

Cracking the Nut: Oral Immunotherapy Conundrums



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Overall Purpose/Goal: To provide excellent case-based reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Rahul Datta, MD, PhD, and Stacie M. Jones, MD (authors); Scott H. Sicherer, MD (editor)

Learning objectives:

1. To describe the process of undergoing oral immunotherapy (OIT) to peanut.
2. To inform potential patients of the risks that may be associated with OIT.
3. To describe approaches to mitigate OIT-associated risks.

Recognition of Commercial Support: This CME has not received external commercial support.

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R.G. is an 8-year-old boy who was diagnosed with peanut allergy at age 1 year after developing hives with peanut butter ingestion. He had no further reactions until age 7 years when he had an anaphylactic reaction after mistakenly consuming peanut. In clinic, parents were concerned that his diet would be more

difficult to control with age, putting him at a higher risk for reactions. After discussing the risks and benefits with the family, we decided to start oral immunotherapy (OIT).

The phase 3 Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE)

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trial demonstrated efficacy when comparing peanut OIT to placebo.¹ OIT begins with an initial daily dose of 3 mg of peanut protein, with updosing every 2 weeks to a maintenance dose of 300 mg followed by 6 months on daily maintenance. Each dose escalation was performed under medical supervision, with subsequent doses given at home. Primary end point was tolerance of 600 mg of peanut protein following the maintenance phase, with 67% of those receiving peanut able to safely consume 600 mg versus 4% with placebo.¹

OIT was approved by the Food and Drug Administration in 2020 under the brand name Palforzia and is indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut.² It is approved for patients ages 4 to 17 years with a confirmed peanut allergy and used alongside a peanut-avoidant diet.² Treatment involves daily ingestion of peanut powder mixed in a food vehicle such as pudding. Contraindications are uncontrolled asthma or a history of eosinophilic gastrointestinal disease.

Two months after starting OIT, R.G. reported sneezing and hives 30 minutes after taking a 40-mg home dose despite a successful clinic dose. He reportedly played soccer shortly after dosing and the dose was consumed on a nearly empty stomach. We reviewed OIT risks and precautions with R.G. and his parents. The following precautions were reviewed with the family: (1) doses should be taken with meals, (2) patient should be monitored for 60 minutes after dosing, (3) exercise and hot showers should be avoided for 3 hours after dosing, and (4) dose adjustments may be needed because of illness such as a viral illness due to an increased risk of a reaction.²

Reactions are common with OIT, but are primarily mild to moderate in nature. Most common are gastrointestinal

symptoms, with 67% of subjects reporting abdominal pain and 37% reporting vomiting during up dosing. Epinephrine was administered to 10.4% of patients. Approximately 2% to 3% of patients developed eosinophilic gastrointestinal disease.²

Two months later, R.G. returned for up dosing and reported a week of abdominal pain immediately after each home dose of 120 mg. We maintained the 120 mg dosing for 2 extra weeks and started H₁ and H₂ blockers. Symptoms resolved and up dosing was resumed. He reached maintenance after which medications were weaned with no further issue. In a potential second scenario, R.G. does not respond to the medications. He was found to have an abnormal endoscopy that demonstrated esophageal eosinophilia. A diagnosis of eosinophilic esophagitis was confirmed and OIT was discontinued. Within 2 weeks, his symptoms resolved. Six months later, a repeat biopsy showed only 2 eosinophils/hpf.

OIT is a treatment for peanut allergy with proven efficacy in increasing tolerance of ingested peanut. Most adverse events are mild to moderate and improve over time. However, OIT is not for everyone. Families must be aware of the risks, benefits, and processes involved with undergoing the treatment. Ultimately, OIT is a shared decision process between the physician, the patient, and the family requiring ongoing education. The patient must maintain a peanut-avoidant diet and access to self-injectable epinephrine for the most beneficial and safe outcomes associated with treatment.

