



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

Sublingual immunotherapy for allergic rhinitis and conjunctivitis

Sublingual immunotherapy (SLIT) for allergic respiratory diseases was first described in 1986 and immediately appeared as a viable alternative to the traditional subcutaneous route. Since then, more than 60 randomized controlled trials have been published, almost all with very favorable results. The average improvement over placebo in symptom score and medication use was always greater than 20%. The results of the clinical trials were pooled in several meta-analyses, which consistently confirmed the efficacy of the treatment. SLIT is characterized by a satisfactory safety profile, its side effects being mainly limited to oral discomfort. Only six anaphylaxes and no fatalities have been so far reported. Due to the good risk:benefit ratio, SLIT is currently being investigated in diseases other than respiratory allergy, such as food allergy and atopic dermatitis.

KEYWORDS: allergic rhinoconjunctivitis ■ efficacy ■ meta-analysis ■ safety ■ SLIT ■ sublingual immunotherapy

In 1986 the use of allergen-specific immunotherapy (SIT) administered by the sublingual route (SLIT) was described for the first time [1]. Until then, the only route of administration for SIT remained subcutaneously (SCIT), which was repeatedly demonstrated to be effective in respiratory allergy. Nonetheless, with SCIT, some risk of severe or even fatal adverse events still remains [2]. The risks can be partly attributed to technical/human errors and can therefore be avoided [3]; however, a large fraction of the severe adverse events reported remain unpredictable, even if all precautions are taken. Based on this, alternative routes of administration were repeatedly approached. Among them, SLIT appeared as a promising route, despite initial skepticism owing to the low doses used and the poor design of the early studies [4]. During the last 15 years, numerous randomized controlled trials confirmed the clinical efficacy of this route and several postmarketing surveys supported the good safety profile of SLIT. Nowadays, SLIT is officially accepted in international documents as a viable alternative to SCIT [4–6] for both adults and children. In addition, thanks to the good safety profile, the use of SLIT has also recently been proposed in non-respiratory allergy, including atopic dermatitis and food allergy [7].

Despite the abundant literature confirming the efficacy of SLIT, some aspects are still debated, such as the optimal maintenance dose, best administration regimen and duration of the treatment. Finally, the wide variability in standardization methods, usually applied using

in-house references, render the published studies difficult to compare.

SLIT for allergic rhinoconjunctivitis

■ Efficacy

To date, the principal indication to SLIT remains allergic rhinoconjunctivitis and most of the clinical data derive from trials conducted in patients with that disease. More than 60 randomized double-blind placebo-controlled trials have been published so far (for review see [6]), two-thirds of them in dust mites and grass allergy.

The majority of trials assessed the effects of SLIT in allergic rhinitis; however, some also evaluated the effects in asthma, although only in few studies was asthma the primary outcome. Only six studies produced completely negative results (no difference vs placebo) [8–13]. In the 60 positive studies, the degree of clinical effect ranged from 10 to 45% over placebo with greater than 20% in about two-thirds. When analyzing the available trials, it was noted that some meta-analyses were continued, subdividing patients for age, allergen or disease (TABLE 1) [14–21]. Four meta-analyses evaluated the use of SLIT considering only allergic rhinitis for symptoms and drug intake [14,17,19,20] (three included patients of all ages [14,19,20] and the fourth only patients aged 5–18 years [17]), all providing results consistently in favor of SLIT versus placebo [22]. The same was evidenced in the two meta-analyses that only took asthma into account [15,17]. Nieto *et al.* questioned the reliability of these meta-analyses, underlining the possible publication

Giovanni Passalacqua^{*1},
Valentina Garelli¹,
Francesca Scilifò¹
& Giorgio Walter
Canonica¹

¹Allergy & Respiratory Diseases, IRCCS
San Martino-IST-University of Genoa,
Padiglione Maragliano, L.go R. Benzi
10, 16132 Genoa, Italy

^{*}Author for correspondence:

Tel.: +39 10 3538908

Fax: +39 10 3538904

passalacqua@unige.it

Future
Medicine

fsg
part of

Table 1. Meta-analyses of sublingual immunotherapy.

