

Anaphylaxis during Peanut Oral Immunotherapy: Looking beyond dose escalation

To the Editor

Peanut Oral Immunotherapy (POIT) is shown to be a safe and efficacious therapeutic option for peanut-allergic patients corroborated by multiple published studies.^{1–3} Limited data exist on anaphylaxis risk and long-term therapy.^{4–6} The aim of our study was to investigate anaphylaxis episodes during dose escalation and maintenance, and identify potential risk factors and avoidable triggers for these.

We examined anaphylaxis episodes in a cohort of 75 subjects who completed real-world POIT in an academic center. Anaphylaxis was defined based on the NIAID criteria.⁷ Records of patients who received POIT over a period of 4 years (2017–2021) were reviewed. The study was approved by the local Institutional Review Board (IRB).

A total of 75 subjects reached a maintenance dose of 300mg of peanut protein (pp) following monthly dose escalation from a starting dose of 2mgpp, as previously described.⁸ Demographics and characteristics of our cohort are shown in Tables 1 and 2. Allergic comorbidities (allergic rhinitis, asthma, atopic dermatitis) were controlled prior to starting POIT. All families were educated on how external factors affect dose threshold and written instructions were provided for avoiding exercise and hot showers within 2 h after dose, not dosing on an empty stomach and stopping or reducing dosing during viral illness after discussion with the treating physician. After reaching the maintenance dose, subjects had the option to maintain or increase it. Multivariable logistic regression was used to examine if any factors were still associated with anaphylaxis after adjusting for those found to be significantly different between patients with and without anaphylaxis. To avoid collinearity, correlated variables ($r > \pm 0.5$) were not included in the same model. The logistic regression estimated odds ratios (ORs) with 95% CIs for anaphylaxis. $p < .05$ was considered statistically significant.

A total of 15 subjects (20%) opted to increase their maintenance dose higher than 300mg (range 450–900mg). Three subjects decided to stay at a lower maintenance dose (150mg) due to experiencing anaphylaxis ($n = 2$) or personal preference ($n = 1$). After completing dose escalation, (approximately 9 months), the maintenance period started (month 1 maintenance). Median maintenance follow-up time for subjects was 25 months (range: 8–42 months), at the time of writing. A total of four subjects discontinued therapy due to eosinophilic esophagitis (EoE)-like symptoms ($n = 1$), taste aversion ($n = 2$), and anaphylaxis during dose escalation ($n = 1$). One

additional subject was lost to follow-up (moved out of state). For the subject with eosinophilic esophagitis-like symptoms, a biopsy was performed after discontinuing therapy, which was negative for a diagnosis of EoE, but the subject decided to stay off therapy.

We identified 13 subjects (17%) who experienced a total of 15 episodes of anaphylaxis during POIT (Table 3). Two subjects (2/13) experienced two episodes of anaphylaxis each. Of the 15 episodes, eight (53%) happened during the dose escalation period and 7/15 (47%) after maintenance was reached. The doses associated with anaphylaxis during dose escalation were: 300mg (1/15), 150mg (3/15), 100mg (1/15), 50mg (2/15), and 5mgpp (1/15). We recorded seven episodes of anaphylaxis during long-term maintenance. Specifically, the 300-mg dose was associated with five episodes of anaphylaxis (5/15), the 450mg with one episode (1/15), and the 600mg with one episode (1/15). The longest follow-up time during which anaphylaxis was observed was 16 months (Figure 1). No episodes occurred after this period.

We noted a statistically significant difference between median levels of baseline peanut-specific IgE and Arah 2; levels were higher in the anaphylaxis group compared with the non-anaphylaxis group (median peanut-specific IgE of 100 versus 14.9 kUA/L, $p = .001$ and median peanut Arah 2 of 65.3 versus 13 kUA/L, $p = .007$, respectively). A statistically significant difference was also noted in median age between the two groups, with older median age (11 vs. 7 years) being associated with anaphylaxis ($p = .001$). We did not find an association with higher (or lower) maintenance dose and anaphylaxis (Table 1).