REFERENCES

1. The PALISADE Group of Clinical Investigators. AR101 Oral immunotherapy for peanut allergy. *N Engl J Med* 2018;379:1991-2001.
2. Aimmune Therapeutics, Inc. Palforzia full prescribing information. Accessed February 1, 2022. https://www.palforzia.com/static/pi_palforzia.pdf

Difficult Cases:

Cracking the Nut: Oral Immunotherapy Conundrums

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Case Report - RG

- 8 year old boy presents with a history of a peanut allergy and atopic dermatitis.
- Peanut allergy was diagnosed at age 12 months after RG developed generalized hives and facial swelling following ingestion of 1 tablespoon of peanut butter.
 - PnIgE = 50 kU/L; Peanut SPT = 8 mm
- Management includes peanut diet restriction and self-injectable epinephrine with ongoing education from his allergist.
- One year ago, RG ate ice cream at a birthday party and immediately developed hives and respiratory distress. Epinephrine and diphenhydramine were given and he was taken to the emergency room where he was monitored 4 hours and discharged to home without further symptoms.
- Parents are concerned that as RG gets older, he may have more accidental ingestions.



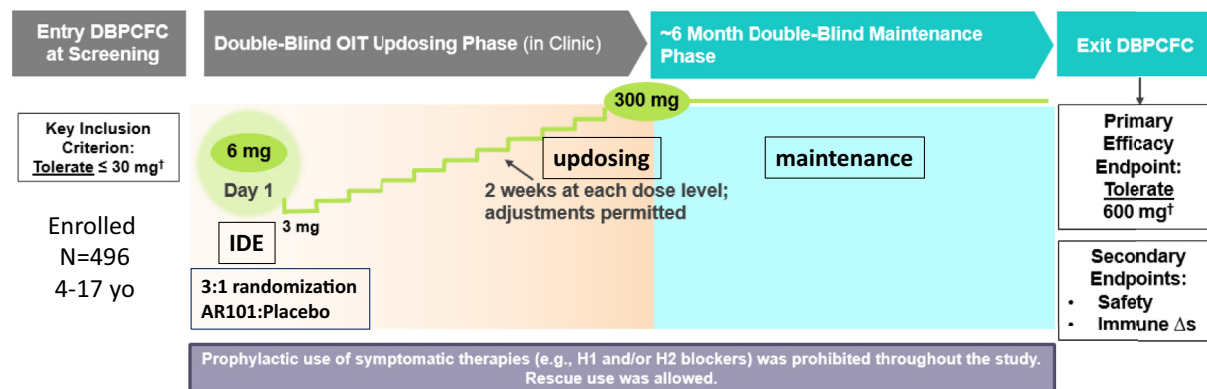
Oral Immunotherapy (OIT)

- Peanut powder ingested in a food vehicle (e.g., applesauce, pudding)
- Antigen is processed in gut-associated lymphoid tissue with antigen up-take by mucosal dendritic cells that further modify immune pathways through regulatory mechanisms dampening Th2-skewed allergic response



PALISADE Trial, Phase 3 – Peanut OIT

Participating countries (66 centers): US, Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, Sweden, UK

