The BTK inhibitor acalabrutinib prevents clinical reactivity during oral peanut challenge in allergic adults

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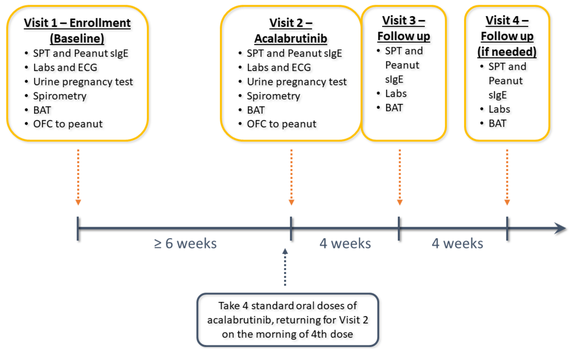
Background

Patients with mast cell disorders are at higher risk for severe anaphylaxis to allergens including medications, foods, and stinging insect venoms. However, there are no known preventative treatments for IgE-mediated reactions including anaphylaxis. Bruton's tyrosine kinase (BTK) is an enzyme thought to be essential for FcεRI signaling in human mast cells and basophils, and thus represents an attractive target for inhibition of anaphylaxis to any allergen. Oral BTK inhibitors are now FDA-approved for treatment of B cell malignancies and are generally well-tolerated. We have previously shown in humanized mice that just two oral doses of the second-generation BTK inhibitor acalabrutinib can completely prevent moderate passive IgE-mediated anaphylaxis and even significantly prevent death during severe anaphylaxis (1). Additionally, in an open-label trial, we have demonstrated that just two standard doses of the first-generation BTK inhibitor ibrutinib suppress food skin prick test area (SPT) by an average of 77% in peanut and tree nut allergic adults (with 44% of all skin tests becoming negative on treatment), and completely abolish IgE-mediated basophil activation (BAT) *ex vivo* (2,3) without any observed toxicity during dosing up to 7 days. We therefore hypothesized that BTK inhibitors can prevent clinical reactivity to foods in food-allergic adults.

Methods

In an open label, proof of concept clinical trial, healthy adults with a history of IgE-mediated peanut allergy were enrolled under the approval of an FDA Investigational New Drug application and the JHU IRB (JHU IRB00223615; NCT05038904). Inclusion criteria included a positive skin test and/or peanut- specific IgE (sIgE) at baseline and an objective clinical reaction to 1,044 mg or less of peanut protein at baseline oral food challenge (OFC). Exclusion criteria included history of bleeding disorder or use of blood thinners; cardiac arrhythmia; cardiovascular disease, use of immunomodulatory agents, including systemic corticosteroids; active infection or latent hepatitis; use of strong CYP3A4 inducers or inhibitors; and pregnancy or nursing. Subjects stopped all antihistamines at least 1 week prior to study visits.

Figure 1: Study design



Subjects underwent baseline SPT using Lincoln Diagnostics Multitest devices and BAT to peanut extract dilutions (Greer; Figure 1). BAT was performed by treating whole blood samples with anti-IgE mAb or peanut extract; percent of basophil activation was determined by CD63 upregulation as assessed by flow cytometry. All subjects underwent a baseline placebo-controlled, single-blinded, graded OFC to peanut to establish their baseline level of clinical reactivity. Symptoms were assessed during OFC using a modified PRACTALL scale (4). At the first sign of objective clinical reaction, the OFC was stopped, and the reaction was treated accordingly. After a minimum 6-week recovery period, subjects then took 4 standard oral doses of 100 mg acalabrutinib every 12 hours and returned on the morning of their 4th dose for repeat OFC, SPT, and BAT. Peanut- and peanut component-sIgEs were measured at each visit by the Johns Hopkins University Dermatology, Allergy and Clinical Immunology (DACI) Reference Laboratory. Subjects underwent laboratory monitoring (complete blood counts with differential, comprehensive metabolic panel) and electrocardiogram (ECG) at all visits to monitor for toxicity.

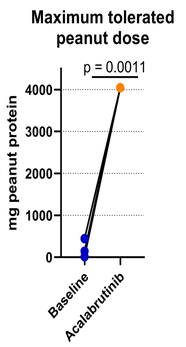
Results

Table 1: Subject baseline characteristics (n = 3)

	Subject 001	Subject 002	Subject 005
Age / Gender	36 / M	34 / M	32 / F
Peanut allergy history (most recent reaction)	Reaction at age 34 with vomiting, generalized urticaria, "feeling of dread", flushing, and rhinorrhea; required epinephrine	Reaction at age 21 with tongue/throat swelling, generalized urticaria, and dizziness; required epinephrine	Reaction at age 30 with generalized urticaria, throat swelling, and abdominal pain
Baseline peanut sIgE	68.5 kUA/L	< 0.1 kUA/L	335 kUA/L
Baseline peanut SPT (wheal)	11 x 16 mm	5 x 7 mm	13 x 25 mm
Atopic comorbidities	Allergic rhinitis, asthma	None	Allergic rhinitis, asthma, other food allergy (soy, egg)
Total IgE	329 kU/L	50.5 kU/L	802 kU/L
Other medical history	GERD, prior appendectomy	Anxiety, multiple concussions	GERD

Figure 2 / Table 2: Acalabrutinib pretreatment prevents clinical reactivity to peanut in peanut allergic adults.