Since peanut-specific IgE and Arah 2 were highly correlated ($r = .91$, $p < .001$), separate models were created for each (Table 2). The odds of anaphylaxis increased as patient age increased (1 year increase in age: adj. OR 1.54, 95% CI: 1.14, 2.07) when adjusting for peanut-specific IgE. As peanut-specific IgE increased, so did the odds of anaphylaxis (1 kUA/L increase: adj OR 1.04, 95% CI: 1.01, 1.08). The odds of anaphylaxis increased as patient age increased (1 year increase in age: adj. OR 1.45, 95% CI: 1.14, 1.85) when adjusting for Arah 2. As Arah 2 increased, so did the odds of anaphylaxis (1 kUA/L increase: adj OR 1.03, 95% CI: 1.01, 1.05).

In terms of clinical presentation, cutaneous symptoms, such as urticaria, angioedema and/or erythema (11/15, 73%) and respiratory symptoms such as wheezing, coughing, and/or dyspnea (11/15, 73%) were noted in most episodes. Only in 2/15 (13%) episodes,

TABLE 1 Demographics and characteristics of patients

	No anaphylaxis (N = 62)		Anaphylaxis (N = 13)		p-Value
	N	Median (Min, Max)	N	Median (Min, Max)	
Age (years)	61	7 (3.0–15.0)	13	11 (6.0,17.0)	.001
Pre-OIT peanut sIgE (kUA/L)	62	14.9 (0.7–100)	12	100 (37.0–100.0)	.001
Pre-OIT peanut Ara h 2 (kUA/L)	62	13 (0.1–100)	12	65.3 (8.3–100)	.007
	N	N (%)	N	N (%)	
Maintenance dose					
300-mg peanut protein or less	62	47 (75.8)	13	12 (92.3)	.276
>300-mg peanut protein		15 (24.2)		1 (7.7)	
Gender					
Female	62	25 (40.3)	13	6 (46.2)	.762
Male		37 (59.7)		7 (53.8)	
Race & Ethnicity					
Asian non-Hispanic	54	8 (14.8)	13	5 (38.5)	.201
White non-Hispanic		38 (70.4)		7 (53.8)	
Hispanic		8 (14.8)		1 (7.7)	
Atopic comorbidities					
Other food allergy	61	48 (78.7)	13	9 (69.2)	.480
Asthma	62	23 (37.1)	13	8 (61.5)	.128
Allergic rhinitis	62	50 (80.6)	13	10 (76.9)	.716
Atopic dermatitis	62	50 (80.6)	13	11 (84.6)	1.000

Values of $p < .05$ were considered statistically significant

TABLE 2 Multivariable logistic regression for anaphylaxis

	Adj. OR	95% Confidence interval		p-Value
Age (years)	1.54	1.14	2.07	.004
Peanut-specific IgE (kUA/L)	1.04	1.01	1.08	.003
Age (years)	1.45	1.14	1.85	.003
Ara h 2 (kUA/L)	1.03	1.01	1.05	.007

gastrointestinal symptoms (nausea, vomiting, and/or abdominal pain) were seen during the anaphylaxis event. No episodes of hypotension or hypoxia were recorded. All anaphylaxis episodes were classified as Grade 3, according to the "World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System".⁹ Epinephrine was used in 11/15 (73%) episodes. One dose was used in 9/15 (60%) events and two doses in 2/15 (13%). Antihistamines were administered in 9/15 (60%) subjects, followed by albuterol in 6/15 (40%) and oral steroids in 3/15 (20%). Overnight hospitalization was required for one subject. This subject was one of the two who received two epinephrine doses to treat the anaphylaxis episode, had asthma as a comorbidity and experienced abdominal pain, generalized pruritus, wheezing and vomiting during the episode (see Table 3).

Identified triggers for anaphylaxis included: exercise (3/15, 20%), viral illness (2/15, 13%), dose taken on an empty stomach

(2/15, 13%), hot shower shortly after dose (1/15, 7%), and accidental peanut exposure (1/15, 7%). In 6/15 episodes (40%) no trigger was identified.

