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Risk Factors and Treatment Outcomes for Oral Immunotherapy-Induced Gastrointestinal Symptoms and Eosinophilic Responses (OITIGER)

Goldberg et al., *JACI in Practice*, January 2020

Presented By: Ellen Stephen, MD (PGY-4)

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Background

- **Oral Immunotherapy (OIT)** is an important emerging therapy for food allergy, but one of the chief concerns about its use as a treatment is the adverse effect profile
  - IgE-mediated or non-IgE mediated symptoms – differentiate by temporal relationship to dose administration

Background

- Authors' prior study (published in *JACI in* 2017) showed that patients who experienced non-IgE mediated GI symptoms showed a significant increase in peripheral blood eosinophil count that then decreased when symptoms subsided
  - Now referred to as **OIT-induced Gastrointestinal Symptoms and Eosinophilic Responses (OITIGER)**
    - Seen in 8-13.7% of patients per prior estimates
  - Observed that after cessation of OIT, symptoms resolved and peripheral blood eosinophilia returned to baseline
  - Their work and several other studies found that most patients with OITIGER who resumed OIT did not develop symptoms again

Methods

- Single-hospital center with an open label OIT program
- Patients >4 years of age with positive skin prick test and/or specific serum IgE **plus** clinical history of IgE-mediated reaction with oral food challenge or accidental exposure in the past year
- 794 patients enrolled (April 2010-October 2015)
  - 614 milk, 130 peanut, 41 egg
- Individualized OIT dosing –
  - started with 4 day induction to find maximum tolerated starting dose (below the eliciting dose on oral challenge) then maintained this dose BID for 24 more days
  - Dose was then increased every 28 days
  - If symptoms developed thought to be related to rate of dosage increase, then **future dose escalations were limited** to 4-fold in 2nd round, 3-fold in 3rd round, and 2-fold in 4th and 5th rounds, then 50% of prior dose for 6th round onward
  - Goal protein dose with no adverse reactions for **full desensitization**: 7,200 mg (milk); 3,000 mg (peanut); 12,000 mg (egg); 4,000 mg (sesame)
  - **Partial desensitization** = able to tolerate > 180 mg (milk), >300 mg (peanut), >240 mg (sesame)

Methods

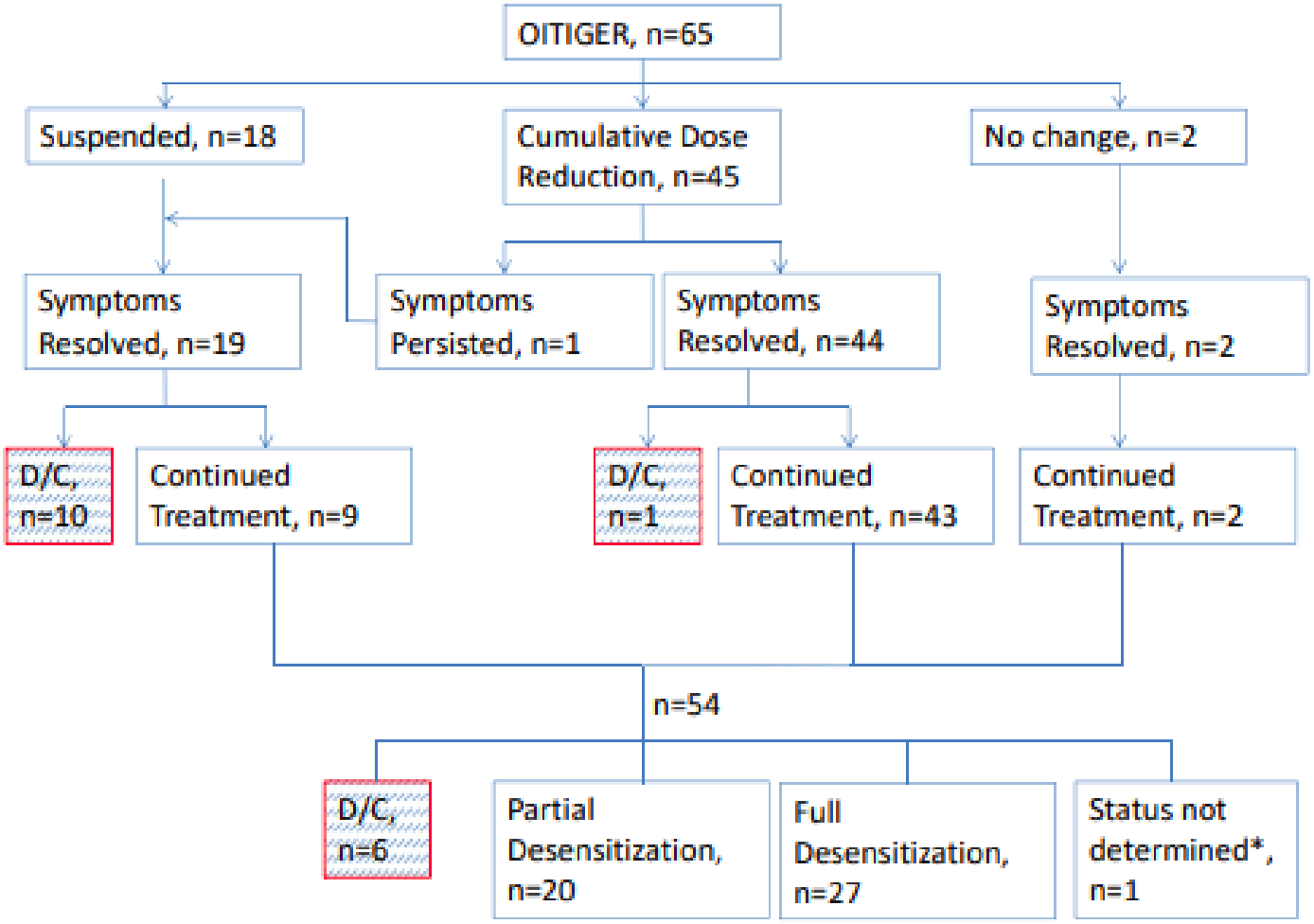
- Patients/parents reported daily (by email or web-based program) whether they tolerated their daily dose(s)
- If GI symptoms reported, they were asked about timing of onset related to timing of dose administration
- Peripheral blood absolute eosinophil count (AEC) was collected at baseline and at the time of each visit for dose increase, as well as at the time of onset of GI symptoms that were not related to timing of dose administration

