A review of the safety of oral immunotherapy in clinical trial and real-world studies

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ABSTRACT

Safety concerns are a barrier to oral immunotherapy (OIT). This review aims to describe OIT safety events and explore potential risk factors and mitigating factors. Published clinical and real-world OIT studies were reviewed for data on safety outcomes in OIT. Gastrointestinal symptoms are one of the most common adverse reactions associated with OIT, and persistent symptoms can be associated with an eosinophilic response. Allergic reactions are increased in OIT compared with avoidance; however, these symptoms tend not to be severe and to decrease over time. Despite OIT, epinephrine usage persists in studies and life-threatening reactions (though rare) have occurred. High baseline food specific immunoglobulin E levels, aggressive dosing, uncontrolled atopic comorbidities, and poor adherence to protocols may contribute to the severity of adverse events. OIT remains a shared decision that incorporates best medical evidence and appropriate patient selection. It requires individualized care and action plans to ensure safe outcomes.

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SAFETY CONSIDERATIONS IN ORAL IMMUNOTHERAPY

Opting to initiate oral immunotherapy (OIT) is a shared medical decision (see section 8), and safety is one of the most important topics to consider as it applies to patient selection, anticipatory guidance, protocols for dosing, parameters for monitoring, algorithms for treatment, and, ultimately, the benefit of long-term therapy. In fact, safety concerns may be the single most important factor for patients when considering OIT and, as such, practitioners and patients alike are often tasked with weighing the benefits against the short- and long-term risks.[1] Most practitioners are able to describe general trends in reported adverse events related to OIT. However, there is heterogeneity of safety reporting across published OIT studies, which makes nuanced discussion about individual risk more difficult.[2] Many patients may choose not to pursue OIT given the well-established incidence of OIT-associated reactions, and other patients may choose not to pursue OIT given the paucity of long-term safety data. However, certain aspects of OIT safety can be described with confidence, including the most common reported adverse reactions as well as risk factors for adverse reactions.

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GASTROINTESTINAL SYMPTOMS IN OIT

Gastrointestinal symptoms are among the most common adverse reactions associated with OIT, and they can include nausea, pain, and vomiting. Persistent symptoms can be associated with a peripheral eosinophilic response. This constellation of symptoms, termed ELORS (eosinophilic esophagitis like oral immunotherapy related syndrome)[3] or OITIGER (oral immunotherapy-induced gastrointestinal and eosinophilic responses),[4] has been reported, in addition to conventional biopsy-proven eosinophilic esophagitis (EoE) in OIT studies. Although some postulate that OIT may directly contribute to the development EoE, others have shown that select patients have evidence of esophageal eosinophilia before initiation of OIT, perhaps supporting the notion of OIT "unmasking" a preexisting disease state.[5]

The reported prevalence of EoE-like symptoms in patients undergoing OIT ranges from 2.7% to 30%, but we do not have reliable data to report true incidences.[6,7] A recent review of 12 clinical trials from 2019 to 2020, which totaled 620 patients reported two EoE diagnoses, which suggests that prevalence may be,

overall, lower than previously estimated.[8] Cessation of OIT treatment seems to result in resolution of symptoms and eosinophilia in many (but not all) patients, and some patients seem to have resolution of symptoms at lowered doses. Some patients, although a minority, may thus opt for EoE management while continuing OIT.[7] Vigilance must be paid toward monitoring for abdominal concerns at all stages of OIT treatment, and the degree of eosinophilia may not correlate directly with symptoms. Much is still unknown about the prevalence, underlying mechanisms, natural history, and preferred interventions for gastrointestinal symptoms associated with eosinophilia in the setting of OIT.