Study (year)	Patients	Disease	Trials	Effect size on symptoms	Effect size on medications	Comment	Ref.
Calamita <i>et al.</i> (2006)	303 adults + children	Asthma	5 pollens 4 mite	-0.38 ($p = 0.07$)	-0.82 ($p = 0.01$)	No change in symptom score Significant reduction in medication score	[15]
Wilson <i>et al.</i> (2005)	959 adults + children	Rhinitis	16 pollens 6 mite	-0.42 ($p = 0.002$)	-0.43 ($p < 0.001$)	Decreased symptoms and medications for rhinitis Asthma not evaluable	[14]
Penagos <i>et al.</i> (2008)	484 children	Rhinitis	5 pollens 4 mite	-0.56 ($p = 0.02$)	-0.76 ($p = 0.03$)	Decreased symptoms and medications for rhinitis No subanalysis feasible	[16]
Penagos <i>et al.</i> (2006)	441 children	Asthma	3 pollen 3 mite	-1.42 ($p = 0.02$)	-1.63 ($p = 0.007$)	Decreased symptoms and medications for asthma	[17]
Compalati <i>et al.</i> (2009)	858 adults + children	Rhinitis Asthma	Mite 8 rhinitis 9 asthma	Rhinitis: -0.95; asthma: -0.95 ($p = 0.02$)	-1.88 ($p = 0.04$)	Significant effect on symptoms and drug intake for both rhinitis and asthma	[18]
Di Bona <i>et al.</i> (2010)	2791 adults + children	Rhinitis	19 grass	-0.32 ($p < 0.0001$)	-0.33 ($p = 0.001$)	Decreased symptoms and medications for rhinitis Greater effect in adults	[19]
Radulovic <i>et al.</i> (2010)	4589 adults + children	Rhinitis	23 grass 8 mite 18 other	SMD: -0.49; ($p < 0.00001$)	-0.32 ($p < 0.001$)	Similar size effect also for medications	[20]
Calderon <i>et al.</i> (2011)	3950 adults + children	Conjunctivitis	35 seasonal 12 perennial	SMD: -0.41; ($p < 0.001$)	-0.1 ($p = \text{NS}$)	Significant difference also for individual symptoms	[21]

NS: Not significant; SMD: Standardized mean difference.

biases, the incorrect reporting and the high heterogeneity testified by the large CIs (certainly owing to the variability in the inclusion criteria, doses, regimens and outcome measures) [23]. Some of the concerns expressed by Nieto *et al.* (especially heterogeneity) remained, nonetheless, valid, even after more recent meta-analyses were published. However, meta-analysis is so far the only way to summarize the results of studies when they are not comparable with each other. In addition, more recent meta-analyses, restricted to house dust mite and grasses [19,20] confirmed the results with a lesser heterogeneity grade. Finally, the superiority of SLIT over placebo was confirmed, also limiting the analysis to conjunctivitis symptoms [21].

Relevant information on SLIT (grass tablets) in allergic rhinitis was obtained in the so-called 'big trials', where more than 200 individuals were enrolled in each study (in some cases up to 600) [12,24–31]. Some of these trials had a dose-ranging design, thus it was possible to demonstrate a dose-dependent clinical effect of SLIT and to identify the optimal maintenance dose for grasses in 15–25 µg major allergen per day (approximately 50-times the monthly dose of SCIT). Finally, a magnitude of clinical effect of 20% or greater over placebo is considered

clinically relevant [32] and in the quoted studies this magnitude ranged from 25 to 50% (TABLE 2) [12,24–31].

The comparison between immunotherapy and drugs is still a matter of debate. In particular, the clinical effects of SLIT can be appreciated only in the long term (months), whereas traditional drugs act immediately. The only available head-to-head trials comparing SLIT as add-on therapy versus inhaled budesonide [33] and montelukast [34] in patients with asthma and rhinitis, respectively, consistently showed a favorable outcome for SLIT, in nasal and bronchial symptoms, and nasal inflammation.

