Subcutaneous Immunotherapy and Sublingual Immunotherapy

Comparative Efficacy, Current and Potential Indications, and Warnings—United States Versus Europe

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KEYWORDS

• SCIT • SLIT • AIT • Immunotherapy • Allergic rhinitis • Allergic asthma

KEY POINTS

- Both SCIT and SLIT are of proven effectiveness in the treatment of allergic rhinitis and allergic asthma with some evidence that both are helpful in selected patients with atopic dermatitis.
- Both SCIT and SLIT modify the underlying immune process resulting in persisting benefits after cessation of treatment.
- The lesser frequency and severity of systemic reactions allows SLIT to be home administered after the first dose.
- SCIT but not SLIT has been demonstrated to be effective using mixtures of multiple, unrelated allergen extracts.
- Although good comparative studies are lacking, available evidence suggests superior short-term efficacy with SCIT.

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INTRODUCTION

Allergy immunotherapy (AIT) was introduced more than a century ago by Leonard Noon as a treatment of allergic rhinitis caused by grass pollen.[1] The subcutaneous injection of increasing and eventually maintenance doses of various seasonal and perennial allergens (subcutaneous immunotherapy [SCIT]) came into widespread use for the treatment of allergic rhinitis, allergic asthma, and allergic sensitization to insect venoms. Although of proved efficacy in allergic rhinitis,[2] allergic bronchial asthma,[3] and Hymenoptera venom sensitivity,[4] the use of SCIT for allergic rhinitis and allergic asthma has been limited by the long course of treatment requiring numerous visits to physicians' offices, by cost, and to some extent by the possibility of local and systemic reactions to the injections. As a result, alternative methods of AIT have been investigated that aim to avoid these SCIT drawbacks by greatly shortening the course of treatment, allowing home administration, or both. Alternatives under active investigation include administering the extract in a limited number of injections intralymphatically, applying the extracts incorporated in a patch (epicutaneously), or treating with modified extracts that are hypoallergenic so that a few large doses are sufficient for a course of treatment.[5] The one alternative approach that has been studied the most and is now an accepted clinical practice is to administer the extract as a liquid or a rapidly dissolving tablet (sublingual immunotherapy [SLIT]).

SCIT and SLIT are directed at modifying immune response to the allergen to which the patient is sensitized and therefore the responses to treatment with these two approaches share many features (**Box 1**). Both have been shown to be effective for allergic rhinitis and allergic asthma and with some support for use in selected patients with atopic dermatitis.[6] There are defined effective doses for most standardized extracts for SCIT, for the SLIT tablets, and liquid ragweed. The sequence of immunologic

Box 1
Shared and differing attributes of SCIT and SLIT

Shared

1. Effective treatment of allergic rhinitis and allergic asthma, with some support for use in selected patients with atopic dermatitis.
2. Defined optimal doses for standardized liquid extracts (SCIT) and SLIT tablets.
3. Underlying immunologic response
   a. Early induction of regulatory T cells.
   b. Later immunodeviation from a predominant Th2 to a Th1 response to the administered allergen.
   c. Suppression of Th17 responses.
4. Evidence for disease modification
   a. Reduction of additional sensitization in monosensitized patients.
   b. Reduction in the development of asthma in patients with allergic rhinitis.
   c. Persisting benefit after stopping an effective course of treatment.