ALLERGIC REACTIONS IN OIT

Allergic reactions, including anaphylaxis, are also common during OIT, with an overall adverse event frequency as high as 98.7% in subjects observed in peanut studies.[9] Although reactions tend to be more frequent during escalation and in early maintenance (such as the first 6 months), they may occur at any point of therapy, from buildup to maintenance phases. Many trials use the Consortium for Food Allergy Research grading system, which categorizes reactions as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (death).[10] In December of 2021, one pediatric death was reported during daily dosing for desensitization to milk.[11] No previous reports of OIT-related fatalities were found; however, some fatalities associated with oral food challenges have been reported.[12] Accurate reports of reaction severity in the setting of OIT may be difficult to compile because there are variations in the use of epinephrine, a theme common to all domains of food allergy treatment. It is important to remember that epinephrine use does not equate to severity of reaction and that the absence of epinephrine use does not mean that anaphylaxis did not occur. The possibility of allergic reactions should be discussed with patients who start OIT, and an emergency action plan and access to medications should be reviewed in detail.

RISK FACTORS FOR ADVERSE EVENTS IN OIT

There are relative risk factors associated with increased adverse events with OIT (see section 9). A multivariate model in a large retrospective analysis showed that, for peanut OIT, baseline allergic rhinitis and asthma were significant predictors of higher rates of adverse events, and another large retrospective review showed that intermittent asthma increased the risk of epinephrine-treated reactions during peanut dose escalation.[3,13] These analyses suggest that control of other atopic disorders may be ideal before initiating OIT.[14] Studies generally have found that large skin prick test and high baseline food specific immunoglobulin E (IgE) levels correlated with an increased risk of adverse events.[3,13,15,16] Although there are no specific cutoff values for which OIT should be modified, providers may use their individual judgment to decide whether reaction-reducing mitigation strategies (smaller dose increments, longer dose intervals) should be considered for patients with high levels of food sensitization.

Beyond clinical parameters, more aggressive protocols (rush immunotherapy) and higher maintenance doses may increase the risk of adverse reactions.[17] Related to protocols, the dose of the food ingested may provide clues to the type of reactions that patients are most at risk of having. One retrospective review found that more ELORS episodes presented at lower peanut OIT doses, whereas epinephrine-treated reactions occurred predominantly at higher peanut OIT doses.[3] Also, poor adherence to OIT guidelines seems to increase the risk of adverse reactions.[3,18] Patients should take OIT doses on a full stomach, and they should avoid exercise and rigorous physical activity after dosing. Patients need to have clear instructions on dose adjustments during illness. Close communication with the care team is essential because doses may need to be held or lowered in the setting of acute fever, respiratory symptoms, and gastrointestinal symptoms. Patients should also be advised about external factors that may augment the likelihood of reaction, including extreme temperatures (hot showers), menses, sleep deprivation, dental and/or oral procedures, and stress.

COMPARING SAFETY IN OIT STUDIES

Reviewing safety across OIT studies broadly is a difficult task because foods have unique allergenic characteristics and patients have unique immune responses. Head-to-head comparisons between clinical trials and real-world studies are challenging due to variations in data collection and safety outcomes. Studies report safety outcomes in various ways, including the frequency of adverse reactions, epinephrine usage, and withdrawal of subjects due to adverse events. Of note, measures of adverse event frequency are reported in different scales (such as events per subject or events per dose), severity (using different severity grading systems), organ systems involved, and extent (such as local versus systemic). The application of data to general populations is limited because data set demographics often skew toward younger white populations.

SAFETY IN SINGLE-FOOD OIT AND MULTIFOOD OIT

Safety in OIT seems to be similar across studied foods, including the most common childhood allergens of milk, egg, and peanut, with peanut being the most studied food (Table 1). A systematic review and meta-

