A Phase 2 Study of Multi Oral Immunotherapy in Multi Food Allergic Patients to Test Immune Markers after Minimum Maintenance Dose using Xolair

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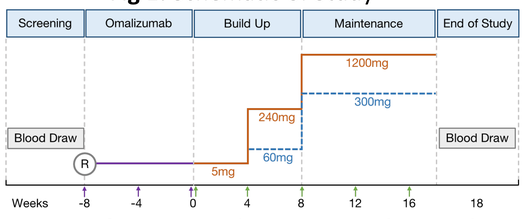
Introduction

- Food allergies affect approximately 8% of children[1] and 10.8% of adults[2] in the United States
- 45% of patients are allergic to multiple foods[2]
- Oral immunotherapy (OIT) has been well studied as a therapeutic option for treating food allergy
- Numerous studies have indicated that sIgG4/sIgE ratio may be a more reliable indicator of desensitization than sIgG4 or sIgE alone[3-4]
- The immune changes associated with varying maintenance doses in multi-allergen OIT (mOIT) have not been directly compared
- This study assesses immunological changes associated with different low maintenance doses preceded by fixed dose omalizumab

Methods

- Phase 2, multi-site mOIT trial
- Participants with 2-5 allergens
  - Peanut
  - Almond
  - Cashew
  - Hazelnut
  - Walnut
  - Pink fish
  - White fish
  - Shellfish
  - Egg
  - Milk
  - Peanut
  - Sesame
  - Soy
  - Wheat
- Pretreated with 3 doses of omalizumab (150 mg) then randomized to receive mOIT to a maintenance dose of 300 or 1200 mg protein containing 2-5 food allergens (Fig 1)

Fig 1: Schematic of Study



- Specific IgG4 and sIgE were obtained at baseline and week 18
- Primary endpoint: to evaluate whether mOIT can induce a ≥25% increase in the specific IgG4/IgE ratio in at least 2 allergens

Results

- Adverse events were also evaluated
- 60 participants (ages 4-20 years) were randomized 1:1 to 300 or 1200 mg treatment groups
- No significant differences in baseline characteristics by treatment arm (Table 1)

Table 1: Baseline Characteristics by mOIT Treatment Arm*

Characteristic	Total (n=60)	Treatment	
		300 mg (n=30)	1200 mg (n=30)
Age in years	10 [4, 20]	10 [4, 20]	10 [4, 17]
Male	41 (68%)	21 (70%)	20 (67%)
Ethnicity			
Hispanic or Latino	1 (2%)	0	1 (3%)
Not Hispanic or Latino	56 (93%)	28 (93%)	28 (93%)
Prefer not to report	3 (5%)	2 (7%)	1 (3%)
Race			
White	24 (40%)	15 (50%)	9 (30%)
Asian	22 (37%)	8 (27%)	14 (47%)
Black or African American	1 (2%)	0	1 (3%)
Multiracial	10 (17%)	5 (17%)	5 (17%)
Prefer not to report	3 (5%)	2 (7%)	1 (3%)
Atopic history			
Allergic dermatitis	48 (80%)	24 (80%)	24 (80%)
Asthma	39 (65%)	21 (70%)	18 (60%)
Allergic rhinitis	42 (70%)	20 (67%)	22 (73%)
Number of food allergies	7 [2, 14]	7 [3, 13]	7 [2, 14]
Omalizumab dose ≥ 0.016 mg/kg/(IU/mL) group (standard dose)**	18 (30%)	9 (30%)	9 (30%)
Weight (kg)	30.1 [17.4, 72.3]	29.4 [17.4, 72.1]	30.5 [17.7, 72.3]

Note: Categorical and continuous variables are reported as count (percent) and median (range), respectively.
* There were no significant differences between the treatment groups.
**Each participant's omalizumab dose was calculated by dividing their 150 mg dose by their weight and total IgE and categorized into 2 groups (< 0.016 mg/kg/(IU/mL) and ≥ 0.016 mg/kg/(IU/mL).