Differing

1. Frequency and severity of systemic reactions (favors SLIT).
2. Clinical efficacy with Hymenoptera venom (favors SCIT) and for food allergy (favors SLIT).
3. Lack of defined optimal doses for SLIT liquids (favors SCIT).
4. Proven effectiveness of multiple allergen mixes with SCIT but not SLIT (favors SCIT).
5. Clinical efficacy (currently available studies favor SCIT).

responses is the same, irrespective of the route of administration and not surprising, similar disease modification has been demonstrated with both forms of AIT. However, there are differences between the two approaches. The most important is the greatly reduced likelihood of SLIT producing systemic reactions, a feature that allows home administration and thus overcomes one of the major drawbacks of SCIT. Although there is some evidence of efficacy of SLIT with Hymenoptera venom[7,8] it is not yet clinically recommended. SLIT for food allergy is still under investigation, but studies show some efficacy and good safety,[9] whereas SCIT for food allergy proved too dangerous for clinical application.[10] There are major drawbacks for SLIT in regard to dosing. First is the lack of defined dosing for most liquid extracts,[11] and second is the lack of demonstrated efficacy of SLIT with multiple allergen mixtures.[12] Finally, there is the question of relative clinical efficacy, with the currently available data favoring SCIT.[13,14]

CLINICAL EFFICACY

Meta-analyses (**Table 1**) and more recent systematic reviews[17,18] have confirmed the effectiveness of SCIT and SLIT for treatment of allergic rhinitis and allergic asthma. Meta-analyses using the Cochrane collaboration method demonstrated significant efficacy of SCIT for symptoms of and medication use for allergic rhinitis[2] and allergic asthma.[3] Similar analyses demonstrated significant improvement in symptoms and medication use for allergic rhinitis[15] with SLIT. Trends favored SLIT for the treatment of allergic asthma[16] but the results did not reach statistical significance perhaps because of a smaller number of studies in this category. A more recent systematic review[17] reported high-quality support for the effectiveness of SCIT for reduction of asthma symptoms and medication use and for reduction of rhinoconjunctivitis symptoms and moderate evidence to support reduction in rhinoconjunctivitis medication use. A companion systematic review of SLIT[18] showed high-quality evidence for reduction in asthma symptoms and moderate-quality evidence to support the reduction in symptoms of rhinoconjunctivitis and in the use of rescue medications for rhinitis and asthma.

A meta-analysis of eight randomized, controlled trials provided moderate support of the use of house dust mite (HDM) extracts by SCIT and SLIT for selected patients with atopic dermatitis who are HDM sensitive. Two of the studies coadministered other allergens.[6]

Table 1
Cochrane collaboration and Cochrane method meta-analyses of SCIT and SLIT for allergic rhinitis and allergic asthma

Study	Method	Number of Studies	Allergens	Number of Subjects	Symptoms Scores SMD (95% CI)	Medication Scores SMD (95% CI)
Allergic rhinitis						
Calderon et al,[2] 2007	SCIT	51	S	2871	−0.73 (−0.97 to −0.50)	−0.57 (−0.82 to −0.33)
Radulovic et al,[15] 2011	SLIT	49	S and P	4589	−0.49 (−0.64 to −0.34)	−0.32 (−0.43 to −0.21)
Allergic asthma						
Abramson et al,[3] 2010	SCIT	88	S and P	3459	−0.59 (−0.83 to −0.35)	−0.53 (−0.80 to −0.27)
Calamita et al,[16] 2006	SLIT	25	S and P	1706	−0.38 (−0.79 to 0.03)	−0.91 (−1.94 to 0.12)

Abbreviations: CI, confidence interval; P, perennial; S, seasonal; SMD, standardized mean difference.

SCIT with Hymenoptera venom[4] and whole body extract of imported fire ants[19] is well accepted as effective in treating sensitivity to the stings of these insects. There are limited data for treating Hymenoptera venom sensitivity with SLIT and it is currently not recommended.[7,8]

An attempt was previously made to treat patients with anaphylactic sensitivity to peanuts with injections of peanut extract. Although the level of sensitivity could be reduced, even the maintenance injections resulted in repeated systemic reactions, so the treatment was deemed a failure.[9] Treatment of hazel nut[20] and peanut allergy[10] with SLIT has been reported to increase tolerance with an acceptable rate of systemic reactions. This treatment, although promising, must still be considered experimental.