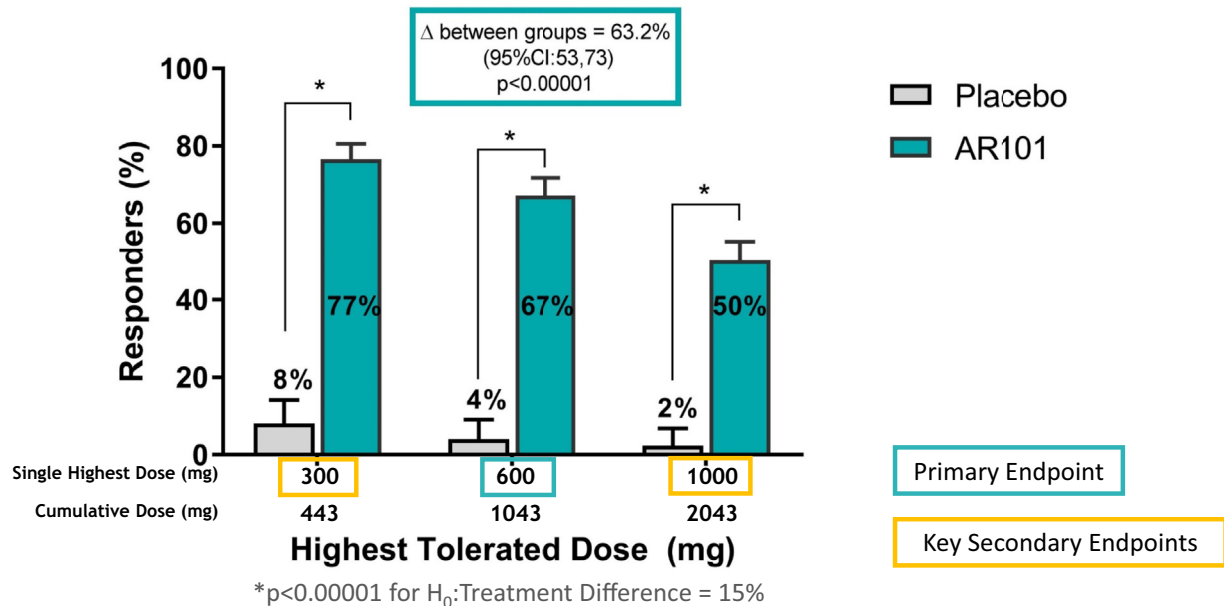


Primary endpoint: Desensitization

[†]600 mg of peanut protein is approximately equal to 2 peanut kernels

www.clinicaltrials.gov; NCT02635776

PALISADE: Efficacy in 4-17 yo, ITT Population (N=496)



Vickery BP, et al. NEJM 2018; 379:1991-2001

FDA approval on January 31, 2020

Palförzia
Peanut (Arachis hypogaea)
Allergen Powder-dnfp



-Indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut

-Approved for use in patients, ages 4-17 years, with confirmed peanut allergy

-Contraindications poorly controlled asthma, EoE, severe anaphylaxis w/in 60d

****PALFORZIA REMS (Risk Evaluation and Mitigation Strategy) Program Enrollment is required due to risk of anaphylaxis**

INITIAL DOSE ESCALATION

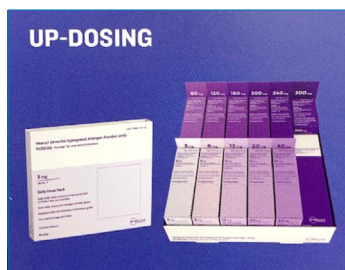


5 Doses on Day 1

0.5 mg, 1 mg, 1.5 mg, 3 mg, 6 mg

- Peanut avoidant diet
- Epinephrine access

UP-DOSING



11 Doses every ~2 weeks

3 mg to 300 mg daily

Maintenance 300 mg daily



Case Continued.....

- Family decides to begin peanut OIT.
 - Two months after starting, RG reports to clinic for an up dosing appointment.
 - Parents report that one week prior, RG exhibited symptoms of sneezing and 4-5 hives that began 30 minutes after he received his dose which was given at school after lunch.
 - On further questioning, several issues are discovered:
 - Shortly after taking the dose, he was playing soccer in gym class
 - Dose was given in a small amount of applesauce with only an apple eaten at lunch
 - Mom confides that RG splits time between his two separated parents and sometimes with his grandmother. He may miss 1-2 doses per week. She wonders if this may have contributed to his anaphylaxis.
-

Palforzia prescribing information

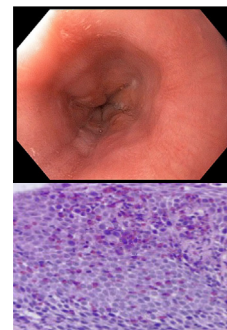
- **Key Points:**
 - Adverse reactions, including anaphylaxis, can occur at any stage of dosing
 - Most dose-related reactions are mild-moderate in severity
 - Anaphylaxis occurred in 9.4% of peanut OIT participants in key studies
 - EoE was diagnosed in <1% of study participants
 - Risks increase with severe or poorly controlled asthma
 - **Recommended Dosing Procedures:**
 - Doses should be taken in a cool vehicle with a meal or meal-size snack
 - Doses should not be missed and should be take at same time of day (preferably evening)
 - No strenuous exercise or hot shower/bath immediately before or 3 hours post-dose
 - Dose adjustments, including holding doses, are needed for fever and illnesses (viral respiratory/gastrointestinal), including acute asthma attacks and menses
 - Dose adjustments or observed doses are needed if 3 or more consecutive doses are missed
- ***Epinephrine Access/Education and Peanut Avoidant Diet are required***
-

Case Continued.....