Finally, there are very few randomized trials directly comparing SLIT with SCIT. The first was randomized, double-blind and double-dummy, but without a placebo arm, which failed to find significant difference between SLIT and SCIT [35]. Another was randomized, double-blind, double-dummy and placebo-controlled, and showed no significant difference in clinical efficacy between the two routes of administration over 2 years in birch-allergic patients [36]. Another recent, randomized, open controlled trial in children with asthma and rhinitis due to mite provided similar results [37]. Finally, a meta-analysis-based comparison between SLIT and

SCIT for grass pollen allergy reported a more prominent effect in favor of SCIT, although this comparison was totally indirect and with high data heterogeneity [38]. Thus, the few head-to-head comparison trials (with a small number of subjects) could not demonstrate a difference between the two routes, whereas an indirect comparison pooling together all the grass pollen studies was in favor of SCIT. In conclusion, no robust evidence so far exists to suggest that one route is superior to the other.

■ Safety

After more than 25 years of clinical use, the satisfactory safety profile of SLIT has been well acknowledged [6,39]. In general, the vast majority (>90%) of side effects of SLIT are represented by local adverse reactions such as oral itching/swelling/burning, nausea and stomach ache. These side effects are usually mild and tend

to disappear after the first doses (<10 days) [40,41]. Systemic side effects, such as rhinitis, asthma and urticaria, are reported to be very rare, and to occur in less than 1% of patients. Only six cases of anaphylaxis [42–46] have been described so far, with some of them not using standardized extracts. Finally, no fatal event has ever been described. Due to the rarity of severe adverse events, no risk factor has so far been clearly identified. Nonetheless, based on common sense and transferring our knowledge about SCIT to SLIT, it is recommended to not administer SLIT to patients with severe/uncontrolled asthma. Also, it is recommended that the first dose of SLIT is administered under medical supervision [6]. Below 5 years of age is generally considered a relative contraindication to SCIT owing to safety concerns [4]; however, postmarketing surveys have clearly shown that SLIT-induced side effects are no more frequent or severe in small

Table 2. Large trials with sublingual immunotherapy.

Study (year)	Age range (years)	Pts (A/P)	Allergen	Duration	Dose preparation	Main positive results over placebo	Ref.
Durham <i>et al.</i> (2006)	18–66	569/286	Grass 3 doses	6 months	15 µg (136 pts) 150 µg (139 pts) 450 µg (294 pts) Phl p5/month Tablets	Drug score -28% (p = 0.012) Symptoms -21% (p = 0.002) only with the highest dose QoL improved. No clinical change with the two low doses	[24]
Dahl <i>et al.</i> (2006)	23–35	316/318	Grass	6 months	450 µg Phl p5/month Cumulative 2.7 mg Tablets	RC symptoms -30% (p = 0.001); RC drugs -38% (p = 0.001); well days -52% (p = 0.004)	[25]
Didier <i>et al.</i> (2007)	25–47	472/156	Grass 3 doses	6 months	240 µg (157 pt) 750 µg (155 pt) 1.2 mg (160 pt)/month Tablets	For 300 and 500 IR Total and individual symptom and drug scores (p < 0.001) RQLQ improved	[26]
Wahn <i>et al.</i> (2009)	4–17	139/139	Grass	8 months	600 µg major allergen/month Tablets	Rhinitis score -28% (p = 0.01) Medications -24% (p = 0.006) Medication free days (p = 0.01)	[27]
Ott <i>et al.</i> (2009)	20–50	142/67	Grass	5 years 4 seasons	Cumulative 1.5 mg major allergen/season	Combined score and symptom score significantly reduced since first season. Symptoms decrease from -33 to 47% (third season). No change in medication scores	[28]
Bufe <i>et al.</i> (2009)	5–16	126/127	Grass	6 min	450 µg Phl p5/month Tablets	Significant reduction in RC symptom score (-24%), asthma score (-64%), RC medications (-34%) and well days (+28%) All p < 0.03	[29]
Blaiss <i>et al.</i> (2011)	5–17	349/358	Grass	6 min	450 g Phl p5/month	Significant reduction in combined score (-26%); QoL -38%	[30]
Nelson <i>et al.</i> (2011)	18–63	213/225	Grass	10 min	450 µg Phl p5/month Tablets	Significant reduction in combined (-20%) and medication score (-20%)	[31]
de Bot <i>et al.</i> (2012)	6–18	126/125	Mite	2 years	4.06 µg Der p1/week Drops	No difference between active and placebo in all parameters	[12]

A/P: Active/placebo; pt: Patient; QoL: Quality of life; RC: Rhinoconjunctivitis; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire.

children than in older age groups [47–49], even when multiple allergens are administered [50].