THE IMMUNOLOGIC RESPONSE

The immunologic response to AIT involves changes in the allergen-specific humoral response, with ultimately a shift from allergen-specific IgE to IgG, and particularly IgG4 responses. These changes in antibody response result from underlying changes in the T-cell responses and it is the latter that are thought to mediate the clinical improvement and ultimate disease modification. The early T-cell response is an increase in allergen-specific regulatory T cells (Tregs) secreting interleukin-10 and sometimes also transforming growth factor-β.[21,22] There is evidence that this initial increase in Tregs is not fully sustained and after one or several years of continuing treatment, the Treg numbers are reduced and the predominant pattern is a shift, again allergen specific, from a T helper (Th) 2 to a Th1 cytokine responses.[22–24] This is known as immune deviation. This same evolving pattern of immunologic changes has been demonstrated with SCIT and SLIT.

Studies with SCIT and SLIT have also demonstrated a suppressive effect of AIT on Th17 cells and their cytokines. After 2 years of SCIT with HDM extract in adults, Th2 and Th17 cells were reduced, Th1 and Tregs were increased, and, strikingly, the decrease in plasma interleukin-17 levels correlated highly with the decrease in symptoms of perennial rhinitis.[25] Sublingual administration of *Dermatophagoides farinae* extract for 48 weeks to children with allergic asthma also decreased symptoms, increased Tregs, and decreased Th17 cells in the peripheral blood.[26]

DISEASE MODIFICATION

Pharmacotherapy of allergic rhinitis and asthma can to variable degrees control the symptoms but has no effect on the underlying immunologic mechanisms and hence has no persisting benefit after treatment is stopped.

Because SCIT and SLIT have been shown to modify the underlying immunologic process, not unexpectedly both modify the progression of the respiratory allergy and impart persistent benefits after stopping a successful course of treatment. Studies with SCIT[27] and SLIT[28] have shown marked reduction in the development of new sensitivities in monosensitized patients, not only during the period of treatment, but also persisting for several years after its discontinuation. Similarly, when children having only allergic rhinitis were treated with either SCIT[29] or SLIT[30] there was a significant reduction in the number who developed asthma. Again this protection has been shown to persist for years after treatment was discontinued.

The most important effect of modifying the underlying immune process, however, is the persisting remission in symptoms that results from 3 to 5 years of treatment with proved effect doses of allergens. Relapses do occur but some patients may experience long-lasting improvement.[28,31]

DEFINED OPTIMAL DOSES

Ideally, to define optimal doses for AIT a dose-response study should be conducted that includes a low dose that is suboptimal and a high dose that either shows no improvement over a lower dose or is associated with unacceptable side effects. It is surprising how seldom such studies of AIT have been conducted. Nevertheless, there are SCIT studies in which a lower, less-effective dose has been included with standardized extracts of ragweed, timothy grass, HDM, cat, and dog.[32] The effective dose of major allergen was within a fairly narrow range (7–19 μg). This suggests that at least for other pollen and animal dander extracts similar doses are likely to be effective. SCIT with *Alternaria* in this dose range has also proved to be effective.[33]

Studies of rapidly dissolving SLIT tablets for grass, ragweed, and HDM have included dose-ranging studies and higher dose safety studies. Thus optimal doses for safety and efficacy have been identified for these tablets.[34–37] For SLIT with liquid extracts, the same studies have not been conducted. Dose-response studies were conducted with liquid ragweed extract[38] and a birch/hazel nut/alder mix.[39] However, the two doses studied in these studies differed by nearly 10-fold leaving unanswered whether intermediated doses might be equally effective. A two-dose study of HDM liquid SLIT found a daily dose of 1 μg Der f 1 ineffective but a dose of 70 μg per day reduced bronchial allergen sensitivity.[40] Again, the efficacy of intermediate doses was not investigated. Except for these studies, there seems to be little scientific basis for many of the SLIT-liquid doses used, and effective treatment has been reported with a 500-fold range in doses.[11]

