Sublingual immunotherapy as an option for effective food allergy treatment

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ABSTRACT

Food allergy sublingual immunotherapy (SLIT) has demonstrated efficacy in inducing desensitization with lower rates of systemic adverse effects than oral immunotherapy (OIT). Long-term SLIT has been shown to induce sustained unresponsiveness, and there is evidence that high-dose SLIT protocols can achieve tolerance that approximates that of OIT. However, the cost of allergenic extract may make long-term, high-dose SLIT prohibitive. Consequently, some allergists have used food allergy SLIT as a temporary bridge to OIT. Other allergists have developed SLIT protocols by using suspensions prepared from whole foods instead of commercially available extracts. Because long-term maintenance dosing regimens for food allergy SLIT have not been standardized, studies are needed to determine the minimum effective doses and duration of food allergy SLIT for various foods. Clarity on these questions may open the door to establishing food allergy SLIT as a viable treatment option.

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Although oral immunotherapy (OIT) for food allergy has been shown to be safe and effective in the outpatient setting, some patients have difficulty tolerating OIT due to persistent gastrointestinal (GI) symptoms, acute hypersensitivity reactions, or taste aversion.[1] Other patients may not have an interest in consuming the food allergen regularly but still wish to gain protection from cross-contamination or accidental ingestion. Still others have concerns about being able to comply with the safety precautions necessary with OIT.[1] Sublingual immunotherapy (SLIT), which uses lower doses of allergen to induce food allergen desensitization in the oral mucosa rather than the small intestine, offers an alternative to OIT due to its ease of dosing and tolerability. Until recently, the excellent safety profile of SLIT was one of its primary selling features, and SLIT was believed to yield more modest levels of desensitization in comparison with OIT.[2] However, recent studies demonstrate that, at higher doses, SLIT can yield tolerance to doses of peanut that approximate results of peanut OIT. SLIT is now getting a closer look as a form of food allergen desensitization that may hit the "sweet spot" for both safety and efficacy in patients who desire protection from accidental food allergen ingestion.

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PATIENT SELECTION

Ease of administration and a favorable tolerability profile makes SLIT a suitable treatment option for a wide variety of patients. SLIT can be practically administered in young children, including toddlers. SLIT is also an attractive modality for patients who have experienced bothersome adverse effects during OIT or who simply prefer a treatment option with a lower risk of systemic reactions. Other patients may prefer SLIT due to fewer dietary and activity restrictions compared with OIT or due to a marked taste aversion to the food allergen. Contraindications to food allergy SLIT have not been well defined but rather have been extrapolated from aeroallergen SLIT. Absolute contraindications include serious immunologic disorders, serious cardiovascular disease, uncontrolled asthma, active eosinophilic esophagitis, cancer, chronic infection, noncompliance, and severe psychological disorders. Pregnancy is a relative contraindication to SLIT initiation. Temporary contraindications to SLIT include inflammation, injury, or surgical intervention in the oral cavity, and acute gastroenteritis.[3,4]

PREPARATION AND ADMINISTRATION

Although a comprehensive discussion of SLIT's mechanism of action is beyond the scope of this practical article, it is detailed in the existing literature.[5,6] SLIT for food allergens is generally administered in the form of liquid drops or spray to the oral mucosa beneath the tongue, which is then held in place for ~2–5 minutes

Table 1 **Sample food sublingual immunotherapy dose escalation protocol by using commercial extracts**

Dose No.	Vial Dilution,** v/v	Concentration, w/v	No. Pumps (50 μL per pump)#	Peanut Protein per Dose,## μg	Egg White Protein per Dose,§ μg	Cow's Milk Protein per Dose,¶ μg	Cashew Protein per Dose,‖ μg
1	1:1000	1:20,000	1	0.25	0.1125	0.2	0.3
2	1:1000	1:20,000	2	0.5	0.225	0.4	0.6
3	1:1000	1:20,000	3	0.75	0.3375	0.6	0.9
4	1:1000	1:20,000	4	1	0.45	0.8	1.2
5	1:100	1:2000	1	2.5	1.125	2	3
6	1:100	1:2000	2	5	2.25	4	6
7	1:100	1:2000	3	7.5	3.375	6	9
8	1:100	1:2000	4	10	4.5	8	12
9	1:10	1:200	1	25	11.25	20	30
10	1:10	1:200	2	50	22.5	40	60
11	1:10	1:200	3	75	33.75	60	90
12	1:10	1:200	4	100	45	80	120
13	1:5	1:100	3	150	67.5	120	180
14	1:5	1:100	4	200	90	160	240
15	1:5	1:100	5	250	112.5	200	300
16	1:2.5	1:50	3	300	135	240	360
17	1:2.5	1:50	4	400	180	320	480
18	1:2.5	1:50	5	500	225	400	600
19	1:1* (undiluted)	1:20	2	500	225	400	600
20	1:1* (undiluted)	1:20	3	750	337.5	600	900
21	1:1* (undiluted)	1:20	4	1000	450	800	1200