There is a certain dose-dependence in side effects, since their occurrence increases as the dose increases; however, so far there is no clear demonstration of a ‘maximum tolerated dose’. A controlled dose-finding study involved 48 grass pollen allergic patients outside pollen season [51]. They received SLIT for 28 days at progressively increasing doses, up to 200 µg Phl p 5 allergen (approximately 40-times the dose given subcutaneously). The incidence of side effects was 74%, all of mild or moderate intensity, the most frequent being irritation of the throat and oral itching. An up dosing phase, as is usually carried out with SCIT, seems to be unnecessary with SLIT and the treatment course can be started immediately with the maintenance dose [24,26,52,53].

Effects on the natural history of respiratory allergy

SIT is recommended as part of the treatment for allergic rhinitis as an adjunct to the pharmacological treatment plan, in order to reduce symptoms and the need for rescue medications. This is named the ‘immediate’ or ‘early’ effect. Nonetheless, it is well known that rhinitis represents an independent risk factor for the subsequent development of asthma and none of the available drugs are capable of modifying this progression. On the other hand, SIT acts as a biological response modifier and induces profound changes in the immune response to allergens, meaning that it can affect the natural history of allergy in the long term [54]. This ‘preventive’ effect was firstly demonstrated with SCIT. In a randomized open controlled study, SCIT was able to significantly reduce the risk of developing asthma after 3 years of follow-up in allergic children with rhinitis only and this effect was maintained 7 years following discontinuation [55]. These results were subsequently replicated with SLIT. An open randomized controlled study involved 113 children suffering from seasonal rhinitis due to grass pollen, who were randomly allocated to medications plus SLIT or medications only [56]. After 3 years, 8/45 SLIT subjects and 18/44 controls developed asthma, with a relative risk of 3.8 for untreated patients. Another open prospective controlled study involved 216 children suffering from rhinitis with/without intermittent asthma [57]. They were randomly allocated 2:1 to drugs plus SLIT or drugs only, and followed for 3 years to detect the presence of persistent asthma. The

prevalence of persistent asthma after 3 years was 1.5% in the SLIT group and 30% in the control group. The preventive and history-modifying effect of SCIT and SLIT are attractive and of potential clinical relevance, although the trials available so far are small, lack a placebo arm and are not double-blind. Thus, more robust data are required to draw a firm conclusion on this point.

Another important aspect concerning the effects on the natural history of respiratory allergy (not shared by standard pharmacological treatments) is the long-lasting effect after discontinuation. This effect has been seen in several SLIT studies in adults and children [40,41,58–60]. According to the literature, the beneficial effects are maintained for 2–6 years after discontinuation of SLIT, with an open study lasting 15 years. Nonetheless, a formal demonstration of this long-lasting effect would require prolonged double-blind controlled studies, which are not feasible from a practical viewpoint.

Unmet needs

Despite the robust proof of the clinical efficacy and long-term effect of SLIT, some aspects need to be better elucidated:

- The candidate patient who would receive the most benefit from SLIT. In this regard no predictive biomarker of efficacy has been identified so far, although some have been suggested [61]. The identification of a biomarker for subsequent clinical response to SLIT (as well as SCIT) would be of primary relevance, also considering the non-negligible cost of the treatment. So far, the treatment is given according to current guidelines and the assessment of its efficacy is only made on a clinical and *a posteriori* basis;
- The adequate maintenance dose required. This has only been clearly established for grass tablets, whereas data are lacking for the other relevant allergens;
- The best administration regimen (preseasonal, coseasonal, pre-/co-seasonal or continuous). According to the literature, for pollen allergies, the pre-/co-seasonal regimen seems to be the best choice, also from an economical viewpoint [62–64], but direct head-to-head comparisons are nowadays scarce;
- The standardization of extracts, which differ greatly in allergen content from one manufacturer to another [65]. Presently, each SLIT manufacturer standardizes their products according to arbitrary in-house reference, although many

extracts report the average content of the major allergens in micrograms. A universal standardization of the extracts would allow better comparison of the various trials and products;

- A universally accepted classification/grading system for side effects does not exist and this fact heavily limits the overall evaluation of the safety of SLIT in real life.