MULTIALLERGEN ALLERGY IMMUNOTHERAPY

There is evidence to support the administration of mixtures of unrelated allergens by SCIT. Four double-blind, randomized, controlled studies have shown clinical efficacy, two in patients with allergic rhinitis[41,42] and two in patients with allergic asthma.[43,44] Two studies are often cited in questioning the efficacy of multiallergen SCIT, but both have fatal flaws in their design. One compared the response to AIT in patients monosensitized to grass who received only grass extract with that in patients polysensitized to grass and other pollens who received a mixture of these pollens This was not a randomized study and immunoblotting revealed that the polysensitized subjects were sensitized to more than twice as many proteins in the grass extract as were those monosensitized, thus providing an alternative explanation for their less robust response to AIT.[45] The second, a study of SCIT for polysensitized children with perennial asthma, used largely seasonal allergens for treatment and omitted cat, dog, cockroach, and mouse extracts from the treatment all of which have been shown to be important allergens for perennial asthma in children. Thus the failure of AIT in this study may have been caused by omission of most of the relevant allergens from the treatment extract.[46]

Although there have been many more recent studies of SLIT than SCIT, all but three have used monotherapy. Two studies used two differing extracts that were administered simultaneously from separate dispensers.[47,48] Both demonstrated efficacy for the two components. Only the third examined truly multiallergen immunotherapy.[12] In this study, subjects were randomized to receive SLIT with a timothy grass extract (containing 19 μg at maintenance), the same dose of timothy grass combined with nine other pollen extracts at 1:100 wt/vol, or placebo. After 10 months the subjects receiving timothy grass monotherapy had significant favorable changes compared with those receiving placebo in titrated skin prick tests, titrated nasal challenge, and timothy grass–specific IgG4, whereas those receiving the same dose of timothy grass combined with other pollen extracts differed significantly from placebo only for titrated

skin prick tests and then to a lesser degree than those receiving timothy grass monotherapy. To date, this is the only study conducted of multiallergen SLIT and raises unanswered questions regarding its suitability for clinical use.

SAFETY

Local Reactions

In a systematic review of 61 randomized controlled trials including 3577 subjects local reactions to subcutaneous injections were reported in 5% to 58% of patients and 3% to 10% of injections.[17] Local reactions may be immediate or delayed and vary from small areas of redness and itching to delayed larger swellings. Although patients with frequent large reactions are at increased risk for systemic reactions, individual large local reactions do not predict a systemic reaction and therefore should not be a basis for dose adjustment.[49]

Local or application site reactions are common with SLIT. Among 3314 adults in the timothy grass SLIT tablet studies, 67% receiving active and 24% receiving placebo reported treatment-related adverse events.[50] In the active treatment group this included oral pruritus in 27%, throat irritation in 23%, ear pruritus in 13%, and mouth edema in 11%. With the highest dose ragweed SLIT tablet, local reactions were less common than with the timothy grass SLIT tablet: oral pruritus 4%, throat irritation 11%, ear pruritus 6%, and mouth edema 7%.[51] Except for localized swelling, which tends to develop only after several days of treatment, the local symptoms occur with the first dose, persist a few minutes, and cease occurring within the first 2 weeks of treatment.

