

Sublingual Immunotherapy for Other Indications

Venom Large Local, Latex, Atopic Dermatitis, and Food



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KEYWORDS

- Sublingual immunotherapy • Food allergy • Latex allergy • Venom allergy
- Atopic dermatitis • Dust mite

KEY POINTS

- Latex sublingual immunotherapy trials have produced evidence for efficacy, but safety concerns exist. In addition, latex extracts are not available in the United States.
- Evidence to support the use of venom sublingual immunotherapy for large local reactions is lacking.
- Dust mite sublingual immunotherapy for atopic dermatitis has produced promising results, but trials using the available US tablet are lacking.
- Food sublingual immunotherapy trials have shown modest efficacy with minimal local reactions, but dose and duration trials are lacking.

INTRODUCTION

With the United States Food and Drug Administration's (FDA) recent approval of standardized sublingual tablets for grasses, ragweed, and dust mites, the scientific data to support the safe and efficacious use of sublingual immunotherapy (SLIT) for allergic rhinitis and asthma are accumulating. These tablets are ideal for furthering SLIT research because they are standardized and reproducibly manufactured, much like medications; however, their FDA indications of use are currently limited. Nevertheless, there are decades of international data regarding less well-known applications of less

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standardized, liquid SLIT drops. This article is a thorough attempt to analyze the prospective clinical trial data regarding these alternative applications of SLIT in order to provide an evidence-based review of the efficacy, safety, and potential indications or limitations of their use for practicing clinicians.

VENOM SUBLINGUAL IMMUNOTHERAPY

The concept of SLIT for venom allergy has a small amount of published data. Two Italian studies regarding the use of SLIT for venom immunotherapy were published in 2008 with optimistic views of this treatment modality.

Severino and colleagues¹ performed a randomized, double-blind, placebo-controlled trial in 30 adult patients with large local reactions to honeybee stings. Patients' local reactions were confirmed via sting challenge and then randomized to honeybee venom SLIT or placebo for 6 months of therapy. Patients in the SLIT group rapidly built up to 35 µg of venom every other day for a total dose of 535 µg monthly. Of the 26 patients who completed the study, a statistically significant reduction in median peak diameter of local reaction was observed in the SLIT group (20.5–8.5 cm), whereas no difference was noted in the placebo group. No adverse reactions to SLIT were reported. The investigators concluded that this study provided a proof of concept regarding the possible utility of SLIT in venom hypersensitivity and admitted that this end point may not be the most clinically important. They suggested this concept warranted further dosing trials and trials regarding patients with systemic reactions to venom stings. This interpretation of the results was debated by Rueff and colleagues,² who cited several methodological flaws in the trial to include differing characteristics of groups, unclear determination of SLIT dosing, and differing interpretation of the same end-point results.

Patriarca and colleagues³ published a case-control study of venom SLIT versus subcutaneous immunotherapy (SCIT) the same year. Forty-one patients with a history of systemic reactions to wasp stings were randomized to receive standard-of-care SCIT (100 µg monthly) versus SLIT (100 µg weekly) via ultrarush buildup protocols. No baseline sting challenges were performed, but immunoglobulin (Ig) E and IgG4 levels were drawn at enrollment and at 6, 12, and 24 months of therapy. Two (9.5%) patients in the SLIT group experienced mild side effects (dysphagia with spontaneous remission and diffuse itching, which resolved with oral antihistamine), whereas 3 (15%) patients in the SCIT group experienced adverse reactions to the same ultrarush buildup protocol. In the SLIT group, no significant changes in IgE and IgG4 levels were observed. In contrast, in the SCIT group, serum-specific IgE levels initially increased, but returned to baseline. IgG4 levels increased significantly at 6 months and remained increased throughout the trial. Four patients had field stings in the SLIT group; each patient experienced a milder reaction than before therapy and only 1 person experienced a systemic reaction (isolated throat constriction). In the SCIT group, 9 patients had field stings, resulting in 8 large local reactions and 1 systemic reaction (dizziness). The investigators argue that this study reveals similar safety and efficacy between venom SCIT and SLIT, but admit that larger randomized controlled trials with standardized sting challenges are needed before venom SLIT can be considered for treatment.

Further research trials into venom SLIT could not be found and no trials seem to be ongoing. Given the lack of data, SLIT for venom allergy cannot currently be recommended. In addition, in an era of flying Hymenoptera venom shortage, it remains difficult to even recommend continuing research into a therapy that would require the use of 4 to 5 times more venom per month compared with SCIT.

