

## Clinical Commentary Review

## Local Side Effects of Sublingual and Oral Immunotherapy

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Sublingual immunotherapy (SLIT) is increasingly used worldwide, and several products have been recently registered as drugs for respiratory allergy by the European Medicine Agency and the Food and Drug Administration. Concerning inhalant allergens, the safety of SLIT is overall superior to that of subcutaneous immunotherapy in terms of systemic adverse events. No fatality has been ever reported, and episodes of anaphylaxis were described only exceptionally. Looking at the historical and recent trials, most (>90%) adverse events are “local” and confined to the site of administration. For this reason, a specific grading system has been developed by the World Allergy Organization to classify and describe local adverse events. There is an increasing amount of literature concerning oral desensitization for food allergens, referred to as *oral immunotherapy*. Also, in this case, local side effects are predominant, although systemic adverse events are more frequent than with inhalant allergens. We review herein the description of local side effects due to SLIT, with a special focus on large trials having a declared sample size calculation. The use of the Medical Dictionary for Regulatory Activities nomenclature for adverse events is mentioned in this context, as recommended by regulatory agencies. It is expected that a uniform classification/grading of local adverse events will improve and harmonize the surveillance and reporting on the safety of SLIT. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

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Allergen immunotherapy (AIT) administered via routes other than the traditional subcutaneous route has been investigated since the beginning of 20th century (for a historical review, see Canonica and Passalacqua<sup>1</sup> and Committee on the Safety of Medicines<sup>2</sup>), but these empirical attempts remained essentially anecdotal for many decades. The interest in noninjection routes of AIT administration was renewed during the 1980s, after official report of deaths due to subcutaneous immunotherapy (SCIT).<sup>3</sup> Indeed, it was subsequently recognized that although a proportion of near-fatal or fatal events was due to avoidable human errors, many of those events remained unpredictable and unavoidable<sup>4,5</sup> although rare. Among the various alternative routes proposed to improve AIT safety and convenience, sublingual immunotherapy (SLIT)<sup>6</sup> emerged as a safe and effective option. SLIT has become gradually accepted and acknowledged in the AIT official documents and guidelines.<sup>7-11</sup> Selected SLIT products (tablets) have been approved recently for clinical use by the Food and Drug Administration in the United States.<sup>12</sup> Since the earliest pioneering trials<sup>6</sup> it has become apparent that untoward events were mainly localized to the site of administration (ie, gastrointestinal tract), and most frequently confined to mouth, lips, tongue, pharynx, and throat. Systemic (not anatomically related) side effects, such as rhinitis, conjunctivitis, ear pruritus, asthma, urticaria, or anaphylaxis, were consistently rare. All those findings were further confirmed in the recent “large” multicenter trials that involved hundreds of patients, as well as in several meta-analyses (see Canonica et al<sup>11</sup>).

In parallel, based on the expected safety profile, the use of sublingual and oral administration of allergens was proposed for food allergy, leading to the practice of oral immunotherapy (OIT) or specific oral tolerance induction. SLIT and OIT with food allergens are less well defined, from the immunological and clinical viewpoints, than the standard SLIT for respiratory allergy because it is not clear whether (1) food SLIT or OIT can induce only a transient desensitization or a sustained tolerance to foods; (2) the desensitization should be maintained with a regular dietary intake; and (c) the immunological changes are long-lasting or only provisional.<sup>13,14</sup> Despite these unsolved questions, SLIT and OIT were reported to be beneficial with cow’s milk, hen’s egg, and peanuts, mainly in children. Also, in the case of food allergy, with oral administration, local adverse events (AEs) were reported as predominant.<sup>15</sup>

We summarize herein the main findings about local side effects of SLIT (for inhalant and food allergens) and of food oral desensitization, to quantify the phenomenon, and to suggest strategies for a standardization of grading and description. The main advantages of using a widely agreed grading system in SLIT are (1) uniformity in reporting and comparing the safety of extracts, doses, and regimens; (2) improved “epidemiological” knowledge on the safety of SLIT; (3) increased value of the

**Abbreviations used**

*AE*- adverse event  
*AIT*- allergen immunotherapy  
*EoE*- eosinophilic esophagitis  
*OIT*- oral immunotherapy  
*SCIT*- subcutaneous immunotherapy  
*SLIT*- sublingual immunotherapy

postmarketing surveillance studies; (4) the possibility of identifying risk factors for AEs; and (5) providing guidelines to doctors and patients on how to respond to a particular AE (ie, to continue, adjust, or stop treatment).