Systemic Reactions

The incidence of systemic reactions to SCIT varies widely with the different doses used in treatment. In the American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology online surveillance survey, data were submitted by allergists on the outcome from 23.3 million injection visits between 2008 and 2012.[52] Systemic reactions were reported as occurring in 9.4 per 10,000 injection visits and of these 0.4 per 10,000 were severe. There was one fatality reported during these 4 years. Although systemic reactions, even anaphylaxis, can occur with SLIT, there have as yet been no reported fatal or near fatal reactions.[53] A review of studies with the timothy grass SLIT tablet reported eight systemic reactions, all mild or moderate, in 2115 subjects receiving active treatment for a systemic reaction rate of 0.38% of patients.[54] In the United States, the Food and Drug Administration's Prescribing Information Guides mandate that recipients of a prescription for SLIT tablets also receive a prescription for and be instructed in the use of autoinjectable epinephrine. The relevance of this mandate was examined in a review of phase III trials conducted with timothy grass SLIT tablets, short ragweed SLIT tablets, and HDM SLIT tablets, which including 8804 subjects treated for 24 to 18 months.[55] Thirteen patients received epinephrine injections for SLIT-tablet related symptoms (8 local and 5 systemic reactions). Four of the systemic reactions occurred with the first dose administered in the physician's office. The fifth occurred on day 6. None of the 5 systemic reactions was considered serious. Patients self-administered epinephrine 8 times, only 3 of which were for SLIT-tablet related symptoms.

COMPARATIVE EFFICACY OF SUBCUTANEOUS IMMUNOTHERAPY AND SUBLINGUAL IMMUNOTHERAPY

In the absence of definitive head-to-head trials, an indirect approach has been used to compare the clinical efficacy of SCIT and SLIT. The reduction in symptoms or

medication use with SCIT or SLIT has been compared with that with placebo by meta-analyses and then the standardized mean differences (SMD) from the meta-analyses for SCIT and SLIT have been compared. In the four meta-analyses cited in **Table 2**, the reduction in SMD for symptom scores and medication use in allergic rhinitis was –0.73 and –0.57, respectively, in 51 studies of SCIT and –0.49 and –0.32 in 49 studies for SLIT. This has been interpreted as suggesting a greater efficacy for SCIT. The results for asthma cannot be compared, because the SMD for symptoms and medication with SLIT did not differ significantly from placebo. The studies in these meta-analyses predate the large randomized, placebo-controlled trials conducted with SLIT tablets. A meta-analysis, limited to commercially available preparations, that separately assessed the response to SCIT, SLIT tablets, and SLIT drops for grass allergic rhinitis found no significant difference between SCIT and SLIT tablets for symptoms or medication use. The results with SLIT drops were much more variable and for symptom reduction the drops were less effective than the tablets.[56]

Direct head-to-head comparisons between SCIT and SLIT are clearly preferable to indirect comparisons of the response to placebo, but there have been problems with the quality of most of these studies. Eleven direct comparisons, all randomized and four placebo-controlled, were reviewed.[13] Overall, the results with SCIT were superior to those with SLIT when compared with placebo and in some instances when compared with each other (see **Table 2**). The problem with interpretation of these studies is that often the SLIT was low-dose, but more important in 9 of 11 studies SLIT was administered every other day or two or three times a week and daily SLIT has been shown to be more effective than thrice weekly even when the latter delivered a higher cumulative dose.[57] There is one study that seems to overcome the shortcomings of many of the previous studies. Optimal treatment regimens for ALK-Abello' subcutaneous (100,000 Standardized Quality units every 2 months) and sublingual timothy grass tablets (75,000 Standardized Quality units daily) were directly compared in a 15-month study, which also included an untreated group.[14] Outcomes included allergen nasal challenges, specific IgG4, and several functional assays of the IgG4 response. The nasal challenge was significantly different from placebo at 3 and

Table 2
Comparative response to SCIT and SLIT in 11 randomized studies

Statistically Significant Differences	Symptoms	Medication	Skin Prick Tests	IgG4	Bronchia/ Nasal Allergen Challenges	Miscellaneous
None reported	3 studies	7 studies	6 studies	4 studies	8 studies	9 studies
SCIT only greater than placebo	3 studies	2 studies	3 studies	6 studies	1 study	1 study
Both greater than placebo	4 studies	2 studies	2 studies	None	1 study	1 study
SLIT only greater than placebo	None	None	None	None	None	None
SCIT greater than SLIT	1 study	None	None	1 study	1 study	None

Adapted from Nelson HS. Subcutaneous immunotherapy versus sublingual immunotherapy: which is more effective? J Allergy Clin Immunol Pract 2014;1:144–9.