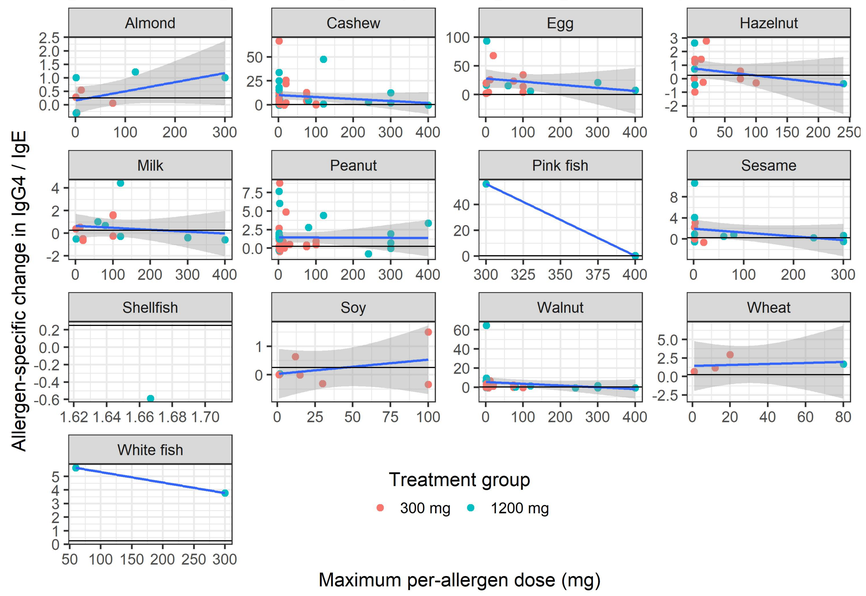
Table 2: Primary and Secondary Endpoints

	300 mg (n=30)	1200 mg (n=30)	Estimate* (95% CI)	P-value*
Primary endpoint: IgG4/IgE ratio increase from baseline ≥ 25% for at least 2 allergens				
Overall	42/60 (70%)		0.70 (0.59, 1.00)	--
By treatment	21/30 (70%)	21/30 (70%)	1.00 (0.29, 3.49)	1.00
Secondary endpoints: IgG4/IgE ratio increase from baseline ≥ 25% for at least...				
...3 allergens	35/46 (76%)		0.76 (0.64, 1.00)	--
	20/25 (80%)	15/21 (71%)	1.58 (0.33, 7.95)	0.73
...4 allergens	18/23 (78%)		0.78 (0.60, 1.00)	--
	9/10 (90%)	9/13 (69%)	3.78 (0.29, 218.16)	0.34
...5 allergens	5/7 (71%)		0.71 (0.34, 1.00)	--
	4/4 (100%)	1/3 (33%)	∞ (0.28, ∞)	0.14

* The probability of success and 95% CI was reported. To determine whether the probability of success differed by treatment arm, Fisher's exact test was used to calculate the odds ratio and 95% CI.

- 70% of all participants showed a change in IgG4/IgE ratio in at least 2 allergens (Table 1)
- No differences in primary endpoint success, focused on the intention-to-treat (ITT) population, by treatment group, by ability to reach maintenance dose, or by number of allergens in the mOIT mix
- No differences in the percentage of doses associated with adverse events between the two treatment groups (19% vs. 17%, P = 0.69)

Figure 2: Change in Allergen-Specific IgG4/IgE Ratio by Maximum Per-Allergen Dose



- Scatter plots color coded by treatment group
- Linear regression line (blue) and 95% confidence band shown
- The solid black line at 0.25 represents the threshold of a 25% increase in allergen-specific IgG4/IgE ratio from screening to week 18
- Spearman's rank correlation was calculated to determine whether there was an association between change in IgG4/IgE ratio and max per-allergen dose
- No associations among any of the allergens

Discussion

- Several publications have explored lower maintenance dosing with single foods and showed evidence of immunological changes[5]
- Our study is the first mOIT trial exploring different low maintenance doses over a short duration of time
- Our data suggests that biomarker changes are induced early and at a lower maintenance dose than previously known
- These findings are important when considering improvements to compliance in long-term dosing of OIT
- Limitations include the lack of comparison to mOIT alone (without omalizumab), small sample size (but comparable to other OIT studies), and free IgE was not measured (ideal given omalizumab can elevate IgE values)

Conclusions

- Our data suggests that biomarker changes are induced early, even at a 300 mg dose for multiple allergens
- Lower allergen maintenance doses will likely be better tolerated and preferred by patients, thus improving adherence
- Larger phase 2 trials are needed to confirm these findings

References

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