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The Safety of Peanut Oral Immunotherapy in Peanut-Allergic Subjects in a Single-Center Trial

G.P. Yu B. Weldon S. Neale-May K.C. Nadeau

Division of Immunology and Allergy, Stanford University, Stanford, Calif., USA

Key Words
Food allergy · Oral immunotherapy · Peanut allergy

Abstract
Background: Peanut allergy is the leading cause of food-related anaphylaxis, and accidental exposures are common. Oral immunotherapy (OIT) has been posited as a potential treatment. ***Methods:*** Patients aged 3–65 years with peanut-specific IgE ≥7 kU/l and/or a positive skin prick test with a history of an allergic reaction to peanut were recruited to undergo an OIT protocol. All adverse reactions were recorded by research staff or patients in real time. ***Results:*** Twenty-four patients received 6,662 doses. Symptoms were mostly mild (84%), and only 3 severe gastrointestinal reactions required the administration of epinephrine. Abdominal pain was the most common reaction, followed by oropharyngeal and lip pruritus. Respiratory symptoms were rare. ***Conclusions:*** In this trial of OIT in adults and children, most reactions were mild.

Peanut allergy, which affects an estimated 0.6% of US adults and more than 1% of children [1], is the leading cause of food-related fatal anaphylaxis in the USA [2]. The standard of care is strict avoidance and readily available injectable epinephrine in case of accidental exposure, which is an unfortunately common occurrence with an estimated incidence of 0.33 exposures per patient year [2]. There is significant resource utilization in the form of ambulatory care and ER visits due to food-related adverse events, estimated by Clark et al. [3] to be 203,000 ER visits per year from 2001 to 2005, and by Branum et al. [4] to have averaged 317,000 ambulatory care and ER visits per year between 2004 and 2006 for food allergy-related diagnoses.

Oral immunotherapy (OIT) has been posited as a possible method of desensitization, with preliminary trials showing efficacy [4–6]. However, given that OIT relies on allergen ingestion on a daily basis at home, there have been concerns about safety. Jones et al. [5] reported reactions following 3.7% of home doses, 2 requiring epinephrine administration. Blumchen et al. [7] reported that 2.6% of buildup and home doses resulted in an objective adverse reaction. Most recently, in a randomized, placebo-controlled trial published by Varshney et al. [6], 47% of patients had clinically relevant adverse events during initial rush dosing, with 2 requiring epinephrine. Importantly, during buildup and home doses none of the peanut patients required epinephrine. To add to the safety database and to demonstrate for the first time safety in adults, we present preliminary safety data from an ongoing phase 1 single-center trial of peanut OIT in adults and children.

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Correspondence to: Dr. Kari C. Nadeau
Division of Immunology and Allergy, Stanford University
269 Campus Drive, CCSR Building, Room 2115
Stanford, CA 94305-5164 (USA)
Tel. +1 650 723 5227, E-Mail knadeau@stanford.edu

Methods

Inclusion criteria required patients to be 3–65 years of age with a peanut-specific IgE ≥7 kU/l and/or a positive peanut skin prick test and a history of an allergic reaction to peanut (table 1). Many of the subjects had had positive oral food challenges to peanut before entering the study. Patients underwent a modified rush day identical to a previously published protocol [4] where increasing amounts of peanut protein were ingested until the maximum dose (cumulative 12 mg peanut protein) was reached or a reaction occurred. The following day, they were brought back to repeat the highest tolerated dose. If there was no reaction within 1 h, they were sent home with daily doses. Patients were instructed to keep a daily diary of doses and any potential reactions with severity determined by subjective assessment (mild, moderate or severe). Patients returned to the Clinical Translational Research Unit (CTRU) every 2 weeks where daily dosing diaries were reviewed and dose escalations occurred to a maximum maintenance dosage of 4,000 mg of peanut protein. Any reactions in the CTRU were graded based on Bock's criteria [7]. Research staff kept in close contact with patients and families to investigate any significant adverse events, and subjects had 24-hour contact information for all study personnel in case of a significant reaction or dosing question.

Results

Twenty-four subjects received 6,662 doses. Twenty-two of these reported symptoms during either home doses or doses in the CTRU. Overall, there were 1,023 symptoms recorded, 84% of which were mild and either self-resolved or resolved with antihistamines, 13% were moderate and 3% were severe. Of the severe reactions, three, in separate patients, were treated with epinephrine. One was given in the CTRU following a dose escalation due to severe abdominal pain not responsive to multiple doses of antihistamines. Two were given at home following previously tolerated doses, one with severe abdominal pain following an episode of diarrhea and the second following multiple episodes of emesis with moderate throat pain unresponsive to antihistamines. For all 3 subjects, a single injection of epinephrine improved the clinical symptoms within a few minutes. None of these reactions resulted in discontinuation of therapy. All home reactions requiring epinephrine were associated with either exercise or bathing following the dose of peanut.