LATEX SUBLINGUAL IMMUNOTHERAPY

As researchers began to expand the potential uses of SLIT in the early 2000s, its applicability to latex allergy became interesting to researchers as well. The published literature regarding latex SLIT began in 2001 when Nucera and colleagues⁴ described a case report of a 23-year-old patient with latex allergy who became able to tolerate 1-hour mucosal and 6-hour cutaneous latex challenge tests after a 3-day rush buildup with latex SLIT. This case was a proof of concept and suggested further research into the treatment modality.⁴

The scientific evidence regarding the topic was advanced in 2002 by Patriarca and colleagues.⁵ Their trial randomized 24 children (8 years old at the youngest) and adult patients into a latex extract versus placebo group in a double-blinded fashion after baseline laboratory tests were drawn and latex hypersensitivity was confirmed via latex-specific challenges (cutaneous, mucosal, conjunctival, and sublingual).⁵ Both groups of 12 patients underwent a 4-day rush protocol followed by daily SLIT maintenance for 3 months. After maintenance, all patients in the latex SLIT group were able to tolerate the maximal cutaneous, mucosal, and sublingual latex exposure challenge times (statistically significantly improved compared with placebo group). No systemic reactions and only mild local reactions were noted. Although this was a small trial, these data suggested that SLIT could be safe and efficacious for the treatment of latex allergy.

In 2004, Cistero Bahima and colleagues⁶ published the results of a case series of 26 latex-allergic patients. These patients followed the ALK-Abello sublingual rush protocol with the European commercially available SLIT-LATEX product. Patients were rushed to 100 μ g of latex protein and then continued every other day (300 μ g weekly) for 9 weeks. After this maintenance phase, the skin prick tests did not significantly reduce in size, but the tolerance of cutaneous exposure did significantly improve, although less drastically than the previous study by Patriarca and colleagues.⁵ This trial also highlighted the potential safety risks of latex SLIT, because 12 of 26 patients (46.2%) experienced at least 1 systemic reaction and 23 of 26 patients (88.5%) reported at least 1 local reaction, predominantly lip itching. Systemic reactions resolved without treatment in 44.7%, with antihistamines alone in 26.3%, with beta-2 agonists alone in 5.3%, and with antihistamines and corticosteroids in 18.4% of patients. One patient was treated with epinephrine twice for separate reactions (immediate dyspnea in 1 case and abdominal pain, headache, cough, dyspnea, rhinitis, and chest tightness in the other). Although these rates were concerning, they could also be at least partially attributed to trial design because all patients were being openly exposed to known allergen.

Bernardini and colleagues⁷ published the robust results of their randomized, double-blind, placebo-controlled trial with 20 latex-allergic pediatric patients (4 to 15 years old) in 2006 after 1 year of SLIT-LATEX treatment and again in 2008 after 3 years of immunotherapy. After randomization, 12 children received 40 μ g of latex extract daily after a 4-day rush protocol. After the first year, this active group was allowed to continue SLIT in an open fashion for the remaining 2 years. At the termination of the blinded trial period, cutaneous exposure tolerance significantly improved, but skin prick testing results and IgE levels remained similar to the placebo group. However, cutaneous tolerance continued to improve after 2 years of SLIT and all patients could complete the latex glove use test after 3 years of therapy. No systemic or local side effects were reported and these data supported the long-term safe and efficacious use of latex SLIT, but the duration of this tolerance after the cessation of SLIT was not evaluated.

After Tabar and colleagues⁸ latex study was published in 2006, latex SCIT was largely abandoned for safety concerns because 81.8% of patients receiving latex immunotherapy experienced systemic reactions. Although the tolerability of SLIT allowed it to remain as a potential immunotherapy modality, its safety continued to be closely monitored. Meanwhile, continued SLIT trials in Europe began to accumulate safety and efficacy of the SLIT-LATEX product.

Nettis and colleagues⁹ published an additional randomized, double-blind, placebo-controlled latex SLIT study in 2007. Patients with asthma or urticaria on latex exposure were randomized to the ultrarush protocol with the SLIT-LATEX extract followed by every-other-day administration of 100 μ g of extract. After 12 months, patients underwent cutaneous challenge and statistically significant improvement was again noted compared with the placebo group. Skin prick testing and reduction of medication use also significantly improved, but IgE levels remained similar to placebo. Three of the 18 patients (17%) reported local oral reactions during the induction phase of the active group, which was similar to the placebo group, and no side effects were noted in the maintenance phase.

Buyukozturk and colleagues¹⁰ published their experiences in 2011 with latex SLIT in health care workers that remained symptomatic despite attempted avoidance. Of the 12 people that agreed to participate in this blinded trial, 8 were randomized in the SLIT group and 4 to placebo. However, 3 of these 8 patients (37.5%) experienced severe systemic reactions (anaphylaxis or severe bronchoconstriction) and withdrew from the trial. The remaining people in the SLIT group again showed improved glove use and decreased skin prick responses compared with placebo, but these results perpetuated safety concerns, especially in health care workers.