### LOCAL SIDE EFFECTS OF SLIT IN RESPIRATORY DISEASES

There are more than 80 randomized double-blind placebo-controlled trials (for review, see Scadding and Brostoff<sup>5</sup> and Canonica et al<sup>11</sup>), and several systematic reviews,<sup>16-24</sup> all confirming the consistent clinical efficacy of SLIT for respiratory allergic diseases, despite substantial heterogeneity due to methodological variability. In the reported studies, the relative efficacy (symptoms and/or medication scores) versus the placebo groups varies from 20% to 40%.

The safety profile of SLIT is overall superior to that of SCIT,<sup>25</sup> no fatalities have been reported, and severe systemic reactions are rare. Over 30 years of clinical use, only few cases of anaphylaxis have been reported.<sup>26</sup> The overall occurrence of systemic side effects is similar between placebo and active groups in most studies. The rate of AEs reported in SLIT trials varies according to the definition used, but local AEs are predominant. Oral side effects are quite frequent and invariably occur in more than 50% (Table I)<sup>27-45</sup> of the patients receiving active SLIT, but their duration commonly does not exceed 10 days, and discontinuation due to such side effects is generally less than 5%. Of note, the occurrence and severity of AEs gradually decline in the subsequent years of treatment, as reported in follow-up assessment of previous trials.<sup>46,47</sup> As mentioned above, local reactions associated with SLIT primarily occur in the mouth, at the site of administration of the allergen vaccine. These include oral itching, throat irritation, and lip/tongue swelling. SLIT can also provoke lower gastrointestinal symptoms.<sup>48,49</sup> Reactions involving the lower digestive tract (diarrhea, nausea, abdominal pain) could be part of "systemic" reactions but, in general, such events are classified as local because they are related to the site of administration. However, in some postmarketing surveys, abdominal pain and diarrhea are included as systemic side effects. The more recent position statement by the World Allergy Organization<sup>50</sup> proposed that lower gastrointestinal tract reactions are considered local reactions, unless they occur with other systemic manifestations, in which case they are classified as systemic reactions. The real-life studies<sup>51-56</sup> show that the overall occurrence of reported AEs (either local or systemic) is lower in postmarketing surveys than in randomized controlled trials. This is probably because many events are judged as minimal by patients and therefore not reported to physicians. Certainly, other variables may intervene, such as personal expectations on efficacy versus discomfort, difficult recall, or time elapsed to the next visit. Nonetheless, most AEs in postmarketing studies are

reported as oral, mild, and self-limiting, with a rate of less than 10 per 1000 doses.

The report and description of local reactions are overall unsatisfactory, making it difficult to compare the reporting among studies, to identify the risk factors, and to recommend appropriate action to take when a reaction occurs. For this reason, a uniform grading system of systemic AEs based on the previously used systems was proposed<sup>57</sup> (Table II). In this context, to better standardize reporting/grading, the World Allergy Organization panel strongly recommended the use of the Medical Dictionary for Regulatory Activities<sup>58-60</sup> (Table III). In this system, AEs are hierarchically classified into 5 levels of detail, starting from the more general (system organ class) to the more specific (lowest level term). Each level better details the AEs and the terminology of the previous one. The World Allergy Organization grading of the systemic side effects associated with SCIT was endorsed by several regional scientific societies.<sup>57</sup> Because the administration of any allergen, regardless of the administration route, can cause systemic adverse effects (including ocular symptoms, asthma, or urticaria), the above-mentioned classification for systemic side effects is also suggested for SLIT.<sup>57,61</sup> With SLIT, the severity of local side effects has been assessed in arbitrary ways across the clinical trials. There is no objective parameter (eg, FEV<sub>1</sub> or blood pressure) to quantify the severity of a local AE; therefore, a certain degree of subjectivity is unavoidable. In general, the severity of local side effects depends on the signs and symptoms and on their duration, keeping in mind that local side effects of SLIT tend to disappear after the initial doses. Another aspect to consider is that if a local side effect causes discontinuation of SLIT, either because of a single event or for the persistence with repeated dosing, this would be a severe event.<sup>57</sup>