A few published studies have reported on long-term safety of POIT. A real-life study of 111 subjects from Israel who reached a maintenance dose of 3000-mg peanut protein, reported that only 2/111 (1.8%) required epinephrine over the long-term follow-up, which ranged from 6 to 75 months (median:18 months).⁴ In a recent US survey study of 55 subjects who previously completed OIT and reached maintenance, fourteen (25%) reported at least 1 reaction within 2 h of peanut ingestion over a median of 2.9 years follow-up period.⁵ Cutaneous symptoms were most common (8/55). Subjects also reported laryngeal/pulmonary (6/55), gastrointestinal (7 /55), and oropharyngeal (5/55) symptoms. Three subjects (5%) had systemic reactions requiring epinephrine.⁵ A pooled analysis of three controlled, phase 3 and two open-label extension multi-center trials of children receiving PTAH (Peanut Arachis hypogaea Allergen Powder-dnfp) for up to 2 years of treatment showed that 829 subjects (out of a total of 944) experienced treatment-related adverse events classified as mild ($n = 497$; 52.6%), moderate ($n = 332$; 35.2%), or severe ($n = 24$; 2.5%).⁶ When adjusted for exposure, these events occurred at a rate 58.7 events/subject - year of exposure during up dosing, but decreased to 14.2, during 300-mg maintenance.⁶ We also noted a decrease in anaphylaxis episodes with longer maintenance time, although this was not systematically examined. A recent trial of peanut OIT in young children between 1 and 3 years

TABLE 3 Subjects experiencing anaphylaxis during therapy (dose escalation and long-term maintenance).

Subject	Age	Gender	Anaphylaxis during up dosing				Anaphylaxis during maintenance				Time on maintenance when episode occurred (total time on maintenance at time of writing = total follow-up time)	AEs during up dosing
			Dose	Symptoms	Trigger	Treatment	Dose	Symptoms	Trigger	Treatment		
1	8	M	-	-	-	-	300	W	Accidental exposure to peanut candy	Albuterol Steroids	2 months (42 months)	Yes
2	8	F	50	V	None identified	IM epinephrine	-	-	-	-	- (discontinued)	Yes
3	9	M	100	OI, AP, H, V	Viral illness	IM epinephrine (2 doses)	600	Tongue and eye angioedema, DIB	Exercise	Epinephrine Benadryl	9 months (37 months)	Yes
4	13	M	-	-	-	-	300	E, AP, V	Exercise	Epinephrine	6 months (26 months)	No
5	6	F	150	W, H	Exercise	Albuterol	300	C, H, A, P	Not identified	Albuterol Benadryl	16 months (30 months)	Yes
6	11	M	150	H, DIB	Hot shower	Albuterol Benadryl	-	-	-	-	- (21 months)	Yes
7	12	M	50	A, H	Viral illness	IM Epinephrine Benadryl Steroids	-	-	-	-	- (18 months)	Yes
8	17	F	150	H, A, SOB, P	None identified	IM Epinephrine Benadryl	-	-	-	-	- (discontinued)	Yes
9	8	M	-	-	-	-	300	C, H	None identified	Albuterol Benadryl Zyrtec	2 months (18 months)	Yes
10	7	M	300	C, E, T	None identified	IM Epinephrine Benadryl Steroids	-	-	-	-	- (15 months)	Yes
11	11	M	-	-	-	-	300	AP, W, V, P	Dosing on empty stomach	IM Epinephrine (2 doses)	5 months (19 months)	Yes
12	10	M	-	-	-	-	450	SOB, T	None identified	IM Epinephrine Benadryl Steroids	4 months (19 months)	Yes
13	13	F	5	C, W	Dosing on empty stomach	Albuterol Benadryl	-	-	-	-	- (15 months)	Yes

Note: Age, gender, dose at which anaphylaxis occurred, trigger of episode, treatment, and AEs during up dosing are all listed for each subject.

Abbreviations: A, angioedema; AEs, Adverse events; AP, abdominal pain; C, cough; DIB, difficulty in breathing; E, erythema; H, hives; OI, oral itching; P, pruritus; SOB, shortness of breath; T, throat swelling/discomfort; V, vomiting; W, wheeze.