Curiously, conflicting efficacy results were published by Gastaminza and colleagues¹¹ in 2011. This double-blind, placebo-controlled study of 28 latex-allergic patients found no significant difference in specific provocation tests or in vitro testing after a year of SLIT-LATEX. This study stopped at the lower dose of SLIT at 40 μ g daily, but still reported 4 patients with mild adverse events (similar to the control group's rate of side effects). This dose of SLIT-LATEX was also the dose used in the Bernardini and colleagues⁷ trial. Because trial designs have differed beyond just SLIT dose, no clear association could be made between tolerability and efficacy of a 210- μ g weekly dose compared with a 300- μ g weekly dose.

Lasa Luaces and colleagues¹² furthered the concept of latex SLIT in 2012 when they published the results of their 12-month open, case-control study of 23 children who were allergic to latex. This trial was the first to argue that the previous randomized, double-blind, placebo-controlled trials had already established the safety and efficacy of latex SLIT. Therefore, this trial was designed to use the known data regarding latex component sensitization patterns to further refine the immunologic changes of SLIT to attempt to find correlations to predict clinical efficacy or safety outcomes. Patients were again rapidly built up to 100 μ g of SLIT-LATEX and continued every other day for 12 months. In summary, although some serologic changes were observed, this trial failed to show consistent significant changes in IgE, IgG4, and basophil activation test, which could help predict patients' safety or efficacy outcomes.

The most recent and largest study regarding latex SLIT was published by Nucera and colleagues¹³ in 2018. This observational (nonblinded) case series of 76 latex-allergic adults again used SLIT-LATEX via standard 4-day rush to 100 μ g of latex protein every other day for 3 years of treatment. Latex IgE, mean wheal diameters of skin prick testing, and provocation tests again significantly improved, but IgG4 levels did not change. The investigators supported the clinical use of SLIT-LATEX for patients with latex allergy.

Rush protocols used in these trials and 2 additional independent trials^{14,15} have provided reasonable evidence to suggest that effective doses of latex SLIT can be safely and rapidly achieved. Regrettably, there are several limitations to these studies. The complexity of the clinical manifestation of latex allergy continues to limit the power of these studies because patients with differing symptoms are often grouped together when exposed to specific challenge tests, but the validity of this assumption could be challenged. In addition, sample sizes remained small, with 20 patients as the largest active arm of a randomized, placebo-controlled trial. There is also a lack of long-term data (1 case report) to suggest sustained efficacy after cessation of SLIT. No ongoing trials were discovered. In addition, although there are reasonable data to support the use latex SLIT, there is no commercially available latex extract in the United States, and therefore it is not yet a viable treatment option.

SUBLINGUAL IMMUNOTHERAPY FOR ATOPIC DERMATITIS

The concept of specific immunotherapy as a treatment of atopic dermatitis has gained popularity specifically for the treatment of dust mite–allergic patients. As such, the investigation of SLIT for the treatment of atopic dermatitis also increased for dust mite–sensitized patients and was the first application of SLIT among the topics of this article.

The first prospective trial investigating the effect of dust mite SLIT was published in 1994. Galli and colleagues¹⁶ divided 60 dust mite–allergic children, aged 6 months to 12 years, into separate groups of atopic dermatitis with allergic comorbidities (rhinitis or asthma) and solely atopic dermatitis. The group of children with atopic dermatitis with comorbidities and half of the children with just atopic dermatitis received thrice-weekly dust mite SLIT for up to 3 years. The remaining children with atopic dermatitis served as a control group. Of the 26 children with atopic dermatitis and other comorbidities receiving dust mite SLIT, 21 had significant improvement in dermatitis scores. Ten of 16 children with atopic dermatitis alone receiving SLIT also experienced significant improvement. Eleven of 18 children in the control group similarly experienced significant improvement ($P < .05$) in atopic dermatitis scores before and after the trial period without treatment. As such, the treatment groups did not improve compared with the control group.

The best evidence supporting the use of SLIT for atopic dermatitis originates from a double-blind, placebo-controlled trial published by Pajno and colleagues¹⁷ in 2007. This trial enrolled 56 children that were 5 to 16 years old with atopic dermatitis with a Scoring Atopic Dermatitis (SCORAD) score greater than 7 and evidence of mono-sensitization to dust mites via skin prick testing or serum-specific IgE. Patients with asthma and food allergy were excluded to attempt to limit confounders. Children were stratified based on their atopic dermatitis severity and randomized to SLIT (approximately 3 μ g each of Der p 1 and Der f 1 weekly) or placebo for 18 months of continuous therapy. This method allowed for blinding, but not true randomization. Data regarding the change in SCORAD, rescue medication use, and visual analog score were collected every 3 months and at the end of therapy. Forty-eight (85%) of the children completed the trial, with the 8 dropouts occurring in the first 6 months (2 active and 6 in the placebo group), with the 2 dropouts from the active group citing worsening dermatitis as their motivation to stop participation. After 9 months of therapy, mean SCORAD improved (10 points) in the SLIT group compared with placebo, and they maintained this improvement for the remaining months. This improvement was statistically significant but also likely clinically significant, as shown by the subsequent first publication of a minimal clinically important difference for the SCORAD as