In addition, there are methodological problems with the published studies, mainly concerning description, sample size calculation and reporting [66,67]. The variability of regimens, doses, patients and outcomes, in fact, result in an unacceptable degree of heterogeneity, which strongly limits the conclusions provided by meta-analyses. Finally, a standardized methodology to conduct clinical trials is urgently needed [6,68,69].

Conclusion

Allergic rhinitis is a major public health concern with significant healthcare costs, also representing an independent risk factor for the development of asthma. SLIT has been consistently shown to be capable of reducing symptoms and medication use in allergic rhinitis and possibly in coexistent asthma [70] for all the relevant allergens. In addition, due to the complex mechanism of action, SLIT profoundly modifies the immune response, thus, its effects last for many years [71]. Finally, SLIT, as well as SCIT, can reduce the risk of asthma onset in children with allergic rhinitis. According to this evidence, SLIT is confirmed to be a viable alternative to SCIT in the treatment of allergic

rhinoconjunctivitis, with a very favorable safety profile and the possibility of expanding the indications to other diseases.

Future perspective

The very favorable safety profile of SLIT suggested new possible applications of the treatment, especially in conditions other than respiratory allergy. At least three exploratory studies used SLIT in food allergy, one with Pru p 3 (lipid transfer protein of peach), one with hazelnut extract and one with peanut [72–74]. All these trials reported positive results in terms of clinical efficacy and immunological effects. In addition, there is abundant literature regarding the efficacy of oral desensitization for cow milk allergy in children [75]. Latex allergy seems to be a promising field of application for SLIT since several trials with positive results have been published involving adults and children [76], with only one completely negative study [77]. Due to the partial discrepancy of the results, latex allergy has not yet been accepted as an indication to SLIT, although standardized extracts are commercially available and used. The use of SLIT has also been proposed in the treatment of extrinsic atopic dermatitis. A double-blind study conducted in 30 children with mite allergy [78] reported a significant effect of SLIT in reducing the SCORAD in mild-to-moderate atopic eczema and a concomitant reduction in the need for rescue medications. Another pilot study showed that SLIT with honeybee venom reduces the diameter of large local reactions upon sting challenge [79].

Executive summary

Background

- Sublingual immunotherapy (SLIT) was first described in 1986.
- The rationale of SLIT is to improve safety and make the treatment more convenient for patients.
- Nowadays there are more than 60 randomized controlled trials with SLIT.
- SLIT is accepted in international guidelines as a viable alternative to the injection route.

SLIT for allergic rhinoconjunctivitis

- The available randomized controlled trials consistently show that SLIT is clinically effective in allergic rhinoconjunctivitis.
- Several meta-analyses confirmed the findings of the individual trials, although the conclusions of those meta-analysis are limited by the great heterogeneity.
- Overall, SLIT is safer than the injection route, both in adults and small children. Only six cases of anaphylaxis and no fatalities have been reported in over 25 years of clinical use.

Effects on the natural history of respiratory allergy

- SLIT can modify the natural course of respiratory allergy by reducing the risk of developing asthma in children with rhinitis.
- Similarly to the injection route, the beneficial effects of SLIT may last several years after its discontinuation.

Future perspective

- Food allergy seems to be a promising field of application for SLIT.
- SLIT for latex allergy is commercially available and is used as such, although more confirmatory data are needed.

Other possible developments include the use of mucoadhesive substances that could improve the contact of allergenic extracts with the oral mucosa, resulting in an enhanced immunological effect, as shown in animal models [80]. The use of adjuvants (either bacterial or DNA-based) in association with SLIT seems to be a feasible and promising approach, as previously demonstrated with SCIT [81], whereas, due to regulatory and marketing problems, the use of recombinant allergens seems likely in the more distant future [82]. Finally, since the oral mucosa (specifically the dendritic cells) is responsible for the presentation of the allergen to the immune system,

there is currently a promising research field dedicated to the development of SLIT extracts in terms of molecular structure to optimize the interactions with APCs [83].