- OIT dosing procedures are carefully reviewed with the family.
 - Two months later, mother calls and reports that RG has developed epigastric abdominal pain within 30-45 minutes of each dose of 120 mg.
 - H1 and H2 blockers are prescribed daily prior to OIT dosing.
 - OIT dose is held at 120 mg x 2 additional weeks with resolution of pain.
 - As OIT up dosing continues to 160 mg, no symptoms occur.
 - He is able to continue his dosing and achieve maintenance (300 mg).
 - Three months into maintenance, he remains symptom-free and he is weaned off the H1 and H2 blockers without issue.
-

Case Continued (second scenario)

- OIT dosing procedures are carefully reviewed with the family.
- Two months later, mother calls and reports that RG has developed epigastric abdominal pain within 30-45 minutes of each dose of 120 mg. H1 and H2 blockers are prescribed daily prior to OIT dosing.
- OIT dose is held at 120 mg x 2 additional weeks with resolution pain.
- As OIT up dosing continues to 160 mg, abdominal returns and persists, prompting a change from an H2 blocker to a PPI.
- One week later, family reports that RG is having trouble tolerating his meals with difficulty swallowing and emesis.
- An esophageal biopsy was performed which shows 100 eos/HPF; OIT was discontinued.
- Within 2 weeks of stopping OIT, GI symptoms resolve. Repeat biopsy six months later shows 2 eos/HPF.



Side effects of OIT – Palforzia package insert

Table 4: Treatment-Emergent Adverse Reactions in ≥ 5% of PALFORZIA-Treated Subjects and ≥ 5% Percentage Points Greater Than Placebo-Treated Subjects in any Dosing Phase (Aged 4 through 17 Years)

System Organ Class / Preferred Term [2]	Study 1 & Study 2 IDE PALFORZIA (N = 709)	Study 1 & Study 2 IDE Placebo (N = 292)	Study 1 & Study 2 Up-Dosing PALFORZIA (N = 693)	Study 1 & Study 2 Up-Dosing Placebo (N = 289)	Study 1 [1] 300 mg PALFORZIA (N = 310)	Study 1 [1] 300 mg Placebo (N = 118)
Gastrointestinal disorders						
Abdominal pain [3]	185 (26.1%)	24 (8.2%)	465 (67.1%)	100 (34.6%)	90 (29.0%)	20 (16.9%)
Vomiting	22 (3.1%)	2 (0.7%)	253 (36.5%)	47 (16.3%)	50 (16.1%)	14 (11.9%)
Nausea	60 (8.5%)	2 (0.7%)	224 (32.3%)	41 (14.2%)	45 (14.5%)	8 (6.8%)
Oral pruritus [4]	62 (8.7%)	9 (3.1%)	216 (31.2%)	30 (10.4%)	51 (16.5%)	7 (5.9%)
Oral paresthesia	13 (1.8%)	7 (2.4%)	94 (13.6%)	11 (3.8%)	23 (7.4%)	2 (1.7%)
Respiratory, thoracic, and mediastinal disorders						
Throat irritation	66 (9.3%)	15 (5.1%)	279 (40.3%)	49 (17.0%)	43 (13.9%)	11 (9.3%)
Cough	18 (2.5%)	1 (0.3%)	221 (31.9%)	68 (23.5%)	61 (19.7%)	22 (18.6%)
Rhinorrhea	9 (1.3%)	4 (1.4%)	145 (20.9%)	50 (17.3%)	46 (14.8%)	9 (7.6%)
Sneezing	24 (3.4%)	8 (2.7%)	140 (20.2%)	31 (10.7%)	33 (10.6%)	5 (4.2%)
Throat tightness	18 (2.5%)	3 (1.0%)	98 (14.1%)	8 (2.8%)	20 (6.5%)	0 (0.0%)
Wheezing	4 (0.6%)	0 (0.0%)	85 (12.3%)	21 (7.3%)	19 (6.1%)	10 (8.5%)
Dyspnea	2 (0.3%)	1 (0.3%)	53 (7.6%)	5 (1.7%)	17 (5.5%)	1 (0.8%)
Skin and subcutaneous tissue disorders						
Pruritus	56 (7.9%)	16 (5.5%)	225 (32.5%)	59 (20.4%)	45 (14.5%)	14 (11.9%)
Urticaria	28 (3.9%)	10 (3.4%)	197 (28.4%)	54 (18.7%)	63 (20.3%)	17 (14.4%)
Immune system disorders						
Anaphylactic reaction [5]	5 (0.7%)	1 (0.3%)	63 (9.1%)	10 (3.5%)	27 (8.7%)	2 (1.7%)
Ear and labyrinth disorders						
Ear pruritus	5 (0.7%)	1 (0.3%)	41 (5.9%)	2 (0.7%)	7 (2.3%)	0 (0.0%)