15 months in the SCIT-treated group, but not in those receiving SLIT. Both AIT approaches induced significant humoral responses compared with placebo, but those with SCIT were of approximately twice the magnitude of those with SLIT.

WARNINGS

There are still some unanswered questions regarding SCIT and SLIT and their use. These include the optimal length of treatment and clarifications regarding absolute and relative contraindications.

It is also important to consider that clinical efficacy of AIT is greatly affected by patient adherence to the treatment regimen. Several studies have suggested that in clinical practice, adherence to SLIT over the intended 3-year course of treatment is variable.[58] SCIT also suffers from less than optimal adherence; however, because it is administered by allergists nonadherence does not go undetected. Furthermore, adherence to SCIT seems to be better than to SLIT. In a pharmacy data study from the Netherlands, 23% completed a projected 3-year course of SCIT compared with only 7% of those prescribed SLIT. The mean duration of persistence with treatment was 1.7 years for SCIT but only 0.6 years for SLIT.[59] However, more research is required to identify reasons for lack of adherence and develop strategies to improve this.

Different regulatory laws in Europe and the United States currently govern registration and licensing of immunotherapy products.[60] In Europe, regulatory guidance has been published in the form of directives 2001/20/EC and 2003/63/EC, which outlined specifications for allergen products in diagnostics and immunotherapy. The bodies involved in the regulatory process are the European Medicines Agency and national health authorities of the individual member states. A marketing authorization for allergen products is achievable by national or centralized procedures and through mutual recognition.[61] However, there is a need for simplifying and standardizing the process to make immunotherapy more widely available.

In the United States, approval of allergen extracts is the responsibility of the Division of Bacterial, Parasitic and Allergenic Products of the US Food and Drug Administration. Allergenic Products Advisory Committee meetings were held in December 2013 and January 2014 to consider the safety and efficacy of the two grass and one ragweed SLIT tablets.[62] All three products received approval in April 2014. The prescribing information for all three products contains a Black Box warning that the tablets can cause life-threatening allergic reactions; should not be administered to patients with severe, unstable, or uncontrolled asthma; require the patient to be observed for 30 minutes following the initial dose; that patients be provided with and trained in the use of autoinjectable epinephrine; and list patients for whom the treatment may not be appropriate because of underlying medical conditions that reduce their ability to survive and serious allergic reaction or who may be unresponsive to epinephrine or inhaled bronchodilators.[63–65] Additional contraindications listed are a history of any severe systemic allergic reaction or any severe local reaction to SLIT, or a history of eosinophilic esophagitis.

REFERENCES

1. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;i:1572.
2. Calderon MA, Alves B, Jacobson M, et al. Allergy injection immunotherapy for sessional allergic rhinitis. Cochrane Database Syst Rev 2007;(1):CD001936.
3. Abramson MJ, Puy RM, Winer JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 2010;(8):CD001186.

