Managing reactions in OIT

David Fitzhugh, MD
Allergy Partners of Chapel Hill

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Disclosures

- AstraZeneca - Speaker
- Allergenis - Medical Advisor / Investor
- Biocryst, CSL - Advisory boards 2021

Overview of Reactions Types in OIT

- Oropharyngeal reactions / side effects
- Cutaneous reactions
- Gastrointestinal reactions / side effects - Immediate and delayed
- Anaphylaxis / ETRs (Epinephrine-treated reactions)
- “Triggered” vs. spontaneous reactions - predisposing cofactors

A little history

Wes Burks, et al 2009 JACI

In the studies to date, peanut and food OIT have a good safety profile, and home dosing is infrequently associated with adverse reactions.[2,6] However, allergic symptoms should be expected, and subjects and their families should be counseled about circumstances associated with an increased possibility of reacting to previously tolerated OIT doses. As OIT for food allergy becomes increasingly studied in research settings, implementing these recommendations and modifications can improve the safety of these experimental protocols.

Pooja Varshney, MD[a]
Pamela H. Steele, CPNP[a]
Brian P. Vickery, MD[a]
J. Andrew Bird, MD[a]
Ananth Thyagarajan, MD[a]
Amy M. Scurlock, MD[b]
Tamara T. Perry, MD[b]
Stacie M. Jones, MD[b]
A. Wesley Burks, MD[a]

Literature sources

Original Article

Oral Immunotherapy for Peanut Allergy: Multipractice Experience With Epinephrine-treated Reactions

Richard L. Wasserman, MD, PhD[a], Jeffrey M. Factor, MD[b], James W. Baker, MD[c], Lyndon E. Mansfield, MD[d], Yitzhak Katz, MD[e], Angela R. Hague, PA-C[f], Marianne M. Paul, BS[c], Robert W. Sugerman, MD[a], Jason O. Lee, MD[b], Mitchell R. Lester, MD[b], Louis M. Mendelson, MD[b], Liat Nacshon, MD[g], Michael B. Levy, MD[g], Michael R. Goldberg, MD, PhD[g], and Arnon Elizur, MD[e] *Dallas and El Paso, Tex; West Hartford, Conn; Portland, Ore; and Tel Aviv and Zerifin, Israel*

352 patients, JACI: IP 2014

Original Article

First Real-World Safety Analysis of Preschool Peanut Oral Immunotherapy

Lianne Soller, PhD[a,b], Elissa M. Abrams, MD[b,c,d], Stuart Carr, MD[e], Sandeep Kapur, MD[f,g], Gregory A. Rex, MD[f,g], Sara Leo, MD[b,h], Per G. Lidman, MD[e], Joanne Yeung, MD[b,i], Timothy K. Vander Leek, MD[e], Mary McHenry, MD[f,g], Tiffany Wong, MD[a,b], Victoria E. Cook, MD, MSc[b,j], Kyla J. Hildebrand, MD, MScCH (HPTE)[a,b], Thomas V. Gerstner, MD[c,d], Raymond Mak, MD[b], Nicole J. Lee, MSc[a,b], Scott B. Cameron, MD, PhD[b,j,*], and Edmond S. Chan, MD[a,b,*] *Vancouver and Victoria, BC, Canada; Winnipeg, MB, Canada; Edmonton, AB, Canada; and Halifax, NS, Canada*

270 patients, JACI: IP 2019

Original Article

Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral Immunotherapy in Children with Peanut Allergy

Katharina Blumchen, MD[a,b], Valerie Trendelenburg, MSc, PhD[b], Frank Ahrens, MD[c], Armin Gruebl, MD[d],

62 patients, JACI: IP 2019

Original Article

Community Private Practice Clinical Experience with Peanut Oral Immunotherapy

Yuliya Afinogenova, MD[a], Tamar N. Rubin, MD[b], Sagar D. Patel, BS[c], Rachel L. Powell, RN[c], Janina M. Gilo, APRN[c], Morgan N. Denno, APRN[c], Gary Soffer, MD[d], Jason O. Lee, MD[c], Louis M. Mendelson, MD[c,†], and Jeffrey M. Factor, MD[c] *New Haven and West Hartford, Conn; and Palm Beach Gardens, Fla*