**1:1 v/v solution is undiluted (peanut, egg white, cow's milk, or cashew) extract, 1:20 w/v. (Stallergenes Greer, Lenoir, NC)*

#Metered dose dropper vials supplied by Edge Pharmaceuticals, Colchester, VT; each pump delivers 50 mL of liquid (after priming with six pumps); each vial holds 15 mL of liquid.

§Concentration of egg white protein in undiluted extract is estimated to be 2250 μg/mL.

¶Concentration of milk protein in undiluted extract is estimated to be 4000 μg/mL, of which 80%–90% is conservatively estimated to be casein.

‖Concentration of cashew protein in undiluted extract is estimated to be 6000 μg/mL.

***Dilutions are made in 50% glycerinated saline solution (Stallergenes Greer, Lenoir NC or ALK-Abello, Hørsholm Denmark).*

##Concentration of peanut protein in undiluted extract is estimated to be 5000 mg/mL, of which 6% is conservatively estimated to be Ara h 2.

before being swallowed or spit out. Dosing for food allergen SLIT begins in the microgram range, builds up to maximum doses in the milligram range, and is prepared as a series of increasingly concentrated dilutions that lead up to an undiluted commercial extract or stock whole-food suspension.[8] Doses are administered once daily in most cases, although some protocols incorporate more frequent dosing. Dose escalation occurs every 1–2 weeks. The author's SLIT dosing schedule, which uses commercial allergen extract, is provided in Table 1. An alternative method of creating SLIT vials from readily available food sources is summarized in Table 2.

SAFETY AND TOLERABILITY

The majority of reactions to food allergen SLIT are local and include oropharyngeal itching and swelling of lips and oral and/or lingual mucosa.[8] These symptoms are generally self-limited and tend to resolve over the course of a few weeks of consistent dosing. Rinsing the mouth with water, eating, and oral antihistamines can be helpful if symptoms do not resolve spontaneously. Systemic reactions to food allergy SLIT are uncommon. A multicenter, randomized clinical trial of peanut SLIT reported that ~95% of doses were symptom-free, once localized oropharyngeal symptoms were excluded.[8] Similarly, low rates of systemic reactions were also noted with hazelnut, milk, and peach SLIT.[9–11]

GI adverse effects are also rare in food allergy SLIT, consistently less common than reported in OIT.[7,10] Isolated cases of biopsy-confirmed eosinophilic esophagitis during the updosing and maintenance phases of aeroallergen SLIT have been reported, and seem to be reversible on SLIT discontinuation.[12] Although this

Table 2 **Creating food allergy SLIT maintenance vials from OIT solutions and/or suspensions***

Food Allergen	Source	Amount	Distilled Water	Flavoring	Maintenance Dose (per 400 μL), mg
Almond	Barney Butter Almond Butter (smooth; Barney Butter, Fresno, CA)	1/8 tsp	To yield 25 mL total volume	Kool-Aid (The Kraft Heinz Co., Glenview, IL) 1/2 tsp	2
Cashew	Artisana Raw Organic Cashew Butter (Premier Organics, Oakland, CA)	1/8 tsp	To yield 25 mL total volume	Kool-Aid 1/2 tsp	2
Chickpea	Bob's Red Mill Garbanzo Bean Flour (Bob's Red Mill Natural Foods, Milwaukie, OR)	625 mg	To yield 25 mL total volume	Kool-Aid 1/2 tsp	2
Coconut	Bob's Red Mill Organic Coconut Flour (Bob's Red Mill Natural Foods, Milwaukie, OR)	3/8 tsp (875 mg)	To yield 25 mL total volume	Kool-Aid 1/2 tsp	2
Egg white	All Whites 100% or Eggland's Best Liquid Egg White (Crystal Farms, New Albany, OH; Eggland's Best LLC, Malvern, PA)	1.1 mL	23.9 mL	Kool-Aid 1/2 tsp	2
Hazelnut	Elmhurst Hazelnut Milk (Elmhurst Milked Direct LLC, Elma, NY)	15 mL	10 mL	Chocolate or strawberry syrup	2
Milk	Organic or irradiated whole milk	3.75 mL	21.25 mL	Chocolate or strawberry syrup	2
Peanut	Peanut butter (Peanut Butter & Co., Santa Cruz Organic, Jif; Peanut Butter & Co, New York, NY; The J.M. Smucker Co., Orrville, OH; Santa Cruz Natural Inc., Chico, CA)	1/8 tsp	To yield 25 mL total volume	Kool-Aid 1/2 tsp	2
Rye	Nuts.com Organic Dark Rye Flour (Nuts.com, Cranford, NJ)	938 mg	To yield 25 mL total volume	Kool-Aid 1/2 tsp	2
Sesame	Max Sesame Tahini Spread (Almondie, Israel)	1/8 tsp	To yield 25 mL total volume	Kool-Aid 1/2 tsp	1.7
Soy	Silk Original Soy Milk (Danone North America, Broomfield, CO)	3.75 mL	21.25 mL	Chocolate or strawberry syrup	2
Sunflower	Sunbutter (SunButter LLC, Fargo, ND)	567 mg	To yield 25 mL total volume	Kool-Aid 1/2 tsp	2
Walnut	Fastachi.com Raw Walnut Butter (Fastachi, Watertown, MA)	1/8 tsp	To yield 25 mL total volume	Kool-Aid 1/2 tsp	1.7
Wheat	Druids Grove Vital Wheat Gluten Flour (Modernist Pantry, Eliot, ME)	178 mg	To yield 25 mL total volume	Kool-Aid 1/2 tsp	2