Methods

- Treatment approach was individualized for each patient based on severity of GI symptoms and AEC (>900 eosinophils/uL)
  - Modifications included:
    - decrease cumulative dose administered (by holding off on monthly dose increase, switching BID to daily dosing, or decreasing the dose itself)
    - suspend OIT until symptoms resolved and AEC returned toward baseline
  - No treatment with PPI or H1/H2 receptor antagonists

Methods

- Statistical analysis was performed using SPSS
  - **Fisher exact test** – used for categorical variables
  - ***t*-test** – used for normally distributed continuous variables
  - **Mann-Whitney test** – used for continuous variables NOT normally distributed
  - **ANOVA** – used for difference between means
  - $p<0.05$ was deemed statistically significant

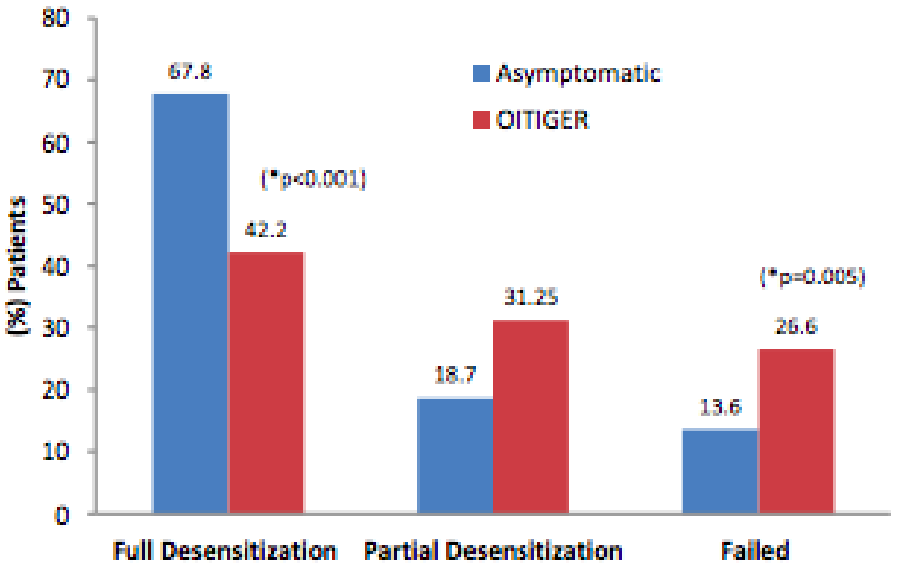

OITIGER, n=65
Suspended, n=18
Cumulative Dose Reduction, n=45
No change, n=2
Symptoms Resolved, n=19
Symptoms Persisted, n=1
Symptoms Resolved, n=44
Symptoms Resolved, n=2
D/C, n=10
Continued Treatment, n=9
D/C, n=1
Continued Treatment, n=43
Continued Treatment, n=2
n=54
D/C, n=6
Partial Desensitization, n=20
Full Desensitization, n=27
Status not determined*, n=1