The most important recommendations, agreed in all guidelines, are that (1) the first dose of SLIT has to be given under medical supervision; (2) patients should be carefully instructed in the use of SLIT, to avoid accidental overdose and to appropriately manage side effects; and (3) uncontrolled asthma remains the major absolute contraindication to any AIT administration.<sup>62</sup> In the United States, a known diagnosis of eosinophilic esophagitis (EoE) is also an official contraindication for some of the Food and Drug Administration—approved products.

### LOCAL SIDE EFFECTS OF SLIT/OIT IN FOOD ALLERGY

Sublingual and oral immunotherapy (SLIT, OIT) routes for treatment of food allergy remain investigational therapies and continue to undergo validation in clinical trials.<sup>63</sup> Subcutaneous rush immunotherapy for peanut allergy has been reported to cause an unacceptably high rate of serious AEs, even during the maintenance phase but has provided a proof of concept that immunomodulation was possible with food allergens.<sup>64,65</sup> Subsequently, in the last 10 years, taking advantage of the improved safety, SLIT and OIT trials have been done with different allergenic foods. SLIT was tested in controlled trials for hazelnut, cow milk, peach, and peanut,<sup>66-71</sup> and OIT was studied with peanut,<sup>72-74</sup> milk,<sup>75-77</sup> wheat,<sup>78,79</sup> and egg<sup>80</sup> (Tables IV and V). Two head-to-head comparisons of SLIT versus OIT for milk and peanut allergy showed that SLIT has generally a more favorable safety profile, whereas OIT affords higher efficacy.<sup>67,72</sup>

**TABLE I.** Local AEs in the “large trials” with SLIT

Author (year)	Patients enrolled	Age range (y)	Allergen (preparation)	Duration	% patients with local AE in the active groups
Dahl (2006) <sup>27</sup>	634	18-65	Grass (tablet)	8 mo	Oral itching, 46%; Mouth edema, 18%; Throat itching, 9%
Durham (2006) <sup>28</sup>	855	18-65	Grass, 3 doses (tablet)	6 mo	75%-90%, not detailed
Didier (2007) <sup>29</sup>	628	18-45	Grass, 3 doses (tablet)	6 mo	Oral itching, 19.7%-25.8%; Mouth edema, 3.2%-6.3%; Throat itching, 9%-14.4%; Tongue edema, 3.2%-5.6%
Ott (2008) <sup>30</sup>	211	8-65	Grass (solution)	4 mo*	69%, not detailed. Most AE defined as local
Wahn (2009) <sup>31</sup>	278	5-17	Grass (solution)	5 mo	Oral itching, 32%; Mouth edema, 13%; Throat itching, 8%
Bufe (2009) <sup>32</sup>	253	5-16	Grass (solution)	6 mo	Oral itching, 33%; Swollen lips, 7%; Throat itching, 10%
Blaiiss (2011) <sup>33</sup>	345	5-17	Grass (tablet)	6 mo	70% overall. Mainly oral itching, oral edema, throat itching, oral swelling. Not detailed
Nelson (2011) <sup>34</sup>	439	18-63	Grass (solution)	6 mo	83% overall. Oral itching, 35%; Mouth edema, 8%; Throat itching, 30%; swollen tongue, 5%
Wahn (2012) <sup>35</sup>	207	4-12	Grass (solution)	6 mo	Oral itching, 72%; Throat itching, 11%
Cox (2012) <sup>36</sup>	473	18-65	Grass (tablet)	6 mo	82%. Mostly oropharyngeal pruritus
DeBot (2012) <sup>37</sup>	257	6-18	Mite (solution)	2 y	Oral-pharyngeal irritation/swelling, 11%; gastrointestinal complaints, 85%
Nolte (2013) <sup>38</sup>	565	18-50	Ragweed, 2 doses (tablet)	1 y	Oral itching, 19%; Mouth/tongue edema, 15%; Throat itching, 26%; pharyngeal edema, 4.2%
Creticos (2013) <sup>39</sup>	784	18-50	Ragweed, 3 doses (tablet)	1 y	Oral/tongue itching, 15%; Mouth edema, 8%; Throat itching, 13%
Bergmann (2014) <sup>40</sup>	509	18-50	Mite, 2 doses (tablet)	1 y + follow-up	Oral/tongue itching 40%; Mouth/tongue edema 35%; Throat itching 33%; Pharyngeal edema 5%
Creticos (2014) <sup>41</sup>	429	18-55	Ragweed (solution)	8 mo	Oral/tongue itching 4%; Mouth edema 6%; Diarrhea/dyspepsia 4%
Mosbech (2014) <sup>42</sup>	604	14-65	Mite, 3 doses (tablet)	1 y	Oral/tongue itching, 2%-19%; Mouth edema, 4%-8%; Throat, itching 3%-7%
Maloney (2014) <sup>43</sup>	1501	5-65	Grass (tablet)	8 mo	Oral/tongue itching, 18%; Mouth edema, 13%; Throat itching, 23%
Wang (2014) <sup>44</sup>	484	14-50	Mite (solution)	1 y	Abdominal pain, swollen tongue, oral pruritus, cheilitis, and mouth edema, all mild and more frequent in the active group (no detail)
Okamoto (2015) <sup>45</sup>	532	12-64	Cedar (solution)	18 mo	Mouth edema, 3.8%; stomatitis and throat irritation, 1.9%; oral itching, 1.1%