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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

References

Papers of special note have been highlighted as:

■ of interest

■ of considerable interest

- Scadding K, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to dust mite. *Clin. Allergy* 16, 483–491 (1986).
- Bernstein D, Wanner B, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J. Allergy Clin. Immunol.* 113, 1129–1136 (2001).
- Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. *J. Allergy Clin. Immunol.* 113, 1117–1121 (2004).
- WHO Position Paper. Allergen immunotherapy: therapeutical vaccines for allergic diseases. Bousquet J, Lockey R, Malling HJ (Eds). *Allergy* 53 (Suppl.), 1–33 (1998).
- Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; WHO. Allergic rhinitis and its impact on asthma. *J. Allergy Clin. Immunol.* 108(Suppl. 5), S147–S334 (2001).
- Canonica GW, Bousquet J, Casale T *et al.* Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 64 (Suppl. 91), 1–59 (2009).
- **Seminal position paper also containing practical guidelines on the use of sublingual immunotherapy (SLIT).**
- Passalacqua G, Compalati E, Canonica GW. Sublingual immunotherapy: other indications. *Immunol. Allergy Clin. North Am.* 31, 279–287 (2011).
- Nelson H, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J. Allergy Clin. Immunol.* 92, 229–236 (1993).
- Guez S, Vatrinet C, Fadel R, André C. House dust mite sublingual swallow immunotherapy in perennial rhinitis: a double-blind placebo controlled study. *Allergy* 55, 369–375 (2000).
- Röder E, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J. Allergy Clin. Immunol.* 119, 892–898 (2007).
- Okubo K, Gotoh M, Fujieda S *et al.* A randomized double-blind comparative study of sublingual immunotherapy for cedar pollinosis. *Allergol. Int.* 57, 265–275 (2008).
- de Bot CM, Moed H, Berger MY *et al.* Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr. Allergy Immunol.* 23, 150–158 (2012).
- Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int. Arch. Allergy Immunol.* 157, 288–298 (2012).
- Wilson DR, Torres L, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Allergy* 60, 3–8 (2005).
- Calamita Z, Saconato H, Bronhara Pelà A *et al.* Efficacy of sublingual immunotherapy in asthma. Systematic review of randomized clinical trials. *Allergy* 61, 1162–1172 (2006).
- 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, 599–609 (2008).
- Penagos M, Compalati E, Tarantini F *et al.* Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in children. Meta analysis of randomized controlled trials. *Ann. Allergy Asthma Immunol.* 97, 141–148 (2006).
- 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, 1570–1579 (2009).
- 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).
- Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst. Rev.* 12, CD002893 (2010).
- **The most up-to-date comprehensive review and meta-analysis of SLIT.**
- Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. *Cochrane Database Syst. Rev.* 6(7), CD007685 (2011).
- Compalati E, Penagos M, Tarantini F, Passalacqua G, Canonica GW. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. *Ann. Allergy Asthma Immunol.* 102, 22–28 (2009).
- Nieto A, Mazon A, Pamies R, Bruno M, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J. Allergy Clin. Immunol.* 124, 157–161 (2009).
- Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass-allergen tablets: a randomised controlled trial in seasonal allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 117(4), 802–809 (2006).
- Dahl R, Kapp A, Colombo G *et al.* Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 118(2), 434–440 (2006).