SLIT = Sublingual immunotherapy; OIT = oral immunotherapy.
**Adapted from Ref. 19.*

Table 3 **Comparison of peanut OIT vs peanut SLIT**

	Peanut OIT	Peanut SLIT
Upper limit of daily maintenance dose (peanut protein)	4000 mg	4000 μg
Efficacy (change in SCD from baseline)	141-fold increase in SCD*	22-fold increase in SCD*
Adverse reactions	Mostly minor, some moderate to severe	Mostly minor
The need for dietary and exercise restrictions during dosing	Yes	No
Sustained unresponsiveness possible	Yes	Yes
Cost of maintenance dosing	Low for whole peanuts or peanut flour; high for commercial product	Low for whole-food SLIT; high for commercial extracts

OIT = Oral immunotherapy: SLIT = sublingual immunotherapy; SCD = successfully consumed dose.
**From Ref. 13.*

has not been the case for food allergy SLIT, there have been reports of food allergy SLIT being associated with delayed GI symptoms. In such cases, spitting out the SLIT solution rather than swallowing may alleviate symptoms.

EFFICACY

A randomized, double-blind, crossover study that directly compared peanut OIT with peanut SLIT in children demonstrated a 22-fold increase in reaction threshold after 12 months of peanut SLIT at a maintenance dose of 3.7 mg/day. However, it is notable that this was significantly lower than the 141-fold increase seen for peanut OIT, which was given at a significantly higher maintenance dose of 2000 mg/day.[13] Studies of aeroallergen SLIT suggest that the immune response in SLIT may be limited by the fixed number of dendritic cells in the sublingual mucosa, and there may not be additional benefit from increasing doses once an effective dose is reached.[14] This, combined with data that demonstrate the efficacy of increased dosing frequency in aeroallergen SLIT, has prompted some centers to develop protocols that use lower doses of food allergen SLIT with higher frequency, up to three times daily.[15] However, the optimal treatment dose has not been clearly elucidated for food allergy SLIT and is likely to be different for individual food allergens. The duration of SLIT seems to be critical to efficacy. The first multicenter, randomized, placebo controlled trial of peanut SLIT showed significant increases in the successfully consumed dose during oral peanut challenge after 68 weeks of active therapy compared with 44 weeks.[8]

A long-term study of peanut SLIT in 48 children ages 1–11 years demonstrated that, after 3–5 years of a daily SLIT dose of 2000 μg of peanut protein, 67% were able to tolerate $\geq$ 750 mg of peanut protein during double-blind, placebo controlled food challenge (DBPCFC), and 25% were able to tolerate $\geq$ 5000 mg. Furthermore, 83% (10/12) of those subjects able to tolerate the highest peanut doses when on DBPCFC were also able to successfully complete an identical DBPCFC after 2–4 weeks without SLIT dosing, which indicated that peanut SLIT at this dose and duration is capable of inducing at least short-term unresponsiveness in a subset of patients (20.8%).[16]

A subsequent study of high-dose peanut SLIT in toddlers demonstrated that, after 36 months of once-daily maintenance SLIT dosing with 4000 μg of peanut protein, 12 of 19 patients randomized to peanut SLIT were able to pass DBPCFC to 4333 mg of peanut protein, and 10 of 19 were able to pass repeated challenge after discontinuing peanut SLIT dosing for a 3-month period.[16] It remains to be elucidated whether the increased efficacy of peanut SLIT in this study was a result of the higher maintenance dose or the young age of the study subjects. A comparison of OIT and SLIT is included in Table 3.