8.7 in 2012.¹⁸ Medication use was also significantly less in the SLIT group. When patients with mild to moderate dermatitis (SCORAD<40) were analyzed separately from severe dermatitis, this effect was noted to be greater for the mild to moderate group and nonsignificant for the severe group. The investigators concluded that SLIT was a safe and effective option to consider in the treatment of patients with mild to moderate atopic dermatitis with dust mite sensitization.

In 2013, Qin and colleagues¹⁹ published the results of their trial of 107 adults with atopic dermatitis with or without atopic comorbidities who were randomized (but not blinded) to receive dust mite SLIT plus medical therapy (levocetirizine and topical mometasone cream) or medical therapy alone for 12 months. Only 84 patients completed the trial and most of the dropouts occurred in the first 6 months at a similar rate between groups. Of the participants who withdrew from the treatment group, the reasons cited were primarily failure to adhere to the protocol and cost. Among the control group, the major reason cited was lack of efficacy. Two patients withdrew from each group because of unspecified adverse events. The statistics were not analyzed on an intention-to-treat basis; however, the trial reported a statistically significant ($P<.05$) higher rate of greater than 60% improvement in SCORAD in the SLIT group (77.8%) compared with the standard-of-care medical therapy group (53.9%). Raw SCORAD scores were not provided, so this improvement could not be compared with the previously mentioned minimal clinically important difference for SCORAD.¹⁸

In 2014, Di Rienzo and colleagues²⁰ published the results of an open, randomized controlled (but again not blinded) study of 27 children aged 5 to 18 years with atopic dermatitis and dust mite sensitization who were treated with dust mite SLIT or medical therapy for 72 weeks. Again, a statistically and clinically significant improvement SCORAD score (mean reduction of -11.9) was noted in the treatment group between baseline and week 72 and between groups at 48 and 72 weeks. No difference was noted in the control group throughout the trial. Although the results are again promising, the lack of blinding continued to introduce possible bias into these studies.

Most recently, in 2017, You and colleagues²¹ published their results of their open trial of SLIT in Korean children and young adults. They treated dust mite-allergic patients with 12 months of SLIT and noted that 19 of 23 (82.6%) had a least 30% decrease in Eczema Area and Severity Index (EASI) score. The mean EASI reduction during the 12 months of SLIT was 6.88, just higher than the minimal clinically important difference of 6.6 determined in 2012.¹⁸ Two patients experienced lip and tongue swelling, which resolved with temporarily withholding SLIT. No systemic reactions were noted. Despite the inherent biases in nonrandomized, nonblinded studies, these data did reveal similar efficacy in patients who were monosensitized to dust mite as well as polysensitized to other aeroallergens and broadened the supportive data to additional ethnic groups as well.

There is an ongoing Brazilian randomized, double-blind, placebo-controlled trial (NCT03388866) continuing to evaluate the efficacy and safety of dust mite SLIT drops. With the FDA approval of a standardized dust mite sublingual tablet, well-designed trials using this product should now be conducted to confirm these optimistic results in the treatment of atopic dermatitis before its widespread use for this indication in the United States.

FOOD-SPECIFIC SUBLINGUAL IMMUNOTHERAPY

Case reports and case series of successful applications of SLIT to food allergy also began receiving attention in the early 2000s.^{22–24} At that time, investigators were

also evaluating the use of SLIT for oral allergy syndrome and the first blinded and controlled trial was published regarding this potential indication. In 2004, Hansen and colleagues²⁵ published their results from a double-blind, double-dummy, placebo-controlled trial of subcutaneous versus sublingual immunotherapy with birch pollen extracts in 40 patients with oral symptoms to apple ingestion. Neither the SCIT nor the SLIT group reported significant symptomatic improvement to an open apple challenge after 2 years of immunotherapy, but unexpectedly the placebo group did have significant improvement. This trial was limited by disease-specific design constraints because subjective symptom scores were the only way to evaluate the results of food challenges, but the lack of blinded challenges likely also biased results. The results argued that neither SCIT nor SLIT improved oral allergy symptoms to apples.