Table 1. Baseline demographic information

Patient letter	Age years	Gender	Peanut-specific IgE, kU_A/l	Skin prick wheal average diameter mm	Clinical history of peanut allergy
A	26	M	20.9	17	Abdominal pain, vomiting, diarrhea, skin and lip pruritus
B	8	M	>100	11	Angioedema, urticaria
C	7	M	>100	9	Abdominal pain, choking
D	6	F	442	9	Facial angioedema
E	5	M	435	30	Urticaria, periorbital swelling, vomiting
F	5	M	342	7	Angioedema, cough
G	11	F	>100	25	Urticaria
H	10	F	12.6	8.5	Drooling, vomiting
I	6	F	249	19.5	Angioedema, coughing, wheezing
J	7	F	>100	21.5	Abdominal pain, vomiting, flushing
K	7	M	153	11	Oral pruritus
L	7	M	54.9	25	Vomiting
M	11	M	>100	2	Urticaria, oropharyngeal swelling, respiratory distress
N	45	M	20.6	10	Abdominal pain
O	11	M	81.9	9	Angioedema, urticaria
P	9	F	48.7	20	Perioral redness, abdominal pain
Q	6	F	59.4	8	Urticaria
R	7	F	32.7	14	Facial angioedema, skin pruritus
S	5	F	7.86	15.5	Urticaria
T	13	M	53.1	8.5	Vomiting, respiratory distress, urticaria
U	8	M	69.7	16.5	Facial angioedema, urticaria, throat pruritus
V	10	M	62.4	17	Facial angioedema, respiratory distress
W	5	F	16.6	17.5	Wheezing, respiratory distress
X	13	M	0.64	9	Allergic conjunctivitis

Any patients who experienced a moderate to severe reaction had their next dose decreased to a dose that was previously tolerated without any adverse symptoms. These patients were also asked to premedicate with H_1 +/- H_2 antihistamines. These two strategies worked well to prevent and attenuate adverse reactions. However, 1 patient (subject F) while on 12 mg of peanut protein had persistent abdominal pain and cough. The parents were not interested in premedicating or treating with antihistamines and the patient dropped out of the study. Of all the symptoms in all subjects, abdominal pain was the most common (34%), followed by oropharyngeal pruritus (25%) and lip pruritus (9%) (fig. 1). Eleven percent of total symptoms occurred in the CTRU at Stanford and 89% occurred at home. On average 13.6% of home doses per patient (range 0–74%) resulted in allergic reactions.

Although not statistically significant due to a small sample size, there seemed to be an increased percentage of dose administrations resulting in reactions around the 25- to 50-mg dose levels (fig. 2). These reactions were generally mild, resolving spontaneously or with antihistamines, although some delayed dose advancement at the next clinic visit. There were no differences in reaction severity or frequency between the adult (n = 2) and pediatric (n = 22) patients, although again this was not statistically significant because of the small sample size.

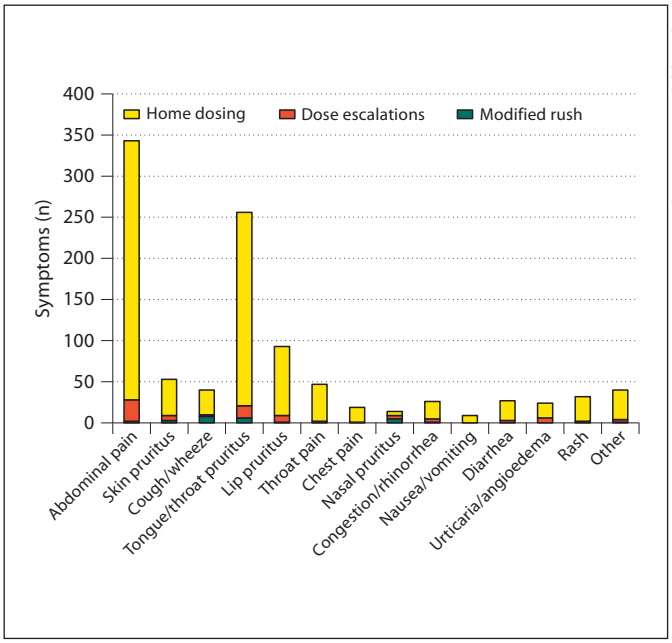

Fig. 1. The total number of symptoms is depicted by the type of symptom and in what situation the reaction occurred (during the modified rush day, a dose escalation appointment or at home).