Subjects' maximum tolerated peanut dose (left panel) is displayed at baseline (blue circles) and while taking acalabrutinib (orange circles). All subjects reacted to 1,044 mg or less of peanut protein at baseline, and all subjects subsequently tolerated the maximum dose of 4,044 mg while taking acalabrutinib. Subject 005 had mild symptoms after the last OFC dose on acalabrutinib that were not severe enough to meet criteria for a positive challenge and did not require treatment.



		Subject 001	Subject 002	Subject 005
Baseline OFC	**Tolerated dose of peanut**	**444 mg**	**14 mg**	**144 mg**
	Subjective symptoms	Generalized pruritus, throat tightness/clearing, severe nausea, heart racing	Dyspnea, dizziness	Generalized pruritus, stomach cramping
	Objective symptoms	Diffuse flushing, conjunctival injection	Periorbital angioedema, facial and truncal urticaria, diffuse erythema	Vomiting, wheezing, diffuse urticaria, conjunctival injection
	Medications given	IM epinephrine x 1, 20 mg cetirizine	IM epinephrine x 1, 20 mg cetirizine, 2 puffs albuterol HFA	IM epinephrine x 2, 20 mg cetirizine, 60 mg prednisone, 8 puffs albuterol HFA*
OFC on acalabrutinib	**Tolerated dose of peanut**	**4,044 mg**	**4,044 mg**	**4,044 mg**
	Subjective symptoms	None	None	Scalp itching
	Objective symptoms	None	None	Flushing over forehead, 1 hive on arm
	Medications given	None	None	None

** After her baseline OFC, Subject 005 was transferred to the emergency department for further management, where she received 25 mg diphenhydramine, 20 mg famotidine, and nebulized albuterol. She was observed for several hours and discharged home.*

Figure 3: Acalabrutinib reduces peanut SPT size and abolishes IgE-mediated basophil activation in peanut allergic adults.

Acalabrutinib treatment (orange circles) reduced SPT size to peanut extract in all subjects compared to baseline (blue circles), but did not affect histamine or saline controls (3A). Additionally, acalabrutinib (orange symbols) completely prevented ex vivo basophil activation to peanut extract and anti-IgE mAb compared to baseline (blue symbols), but did not affect activation responses to fMLP as expected (3B).

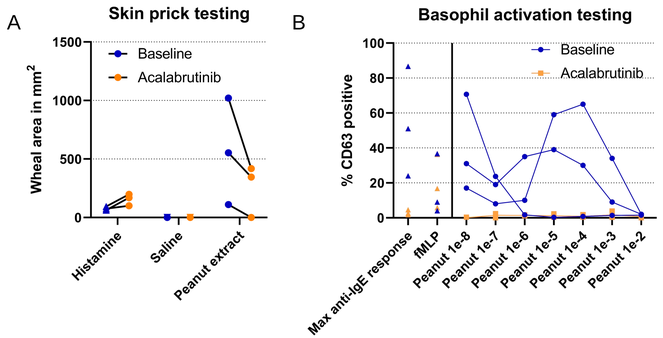


Figure 4: Acalabrutinib does not affect peanut- or component-sIgE.

Acalabrutinib did not alter subjects' levels of total IgE (4A), peanut sIgE 4B), peanut component sIgEs (4B), or quantitative immunoglobulins (data not shown) compared to baseline.

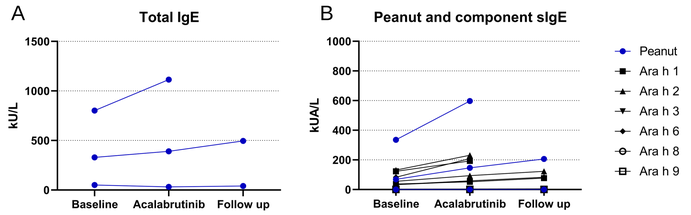


Table 3: Adverse events summary

Four doses of acalabrutinib treatment were generally well tolerated. None of the subjects experienced any adverse symptoms during treatment with acalabrutinib. Subjects 002 and 005 experienced medical events that were judged to be unrelated to acalabrutinib or study procedures (blue text). Subjects 002 and 005 displayed changes in laboratory values (red text), of which only transient neutropenia in Subject 002 was judged to be possibly related to acalabrutinib. No ECG changes were observed after acalabrutinib therapy.

	Subject 001	Subject 002	Subject 005
Symptoms	None	None	None
Events	None	• Fall while walking dog, resulting in left knee and wrist injuries prior to taking acalabrutinib • Car accident on his way to Visit 3 • Fall while snowboarding, resulting in left shoulder injury after Visit 3	• Contracted COVID-19 prior to taking acalabrutinib

Laboratory abnormalities — None

	Baseline	Acala-brutinib	Follow-up
Absolute neutrophil count (K/ mm³)	2.65	1.22	2.20
Alkaline phosphatase (U/L)	97	94	136
AST (U/L)	n/a*	39	42
ALT (U/L)	40	33	90

	Baseline	Acala-brutinib	Follow-up
White blood cell count (K/ mm³)	10.95	11.13	(future)
Hemoglobin (g/dL)	12.2	11.9	(future)

** Sample was hemolyzed*

Summary and Conclusions

BTK inhibitors are promising novel therapies that can prevent IgE-mediated anaphylaxis in humans with rapid onset and minimal toxicity. This clinical trial is still enrolling and will be informative of BTK inhibitors' potential for use as episodic short-term therapies for situations that carry a high risk for anaphylaxis in patients with mastocytosis, including allergen immunotherapy and desensitization to foods or drugs.

References

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