A subsequent study published by Mauro and colleagues²⁶ in 2011 also failed to find significant benefit in either birch SCIT or SLIT for apple oral allergy syndrome. As such, recombinant Mal d 1 extracts were created and initial studies found the antigen could induce immunologic effects *in vivo*.²⁷ More recently, in 2018 a clinical trial by Kina-ciyani and colleagues²⁸ showed the efficacy of recombinant Mal d 1 for the treatment of birch pollen-related food allergy, suggesting that further investigations using recombinant allergens may improve clinical efficacy.

The first trial to show clinical efficacy for SLIT in the treatment of systemic food allergy was published in 2005 by Enrique and colleagues.²⁹ This was a multicenter, randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of hazelnut sublingual extracts in the treatment of hazelnut allergy. A total of 23 patients with a clinical history of hazelnut allergy, positive hazelnut skin prick testing, and a positive double-blind hazelnut oral challenge were randomized to receive hazelnut extract or placebo for 12 weeks after a 4-day rush buildup protocol. Three cutaneous systemic reactions were observed (0.2% of doses) and all resolved with oral antihistamines alone. Local reactions (oral itching) were noted in 7.4% of doses. After completion, the mean dose of hazelnut that provoked objective symptoms increased significantly from 2.29 g to 11.56 g in the SLIT group. No significant changes were noted in the placebo group. In addition, 5 of 11 patients (45%) tolerated the maximum dose of 20 g of hazelnut challenge in the SLIT group, but only 1 of 11 patients (9%) in the placebo group could tolerate this dose.

The same research group then published a follow-up study in 2008 in which patients in the hazelnut group had the opportunity to undergo another food challenge 1 year after the previous study officially ended.³⁰ Seven of the 11 patients consented to and underwent this additional challenge. In the interim, 2 patients remained on SLIT as prescribed, 3 stopped maintenance drops 3 to 4 months after study completion, and 2 reported intermittent compliance with drops. The mean provoking dose increased again to 14.57 g, which was significantly increased from baseline and the initial trial's exit food challenge. Five of the 7 (71%) patients could tolerate the maximal dose of 20 g of hazelnut, but 1 patient who could previously tolerate this dose lost immunologic protection. The study established SLIT as a safe and effective potential long-term tool for the treatment food allergy even without rigorous dosing controls used in clinical trials.

Soon afterward, in 2009, Fernandez-Rivas and colleagues³¹ published their results for the use of SLIT for peach allergy. Fifty-six adult patients with IgE-mediated peach allergy confirmed by peach skin testing or serum-specific IgE testing and positive double-blind, placebo-controlled oral peach challenges were randomized to receive 6 months of SLIT or matching placebo. A total of 4944 doses were given during the trial and 1356 adverse reactions were deemed potentially related to the trial; 1344 were in the active group and 12 in the placebo group, and they were overwhelmingly

local reactions (1328 or 98.8%). Nineteen systemic reactions were noted (16 in active and 3 in placebo groups) and 15 were in the buildup phase of the trial. All of the systemic reactions were considered mild and none required epinephrine for treatment. Sublingual immunotherapy resulted in the tolerance of greater than 3-fold more peach at the end of the trial compared with beforehand. No change was noted in the placebo group. This improvement did not translate to a statistically significant difference between groups ($P = .21$). However, secondary end points of skin test reactivity and IgG4 levels did reach significant improvement levels. The therapy's safety profile and modest improvements in various outcomes motivated an optimistic view that SLIT could have a potential role for the treatment of food allergy and that SLIT would be possible for a variety of foods.

This concept was advanced by a trial by Gomez and colleagues,³² who evaluated the effect of 12 months of peach SLIT on peanut allergy given the cross reactivity of Pru p 3 with Ara h 9. In this case-control trial, 48 peach-allergic patients were divided into groups of 12 based on their peanut allergy status (allergic, sensitized, or tolerant) as well as a control group. In this Mediterranean population, peach SLIT seemed to protect against peach reactions as well as peanut reactions because a significant increase in oral tolerance of peanut protein was observed in those patients with concomitant peanut allergy. This trial was limited by its lack of blinding, and questions remain regarding the extrapolation of this effect to other geographic locations given the varying sensitization profiles to peanut components, but the concept of improving tolerance using cross-reactive allergens is intriguing.

The application of SLIT to the treatment of peanut allergy was first published in 2011 by Kim and colleagues.³³ This randomized, double-blind, placebo-controlled trial of 18 children entailed a 6-month buildup phase followed by 6 months of maintenance-dose immunotherapy. Peanut protein tolerance and immunologic end points were evaluated. The most notable result was that the treatment group could tolerate statistically significant, 20-times more protein than the placebo group (median, 1710 vs 85 mg) during the final food challenge. Entry food challenges were not performed so comparison with baseline levels of tolerance was not possible. Adverse reactions were reported in 11.5% of peanut doses, most commonly oral itching, and 8.6% of placebo doses, most commonly skin itching. No epinephrine was required to treat reactions. The investigators used these data to argue that SLIT for peanut allergy was safe and efficacious and deserved further investigation.