783 patients, JACI: IP 2020

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 22, 2018 VOL. 379 NO. 21

AR101 Oral Immunotherapy for Peanut Allergy

The PALISADE Group of Clinical Investigators*

ABSTRACT

551 patients

Oropharyngeal symptoms

- Fairly common
- Palisade / AR 101: 41% active, 16% placebo
- Blumchen: 60% active, 26% placebo
- NEFATC: 48% during build
- More common during escalation than maintenance

Oropharyngeal symptom management

- Typically, self-limited
- Can monitor with no treatment, treat prn, or if consistent, treat with long-acting AH
- Sometimes this is true OAS/Arah8 related, so might consider environmental SCIT prior to initiating OIT

Cutaneous reactions

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New Haven and West Hartford, Conn; and Palm Beach Gardens, Fla

Build-up (8% hives during maintenance)

Cutaneous symptoms	
Hives	216 (28)
Angioedema	79 (10)
Atopic dermatitis	21 (3)
Other rash	52 (7)
Skin itching	135 (17)
Itchy eyes	48 (6)

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AR101/Palisade: 31% active, 18% placebo in build

Cutaneous reaction management

- Typically, can be managed with AH unless progressive systemic reaction
- Notably, Atopic Derm can flare during OIT, though this isn’t that common (only 3% of patient in build from NEFATC)
- If recurrent / untriggered urticaria, a dose back-down would be indicated
- If recurrent, would also search for underlying triggers, like exertion, empty stomach, etc.

GI side effects

- Extremely common during OIT and probably the most challenging management issue
- Important to distinguish immediate from delayed GI symptoms
- The former are generally IgE-mediated, whereas the latter are often eosinophilic in nature

Characteristic	Patients with at least 1 episode, n (%)
Gastrointestinal symptoms	
Abdominal pain	533 (68)
Oral itch	375 (48)
Vomiting	218 (28)
Nausea	123 (16)
Reflux	101 (13)

Note: only 13% in maintenance

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New Haven and West Hartford, Conn; and Palm Beach Gardens, Fla

GI side effect treatment options

- If untriggered, consider decreasing the dose and/or extending the interval
- H2 blockade or PPI may be helpful but I prefer dose / interval adjustment
- Probiotics (will discuss separately)
- ELORS = EoE-like OIT-Related Syndrome - typified by vomiting several hours after dosing. Consider checking CBC and dose decrease / interval increase. (to be reviewed in detail tomorrow by Dr. Wasserman).

Anaphylaxis / ETRs

- This is what scares everyone! (Patients, parents, and providers)
- Not common, but does happen
- Frequently (but not always), these are triggered and at least theoretically, avoidable to some degree

Frequency of ETRs

- Wasserman, 2014
  - Build: 0.7 ETRs per 1000 doses
  - Maintenance: 0.2 ETR per 1000 doses
- NEFATC, 2020
  - Build 0.6 ETR per 1000 doses
  - Maintenance 0.5 ETR per 1000 doses (year 1 maintenance)
- Chan, 2019
  - Overall: 0.3 ETR per 1000 OIT doses (build and maintenance combined)
- Of note, annualized rate of accidental exposure PN reactions in PN-allergic children around 12%, of which 2/3 were moderate or severe (Clarke, 2011)

Risk factors for ETRs

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TABLE V. Multivariable regressions for systemic reactions in build-up and maintenance phases