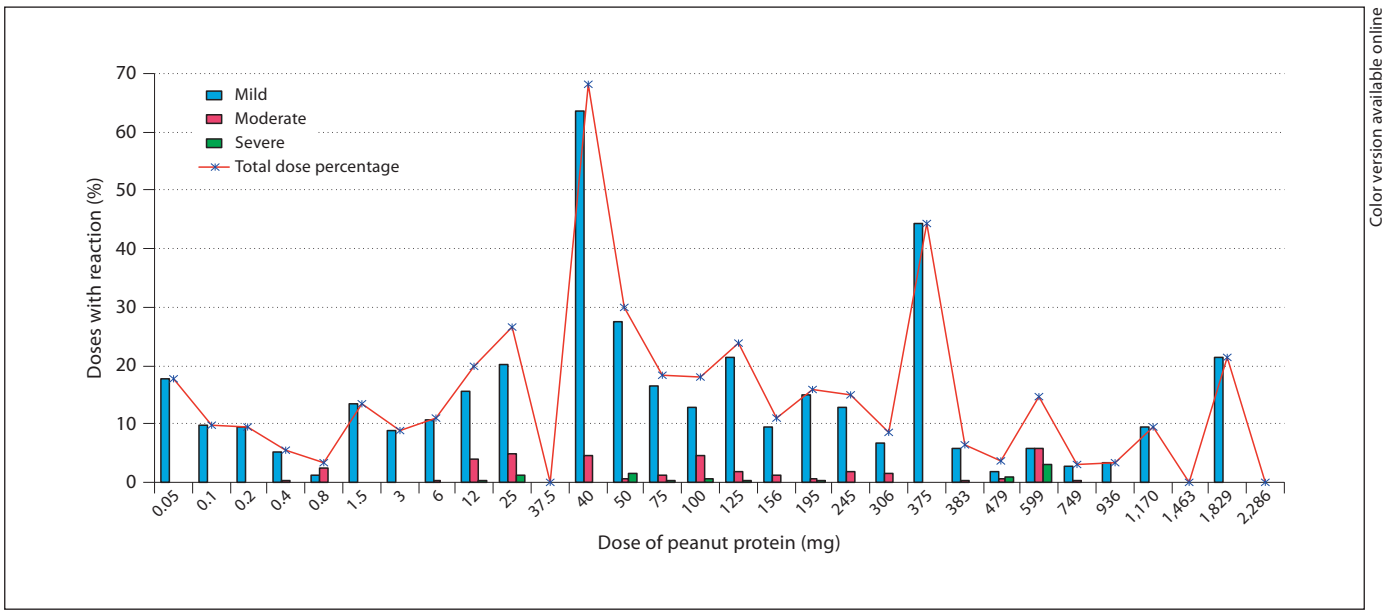

Fig. 2. The above graph demonstrates the percentage of doses at each dose level that resulted in any reaction (line). Reactions were categorized by the patient (for home doses) or practitioner (for doses in the CTRU) as mild, moderate, or severe.

Discussion

The safety of OIT for peanut allergic patients has long been a concern in the design and implementation of trial protocols [8–12]. Since OIT necessitates ingesting the offending food, and ingestion of peanut allergen is responsible for more anaphylactic deaths than any other food allergen, it is easy to understand the trepidation of doctors and patients. However, peanut allergy is also a disease without an available modifying treatment and we live in a society where accidental exposures are almost unavoidable.

Several well-conducted pilot studies have indicated that although respiratory reactions to carefully administered peanut OIT occur, they may not be frequent [4–6, 13] and our data supports the hypothesis that peanut OIT can be done safely. These data must be viewed with scrutiny, however, given the small sample sizes. Key components of safely administering an OIT regimen include experienced study personnel, extensive patient education, adherent patients and families, and ready access to lifesaving therapies at the study site and at home.

As has recently been published, OIT is not yet ready to be considered the standard of care, and should only be conducted within the rigors of an IRB-approved and monitored research study [8, 12]. Several aspects of OIT need to be understood prior to routine implementation. More research is needed to further delineate how to individualize treatment, determine which patients must be treated with the most caution, which can move through the dosing ladder with greater speed and how to best prevent reactions. Certain dosing levels may be more likely to cause reactions or may function as 'threshold' doses, a dose level at which an individual subject has more reactions. Escalations may need to be slowed around these dose levels and may be able to be advanced more quickly once higher levels are reached. The optimal goal dose for OIT should be investigated. Furthermore, more biochemical data is needed to help practitioners understand which patients will only become desensitized, thereby necessitating ongoing daily dosing, and which will become tolerant to peanuts, and how to know when an individual has crossed from the former into the latter category.

There are several ongoing studies looking at the safety and efficacy of peanut OIT in mostly pediatric populations. Our study is ongoing in both adults and children, and further phase 2 and 3 studies are needed to obtain optimal methods for best clinical practices and doses for peanut OIT.

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