Table 1 **Overview of selected peanut OIT studies**

Study; Country	Design	Subjects, *n* (% boys)/ age range/therapy	Dosing	Overall Adverse Event Frequency: % Subjects	Reaction Severity and/or Classification*	Systemic Reactions, % subjects	Subjects Withdrawn Due to Adverse Events While on OIT, *n* (%)	Epinephrine Administered, % subjects	No. Life-Threatening Events that Required Resuscitation
PALISADE Group of Clinical Investigators, *et al.*,[9] 2018; United States	Double-blind, placebo controlled, phase III trial	372 (56)/4–17y/OIT; 124 (61)/4–17 y/placebo	Initial dose escalation, buildup phase, and maintenance dose of 300 mg daily, over a 12-mo trial duration	OIT: 98.7; placebo: 95.2	OIT: 34.7% (mild), 59.7% (moderate), 4.3% (severe); placebo: 50.0% (mild), 44.4% (moderate), 0.8% (severe)	OIT: 14.1; placebo: 3.2	43 (11.5)	OIT: 14; placebo: 6.5	0
Vickery *et al.*,[22] 2017; United States	Single-center clinical trial	40 (70)/9–36 mo/OIT	Initial dose escalation, 42 wk buildup, with double-blinded assignment to 300 mg or 3000 mg daily maintenance dosing	95	85% (mild), 15% (moderate), 0% (severe)	Not specified	2 (5)	2.5	0
Wasserman *et al.*,[3] 2019; United States	Single-center retrospective study	270 (60)/4–18 y/OIT	Initial dose escalation, buildup to 3000 mg, then 2000 mg once or twice a day as maintenance	81	Nonepinephrine treated reactions in 58% of the patients; GI only symptoms in 37% of the patients	Not specified	18 (7)	23 (of whom 8% required 2 doses, and 3% required 3 doses)	0
Chinthrajah *et al.*,[23] 2019; United States	Randomized, double-blind, placebo controlled phase II study	60 (65)/9–13/peanut OIT then discontinuation; 35 (66)/8–17 y/peanut OIT then daily dosing of 300 mg; 25 (76)/9–16 y/placebo	Buildup to 4000 mg over 104 wk, then 300 mg daily for 52 wk, or discontinuation	OIT-discontinuation: 95 (year 1), 73 (year 2), 2 (year 3); OIT 300 mg: 91, 65, 20; placebo: 64, 26, 5	Highest severity grade (range 1–3 in this study) of events: OIT-discontinuation: 2% (year 1), 5% (year 2), 0% (year 3); OIT-300 mg: 0%, 3%, 0%; placebo: 4%, 0%, 0%	Not specified	OIT-discontinuation: 1 (2); OIT-300 mg daily: 1 (3)	Year 1: 19 (n = 18/95); year 2: 13 (n = 12/95); year 3: discontinuation 0 (n = 0/60), 300 mg 6 (n = 2/35)	0

Table 1 **Continued**

Study; Country	Design	Subjects, *n* (% boys)/ age range/therapy	Dosing	Overall Adverse Event Frequency: % Subjects	Reaction Severity and/or Classification*	Systemic Reactions, % subjects	Subjects Withdrawn Due to Adverse Events While on OIT, *n* (%)	Epinephrine Administered, % subjects	No. Life-Threatening Events that Required Resuscitation
Blumchen *et al.*,[24] 2019; Germany	Randomized, double-blind, placebo controlled trial	31 (61)/5–10 y/OIT; 31 (61)/4–11 y/ placebo	Buildup period to 125 mg or 250 mg daily based on initial oral challenge over a maximum of a 14-mo period, followed by maintenance for 8 wk	OIT: 90; placebo: 77	Severity grade I, II, III, IV, V for OIT: 23%, 37%, 33%, 23%, 0%; placebo: 16%, 32%, 42%, 13%, 3.2%	OIT: 10; placebo: 13	2 (6)	OIT: 3 ($n = 1$, accidental non-peanut ingestion); placebo: 3 ($n = 1$)	0

OIT = Oral immunotherapy; GI = gastrointestinal.
**Percentage of reactions, unless otherwise specified.*

analysis published in 2017 reviewed safety data from 31 OIT, sublingual immunotherapy, and epicutaneous immunotherapy trials, which were predominantly OIT, and in egg, milk, and peanut.[2] In subanalyses of pooled safety data in OIT only, local and systemic reactions were increased in OIT compared with controls (risk ratio in controls, of not experiencing a local reaction of 2.14 (95% confidence interval, 1.47–3.12); systemic reaction of 1.16 (95% confidence interval, 1.03–1.30), and there were no fatalities across all studies overall, including randomized controlled trial and nonrandomized OIT trials. In a subanalysis that investigated conventional and rush OIT protocols, both were found to have increased local reactions in treatment groups compared with controls. Of note, only five studies included in this review (four RCTs and one nonrandomized) were included in the systemic reaction meta-analysis, and seven RCTs in the local reaction meta-analysis, with the investigators citing varied safety reporting methods as the reason for this limitation of data-pooling.[2]