GI events
are most
common

Systemic
reactions
in ~10%

Practical factors impacting OIT success

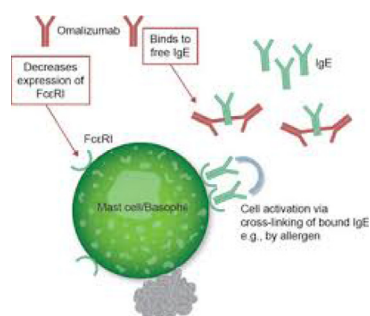
OIT is not the right fit for every patient

- **Problem:** Dosing issues – taste and vehicle issues
 - **Solutions:** change/alternate vehicle to mask taste, provide variety
 - Never cook in food or heat peanut OIT
- **Problem:** Dosing fatigue
 - **Solutions:** review benefits, consider alternate treatment and OIT discontinuation
- **Problem:** Dose adjustments for illness/menses
 - **Solutions:** OIT access line for recommendations
 - Observed dosing after 3 or more missed doses with potential dose reduction
 - Hold doses or pretreat during early menses cycle – monitor for pattern
- **Problem:** Anxiety with dosing
 - **Solutions:** Suggest counseling; discuss discontinuation (risk:benefit assessment)
- **Problem:** Lifestyle disruptions for child/family
 - **Solutions:** Creative dosing scheme vs. discontinuation vs. alternate treatment

Summary

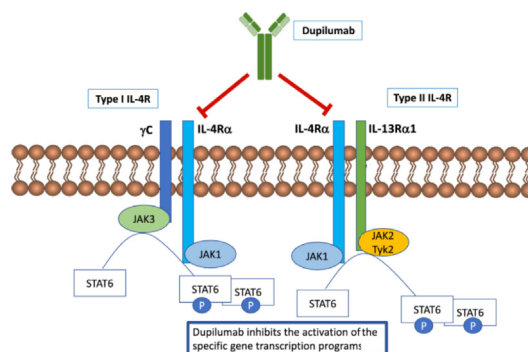
- Oral immunotherapy is a new FDA-approved treatment for managing food allergy.
- OIT has positive efficacy and benefit for many people who undergo the treatment. Patients and families often report a significant improvement in their overall well-being.
- Most adverse events are mild-moderate, manageable and improve over time.
- Families must be aware of the risks, benefits, and process involved with undergoing the treatment.
- Ultimately, oral immunotherapy is a ***shared decision process*** between the physician, the patient, and the family. Like all treatment, OIT must be tailored to the patient and family needs and goals.

Future therapy under investigation: *OIT plus biologic agents*



Dupilumab
FDA Indications:
Atopic dermatitis,
Asthma,
Chronic
rhinosinusitis with
nasal polyposis

Omalizumab
FDA Indications:
Allergic Asthma,
Chronic Idiopathic
Urticaria



Thank You!

- Any Questions?
