroids.

Efficacy of SCIT in rhinitis

- SCIT in properly selected patients with allergic rhinitis resulted in a significant reduction in symptom scores and medication use.
- Simultaneous administration of more than one allergen extract was clinically effective; this is relevant in polysensitized patients.

Safety of SCIT

- SCIT is well tolerated in most patients and anaphylactic reactions are rare.
- However, the risk of severe reactions requires that the anticipated benefit attributed to the treatment must be weighed against such potential risk.

Efficacy of sublingual immunotherapy in asthma

- SLIT is effective in children with allergic asthma as demonstrated by meta-analyses.
- The evidence for efficacy in adults is less solid.
- In one meta-analysis, a number needed to treat of 3.7 was calculated, which is comparable to the value of 3.0 reported for SCIT.

Efficacy of SLIT in rhinitis

- The updated global meta-analysis, including 49 randomized controlled trials found significant reductions for symptoms and medication scores in favor of the active treatment.
- Concerning house dust mites, a meta-analysis showed promising evidence for efficacy, but more data derived from large population-based high-quality studies are needed.
- A meta-analysis limited to studies on grass pollen allergy found that SLIT significantly reduced both symptoms and medication use in a dose-dependent manner.

Safety of SLIT

- The most common adverse events are local reactions in the oropharynx and in the GI tract after the extract is swallowed.
- Systemic reactions such as asthma, rhinitis or urticaria are quite rare, and anaphylactic reactions are extremely rare.
- In any case, SLIT should not be considered a completely safe method of allergen-specific immunotherapy and needs to be applied following the correct indication, prescription and follow-up by specialists.

Future perspective

- Introduction of new materials, concerning active components, such as recombinant allergens, modified allergens, hypoallergenic isoforms and tolerogenic peptides, as well as adjuvants to enhance the efficacy are likely to further improve allergen-specific immunotherapy.
- Concerning SLIT, the formulation in tablets ensures optimal products for both patients and regulatory authorities.
- New routes of administration, based on intralymphatic and epicutaneous administration, showed encouraging results in first studies and warrant further investigation.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Pucci S, Incorvaia C: Allergy as an organ and a systemic disease. *Clin. Exp. Immunol.* 153(Suppl. 1), 1–2 (2008).

- 2 Bousquet J, Lockey R, Malling HJ: Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J. Allergy Clin. Immunol.* 102(4), 558–562 (1998).

- Established the scientific standards for allergen immunotherapy.

- 3 Bousquet J, Khaltav N, Cruz AA (Eds); World Health Organization, GA(2)LEN, AllerGen: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(Suppl. 86), 8–160 (2008).