\*Three seasons, coseasonal regimen.

**TABLE II.** Grading system for SLIT local AEs (see Table III for the Medical Dictionary for Regulatory Activities codes)

Symptom/sign (see Table I)	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	<ul style="list-style-type: none"> <li>• Not troublesome</li> </ul> AND <ul style="list-style-type: none"> <li>• No symptomatic treatment required</li> </ul> AND <ul style="list-style-type: none"> <li>• No discontinuation of SLIT because of local side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Troublesome</li> </ul> OR <ul style="list-style-type: none"> <li>• Requires symptomatic treatment</li> </ul> AND <ul style="list-style-type: none"> <li>• No discontinuation of SLIT because of local side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Grade 2</li> </ul> AND <ul style="list-style-type: none"> <li>• SLIT discontinued because of local side effects</li> </ul>	The treatment is discontinued but there is no subjective and/or objective description of the severity from the patient/physician

Each local AE can be early (&lt;30 min) or delayed.

This difference in safety and efficacy is likely related to significantly higher daily maintenance doses used in OIT (range, 300 mg to 4 g) compared with SLIT daily maintenance dose of approximately 1.3 to 7 mg. In a study comparing milk SLIT with milk OIT, following 48 weeks of daily SLIT dosing with 7 mg of milk protein, 1 of the 10 subjects passed an oral food challenge to 8 g of milk protein. In contrast, among the subjects treated with 1 g of milk OIT, 7 subjects passed and among those treated with 2 g milk OIT, 9 passed an oral food challenge to 8 g of milk protein. Unexpectedly, peanut SLIT trial has reported a

high dropout rate, presumably because of the perceived low therapeutic benefit and potentially AEs.<sup>70</sup> The AEs associated with food SLIT are usually mild and predominantly limited to the local oropharyngeal mucosa. No anaphylaxis or development of EoE has been reported with food SLIT (Table IV). OIT continues to be evaluated in clinical trials with cow's milk, egg, or peanut,<sup>72-82</sup> although the number of patients treated and carefully monitored for food allergy is largely inferior than for inhalant allergens (thousands of patients involved in clinical trials). Severe systemic reactions occur quite infrequently during

