

Exploiting Nut Cross Reactivity to Facilitate Real World Treatment of Tree Nut Allergy

Richard L. Wasserman MDPHd , Hugh H. Windom MD ,
Daria Lie PA-C , Deanna M. Pence RRT , Jean Ly MD

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1 Exploiting Nut Cross Reactivity to Facilitate Real World Treatment of Tree Nut Allergy

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3 Richard L. Wasserman, MD, PhD^{1,2}, Hugh H. Windom, MD³, Daria Lie, PA-C¹, Deanna M. Pence, RRT¹,

4 Jean Ly, MD³

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6 1. Allergy Partners of North Texas, Dallas, Texas

7 2. Medical City Children's Hospital, Dallas, Texas

8 3. Windom Allergy Asthma and Sinus, Sarasota, Florida

9 Corresponding Author:

10 Richard L. Wasserman, MD, PhD

11 7777 Forest Lane, Suite B-332

12 Dallas, Texas 75230

13 Telephone: (972) 566-7788

14 Telefacsimile: (972) 566-8837

15 drichwasserman@gmail.com

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Keywords: oral immunotherapy, tree nut allergy, cashew allergy, pistachio allergy, walnut allergy, pecan allergy, tree nut cross-reactivity, oral food challenge, food allergy

Abbreviations/Acronyms:

IRB – institutional review board

OFC – oral food challenge

OIT – oral immunotherapy

sIgE – specific IgE

SPT – skin prick test

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Oral immunotherapy (OIT) for food allergy has become increasingly common among practicing allergists¹. Tree nut allergy accounts for ~33% of food-induced anaphylaxis fatalities and only 9% outgrow their allergy^{2,3}. