Peanut Oral Immunotherapy: Current State & New Directions

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Disclosures

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Objectives

1. Describe the current burden of food allergy
2. Demonstrate understanding of a typical oral immunotherapy protocol
3. Broadly outline currently known pathophysiologic understanding of oral immunotherapy
4. Discuss utility of peanut oral immunotherapy (OIT) for food allergy treatment in older children compared to preschool age populations

Background

• Food allergy is a significant public health concern
  – Up to 8% of children in developed world\textsuperscript{1,2}
  – Peanut allergy affects 1.5-3% of all children\textsuperscript{3,4}
  – Significant morbidity & negatively influence quality of life with significant financial burden\textsuperscript{5,6,7}
  – Risk of peanut-induced anaphylaxis from accidental exposure is substantial\textsuperscript{8}
Oral Immunotherapy (OIT)

Definitions

• **Desensitization**: a temporary increase in the threshold for reactivity in which maintenance of the desensitized state requires continued exposure to prevent the recurrence of reactivity

• **Sustained unresponsiveness (SU)**: No increase in reactivity after discontinuing immunotherapy treatment, typically assessed with an oral food challenge (OFC) after a certain timeframe following stopping treatment (weeks to months)
  – **Remission**: a state of nonresponsiveness after discontinuing immunotherapy. “Disease quiescence of unknown duration”.

• **Double blind placebo controlled food challenge (DBPCFC)**: a gradual dose-escalating protocol, usually over 2-3 hours, to a defined dose of food protein (usually equivalent of 1 serving or more), and symptoms occurring at a particular dose are noted and challenge stopped if needed. Allergen and placebo are given on separate days
OIT

- Accomplished by mixing the allergenic food into a vehicle and ingesting it in gradually increasing doses
- Has been considerable variation in protocols used with regard to dosing, the type of food used, length of therapy

300mg peanut protein =
How does OIT work?

Research settings

FIG 1. Schematic representation of the typical approach to OIT

Wood RA, Food allergen immunotherapy: Current status and prospects for the future. JACI 2016; 137:973-82

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AR101 Oral Immunotherapy for Peanut Allergy

The PALISADE Group of Clinical Investigators

NEJM November 2018
PALISADE Study

Six month build-up; Maintenance Dose: 300mg for six months

DESENSITIZATION

FDA Approval

- Jan 2020
- Peanut (Arachis hypogaea) Allergen Powder-dnfp (AR 101)
- Only FDA approved treatment for food allergy
- Indication: help reduce the severity of allergic reactions to peanuts, including anaphylaxis, in children aged 4 through 17 years old with a confirmed diagnosis of peanut allergy.
- Not a cure, and PALISADE did not measure sustained unresponsiveness/remission
- Black Box warning for anaphylaxis risk from therapy itself
  – Risk Evaluation and Management System (REMS)
OIT Mechanisms (B-cell responses)

It is unknown why some subjects experience loss of desensitization or remission, characterized by recurrence of clinical reactivity and loss of suppression of SPT and BAT, while some achieve sustained unresponsiveness (SU), characterized by the continued lack of clinical reactivity and suppression of SPT and BAT despite discontinuation of OIT.

Barshow et al. Figure 1: B-cell and effector cell responses

OIT Mechanisms (T-cell responses)

Barshow et al. Figure 2: T-cell responses
Oral Immunotherapy (OIT) Limitations

- “Increases the risk of the thing you are trying to prevent”
- Many patients can successfully avoid their allergen for many years without an adverse reaction, so why start a therapy that gives you a ~1 in 6 chance of getting an allergic reaction that requires using epinephrine?
- A recent meta-analysis by Chu et al11 noted a higher rate of anaphylaxis (16.5%) during peanut OIT compared with avoidance (2.70%), and concluded avoidance is safer in older children.
- Shared decision making with patients & families is critical

What about very young kids (<4 years old?)
Early Age Peanut OIT

**Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective**

- 37 children age 9-36 months with suspected or known peanut allergy who reacted on entry food challenge → Randomized to 300mg or 3000mg doses
- Primary endpoint: after 3 maintenance years, sustained unresponsiveness 4 weeks (4-SU) after stopping therapy (consume 5000mg peanut protein during exit food challenge). *Median age: 28.5 months*
- 29 of 37 (78%) in the intent-to-treat analysis achieved 4-SU over a median of 29 months with no difference between 300mg and 3000mg maintenance doses → 300mg arm, 17 of 20 [85%]; 3000 mg arm, 12 of 17 [71%]; p=.43
- OIT-treated children were 19 times more likely to successfully consume dietary peanut than matched standard-care controls
- **There were no AEs that met serious AE criteria, and only 1 participant required epinephrine for 1 systemic reaction at home. **NOT PLACEBO CONTROLLED

Early Age Peanut OIT

**First Real-World Effectiveness Analysis of Preschool Peanut Oral Immunotherapy**

- Preschoolers (9-70 months) with at least 1 objective reaction to peanut, received a follow-up oral food challenge (OFC) to cumulative 4000mg protein after 1 year on 300 mg peanut daily maintenance dose.
- Primary endpoint: Proportion of patients with negative follow-up OFC (Desensitization, not sustained unresponsiveness).
- **Median age: 26.5 months**
- Of the 117 patients who successfully completed 1 year of OIT and subsequently underwent a cumulative 4000mg follow-up OFC, **92 (78.6%) had a negative OFC and 115 (98.3%) tolerated a cumulative dose of greater than or equal to 1000 mg**
- Two patients (1.71%) received epinephrine associated with peanut OIT, and 1 (0.85%) went to the emergency department.
- **NOT PLACEBO CONTROLLED**
Early Age Peanut OIT

Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study

Lancet 2022

- Children aged 12-48 months reactive to 500 mg or less of peanut protein during entry double-blind, placebo-controlled food challenge (DBPCFC). Median age: 39.3 months.
- Participants randomly assigned 2:1 to receive peanut oral immunotherapy at 2000mg peanut protein daily dose (n=96) or placebo (n=50) for 134 weeks (~2.5 years) followed by 26 weeks (~6 months) of avoidance.
- Primary outcome: desensitization at the end of treatment (week 134), and remission after avoidance (week 160), as the key secondary outcome, assessed by DBPCFC to 5000 mg.

- 68 of 96 participants (71%) who received peanut oral immunotherapy compared with 1 of 50 (2%) who received placebo met the primary outcome of desensitization.
  - Median cumulative tolerated dose during the week 134 exit food challenge was 5005 mg for peanut OIT versus 5 mg for placebo.
- After 6 months of avoidance, 20 of 96 participants (21%) receiving peanut oral immunotherapy compared with 1 of 50 (2%) receiving placebo met remission criteria
  - POISED: median age 11 years; after 104 weeks of peanut OIT (maintenance dose: 4000mg), 20% achieved remission to 4000mg cumulative dose assessed by DBPCFC after 26 week treatment discontinuation.
• Younger age and lower baseline peanut-specific IgE were only factors predictive of remission by multivariate regression analysis
AUC=0.8072

A contour plot of predicted **probability of remission** from the logistic regression model plotted against baseline peanut-specific IgE and age at screening.
### IMPACT Study

- **71% of those who started OIT at younger than 24 months achieved remission, but this was only 12% of the total study population**
  - 35% of those age 24-35.9 months
  - 19% of those aged 36-47.9 months

### IMPACT Study

- An 8000mg open label feeding was attempted for those patients who achieved remission (~26 peanuts)
- **17 of 20 (85%) participants receiving peanut OIT and one who received placebo passed**
  - 1 receiving peanut OIT did not pass
  - 2 participants also receiving OIT had undetermined status because the full dose was not eaten, but no symptoms were reported
IMPACT Study

- Most participants (98% with peanut oral immunotherapy vs 80% with placebo) had at least one oral immunotherapy dosing reaction, predominantly mild to moderate and occurring more frequently in participants receiving peanut oral immunotherapy
- 35 oral immunotherapy dosing events with moderate symptoms were treated with epinephrine in 21 participants receiving peanut oral immunotherapy (22% of participants)
- Higher proportion of at-home epinephrine administrations during maintenance compared with build-up and more epinephrine administrations with oral immunotherapy doses higher than 600mg
- Three of 96 participants receiving OIT were referred for evaluation and endoscopy for eosinophilic esophagitis due to persistent symptoms. Two were documented to resolve after stopping OIT, and one had persistent disease

**PER PROTOCOL GROUP**

Figure S2. Immunologic Changes over the Course of the Study

+: change from pretreatment in placebo participants
*: between placebo and pnOIT group
#: for desensitized/remission vs both not desensitized/no remission vs desensitized/no remission in pnOIT per protocol outcome groups
*, #, + → p<0.05
**,##, ++ → p<0.01
IMPACT Study

• Remission data showing younger age and lower baseline IgE as predictors combined with observed increases in IgE and SPT reactivity in the placebo group suggest a **window of opportunity** for intervening in the natural history of peanut allergy.
Early Age Peanut OIT

• Together, all three of these studies demonstrate that OIT in younger ages is safer and may have improved efficacy outcomes
• Theorized reasons for differences in safety and efficacy in younger children and preschoolers include that these children may have more “immunoplasticity” & less established food allergy.
• They also may not experience subjective symptoms, aversion, and fear of their food allergens, which makes them more adherent and less likely to withdraw from OIT than older children.

At UVA...
UVA OIT Program

• Started formal peanut OIT program in Fall 2020 focused on 6 month-3 year olds
• No formal entry food challenge, but documented clinical reaction history plus positive skin prick test and/or positive serum specific IgE testing required
  – If never ingested, often offer entry food challenge to confirm allergic diagnosis depending on testing results & start OIT at highest tolerated dose
• 10 step up-dose protocol starting at ~7-14mg peanut protein per dose and ends at ~333mg per dose
• Use commercially available peanut powder (PB2) mixed into vehicle the child enjoys eating (applesauce, pureed vegetables, etc.)
• Written informed consent signed before starting

UVA OIT Program

• Currently have 18 patients started on early peanut OIT protocol
  – 5 currently undergoing build-up
  – 10 reached maintenance; none have completed 1 year yet
  – 1 withdrew due to reaction at home while on first dose of 14mg (hives, lip swelling, and coughing; Epi not given, left ED without being seen)
  – 2 lost to follow-up (1 was having hives with each up dose and also moved out of state)
  – No reported use of epinephrine
  – Of the 15 patients on per-protocol:
    • 8 patients developed mild, erythematous rash or small number of hives with up-dosing treated with cetirizine, but were able to continue or complete up-dosing
    • 1 patient developed mild loose stools and abdominal pain treated with famotidine that resolved 3 months after achieving maintenance dosing
UVA OIT Program

- **Median age at OIT start:** 12 months
- 61% male
- Median (IQR) peanut SPT at OIT start: 5.5mm [4-22]
- Median (IQR) peanut serum IgE at OIT start: 7.2kU/L [0.34-26.1]*
- Median (IQR) Ara h2 serum IgE at OIT start: 11.7kU/L [<0.10-45.1]*
  - *Not all patients had serum testing prior to starting OIT
- Once 1 year of maintenance completed, will repeat skin prick and IgE blood tests on therapy to determine if oral food challenge can be attempted
- If pass food challenge while on therapy, will offer options of discontinuing formal therapy and eating peanut in the diet frequently (at least 3 times per week), or continuing therapy indefinitely
- Stay tuned...

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Questions?

Bibliography

Bibliography


- Median peanut SPT at OIT start: 9mm [4-22]
- Median peanut serum IgE at OIT start: 1.32kU/L [0.34-26.1]
- Median Ara h2 serum IgE at OIT start: 0.58kU/L [<0.10-45.1]