Results

- 65 patients met the criteria for OITGER (3+ episodes/month of GI symptoms not temporally related to OIT dose administration)
  - 55 milk, 9 peanut, 1 egg
- 45 patients (69.2%) underwent treatment modifications
  - 43 patients had cumulative dose reduction by median of 50% [IQR 50-66.7%]
    - 1 patient refused to take new dose
  - Dose increases started again after median 29 days [IQR 20-56], 65% got once a day dosing, 35% got BID dosing
  - 2 patients suspended further dose increases for 2 or 3 months, respectively
  - 1 patient was still symptomatic with cumulative dose reduction, so ultimately suspended treatment
- 18 patients suspended treatment (27.7% -- 15 because of symptoms and 3 because of non-adherence)
  - 9 patients who suspended then restarted OIT after median 19 days, oral food challenge was used to determine **new current tolerated dose**
- 2 patients with no change to treatment, symptoms resolved

Results

- Patients with OITIGER had poorer treatment outcomes than asymptomatic patients
  - Less likely to reach full desensitization ($p<0.001$)
  - Longer median duration of treatment to reach full desensitization (295 vs. 229 days)
  - Higher OIT failure rate ($p=0.005$)

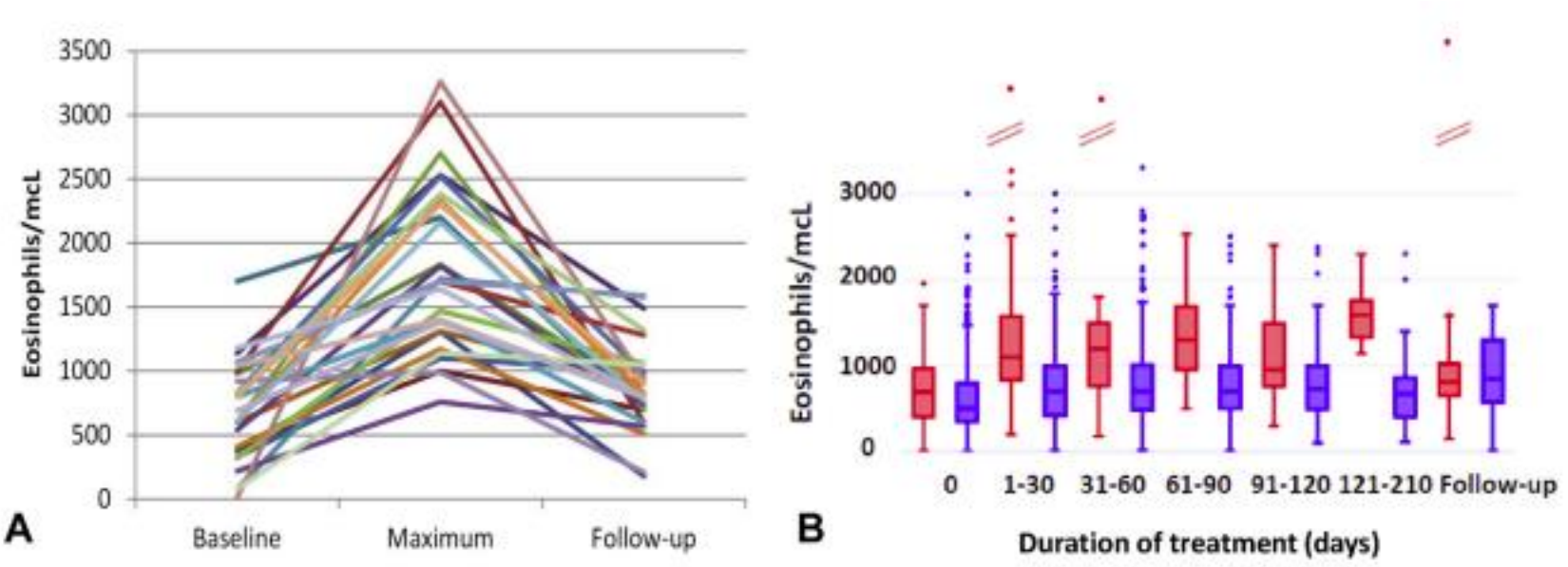


Results

- Still, 73% of patients with OITIGER did achieve partial desensitization, which may mean protection in case of accidental food exposure
- Of the patients who **continued OIT after initial OITIGER symptom resolution**, 50% did achieve full desensitization, 37% reached partial desensitization and 11.1% stopped OIT (2/3 because of symptoms, others for unrelated reasons)
  - [1 patient was still in dose escalation at time of data analysis]
  - 18.5% of patients had **OITIGER symptoms recur** after restarting OIT, but 50% of those ultimately achieved full desensitization and 10% achieved partial desensitization after further treatment reduction