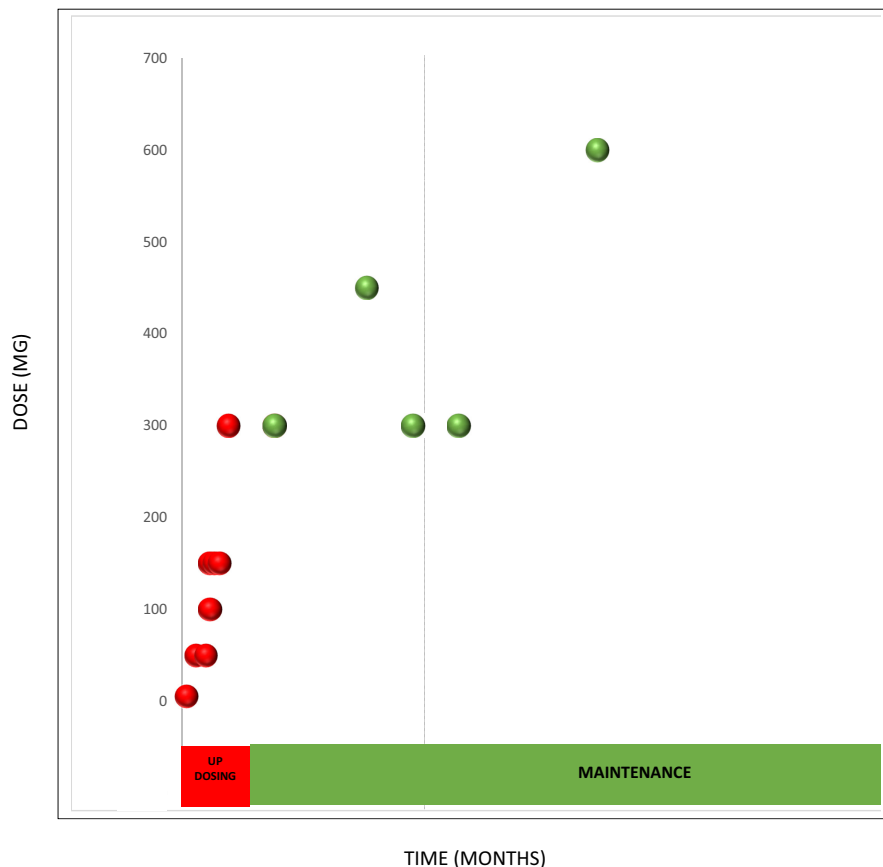


FIGURE 1 Anaphylaxis episodes during up dosing and maintenance—time and maintenance dose.

of age (median:39.3 months) reported younger age and lower baseline peanut-specific IgE as important factors predicting disease remission, following a long-term observation period of 160 weeks.¹⁰ Our population included older children (3–17 years old), but we also found a significant association between younger age, lower peanut-specific IgE, and peanut-specific Ara h 2 with better outcome (less likely to experience anaphylaxis during dose escalation and maintenance).

In summary, anaphylaxis episodes during POIT can occur both during dose escalation and maintenance phases. In our real-world cohort, we observed anaphylaxis in 17% of subjects with 53% of episodes occurring during the dose escalation period and 47% after maintenance was reached. Anaphylaxis was often the result of previously reported avoidable triggers and patients must be educated on these in an effort to prevent adverse outcomes. Education should include physician input on avoidable triggers as well as epinephrine refresher training for both caregivers and subjects of appropriate age. Additionally, age and levels of baseline peanut-specific IgE and Ara h 2 were significantly different between the group experiencing anaphylaxis compared with the non-anaphylaxis group, with older subjects, and those with higher baseline levels, being more likely to experience anaphylaxis. Multivariable analysis confirmed that the odds of anaphylaxis increased as patient age increased when adjusting for peanut-specific IgE and Ara h 2. As peanut IgE and Ara h 2 increased, so did the odds of anaphylaxis.

Limitations of our work include a relatively small sample size, data from a single center, and retrospective review of anaphylaxis episodes. Future studies on long-term therapy and in larger population cohorts will be required to further investigate these findings.

CONFLICT OF INTEREST

A Blackman reports no conflicts of interest. K Stagers reports no conflicts of interest. A Anagnostou serves as PI for Aimmune Therapeutics Peanut Oral Immunotherapy phase 3 trials and receives Institutional funding, and has served as Advisory Board member for DBV Technologies.

PEER REVIEW

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