The same group of researchers published a follow-up study in 2019, which evaluated the long-term outcomes of peanut SLIT.³⁴ This open-label cohort study evaluated 48 children who consumed 2 mg/d of peanut SLIT for 3 to 5 years by means of double-blind, placebo-controlled food challenge of up to 5 g of peanut protein. On completion, 32 (67%) of the 48 children could tolerate 750 mg of peanut protein, 12 (25%) of the 48 could tolerate the entire 5-g peanut challenge, and 10 (21%) could tolerate the 5-g peanut challenge again 2 to 4 weeks after cessation of SLIT, showing sustained unresponsiveness. The therapy was associated with side effects, mostly oropharyngeal itching, in 4.8% of doses (representing 94% of patients), which required antihistamines after 0.21% of doses, and no epinephrine was required. The investigators again argued that this trial showed meaningful desensitization in most children.

Fleischer and colleagues³⁵ published the initial findings and Burks and colleagues³⁶ published the long-term and most convincing data to support peanut SLIT in 2015. This multicenter, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of peanut SLIT found that 14 of 20 (70%) patients in the treatment group (of up to 1386 μ g of peanut protein) could tolerate 5 g of peanut powder or a 10-fold increase in the amount of protein at 44 weeks of therapy compared with their

baseline oral challenge. Only 3 of 20 (15%) patients in the placebo group could tolerate this level of peanut protein. Data were promising that longer duration would provide additional benefit, so the trial was opened and the placebo group was started on peanut SLIT at a higher dose of 3696 μ g. Both groups continued for a total of 3 years of active therapy. Patients subsequently underwent oral challenge at 2 and 3 years of active therapy. Patients who could tolerate a full 10-g oral peanut challenge at 3 years discontinued SLIT for 8 weeks and then underwent an additional oral peanut challenge. Four patients were able to complete this entire protocol and were determined to show sustained unresponsiveness to peanut. Adverse reactions were noted in 18.3% of doses, but typically were mild oral symptoms. No epinephrine was required. Significant differences in oral peanut tolerance were not noted between the 1386- μ g and the 3696- μ g dose SLIT groups at the end of the trial. This fact suggests that more than a 2.3-mg increase in daily protein exposure is needed to suggest that a higher dose of SLIT will provide additional clinical protective benefit. Although only 4 of the original 40 patients achieved sustained unresponsiveness, all patients who completed the trial experienced modest levels of desensitization. However, the high rate of dropout, with the most common reason being participant decision, suggested that SLIT patients were not finding the clinical benefit worth the daily drops and oral side effects.

Two additional clinical trials provided data regarding the use of SLIT for food allergy by comparing the safety and efficacy of SLIT with oral immunotherapy (OIT) in the treatment of cow's milk allergy³⁷ and peanut allergy.³⁸ Both trials made the same general conclusions that OIT could be more effective than SLIT, but this benefit comes at the expense of a higher rate of systemic reactions. Despite many controlled OIT trials, randomized controlled trials using SLIT could not be found for patients with hen's egg allergy. There is an ongoing trial evaluating the safety and efficacy of a peanut SLIT product with adjuvant (NCT03463135) as well as an ongoing trial of early intervention with peanut SLIT in peanut-allergic patients less than 4 years old (NCT02304991). The trials discussed earlier suggest that some immunologic tolerance can be created given sublingual exposures to known allergens with minimal side effects.

SUMMARY

Because this is a summation of the available prospective controlled clinical trials (Table 1), there is a clear lack of long-term outcome data, and few foods have been studied. At present, there are no commercially available food SLIT extracts approved by the FDA, making any food SLIT an off-label therapy. Most importantly, the SLIT dose required to prevent systemic reactions to accidental exposures remains unknown. Until these issues are resolved, the use of this modality cannot be recommended in the United States beyond research settings.