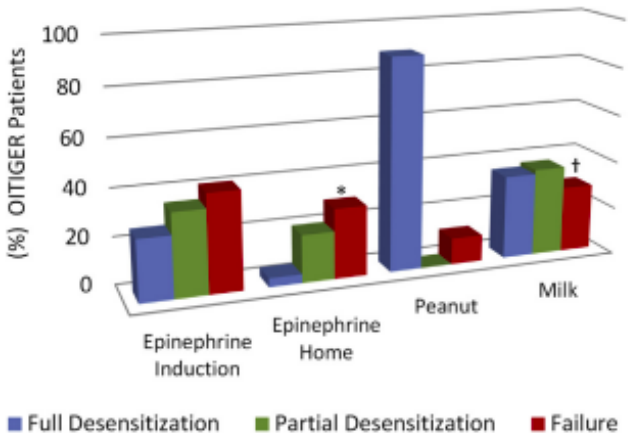
Results

- Patients with OITIGER who then resumed OIT showed AEC return to baseline during long-term follow up (>3 to 26 months)
- Part (B): Asymptomatic patients (blue) showed initial increase in AEC after allergen introduction but then it remained stable vs. OITIGER patients (red) who showed steady increase in AEC over the first 90 days of treatment



Results

- *What risk factors contribute to treatment failure in patients with OITIGER who stopped vs. those who were able to restart OIT and reach full or partial desensitization?*
- Table 1: No significant differences in age, sex, asthma status, starting dose, fold increase in dosing, or epinephrine usage during induction & no difference in baseline eosinophil count or the increase in eosinophils
  - But those who failed were more likely to be undergoing treatment for milk than peanut ($p<0.15$)
  - Failure and partial desensitization groups had significantly more use of epinephrine at home ($p<0.35$) --- suggests higher frequency of anaphylactic-type reactions (IgE-mediated)



Results

- Risk factors for developing OITIGER in milk-OIT patients (univariate and multivariate regression analyses were performed
  - Higher median starting dose (480 mg vs. 45 mg) in those who developed OITIGER within first month of treatment
    - Starting dose >120 mg milk : odds ratio 7.14 of developing OITIGER
  - Significantly greater dose escalation from starting dose to round 2
    - Initial dose increase >4-fold: odds ratio 2.18
  - Higher baseline AEC (and maximum AEC too)
    - Baseline AEC > 600/uL: odds ratio 3.2

Discussion

- Largest cohort of patients with OITIGER symptoms in which treatment modifications, clinical outcomes, and risk factors have been examined
- In the past, patients with OITIGER would be considered treatment failures – but in this study, more than 2/3 of patients achieved at least partial sensitization (50% full desensitization) by modifying or pausing OIT
- More than 80% of patients with revised regimen did NOT have recurrent OITIGER, of those that did—60% were addressed by additional modifications
- Eosinophil-driven pathway is affected by modified dosing regimen (given the trends in AEC that were observed)
- These results were not affected by additional treatment (no PPI/H2 blockers were used)

Discussion

- Mechanism for desensitization in OIT may be due to increases in IgG4 or decreases in basophil reactivity
  - Prior studies found increase in IgG4 is associated with pediatric EoE, OIT does cause increase in IgG4
    - Patients with OITIGER may have had pre-existing subclinical EoE unmasked when treatment started (vs. induction of EoE-type disease by the OIT)
  - Suppressing IL-4/IL-13 axis during OIT may lead to reactive increase in IL-5 pathway, hence the increase in peripheral AEC
    - Transient increase in AEC seen after starting dupilumab supports this
    - Dose adjustment seems to modify this effect—since many patients were able to tolerate OIT after adjustment

Discussion

- Risk of developing OITIGER is related to the amount of allergen exposure in the individual who is prone to these heightened eosinophil responses
  - Higher peripheral blood eosinophilia at baseline
  - Faster rate of escalation of OIT dosing
- In high-risk patients (with high baseline AEC), consider lower starting dose and/or slower dosing regimen

Limitations

- This OIT program uses individualized dosing during the build-up phase rather than a fixed build-up schedule --- may not be able to generalize the identified risk factors to other research protocols/populations
- 14 patients discontinued OIT because of OITIGER symptoms, unclear if their symptoms would have been reversible with treatment modification
  - More research needs to be done to differentiate those who progress to EoE-type disease from those who will eventually have resolution of symptoms
- Patients/parents were reluctant to allow GI endoscopies – these would be required to fully characterize this disease entity and monitor response to treatment
  - Only a few patients in prior studies have had biopsy – likely those with most severe symptoms, not representative
- In 15% of patients the maximal AEC was the one taken before onset of clinical symptoms but the symptoms may lag behind peripheral eosinophilia

Thank you!

Any questions?

Works Cited

- https://www.gfs.com/en-us/ideas/label-reading-for-food-allergens
- Goldberg MR et al. Oral immunotherapy-induced gastrointestinal symptoms and peripheral blood eosinophil responses. *J Allergy Clin Immunol* 2017;139:1388-1390.e4