APPLICATIONS IN CLINICAL PRACTICE

Most of the research on food allergy SLIT has been focused on the use of SLIT as an alternative to other forms of immunotherapy, such as OIT or epicutaneous immunotherapy. This is, indeed, how food allergy SLIT is largely used in clinical practice. However, there is also experience in using food allergy SLIT as a transition, or a bridge, to OIT in patients who have a history of experiencing intolerable adverse effects in the early phases of OIT or who have an especially low threshold of reactivity to their food allergen.[17] Pretreatment with SLIT before OIT has been shown to dramatically reduce the overall rates of adverse reactions.[13] In clinical practice, this approach has been used for a wide variety of food allergens, including peanut, tree nuts, milk, egg, soy, wheat, seafood, and

legumes. Most studies of food allergy SLIT to date have reviewed safety and efficacy of single-allergen SLIT.[8–11] In an effort to personalize treatment to a patient's particular allergens, multiallergen SLIT is common in clinical practice, both as a standalone treatment and as a transition to OIT. Well-designed studies of multifood SLIT are needed to clearly establish efficacy of such protocols.

LIMITATIONS

In contrast to SCIT or OIT, the number of dendritic cells capable of antigen capture in the sublingual space is limited. Consequently, there exists a ceiling on the quantity of allergen than can be effectively introduced to the immune system via SLIT at any given time. In fact, studies of aeroallergen SLIT have demonstrated poorer outcomes with multiallergen SLIT when compared with treatment for timothy grass alone.[18] In theory, competitive inhibition for dendritic cells in the sublingual mucosa might be a barrier to effective multifood allergy SLIT.

Cost is also a limitation of food allergy SLIT. Commercial allergen extracts from which most SLITs are prepared are expensive to procure, and the studies that demonstrated the highest SLIT efficacy used high doses of undiluted extract with extended courses of maintenance therapy. Due to maximum concentrations of commercially available extracts, peanut SLIT protocols that provide a target dose of 4000 μg of peanut protein would require 800 μL of undiluted peanut extract daily, and the extract alone would cost >$10,000 for a 36-month course of therapy (Stallergenes Greer, personal communication, November 1, 2021). These financial realities might impact the commercial viability of a food allergy SLIT product and limit industry investment into research and development for food allergy SLIT. In an effort to improve accessibility of food allergy SLIT to patients, some practices have pivoted to administering food allergy SLIT with office-prepared OIT solutions and/or suspensions that are made from whole-food products rather than commercial allergen extracts.[19] Although this does reduce cost, the stability and efficacy of sublingual treatment with these solutions and/or suspensions has not been established.

CONCLUSION

SLIT for food allergens has demonstrated a favorable safety profile in comparison with OIT, and high-dose SLIT has also been shown to have efficacy that approaches that of OIT. This makes SLIT an attractive option for patients with taste aversion to food allergens or intolerable adverse effects from OIT, whether the SLIT is used as a temporary bridge to OIT or as a standalone treatment. However, the high cost of commercially available food allergen extract may result in high-dose SLIT being cost prohibitive. Additional research is needed to determine if lower doses of SLIT can achieve sufficient protection from accidental food allergen ingestion. Furthermore, studies are needed to assess the safety and efficacy of SLIT prepared from whole-food products. Also, the safety and efficacy of multifood SLIT requires investigation. Investment into research to answer these outstanding questions will be instrumental in enabling food allergen SLIT to meet its potential as a safe and efficacious option for the treatment of food allergy.

CLINICAL PEARLS

- SLIT for food allergies is safe, with a lower rate of systemic reactions than OIT; most reactions to food SLIT are self-limited and localized to the oropharynx.
- Food allergy SLIT modifies molecular markers of food tolerance and promotes B- and T-cell anergy.
- Food allergy SLIT significantly increases the threshold of reactivity compared with placebo, and peanut SLIT has been shown to induce sustained unresponsiveness.
- Limitations of food allergy SLIT include a finite capacity for allergen capture by dendritic cells in the sublingual mucosa and the high cost of allergen extract needed to maintain long-term therapeutic dosing.
- Future directions for study include optimization of the maintenance dose and the frequency and the evaluation of the safety and efficacy of multifood SLIT and SLIT prepared from whole foods.

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