With the accumulating data supporting the use of SLIT for allergic rhinitis and asthma, it is only natural to evaluate how this treatment modality could be used in different allergic diseases. To summarize, there are several randomized, double-blind, placebo-controlled trials to support the use of SLIT in food allergy (hazelnut, peach, and peanut specifically) with acceptable tolerability and modest efficacy. The role of this therapy in the future treatment of food allergy remains unclear given its limited efficacy and the availability of other modalities undergoing research. There is 1 randomized, double-blind, placebo-controlled trial to support the safe and efficacious use of dust mite SLIT in children with mild to moderate atopic dermatitis, but these data have not been confirmed with the current FDA-approved dust mite tablet. Although there are several randomized, double-blind, placebo-controlled trials to

Table 1
Clinical trials for sublingual allergen immunotherapy

Investigators, Year	Patients (Age in Years)	Allergen (Dose)	Design/ Duration (mo)	Outcome Assessed	Efficacy	Safety
Severino et al, ¹ 2008	30 (44 mean)	Honeybee venom (535 µg monthly)	RDBPC (6)	Mean peak local reaction to sting challenge, specific IgE, specific IgG	Treatment: mean reduction from 20.5 to 8.5 cm ⁹ ($P = .014$) NS change in IgE. IgG increased ($P = .03$) Placebo: mean reduction from 23.0 to 20.5 ($P = NS$) NS change in IgE or IgG	Treatment: no reactions to treatment or sting Placebo: no reactions to treatment. One episode of isolated systemic urticaria to sting
Patriarca et al, ³ 2008	41 (14–71)	Wasp venom (SLIT 100 µg weekly vs SCIT 100 µg monthly)	Case control (24)	SPT size, specific IgE, specific IgG4, rate of SR to field sting	SLIT: NS change in SPT IgE or IgG4 SCIT: NS change in SPT or IgE, but IgG4 increased ($P = .001$)	AR to therapy: SLIT 9.5%, SCIT 15% SR rate to field sting: SLIT 25%, SCIT 11%
Patriarca et al, ⁵ 2002	24 (8–64)	Latex (300 µg weekly)	RDBPC (3)	Glove use, conjunctival challenge, sublingual challenge, specific IgE, specific IgG4	Treatment: all could tolerate specific challenges. NS change in IgE Placebo: NS change in specific challenges, IgE, and IgG4	Treatment: no side effects to therapy or challenges Placebo: no side effects to therapy or challenges
Bernardini et al, ⁷ 2006	20 (4–15)	Latex (210 µg weekly)	RDBPC (12)	Glove use, rubbing test, SPT, specific IgE	Treatment: significant improvement in glove use ($P < .0005$) and rubbing test ($P < .0005$). NS change in SPT or IgE Placebo: NS change in glove use, rubbing test, SPT, or IgE	No side effects were reported in either group

Nettis et al, ⁹ 2007	35 (18–47)	Latex (300 µg weekly)	<i>RDBPC</i> (12)	Glove use, specific bronchial provocation, symptom/medication score, SPT, specific IgE	Treatment: significant improvement in glove use, specific bronchial provocation, symptom/medication score, SPT results at 12 mo. NS change in specific IgE Placebo: NS changes at 12 mo	Treatment: AR rate 17% of patients (mouth itching/burning, angioedema) Placebo: AR rate 6% (asthma exacerbation)
Buyukozturk et al, ¹⁰ 2010	12 (26–32)	Latex (300 µg weekly)	<i>RDBPC</i> (12)	Glove use, symptom/medication score	Treatment: significant improvement in glove use ($P = .01$) and symptom/medication scores ($P = .035$) Placebo: NS change in glove use or symptom/medication score	Treatment: 2 patients experienced serious SRs prompting trial discontinuation. One patient experienced dyspnea, which improved with beta agonist but also stopped the trial Placebo: no ARs reported
Gastaminza et al, ¹¹ 2011	28 (24–57)	Latex (210 µg weekly)	<i>RDBPC</i> (12 + 12)	Glove use, conjunctival challenge, SPT, specific IgE, basophil activation test	NS difference in any of the measured outcomes	Treatment: 4 mild reactions during buildup Placebo: 5 mild reactions during buildup; 2 patients withdrew because of ARs
Lasa-Luaces et al, ¹² 2012	23 (5–18)	Latex (300 µg weekly)	Case control (12)	Conjunctival challenge, SPT, specific IgE and IgG4, BAT	Treatment: NS change in IgE or BAT at 12 mo. Significant improvement in SPT ($P < .05$), conjunctival challenge ($P = .05$), IgG4 levels ($P < .05$) at 12 mo	Treatment: AR rate 33% of patients during buildup and 28% during maintenance reported local symptoms Placebo: none reported