- 26 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).
- 27 Wahn U, Tabar A, Kuna P, Halken S, Montagut A, De Beaumont O. Efficacy and safety of 5 grass pollen sublingual immunotherapy in pediatric allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 123(1), 160–166.e3 (2009).
- 28 Ott H, Sieber J, Brehler R *et al.* Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 64, 179–186 (2009).
- 29 Bufe A, Eberle P, Franke-Beckmann E *et al.* Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J. Allergy Clin. Immunol.* 123, 167–173 (2009).
- 30 Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J. Allergy Clin. Immunol.* 127, 64–71 (2011).
- 31 Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J. Allergy Clin. Immunol.* 127, 72–80 (2011).
- 32 Canonica GW, Baena Cagnani C, Bousquet J *et al.* Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 62, 317–324 (2007).
- **Systematic assessment of the requirements and unmet needs in clinical trials with SLIT.**
- 33 Marogna M, Spadolini I, Massolo A *et al.* Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen. *Ann. Allergy Asthma Immunol.* 102(1), 69–75 (2009).
- 34 Marogna M, Colombo F, Spadolini I *et al.* Randomized open comparison of montelukast and sublingual immunotherapy as add-on treatment in moderate persistent asthma due to birch pollen. *J. Invest. Allergol. Clin. Immunol.* 20(2), 146–152 (2010).
- 35 Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin. Exp. Allergy* 26, 1253–1261 (1996).
- 36 Khinchi S, Poulsen LK, Carat F, André C, Malling HJ. Clinical efficacy of sublingual swallow and subcutaneous immunotherapy in patients with allergic rhinoconjunctivitis due to birch pollen. A double blind double dummy placebo controlled study. *Allergy* 59(1), 45–53 (2004).
- 37 Eifan AO, Akkoc T, Yildiz A *et al.* Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. *Clin. Exp. Allergy* 40(6), 922–932 (2010).
- 38 Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J. Allergy Clin. Immunol.* 130, 1097–1107 (2012).
- 39 Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J. Allergy Clin. Immunol.* 117, 1021–1035 (2006).
- 40 Didier A, Worm M, Horak F *et al.* Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 128, 559–566 (2011).
- 41 Durham SR, Emminger W, Kapp A *et al.* Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J. Allergy Clin. Immunol.* 125, 131–138 (2010).
- 42 Dunskey E, Goldstein MF, Dvorin MJ, Belecanec G. Anaphylaxis due to sublingual immunotherapy. *Allergy* 61, 1235 (2006).
- 43 Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 61, 1236 (2006).
- 44 Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 62, 567–568 (2007).
- 45 Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy* 63, 374 (2008).
- 46 de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 64, 963–964 (2009).
- 47 Agostinis F, Tellarini L, Falagiani P, Canonica GW, Passalacqua G. Safety of SLIT in very young children. *Allergy* 59, 675–676 (2004).
- 48 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, 254–258 (2005).
- 49 Di Rienzo V, 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, 560–564 (2005).
- 50 Agostinis F, Foglia C, Landi M *et al.* The safety of sublingual immunotherapy with one or multiple pollen allergens in children. *Allergy* 63, 1637–1639 (2008).
- 51 Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 61, 181–184 (2006).
- 52 Rodriguez F, Boquete M, Ibanez MD, de la Torre-Martinez F, Tabar AI. Once daily sublingual immunotherapy without up dosing – a new treatment schedule. *Int. Arch. Allergy Immunol.* 140, 321–326 (2006).
- 53 Agostinis F, Foglia C, Bruno ME, Falagiani P. Efficacy, safety and tolerability of sublingual monomeric allergoid in tablets given without up-dosing to pediatric patients with allergic rhinitis and/or asthma due to grass pollen. *Eur. Ann. Allergy Clin. Immunol.* 41, 177–180 (2009).
- 54 Canonica GW, Passalacqua G. Disease modifying effect and economic implications of sublingual immunotherapy. *J. Allergy Clin. Immunol.* 127, 44–45 (2011).
- 55 Jacobsen L, Niggemann B, Dreborg S *et al.* Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 62, 943–948 (2007).
- 56 Novembre E, Galli E, Landi F *et al.* Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 114, 851–857 (2004).
- 57 Marogna M, Tomassetti D, Bernasconi A *et al.* Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann. Allergy Asthma Immunol.* 101, 206–211 (2008).
- 58 Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J. Allergy Clin. Immunol.* 126, 969–975 (2010).
- 59 Di Rienzo V, Marcucci F, Puccinelli P *et al.* Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin. Exp. Allergy* 33, 206–210 (2003).
- 60 Tahamiler R, Saritzali G, Canakcioglu S. Long-term efficacy of sublingual immunotherapy in patients with perennial rhinitis. *Laryngoscope* 117, 965–969 (2007).