Results from one phase I study suggest that multifood OIT has a similar safety profile to single-food OIT.[19] This study compared peanut-only OIT versus multiple-food OIT (peanut plus up to five additional allergens) and showed no serious adverse events.[19] Overall reaction rate measures were similar between multifood and peanut-only OITs during phases of initial escalation day ($p = 0.22$), dose escalation ($p = 0.31$), and home dosing ($p = 0.65$), with equal numbers of the subjects requiring epinephrine in each group (multi-OIT usage in 2/25 patients in 0.02% of 12,030 doses versus single-OIT usage in 2/15 patients in 0.03% of 7830 doses; $p = 0.67$).[19] In addition, the total number of allergens did not increase the risk of severe reactions.

TRENDS AND CLINICAL IMPLICATIONS FOR PATIENTS

Despite nonstandardized reporting methods, safety trends do emerge when considering foods that are commonly studied. First, reactions in the setting of OIT are often not severe. Second, the frequency of life-threatening reactions that require resuscitation are rare, although, importantly, can occur. Such events have been reported in patients with suboptimal asthma control who required intensive care unit management, including one report of a milk OIT patient[16]; and another of three OIT patients (two on milk, one on egg).[14] Third, epinephrine administration varies and likely is influenced by subject and/or caregiver and health care provider judgement. Epinephrine administration in OIT studies ranges from 0% to 30% of subjects. Fourth, a significant number of subjects withdraw from OIT studies due to adverse events, up to 20% of subjects.

INCREASING SAFETY IN OIT

Identifying modifiable risk factors is a first step toward improved safety. Allergic comorbidities, such as asthma and allergic rhinitis, should be well controlled before starting OIT and for the duration of OIT.[14] Protocols and schedules should be explained in detail before OIT initiation, and there should be appropriate supervision of daily dosing at home. Counseling about the importance of adherence to dosing instructions is paramount, with attention paid to dosing on a full stomach, limiting exercise after dosing, and decreasing and/or holding doses during illness. Patients need to remain in close communication with providers to make individualized dosing decisions. Education around appropriate and prompt treatment of symptoms is essential, as is ensuring access to appropriate medications, *e.g.,* epinephrine. Investigation is on-going to identify adjunct therapies that may improve safety outcomes in OIT (see section 10). The most studied therapy is omalizumab, a recombinant humanized anti-IgE antibody, which has previously been shown to reduce adverse reactions with milk OIT.[20] Currently, other trials are underway that are examining dupilumab, a fully human monoclonal IgG4 antibody that blocks interleukin 4 and interleukin 13 signaling, with hopes for improved safety and efficacy outcomes.[21] Other potential adjunct therapies currently being studied include probiotics and herbal medications.

CONCLUSION

Safety issues around OIT are exceedingly important to understand, discuss, and anticipate when initiating therapy. When considering OIT, patients and families should be aware that reaction rates and dropouts rates due to adverse events are suggestive of safety concerns for a notable percentage of patients. Epinephrine use persists and is not always eliminated, despite meeting goal OIT dosing for many patients. OIT reactions can occur at any time, with augmenting factors such as exercise or illness playing an important role (see section 9), and there is evidence that more severe baseline allergy may predict worse outcomes. Increased adverse events in OIT may be more frequent during the buildup phases, but, generally, these reactions decrease over time and tend to be mild in the long term. To distill these points down into a single sentiment, practitioners must counsel that OIT is not a putative "cure" for food allergy. OIT remains a shared decision that incorporates best medical evidence and appropriate patient selection. It requires individualized care and action plans to ensure safe outcomes.

CLINICAL PEARLS

- Gastrointestinal symptoms are associated with OIT, and these are the most common symptoms that lead to withdrawal from OIT.
- Allergic reactions associated with OIT are often not severe, but epinephrine usage persists in almost all OIT studies.
- Safety outcomes in OIT can be improved with proper patient selection and protocol adherence.

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