- 4 Noon L, Cantab BC, Eng FR: Prophylactic inoculation against hay fever. *Lancet* 177 (4580), 1572–1573 (1911).
- **Introduced allergen immunotherapy.**
- 5 Frankland A, Augustin R: Prophylaxis of summer hay fever and asthma: a controlled trial comparing crude grass pollen extract with the isolated main protein components. *Lancet* 266(6821), 1055–1058 (1954).
- **The first controlled trial on allergen immunotherapy.**
- 6 Lockey RF, Benedikt LM, Turkeltaub PC, Bukantz SC: Fatalities from immunotherapy (IT) and skin testing (ST). *J. Allergy Clin. Immunol.* 79(4), 660–677 (1987).
- 7 Scadding GK, Brostoff J: Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin. Allergy* 6(5), 483–491 (1986).
- 8 Canonica GW, Passalacqua G: Noninjection routes for immunotherapy. *J. Allergy Clin. Immunol.* 111(3), 437–448 (2003).
- 9 Abramson MJ, Puy RM, Weiner JM: Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am. J. Respir. Crit. Care Med.* 151(4), 969–974 (1995).
- 10 Abramson MJ, Puy RM, Weiner JM: Allergen immunotherapy for asthma. *Cochrane Database Syst. Rev.* 4, CD001186 (2003).
- 11 Abramson MJ, Puy RM, Weiner JM: Injection immunotherapy for asthma. *Cochrane Database Syst. Rev.* 8, CD001186 (2010).
- **Updated meta-analysis on subcutaneous immunotherapy.**
- 12 Calderon MA, Alves B, Jacobson M *et al.*: Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst. Rev.* 1, CD001936 (2007).
- 13 Nelson H: Multiallergen immunotherapy for allergic rhinitis and asthma. *J. Allergy Clin. Immunol.* 123(4), 763–769 (2009).
- 14 Ciprandi G, Alesina R, Ariano R *et al.*: Characteristics of patients with allergic polysensitization: the POLISMAIL study. *Eur. Ann. Allergy Clin. Immunol.* 40(3), 77–83 (2008).
- 15 Committee on Safety in Medicine: CSM update: desensitizing vaccines. *BMJ* 293 (6552), 948 (1986).
- 16 Møllerup MT, Hahn GW, Poulsen LK, Malling H: Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment. *Clin. Exp. Allergy* 30(10), 1423–1429 (2000).
- 17 Schiappoli M, Ridolo E, Senna G *et al.*: A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. *Clin. Exp. Allergy* 39(10), 1569–1574 (2009).
- 18 Bousquet J, Brozek J, Bachert C *et al.*: The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper. *Allergy* 64(12), 1737–1745 (2009).
- 19 Rezvani M, Bernstein DI: Anaphylactic reactions during immunotherapy. *Immunol. Allergy Clin. North Am.* 27(2), 295–307 (2007).
- 20 Wilson DR, Torres-Lima M, Durham S: Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 60(1), 4–12 (2005).
- 21 Olaguibel JM, Alvarez Puebla MJ: Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J. Investig. Allergol. Clin. Immunol.* 15(1), 9–16 (2005).
- 22 Penagos M, Passalacqua G, Compalati E *et al.*: Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 133(3), 599–609 (2008).
- 23 Calamita Z, Saconato H, Pela AB, Atallah AN: Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 61(10), 1162–1172 (2006).
- 24 Penagos M, Compalati E, Tarantini F *et al.*: Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3–18 years of age: a meta analysis of randomized placebo-controlled, double blind trials. *Ann. Allergy Asthma Immunol.* 97(2), 141–148 (2006).
- 25 Radulovic S, Calderon MA, Wilson D, Durham S: Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst. Rev.* 12, CD002893 (2010).
- **The updated meta-analysis on sublingual immunotherapy.**
- 26 Compalati E, Passalacqua G, Bonini M, Canonica GW: The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy* 64(11), 1570–1579 (2009).
- 27 Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G: Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J. Allergy Clin. Immunol.* 126(3), 558–566 (2010).
- 28 André C, Vatrinet C, Galvain S, Carat F, Sicard H: Safety of sublingual swallow immunotherapy in children and adults. *Int. Arch. Allergy Immunol.* 121(3), 220–234 (2000).
- 29 Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G: The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin. Exp. Allergy* 35 (5), 565–571 (2005).
- **Systematic review demonstrates that, in contrast to subcutaneous immunotherapy, there is no dose dependence of safety for sublingual immunotherapy.**
- 30 Rienzo VD, Minelli M, Musarra A *et al.*: Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin. Exp. Allergy* 35(5), 560–564 (2005).
- 31 Fiocchi A, Pajno G, La Grutta S *et al.*: Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann. Allergy Asthma Immunol.* 95(3), 254–258 (2005).
- 32 André C, Fadel R: Anaphylaxis caused by allergen sublingual immunotherapy? *Allergy* 62 (10), 1220–1221 (2007).
- 33 de Groot H, Bijl A: Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 64(6), 963–964 (2009).
- 34 Cochard MM, Eigenmann PA: Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy. *J. Allergy Clin. Immunol.* 124(2), 378–379 (2009).
- 35 Incorvaia C, Mauro M: Do indications to sublingual immunotherapy need to be revised? *J. Allergy Clin. Immunol.* 125(1), 277–278 (2010).
- 36 Passalacqua G, Durham SR: Global Allergy and Asthma European Network: Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J. Allergy Clin. Immunol.* 119(4), 881–891 (2007).
- 37 Shekelle PG, Woolf SH, Eccles M, Grimshaw J: Clinical guidelines: developing guidelines. *Br. Med. J.* 318(7183), 593–596 (1999).
- 38 Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S: Sublingual immunotherapy with once daily grass allergen tablet: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 117(4), 802–809 (2006).
- 39 Didier A, Malling HJ, Worm M *et al.*: Optimal dose, efficacy, and safety of once daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* 120(6), 1338–1345 (2007).

- 40 Wahn U, Tabar A, Kuna P *et al.*: SLIT Study Group: Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 123(1),160–166 (2009).
- 41 Canonica GW, Bousquet J, Casale T *et al.*: Sublingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 64(Suppl. 91), 1–59 (2009).
- ■ **Established the scientific standards for sublingual immunotherapy.**
- 42 Van Metre TE, Adkinson NF Jr: Immunotherapy for aeroallergen disease. In: *Allergy. Principles and Practice*. Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW (Eds). Mosby, St Louis, MO, USA 1327–1343 (1988).
- 43 Passalacqua G, Lombardi C, Troise C, Canonica GW: Sublingual immunotherapy: certainties, unmet needs and future directions. *Eur. Ann. Allergy Clin. Immunol.* 41(6), 163–170 (2009).
- 44 Nagata M, Nakagome K: Allergen immunotherapy in asthma: current status and future perspectives. *Allergol. Int.* 59(1), 15–19 (2010).
- 45 Bilò BM, Bonifazi F: Hymenoptera venom immunotherapy. *Immunotherapy* 3(2), 229–246 (2011).
- 46 Incorvaia C, Mauro M, Cappelletti T *et al.*: New applications for sublingual immunotherapy in allergy. *Recent Pat. Inflamm. Allergy Drug Discov.* 3(2), 113–117, (2009).
- 47 Kamdar T, Bryce PJ: Immunotherapy in food allergy. *Immunotherapy* 2(3), 329–338 (2010).
- 48 Novak N: Allergen specific immunotherapy for atopic dermatitis. *Curr. Opin. Allergy Clin. Immunol.* 7(6), 542–546 (2007).
- 49 Senti G, Prinz Vavricka BM, Erdmann I *et al.*: Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. *Proc. Natl Acad. Sci. USA* 105(46), 17908–17912 (2008).
- 50 Senti G, Graf N, Haug S *et al.*: Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. *J. Allergy Clin. Immunol.* 124(5), 997–1002 (2009).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.