- 61 Senna G, Calderon M, Makatsori M, Ridolo E, Passalacqua G. An evidence-based appraisal of the surrogate markers of efficacy of allergen immunotherapy. *Curr. Opin. Allergy Clin. Immunol.* 11, 375–380 (2011).
- 62 Pajno G, Caminiti L, Vita D *et al.* Direct comparison between continuous and co-seasonal regimen for sublingual immunotherapy in children with grass allergy. *Pediatr. Allergy Immunol.* 22, 803–807 (2011).
- **First published head-to-head comparison between two different treatment regimens.**
- 63 Calderon MA, Birk AO, Andersen JS, Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. *Allergy* 62, 958–961 (2007).
- 64 Lombardi C, Incorvaia C, Braga M, Senna G, Canonica GW, Passalacqua G. Administration regimens for sublingual immunotherapy: what do we know. *Allergy* 64, 849–854 (2009).
- 65 Sander I, Fleischer C, Meurer U *et al.* Allergen content of grass pollen preparations for skin prick testing and sublingual immunotherapy. *Allergy* 64, 1486–1492 (2009).
- 66 Calderon M, Mösges R, Hellmich M, Demoly P. Towards evidence-based medicine in specific grass pollen immunotherapy. *Allergy* 65(4), 420–434 (2009).
- 67 Bousquet PJ, Brozek J, Bachert C *et al.* The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper. *Allergy* 64(12), 1737–1745 (2009).
- 68 Bousquet J, Schünemann HJ, Bousquet PJ *et al.* How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA(2) LEN statement. *Allergy* 66, 765–774 (2011).
- 69 Casale TB, Canonica GW, Bousquet J *et al.* Recommendations for appropriate sublingual immunotherapy clinical trials. *J. Allergy Clin. Immunol.* 124, 665–670 (2009).
- 70 Passalacqua G, Canonica GW. Specific immunotherapy in asthma. Efficacy and safety. *Clin. Exp. Allergy* 41, 1247–1255 (2011).
- 71 Passalacqua G, Canonica GW. Specific immunotherapy: beyond clinical scores. *Ann. Allergy Asthma Immunol.* 107(5), 401–406 (2011).
- 72 Enrique E, Pineda F, Malek T *et al.* Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J. Allergy Clin. Immunol.* 116, 1073–1079 (2005).
- 73 Fernández-Rivas M, Garrido Fernández S, Nadal JA *et al.* Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. *Allergy* 64(6), 876–883 (2009).
- 74 Kim EH, Bird JA, Kulis M *et al.* Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J. Allergy Clin. Immunol.* 127, 640–646 (2011).
- 75 Passalacqua G, Landi M, Pajno G. Oral immunotherapy in cow milk allergy. *Curr. Opin. Allergy Immunol.* 12, 271–277 (2012).
- 76 Nettis E, Delle Donne P, Di Leo E *et al.* Latex immunotherapy: state of the art. *Ann. Allergy Asthma Immunol.* 109(3), 160–165 (2012).
- 77 Gastaminza G, Algorta J, Uriel O *et al.* Randomized, double-blind, placebo-controlled clinical trial of sublingual immunotherapy in natural rubber latex allergic patients. *Trials* 9(12), 191 (2011).
- 78 Pajno GB, Caminiti L, Vita D *et al.* Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J. Allergy Clin. Immunol.* 120, 164–170 (2007).
- 79 Severino M, Cortellini G, Bonadonna P *et al.* Sublingual immunotherapy for large local reactions caused by honeybee sting: a double-blind, placebo-controlled trial. *122*(1), 44–48 (2008).
- 80 Saint-Lu N, Tourdot S, Razafindratsita A *et al.* Targeting the allergen to oral dendritic cells with mucoadhesive chitosan particles enhances tolerance induction. *Allergy* 64, 1003–1013 (2009).
- 81 O'Hehir RE, Sandrini A, Anderson GP, Rolland JM. Sublingual allergen immunotherapy: immunological mechanisms and prospects for refined vaccine preparation. *Curr. Med. Chem.* 4, 2235–2244 (2007).
- 82 Cromwell O, Häfner D, Nandy A. Recombinant allergens for specific immunotherapy. *J. Allergy Clin. Immunol.* 127, 865–872 (2011).
- **Comprehensive review on the published and ongoing trials with recombinant allergens.**
- 83 Novak N, Bieber T, Allam JP. Immunological mechanisms of sublingual allergen-specific immunotherapy. *Allergy* 66(6), 733–739 (2011).