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Table 1
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Investigators, Year	Patients (Age in Years)	Allergen (Dose)	Design/ Duration (mo)	Outcome Assessed	Efficacy	Safety
Galli et al, ¹⁶ 1994	60 (0.5–12)	HDM (?)	RCT (36)	Physician-assessed dermatitis score	All groups improved. NS difference between the groups	No side effects to treatment were reported
Pajno et al, ¹⁷ 2007	58 (5–16)	HDM (3.2 µg Der p1 and 2.6 µg Der f1 weekly)	RDBPC (18)	SCORAD, VAS	Significant improvement in SCORAD between groups beginning at 9 mo of SLIT ($P = .025$), which was most pronounced in mild-moderate AD. NS change in VAS	Treatment: AR rate of 14% reporting local reaction. SR rate of 7% (2 patients) who experienced itching and flares and were ultimately excluded Placebo: no reported AR
Qin et al, ¹⁹ 2014	107 (18–46)	HDM (50 µg Df protein daily)	RCT (12)	Compliance rate, drug scores, SCORAD, VAS, IgG4	Treatment: significantly less drug score after 6 mo ($P < .01$), improved total efficacy at 12 mo ($P \leq 0.05$), improved VAS at 12 mo ($P < .05$), and higher IgG4 ($P < .01$) at 6 mo. NS difference in compliance rates	Treatment: 4 patients reported mild events, 2 patients withdrew because of AR Placebo: 3 patients reported mild events, 2 patients withdrew because of AR. No severe adverse effects were reported
Di Rienzo et al, ²⁰ 2014	27 (5–18)	HDM (50% Df/50% Dp)	RCT (18)	SCORAD, VAS	Treatment: Mean SCORAD improved compared with baseline and placebo group ($P = .02$) at 12 and 18 mo	Treatment: AR rate 17% of patients Placebo: AR rate 7% of patients

Enrique et al, ²⁹ 2005	23 (19–53)	Hazelnut (38 µg Cor a1 and 24 µg Cor a8 daily)	RDBPC (3)	Oral challenge, specific IgE, IgG4 and IL-10	Treatment: significant improvement in oral tolerance ($P = .02$), IL-10 ($P < .05$), and IgG4 ($P < .05$). NS difference in placebo group outcomes. Oral tolerance was significantly more in treatment compared with placebo group ($P < .05$)	Treatment: SR rate 8% of patients Placebo: SR rate 9%. NS difference SR rate between groups. Local reactions observed in 7.4% of doses, but not specified from which groups
Fernandez-Rivas et al, ³¹ 2009	56 (29 mean)	Peach (30 µg Pru p3 weekly)	RDBPC (6)	Oral challenge, SPT, specific IgE and IgG4	Treatment: significant improvement in oral tolerance ($P = .005$), SPT ($P < .05$), IgE ($P = .001$), and IgG4 ($P = .01$) Placebo: significant increase in IgE only ($P = .03$). Only SPT ($P < .05$) and IgG4 ($P = .02$) levels were significantly different between groups	Treatment: local reaction rate of 89% and SR rate 13% of patients Placebo: local reaction rate of 28% and SR rate 17%. NS difference SR rate between groups
Kim et al, ³³ 2011	18 (1.6–10.5)	Peanut (2000 µg weekly)	RDBPC (12)	Oral challenge dose, SPT, BAT, specific IgE and IgG4, IL-5, IL-13, IL-10, IFN- γ and regulatory T cells	Between groups, there were significant improvements in oral tolerance ($P = .011$), SPT ($P < .02$), BAT (0.009), IL-5 ($P = .015$), peanut IgE ($P = .02$), and IgG4 levels ($P = .014$). NS change in IL-13, IL-10, IFN- γ levels, or Treg numbers between groups	Treatment: local reaction rate of 11.5% and 0.28% of doses required treatment Placebo: local reaction rate of 8.6% and none required treatment. No epinephrine was required for either group

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Table 1
(continued)

Investigators, Year	Patients (Age in Years)	Allergen (Dose)	Design/ Duration (mo)	Outcome Assessed	Efficacy	Safety
Fleischer et al, ³⁵ 2013	40 (12–37)	Peanut (1386 µg daily)	RDBPC (11)	Oral challenge dose, SPT, BAT, specific IgE and IgG4	Significant increase in oral tolerance in treatment group ($P<.01$), but NS different than placebo at 44 wk. Also a decrease in BAT ($P<.008$), increase in IgG4 ($P<.001$) in treatment group. NS difference in peanut IgE levels or SPT response	Treatment: local reaction rate of 40.1% Placebo: local reaction rate of 0.6%. Only 1.1% of doses required treatment, including 1 dose of epinephrine for the study during this blinded stage (SLIT group)

Abbreviations: AR, adverse reaction; BAT, basophil activation test; Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; HDM, house dust mite; IFN, interferon; IL, interleukin; NS, nonsignificant; RCT, randomized controlled trial; RDBPC, randomized, double-blind, placebo-controlled; SPT, skin prick test; SR, systemic reaction; Treg, regulatory T cell; VAS, visual analog scale.

support the use of SLIT-LATEX, this product is not available in the United States and extrapolation of these effects to “homemade” latex extracts is unsubstantiated. In addition, there is insufficient evidence to support the use of SLIT for venom hypersensitivity at this time.

DISCLOSURE STATEMENT

The authors have nothing to disclose.

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