4. Boyle RJ, Elremelli M, Hockenhull J, et al. Venom immunotherapy for preventing allergic reactions to insect stings. Cochrane Database Syst Rev 2012;(10):CD0008838.
5. Nelson HS. New forms of allergy immunotherapy for rhinitis and asthma. Allergy Asthma Proc 2014;35:271–7.
6. Bae JM, Choi YY, Park CO, et al. Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 2013;132:110–7.
7. Patriarca G, Nucera E, Roncallo C, et al. Sublingual desensitization in patients with wasp venom allergy: preliminary results. Int J Immunopathol Pharmacol 2008;21:669–77.
8. Severino MG, Cortellinii G, Bonadonna P, et al. Sublingual immunotherapy for large local reactions caused by honeybee sting: a double-blind, placebo-controlled trail. J Allergy Clin Immunol 2008;122:4–8.
9. Nelson HS, Lahr J, Rule R, et al. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol 1997;99:744–51.
10. Burks AW, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol 2015;135(5):1240–8.e1-3.
11. Cox L, Larenas Linnemann D, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. J Allergy Clin Immunol 2006;117:1021–35.
12. Amar SM, Harbeck RJ, Sills M, et al. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. J Allergy Clin Immunol 2009;124:150–6.
13. Nelson HS. Subcutaneous immunotherapy versus sublingual immunotherapy: which is more effective? J Allergy Clin Immunol Pract 2014;1:144–9.
14. Aasbjerg K, Backer V, Lund G, et al. Immunological comparison of allergen immunotherapy tablet treatment and subcutaneous immunotherapy against grass allergy. Clin Exp Allergy 2014;44:417–28.
15. Radulovic S, Wilson D, Calderon M, et al. Systematic reviews of sublingual immunotherapy (SLIT). Allergy 2011;66:740–52.
16. Calamita Z, Saconato H, Pela AB, et al. Efficacy of sublingual immunotherapy in asthma: systematic review of randomize-clinical trials using the Cochrane collaboration method. Allergy 2006;61:1162–72.
17. Erekosima N, Suarez-Cuervo C, Ramanathan M, et al. Effectiveness of subcutaneous immunotherapy for allergic rhinoconjunctivitis and asthma: a systematic review. Laryngoscope 2014;124:616–27.
18. Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA 2013;309:1278–88.
19. Tankersley MS. The stinging impact of the imported fire ant. Curr Opin Allergy Clin Immunol 2008;8:354–9.
20. 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 2005;116:1073–9.
21. Jutel M, Akdis MN, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosa allergen in normal immunity and specific immunotherapy. Eur J Immunol 2003;33:1205–14.
22. Bohle B, Kinaciyan T, Gerstmayr M, et al. Sublingual immunotherapy induces IL-10-producing T regulator cells, allergen-specific T-cell tolerance, and immune deviation. J Allergy Clin Immunol 2007;120:707–13.

23. Mobs C, Ipsen H, Mayer L, et al. Birch pollen immunotherapy results in long-term loss of Bet v 1-specific Th2 responses, transient TR1 activation, and synthesis of IgE-blocking antibodies. J Allergy Clin Immunol 2012;130:1108–16.
24. Hamid QA, Schotman E, Jacobson MR, et al. Increases in IL-121 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. J Allergy Clin Immunol 1997;99:454–60.
25. Li CW, Lu HG, Chen DH, et al. In vivo and in vitro studies of Th17 response to specific immunotherapy in house dust mite-induced allergic rhinitis patients. PLoS One 2014;9:e91950.
26. Tian M, Wang Y, Lu Y, et al. Effects of sublingual immunotherapy for *Dermatophagoides farina* on Th17 cells and CD4+CD25+ regularity T cells in peripheral blood of children with allergic asthma. Int Forum Allergy Rhinol 2014;4(5):371–5.
27. Pajno G, Barberio G, De Luca F, et al. Prevention of sensitization in asthma children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31:1392–7.
28. Marogna M, Spadolini I, Massolo A, et al. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. J Allergy Clin Immunol 2010;126:969–75.
29. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-8 on the PAT study. Allergy 2007;62:943–8.
30. Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. Ann Allergy Asthma Immunol 2008;101:206–11.
31. Ebner C, Kraft D, Ebner H. Booster Immunotheapy (BIT). Allergy 1994;49:38–42.
32. Nelson HS. Subcutaneous immunotherapy for optimal effectiveness. Immunol Allergy Clin North Am 2011;31:211–26.
33. Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to *Alternaria alternata* in children. J Allergy Clin Immunol 2011;127:502–8.
34. 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 2007;120:1338–45.
35. Durham SR, Yang WH, Pedersen MR, et al. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117:802–9.
36. Nolte H, Amar N, Bernstein DI, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. Ann Allergy Asthma Immunol 2014;113:93–100.
37. Nolte H, Malone J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol 2015;135(6):1494–501.
38. Skoner D, Gentile D, Bush R, et al. Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen. J Allergy Clin Immunol 2010;125:660–6.
39. Valovirta E, Jacobsen L, Ljorring C, et al. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. Allergy 2006;61:117–83.
40. Bush RK, Swenson C, Fahlberg B, et al. House dust mite sublingual immunotherapy results of a US trial. J Allergy Clin Immunol 2011;127:974–81.
41. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. N Engl J Med 1965;271:675–9.
42. Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollenosis. JAMA 1967;201:915–7.

43. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children: a 14-year study. Pediatrics 1968;42:793–802.
44. Reid MJ, Moss RB, Hsu YP, et al. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. J Allergy Clin Immunol 1986; 78:590–600.
45. Bousquet J, Becker WM, Heijjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollen and to multiple pollen species. II. Efficacy of double-blind placebo-controlled specific immunotherapy with standardized extracts. J Allergy Clin Immunol 1991;88:43–53.
46. Adkinson NR Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324–31.
47. Marogna M, Spadolini I, Massolo A, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. Ann Allergy Asthma Immunol 2007;98:274–80.
48. Swamy RS, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. J Allergy Clin Immunol 2012;130:215–24.
49. Lieberman P, Tankersley M. Significance of large local reactions that occur during allergen immunotherapy. J Allergy Clin Immunol Pract 2015;3:310–1.
50. Nelson HS. Oral/sublingual phlegm pretense grass tablet (grazax/grastek) to treat allergic rhinitis in the USA. Expert Rev Clin Immunol 2014;10:1437–51.
51. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol 2013;131:1342–9.
52. Epstein TG, Liss GM, Murphy-Berendts K, et al. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. J Allergy Clin Immunol Pract 2014;2:161–7.
53. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J 2014; 7(1):6. Available at: http://www.waojournal.org/content/7/1/6.
54. Maloney J, Durham S, Skoner D, et al. Safety of sublingual immunotherapy timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma. Allergy 2015;70:302–9.
55. Maloney J, Casale TB, Lockey RF, et al. Epinephrine use in clinical trials of sublingual immunotherapy tablets for treatment of allergic rhinitis with/without conjunctivitis. Abstract presentation, Annual Meeting, American Academy of Allergy, Asthma and Immunology. Houston, Texas, 20–24 February 2015.
56. Nelson H, Carter S, Allen-Ramey F, et al. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. J Allergy Clin Immunol Pract 2015;3(2):256–66.e3.
57. Bordignon V, Parmiani S. Variation of the skin endpoint in patients treated with sublingual specific immunotherapy. J Investig Allergol Clin Immunol 2003;13: 170–6.
58. Senna G, Caminati M, Canonica GW. Safety and tolerability of sublingual immunotherapy in clinical trials and real life. Curr Opin Allergy Clin Immunol 2013; 13(6):656–62.
59. Kiel MA, Roder E, van Wijk RG, et al. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol 2013;132:353–60.e2.
60. Bonini S. Regulatory aspects of allergen-specific immunotherapy: Europe sets the scene for a global approach. World Allergy Organ J 2012;5(10):120–3.

61. Kaul S, May S, Lüttkopf D, et al. Regulatory environment for allergen-specific immunotherapy. Allergy 2011;66(6):753–64.
62. Available at: http://www.fda.gov/Advisory. Accessed June 15, 2015.
63. Prescribing information GRASTEK. Whitehouse Station (NJ): Merck Sharp & Dohme Corporation; 2014.
64. Prescribing information RAGWITEK. Whitehouse station (NJ): Merck Sharp & Dohme Corporation; 2014.
65. Prescribing information ORALAIR. Lenoir (NC): Greer Laboratories; 2014.