**TABLE III.** Description of the local side effects related to SLIT (MedDRA 14.1)

Anatomic district	Local side effect	MedDRA preferred term	MedDRA code	MedDRA low-level term
Mouth/ear	Altered taste perception	Dysgeusia	10013911	Taste alteration
	Itching of lips	Oral pruritus	10052894	Itching mouth
	Swelling of lips	Lip swelling	10024570	Swelling lips
	Itching of the oral mucosa	Oral pruritus	10052894	Itching mouth
	Swelling of the oral mucosa	Edema mucosal	10030111	Mucosal swelling
	Itching of the ears	Ear pruritus	10052138	Ear pruritus
	Swelling of the tongue	Swollen tongue	10042727	Tongue swelling nonspecific
	Glossodynia	Glossodynia	10018388	Glossodynia
	Mouth ulcer	Mouth ulceration	10028034	Mouth ulcer
	Tongue ulcer	Tongue ulceration	10043991	Tongue ulceration
	Throat irritation	Throat irritation	10043521	Throat irritation
	Uvular edema	Pharyngeal edema	10034829	Pharyngeal edema
	Upper gastrointestinal	Nausea	Nausea	10028813
Stomachache		Abdominal pain upper	10000087	Stomachache
Vomiting		Vomiting	10047700	Vomiting
Lower gastrointestinal	Abdominal pain	Abdominal pain	10000081	Abdominal pain
	Diarrhea	Diarrhea	10012735	Diarrhea

MedDRA, Medical Dictionary for Regulatory Activities.

OIT clinical trials; estimated rates of anaphylaxis are about 0.01% of all doses across various studies on peanut and milk OIT. However, less severe systemic AEs are common and in trials of cow's milk OIT, about 10% of patients discontinue because of side effects.<sup>83</sup> Nonetheless, by far, the most commonly reported side effects of OIT are gastrointestinal manifestations, including nausea, abdominal pain, vomiting, and diarrhea (Table V). The gastrointestinal symptoms are usually not associated with other organ system symptoms and may occur chronically, without close temporal relationship with the OIT dose. In most patients, these gastrointestinal symptoms resolve with continuation of OIT, although EoE is reported by some patients treated with food OIT. The meta-analysis of the published reports estimated about 2% of the patients developing biopsy-proven EoE.<sup>84</sup> In some patients, EoE goes into remission with the discontinuation of food OIT, whereas in others, it persists despite discontinuation of OIT.<sup>75,76,85,86</sup> Therefore, at this time it is unclear whether OIT induces EoE or unmasks an underlying condition in the predisposed patients. A known diagnosis of EoE or chronic symptoms suggestive of gastrointestinal pathology remains an absolute contraindication for initiation of any food OIT, as well as for tablet-based inhalant AIT, at least in the United States. Local oropharyngeal symptoms are also very common during OIT; they are most common during the initial stages of OIT and tend to subside with continued OIT (Table V). Pretreatment or concomitant treatment with anti-IgE and food OIT reduces the frequency of serious AEs during dose escalation as well as during maintenance but anti-IgE has no significant effect on chronic gastrointestinal complications.<sup>87-91</sup> It should be noted that in food OIT, reactions to previously tolerated maintenance doses may occur in the setting of so-called augmentation factors, which include febrile illness, asthma exacerbation, exercise, and dosing on an empty stomach.<sup>79,82,92</sup> Therefore, patients undergoing food OIT are given specific instructions to ingest the OIT dose at the same time of the day (as much as possible), to eat a meal before ingesting the OIT dose, and to avoid exercise or any significant

physical activity within 2 hours of ingesting the food-OIT dose. Similar to inhalant SLIT,<sup>93</sup> uncontrolled asthma is a contraindication to initiation of food SLIT or OIT. To further minimize the risk of untoward reactions, patients need to receive very specific instructions regarding dosing and reporting of the AEs. Patients need to be taught how to recognize allergic symptoms and when to administer intramuscular epinephrine. Every patient being treated with food SLIT or OIT should receive the prescription for an epinephrine autoinjector and be trained in its proper administration.<sup>94</sup> For both SLIT and OIT with foods, dose escalations should occur under physician supervision in the medical setting, followed by maintenance dosing at home.<sup>13</sup> An additional issue affecting safety of food SLIT and OIT concerns the missed doses. In the first years of SLIT and SCIT, the treatment effect appears to be temporary and dependent on the regular daily administration of the doses. When daily dosing is interrupted because of the concurrent illness, depending on the number of days missed, dose reduction may be necessary as well as administering the dose under supervision in the office. In many trials of food OIT, if 2 doses are missed, dosing can be restarted at home at the same dose level; if 3 to 4 doses are missed, the same dose is administered under supervision, and if 5 or more doses are missed, dose reduction is recommended with administration under supervision. At this time, only a physician-supervised oral food challenge can determine the level of tolerance afforded by SLIT or OIT and the permanence of such effect, by repeat food challenge following a period of purposeful discontinuation of dosing for 4 to 6 weeks.<sup>69,85,92</sup> Concerning the missing doses for inhalant SLIT, there is so far no evidence-based recommendation. At least with tablets, where the maintenance dose is given since starting, at any interruption the fixed maintenance dose must be administered. If a build-up dose is prescribed, the precautionary suggestion is to restart with this build-up dose if the interruption is more than 1 month.

No fatalities have been so far reported in clinical trials or from clinical experience of food SLIT and OIT.

**TABLE IV.** Adverse reactions reported by actively treated subjects from randomized clinical trials of food SLIT

Author (year)	Patients in the active arm	Age (y)	Food	Duration	% Doses associated with AE in the active group
Enrique et al <sup>66</sup> (2005)	12	Mean 29.2 (19-53)	Hazelnut	8-12 wk	Local reactions: 109 of 1466 doses = 7.4%; of these, 94.9% were oral/pharyngeal, 4 patients had transient gastrointestinal complaints on 1 occasion each Systemic reactions: 0.2%, all mild; 1 active patient with delayed urticaria and 1 active patient with facial urticaria
Fernandez-Rivas et al <sup>68</sup> (2009)	37	Mean 29.1	Peach (Pru p 3)	6 mo	Local reactions: 1328 of 3378; of these, 94.9% were oral-pharyngeal, 5.1% transient gastrointestinal complaints Systemic reactions: 16 of 3378, all mild
Kim et al <sup>69</sup> (2010)	11	Median 5.8 (2.8-10.5)	Peanut	12 mo	Any symptom: 11.5%; Local: Oral-pharyngeal, 9.3%; Gastrointestinal, 1.2% Systemic: Skin, 0.6%; Upper respiratory, 1.4%; Chest, 0.05%
Keet et al <sup>67</sup> (2012)	SLIT-10; OIT-20	Median 8 (6-11)	Cow's milk	60 wk	Escalation phase Any symptom, 30.3% Oral, 26.8% Gastrointestinal, 2.97% Upper respiratory, 0.59% Lower respiratory, 0.45% Multisystem, 0.1% Maintenance phase Any symptom, 28.3% Oral, 28% Gastrointestinal, 0.38% Upper respiratory, 0.2% Lower respiratory, 0.02%
Fleischer et al <sup>70</sup> (2013)	20	13.5-18.5	Peanut	44 wk	Initial dose-escalation day Any symptom, 24.6% Local oral-pharyngeal, 21.9% Skin, 2.1% Respiratory, 4% Gastrointestinal, 1.3% Moderate symptoms, 0.2% Severe symptoms, 0% Build-up phase Any symptom, 36.4%, all mild Local oral-pharyngeal, 33.6% Skin, 2.8% Respiratory, 1.4% Gastrointestinal, 0% Maintenance phase Any symptom, 41.5%, all mild Local oral-pharyngeal, 38.8% Skin, 1.3% Respiratory, 2.2% Gastrointestinal, 0.9%
Burks et al <sup>71</sup> (2015)	40	Median 16 (interquartile range, 14-18)	Peanut	3 y	Any symptom, 18.2%; all mild Local oral-pharyngeal, 17.9% Skin, 0.15% Respiratory, 2.1% Gastrointestinal, 0.2% No moderate or severe symptoms



