Efficacy, effectiveness and other patient-centered outcomes of oral immunotherapy

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ABSTRACT

Oral immunotherapy (OIT) is the medically supervised ingestion of a food allergen. Understanding of the expected outcomes of OIT allow for risk-benefit assessments for patient-centered decisions. The efficacy of OIT to achieve desensitization in children has been confirmed in multiple meta-analyses, even with vastly disparate study populations and methodologies. Most children initiated on OIT will achieve the ability to eat more allergen before experiencing an allergic reaction than if they continue to avoid their allergen. This effect is diminished without regular ingestion. Previous meta-analyses showed increased allergic reactions on OIT versus avoidance or placebo due to the dosing itself; however, a recent meta-analysis showed that peanut OIT in children did not lead to an increase in allergic reactions. Analysis of emerging data suggests that OIT may reduce reactions to accidental exposures over time. Important patient-centered outcomes, including reaction avoidance or amelioration, and psychosocial impacts and/or quality of life, and studies of more demographically representative populations are also necessary.

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Knowledge of the outcomes of oral immunotherapy (OIT) is of paramount importance when considering the risk and benefits of treatment. However, is important to recognize that there are vast differences in populations studied and the methodologies used.[1] For example, the Japanese Food Allergy Guidelines[2] and the European Academy of Allergy and Clinical Immunology guidelines[3] suggest that OIT is offered to children who are expected to have persistent food allergy. In contrast, preschool and infant OIT are gaining evidence.[4–6] These population differences bring different risks, benefits, and methodologic approaches. Furthermore, OIT has been conducted in a subset of the population of individuals with allergy. A recent survey showed that most families of individuals with food allergy are not familiar with OIT and that the main factor associated with OIT knowledge was high income, which thus highlights one of the disparities to access OIT.[7]

From a methodologic perspective, studies have differed with respect to dose, time, foods, patient selection, immunologic markers, adjuvants, and other factors. Food Allergy Research and Education[8] recently met to discuss gaps in OIT knowledge. The lack of standardization as well as a need for studying a more diverse patient population factored prominently. Many foodstuffs have been used for OIT, including pharmaceutical products and various formats of store-bought or home-baked foods. Baked milk (BM) or baked egg (BE) introduction to children tolerant to BM and/BE or BM and/or BE OIT in children allergic to BM and/or BE have also been explored. These approaches have unique considerations and risks beyond the scope of this article.[9]

Given the rapid innovations in OIT, it will be important to continue to evaluate modern evidence. Perrett *et al.*[10] noted that the accumulation of experiential and scientific knowledge is expected to drive more accessible, effective, and safer OIT. With the above-mentioned caveats that the heterogeneity of studies can limit firm conclusions of some outcomes, the efficacy, effectiveness, and patient-centered outcomes of OIT have been addressed in many key studies. This article concentrates on the results of meta-analyses to provide the broadest lens in addition to highlighting a few illustrative studies. A summary of the evidence is presented in Table 1.

EFFICACY

Efficacy is usually understood to be how well a treatment works in the rigor of a trial setting. Most studies

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used desensitization as the main efficacy measure. Desensitization is the ability to tolerate a defined amount of the allergic food without having an allergic reaction. In trials, desensitization is often defined by comparing oral food challenges (OFC) before and after OIT. Desensitization is measured while continuing routine ingestion of the allergen.[11] Meta-analyses have confirmed the profound efficacy of desensitization from OIT. A comprehensive meta-analysis of allergen immunotherapy for food until March 2016 was conducted for the European Academy of Allergy and Clinical Immunology.[12] Desensitization by OIT was assessed in 18 randomized controlled trials (RCT) and 5 case controlled trials of predominantly cow's milk, hen's egg, and peanut, with a comparator of either usual care or avoidance, or placebo.[12] OIT-induced desensitization with a relative risk (RR) of 0.14 (95% confidence interval, 0.08–0.24).[12] A subgroup analysis by age found a statistical improvement in desensitization that was not found in adults.[12] Chu *et al.*[13] performed a meta-analysis of RCTs of peanut OIT versus no OIT up to December 2018, which focused on anaphylaxis, allergic or adverse reactions, epinephrine use, and quality of life (QOL). They included 12 trials of 1041 individuals, predominantly children (median age, 8.7 years), and concluded with high certainty that peanut desensitization was effectively induced with OIT (RR 12.42 [95% confidence interval, 6.82–22.61]).

Most recently, de Silva *et al.*[1] performed a meta-analysis to support the upcoming Global Allergy and Asthma European Network guidelines. They focused on RCTs of OIT to any food with or without a biologic adjuvant compared with placebo or routine management until April 2021. Their outcomes of interest were desensitization, sustained unresponsiveness (SU), adverse reactions, QOL, and cost-effectiveness. They included 36 trials with 2126 participants, predominantly children. OIT achieved desensitization for peanut, cow's milk, and hen's egg allergy. The number needed to treat to increase tolerance to a single dose of 300 mg or 1000 mg of peanut protein was only two.

Of special interest due to the young age of the participants, the Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children RCT (known as the IMPACT study) studied peanut OIT to 2000 mg/day or placebo in 146 children with proven peanut allergy (12 to <47 months) reactive to <500 mg.[6] The desensitization end point of passing 5000 mg challenge after 2.5 years was met by 71% by intention to treat versus by 2% on placebo. These results illustrated that proven peanut allergy was persistent over years and that the desensitization outcome had similar success rates to reports in other children.

Predictors of successful OIT may include laboratory parameters of lower immunologic parameters (*e.g.*, lower specific immunoglobulin E (IgE) levels, lower basophil activation tests) and clinical factors. Increasing knowledge of predictive factors and their management is expected to guide risk assessment, personalized regimens, and the need for adjuvants.[4,14,15] In summary, the meta-analyses are in clear agreement of the efficacy of OIT to achieve desensitization in children, despite remarkable differences in populations and trial methodologies. There are limited data available for adults.

EFFECTIVENESS

Effectiveness is assessed in the real-world use of a treatment. A benefit of real-world implementation of OIT is personalization. Conversely, further heterogeneity is introduced in the populations, rigor of diagnoses, methodologies, and outcomes. Some studies report success as reaching a certain dose and some studies by a defined OFC. For peanut, two cohorts of predominantly clinically diagnosed children with peanut allergy are informative.[16,17] In 270 patients, ages 4–18 years, on OIT to a target daily maintenance dose of 3000 mg of peanut protein, 214 of 270 patients (79%) achieved desensitization.[16] Neither history of anaphylaxis or asthma, nor OIT-related epinephrine use or gastrointestinal adverse effects were associated with successful desensitization.[16] Younger age and lower specific IgE levels were associated with success.[16] Soller *et al.*[17] reported on 185 preschool children (9–70 months) on OIT with various approaches to a target maintenance dose of 300 mg of peanut protein. The maintenance dose was achieved in 161 of 185 (87.0%) and 117 of 161 preschoolers underwent food challenge to 4000 mg peanut protein, in whom 78.6% tolerated the 4000 mg and 98.3% tolerated the 1000 mg cumulative dosing.[17]

Another real-life experience of 296 children (ages > 5 years, diagnosed with milk allergy by open OFC) who underwent open-label milk OIT over an 11-year period reported that 136 achieved ongoing ingestion of 20 mL of milk/day and 45 were able to maintain <20 mL a day.[18] Discontinuation occurred in 71 of 296 children (24%), and 44 of 296 (15%) were lost to follow up.[18] This large real-world study highlighted that long-term support is required.

Overall, desensitization demonstrated in clinical trials has been replicated in some real-world settings. Younger age may be a predictor of successful desensitization. Milk may be a more difficult food to desensitize than peanut with current approaches, although more data are needed to directly compare foods. An important consideration for effectiveness concerns the difficulties in the real-world implementation of OIT, as was recently reviewed.[10] Some of the barriers include food selection for foods with few studies, risk stratification, access to OIT services, adjuvant approaches, compliance, and the need for multidisciplinary care.

OTHER POTENTIAL OUTCOMES

There is a need for more patient-centered outcomes than those based on OFC or achieving a target dose of daily ingestion.[19,20]

SU

SU is the ability to maintain the threshold increase achieved during desensitization without regular ingestion of the allergen but does require ongoing intermittent exposure.[11] In brief, typically after completing months to years on maintenance dosing, OFC is conducted. If this OFC produces no symptoms, then maintenance dosing is suspended for weeks and/or months and another OFC is performed. If this OFC produces no symptoms, then the individual has achieved SU to that dose. SU is fulsomely covered elsewhere.[21] A few points will be highlighted here. Although individual studies have reported outcomes of SU typically in single-digit percentages, the available pooled data are low quality for the achievement of SU to peanut and hen's egg, and too limited for conclusions about other foods.[1] Furthermore, a meta-analysis did not show a clear relationship between the duration of treatment and SU.[1]

The importance of standardizing the definition of SU is illustrated by two recent studies. In a small study by Davis *et al.*[22] after 12 months of OIT to a target of 3900 mg of peanut protein daily, maximum dose OFCs were offered. The mean maximum cumulative tolerated dose increased by 12,063 mg and then, after 1 month of avoidance, decreased by 7593 mg. The finding that patients remain reactive to high doses suggests that patients remain at risk for reactions, especially if their threshold is decreased. In another study, a phase II study of peanut OIT, desensitization was achieved to 4000 mg of peanut protein but reduction to a daily dose of 300 mg daily or discontinuation led to a reduction of desensitization.[23]

In the IMPACT study,[6] after 2.5 years of peanut OIT (or placebo), the children had 26 weeks of avoidance to assess SU, defined as no allergic reaction to 5000 mg of peanut protein. Overall, 21% achieved SU (versus 2% in the placebo group).[6] In the youngest age category (<24 months), 71% achieved SU and, in the oldest age group (36–47.59 months), only 19% achieved SU.[6] In addition to the 21% of children who achieved SU as defined, the majority of children (57%) who were treated could consume 1755–3755 mg of peanut protein without an allergic reaction.[6] The results of this study again illustrate the importance of dose in the definition of SU and is both exciting for the possibility of high success rates in young children but also suggestive of a narrow developmental time window to achieve SU.

Complete tolerance to the food without ongoing ingestion cannot be concluded from trials.[11] To put this finding in context, the standard of care of allergy management for both the primary prevention of allergy[24] and for the secondary prevention of allergy (prevent allergy recurring in an individual in whom it was outgrown)[25] is to include the food in the diet routinely because a known risk factor for the development or recurrence of food allergy is prolonged avoidance. Overall, the current state of the art is that, although SU may be achieved in a subset of individuals undergoing OIT, it greatly depends on the definition of unresponsiveness. In summary, results of trials suggest SU may be influenced by the age of the patient, time, and dosing. Currently, there is an expectation that patients who initiate OIT will require ongoing, regular exposure.

REACTION AVOIDANCE: ACCIDENTAL EXPOSURES

Reaction avoidance can be considered under two lenses: (1) reactions due to the dosing of OIT, which is often considered safety,[26] and (2) avoiding reactions from accidental exposures.

Safety

Briefly, for safety, the meta-analysis of Chu *et al.*[13] found high-certainty evidence that OIT increased allergic and anaphylactic reactions (more than threefold) and epinephrine use (more than twice as many uses) versus avoidance or placebo. In contrast, de Silva *et al.*[1] found that OIT did not increase the number of adverse reactions or severe reactions in children undergoing peanut OIT. Cow's milk and hen's egg allergy OIT was associated with more allergic reactions, although typically mild.[1]

Cross-Contamination and "Bite-Proof" Protection

A demonstrated tolerance to a 30-mg peanut protein dose, it is suggested, may allow ingestion of cross-contaminated or "may contain" foods, although there is significant variability in precautionary labeling standards, which creates difficulties in understanding the content of allergens and in advising patients.[27] To achieve "bite-proof" protection, the threshold of an allergic reaction would be higher than trace amounts expected from cross-contamination. For peanut, 300 mg of peanut protein is approximately one peanut kernel or approximately one-quarter teaspoon of peanut butter.

The effect of desensitization on the risk of an allergic reaction to peanut-containing packaged food was considered with mathematical modeling.[28] An expected RR reduction of allergic reaction > 95% may be achieved by increasing the reaction threshold from <100 to 300 mg or from <300 to 1000 mg of peanut protein. The daily OIT maintenance dose typically produces an eliciting dose many times higher on OFC, and presumed accidental exposure protection has been extrapolated from the OCF

Table 1 **Outcomes of Oral Immunotherapy**

Factor	Summary of Evidence*
Efficacy	OIT induces desensitization as demonstrated in multiple meta-analyses; studied populations are limited in diversity
Effectiveness	Real-life studies show the ability to bring OIT to the clinic and achieve desensitization; wide clinical implementation of OIT has multiple barriers for patients and/or families and providers and/or the health care system
SU	A subset of patients may achieve an SU state, which allows a pause in dosing of the maintenance OIT dosing with maintaining desensitization to a defined dose; SU may be more likely to be achieved in young children, SU may not be robust to challenge with high doses and/or threshold lowering factors, *e.g.*, exercise; with the available evidence, ongoing allergy to the OIT food is expected and ongoing ingestion of the food allergen(s) is required in most individuals to maintain desensitization
Reaction avoidance	Peanut OIT has been demonstrated to cause more reactions than avoidance or placebo in two meta-analyses,# with the most recent meta-analysis§ showing similar reaction rates in both groups; OIT doses can cause reactions on ingestion; OIT may protect against accidental exposures (cross-contamination and bite-proof) after years of treatment
Expansion of diet	May not be a priority for patients; milk especially may be important for nutrition and growth; dietary milk can be supported by OIT
Psychosocial impact	Individual studies have variable effects on QOL; QOL improvement not demonstrated in a meta-analysis; further patient-centered research is needed

OIT = Oral immunotherapy; SU = sustained unresponsiveness; QOL = quality of life.
**See the text for details.*
#Adapted from Refs. 12, 13.
§Adapted from Ref. 1.

findings. For example, in a pivotal trial, a 300 mg daily dose of peanut protein allowed 63.2% of children ages 4–17 years to tolerate 1000 mg (cumulative) peanut protein without allergic reaction versus only 2.6% of children treated with placebo.[29] Studies continue to explore dosing considerations and protection.

Although not demonstrated in meta-analyses, there is emerging direct evidence that OIT may provide the reduction in accidental reactions. A recent large study demonstrated that, in the second year of peanut OIT, accidental reactions decreased from 9% in year 1 to 2% in year 2 for peanut OIT compared with the placebo arm of 12% in year 1 to 16% in year 2.[23] Furthermore, a brief report of 62 children who received peanut OIT to a median maintenance dose of 125 mg of peanut protein or placebo for ~16 months showed that 45.2% versus 16.7%, respectively ($p = 0.026$) had an accidental reaction to peanut.[30]

"FREE EATING"

If the threshold of reaction has been increased far above expected serving sizes, then it is possible that, rather than eat a prescribed amount of food for OIT, a person could eat the food freely.[21] As with all aspects of OIT, risk-benefits need to be considered. Reactions can happen years into maintenance dosing of OIT. As an illustrative example, in a long-term real-life study of milk OIT, two patients reported using epinephrine after 9 years of daily milk consumption.[18] One of these reactions occurred in a child freely eating milk and was thought to be due to a lowered reaction threshold due to exercise.[18] This situation highlights that, if an individual is considered for "free eating," then an informed discussion that covers key safety issues, including the understanding of factors that lower the allergic threshold (including exercise, illness, pauses in routine ingestion), recognition of allergic reactions, asthma control, and access to epinephrine autoinjectors, is essential.

EXPANSION OF THE DIET

The importance of expansion of the diet may differ according to the food and may have varying benefits. For example, the ingestion of cow's milk in the context of OIT has been demonstrated to increase the height of children.[31] However, dietary expansion is not typically listed as a top outcome important to patients. For example, in a 2019 survey of 123 families, a fear of a fatal food reaction and a desire to decrease risks of reaction rather than to incorporate the allergenic food in the diet was the main motivator for seeking OIT.[19]

REACTION AMELIORATION

The ability to study reaction amelioration, or the reduction of the severity of allergic reactions if they do occur, is hampered by varying severity definitions. Given that the fear of a fatal reaction[19] is a key motivator for patients, reducing the severity of allergic reactions is an important patient-centered outcome, which requires additional direct data.

PSYCHOSOCIAL IMPACT

The anxiety that comes with a diagnosis of food allergy is significant, as was recently reviewed.[32] Families and individuals affected by food allergy struggle with a lack of information, media coverage of worst-case scenarios, labeling deficiencies, and the burden of needing to control every risk. A hope of OIT is that it can reduce anxiety and uncertainty through a sense of control. Although some individual studies have shown improvement of QOL, so far, this finding has not been clearly demonstrated in meta-analyses. Nurmatov *et al.*[12] concluded that, at the time, there was not enough data on QOL to make conclusions, and Chu *et al.*[13] found that improvement in QOL was not demonstrated between peanut OIT and avoidance or placebo. In the study by de Silva *et al.*,[1] they concluded that too little information was available to determine if OIT affects QOL. A notable limitation of QOL assessment for OIT is that there is a need for a validated comprehensive measurement of the psychosocial impact of food allergy treatment.[33] It has been recommended that each family's treatment goal and the individualized maintenance dose of OIT required to achieve that goal should be clarified in advance of OIT.[8] It is clear that high-quality research of outcomes important to the patient is needed.

CLINICAL PEARLS

- Clinical trials and real-life studies have enormous variability in population and methodology and outcomes.
- The efficacy of OIT to achieve desensitization has been clearly demonstrated in multiple trials and meta-analyses.
- Analysis of the available data shows that the majority of individuals initiated on OIT will need to maintain deliberate ingestion of their food allergen to maintain desensitization.
- Previous meta-analyses showed increased allergic reactions on OIT versus avoidance or placebo; a recent meta-analysis showed that peanut OIT in children did not lead to an increase in allergic reactions versus avoidance or placebo.
- Important patient-centered outcomes of SU, QOL, and demographically representative populations require further study.

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