Parameter	n (%)	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Systemic reactions during the build-up phase					
Age (per increase in 1 SD of age)	—	1.23 (1.00-1.51)	.05	1.20 (0.93-1.53)	.16
Sex (male vs female)	Male 45 (9.3%) Female 33 (11.1%)	0.82 (0.51-1.3)	.42	0.85 (0.51-1.45)	.56
Pre-OIT peanut IgE (per increase in 1 SD of pre-OIT peanut IgE)	—	1.66 (1.27-2.16)	<.0001	1.65 (1.24-2.20)	.001
Has patient required epinephrine for peanut allergy before OIT (yes vs no)	Yes 24 (13.1) No 52 (9.4)	1.45 (0.87-2.43)	.16	1.05 (0.58-1.91)	.88
Presence of eczema (yes vs no)	Yes 29 (8.9) No 49 (10.7)	0.82 (0.51-1.33)	.41	0.93 (0.54-1.59)	.78
Presence of asthma (yes vs no)	Yes 43 (10.4) No 34 (9.2)	1.15 (0.71-1.84)	.58	0.85 (0.51-1.45)	.56
Duration of buildup (per increase in 1 SD of duration of buildup)	—			1.32 (1.05-1.65)	.016
Systemic reactions during the maintenance phase					
Age (per increase in 1 SD of age)	—	1.28 (1.07-1.54)	.007	1.24 (1.01-1.54)	.04
Sex (male vs female)	Male 70 (16.2) Female 61 (22.9)	0.65 (0.44-0.96)	.03	0.62 (0.40-0.96)	.03
Pre-OIT IgE (per increase in 1 SD of pre-OIT IgE)	—	1.81 (1.46-2.24)	<.0001	1.64 (1.31-2.07)	<.0001
Has patient required epinephrine for peanut allergy before OIT (yes vs no)	Yes 39 (24.4) No 79 (16.2)	1.67 (1.08-2.58)	.02	1.51 (0.93-2.46)	.09
Presence of eczema (yes vs no)	Yes 49 (17.3) No 82 (19.8)	0.85 (0.57-1.25)	.41	—	—
Presence of asthma (yes vs no)	Yes 75 (20.9) No 56 (16.7)	1.32 (0.90-1.93)	.16	—	—
Presence of systemic reaction during buildup (yes vs no)	Yes 31 (34.9%) No 100 (15.9%)	4.01 (2.56-7.25)	<.0001	3.09 (1.73-5.53)	<.0001

Triggered reactions

- Significant cofactors that have been implicated in systemic reactions:
  - Exercise / overheating (particularly within 2-3 hrs of dosing)
  - Fasting / dose on empty stomach
  - Concurrent illness (particular fever)

- Lesser but still potentially important
  - Menses
  - NSAIDs
  - Sleep deprivation

Does a patient have to go to the ED if ETR?

- While ETRs happen, we have the opportunity to educate patients routinely during OIT at each visit
- Prompt administration of Epi with early recognition
- Ability to monitor remotely (FaceTime, etc)
- Pandemic concerns
- Reactions for which Epi was not given that really deserved ED!
- Every reaction needs prompt assessment (thus -> clinician availability!)

Dose Adjustments, triggered reactions

- For a triggered reaction with obvious cause:
  - Usually make short-term decrease for 1-2 days at 50% reduction
  - Reinforce dosing rules!

Dosing adjustment, no identifiable cause

- There is a fair amount of art here, not dissimilar to adjustments for SCIT
- If severe, usually decrease by 25-50% and extend interval to 4 weeks
- Consider building intermediate dosing steps (“sensitive build”)
- If already at an acceptable maintenance dose (thus, reaction happened at 1000 mg peanut protein, for instance), consider decreasing to lower maintenance and holding indefinitely

Dosing adjustments, short-term illness

- 1-2 missed days: no change
- 3-6 missed days: decrease by 50% for each day over 2 days (thus, for 4 missed days, use 2 days at lower dose and back to usual dose day 3 of restart)
- 7+ missed days: reducing in office at discretion

Dosing adjustment, GI symptoms

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/al to 4 weeks

dose (“low/slow” protocol)

RS suspected

Very gradual protocol, reaching 200 mg PP in 33 steps

Probiotics???

- Some hints that probiotics may help with sustained unresponsiveness but not well-controlled (PPOIT vs. placebo/placebo, Mimi Tang 2017)
- This is being addressed in a follow-on study with PPOIT vs. POIT but this has not reported yet
- In practice, I frequently use probiotics. They seem to help with intermittent GI symptoms, but there is no compelling data for this that I am aware. Nevertheless, seems to help many patients with mild persistent GI symptoms.

Back to the beginning

TABLE II. Recommendations for future oral immunotherapy investigations

Hold daily dose if febrile or ill with symptoms of viral illness (eg, upper respiratory tract infection, gastroenteritis).
Resume dosing at home if <3 missed daily doses.
Return to research unit for observed dose if 3-5 missed daily doses.
Consider repeat desensitization or significant dose reduction if >5 missed daily doses.
Closely monitor lower and upper respiratory symptoms.
Initiate asthma controller medication if needed.
Perform peak flow and spirometric monitoring.
Ensure optimal control of allergic rhinitis.
Take daily OIT dose with meal or snack
In subjects with exercise-induced symptoms, limit exertion for 2 hours after dosing.
Closely monitor during menstrual cycle, especially when coupled with infection or exercise.

Burks, 2009

Acknowledgements

- Aerik Williams, MD
- Neetu Talreja, MD
- Richard Wasserman, MD
- All of our patients!

Last but not least