**TABLE V.** Adverse reactions reported by actively treated subjects from selected clinical trials of food OIT

Author (year)	Patients in the active arm	Age	Food	Duration	% Doses associated with AE in the active group
Jones et al <sup>74</sup> (2009)	29	57.5 mo (12-111 mo)	Peanut	3 y	Initial dose escalation Any symptom, 92% Mild sneezing/itching/laryngeal symptoms, 69% Mild/moderate nausea or abdominal pain, 44% Mild diarrhea/emesis, 21% Needing epinephrine: 4 patients (10%) Build-up phase and maintenance phase Any symptom, 46% Upper respiratory, 1.2% Skin, 1.1% Treatment with epinephrine after home dosing: 2 subjects, each had 1 episode
Blumchen et al <sup>81</sup> (2010)	23	3.2-14.3y	Peanut	9 wk	Initial dose escalation Any symptom, 7.9% Gastrointestinal, 3.5% Skin, 3.2% Respiratory, 2.8% Upper respiratory, 1.6% No treatment with epinephrine Build-up phase and maintenance phase Any symptom, 2.6% Gastrointestinal, 0.9% Skin, 0.4% Respiratory, 1.3% Upper respiratory, 0.2% No treatment with epinephrine 4 subjects were discontinued because of asthma worsening
Anagnostou et al <sup>75</sup> (2014)	49	7-16 y	Peanut	6 mo	The entire course of OIT Oral pruritus, 6.3%; Abdominal pain, 2.6%; Nausea, 2.2%; Vomiting, 0.75%; Diarrhea, 0.03% Urticaria, 0.16%; Angioedema, 0.4%; Erythema, 0.23% Rhinitis, 0.37%; Wheezing, 0.41% Laryngeal edema, 0.01% Use of inhaled bronchodilator, 0.35% Use of intramuscular epinephrine, 0.01%
Burks et al <sup>82</sup> (2012)	55	5-11 y	Egg	2 y	Initial dose escalation Any symptom, 27.4% Oral-pharyngeal, 13.8% Respiratory, 9.8% Gastrointestinal, 9.5% Skin, 8.1% Other, 3.5% Mild symptoms, 16.7% Moderate symptoms, 3.7% Build-up phase Any symptom, 35.9% Oral-pharyngeal, 19.7% Respiratory, 13.4% Gastrointestinal, 8.8% Skin, 5.8% Other, 3.2% Mild symptoms, 22.1% Moderate symptoms, 1.9% Maintenance phase Any symptom, 24.2% Oral-pharyngeal, 15.1% Respiratory, 7.4% Gastrointestinal, 5.1% Skin, 4.2% Other, 2.1% Mild symptoms, 13.7% Moderate symptoms, 0.6%

(continued)

TABLE V. (Continued)

Author (year)	Patients in the active arm	Age	Food	Duration	% Doses associated with AE in the active group
Longo et al <sup>77</sup> (2008)	30	7-15 y	Milk	1 y	Rush escalation Mouth/lip/tongue pruritus or swelling, 100% Abdominal pain, 75% Erythema/urticaria, 48% Mild asthma, 35% Epinephrine used in 4 patients Maintenance (at home): Emergency department admission and epinephrine treatment: 2 patients; No details on other AEs

## CONCLUSIONS

SLIT and OIT are forms of allergen-specific immunotherapy. SLIT with inhalant allergen has a more favorable profile and comparable efficacy to subcutaneous AIT. SLIT with foods has a superior safety but inferior efficacy compared with food OIT. Food SLIT and OIT remain currently within the realm of research, and desensitization procedures must always be carried out under medical supervision. For inhalant SLIT, many commercial products are available worldwide, and some of them are officially approved by the Food and Drug Administration and the European Medicine Agency. Local side effects with inhalant SLIT are quite common, but invariably mild and self-limiting, whereas systemic side effects are rare and anaphylaxis is an exceptional event.

SLIT and OIT represent alternative forms of food AIT that are generally safe with most treatment-emergent adverse reactions being mild and local in nature.

## SUMMARY

- The safety of SLIT is overall superior than that of SCIT for rhinitis with/without asthma, provided that asthma is controlled.
- SLIT in tablets, as approved, is safe. The first dose must be given under direct medical supervision.
- The use of a standardized classification/grading of systemic and local (for SLIT) AEs is recommended.
- Uncontrolled asthma (symptoms present despite maximal inhalatory treatment) represents an absolute contraindication to start AIT.
- Local (mouth) lesions or undefined gastrointestinal disorders should represent a relative contraindication to the initiation of SLIT, unless properly diagnosed.
- There is no evidence-based recommendation on how to resume a discontinued SLIT. However, because the approved AIT tablets usually start with a maintenance dose, or with a very short build-up, this approach is suggested independent of the discontinuation occurred.
- Oral/sublingual desensitization for food allergy still remains an experimental approach, to be used only under strict medical supervision.

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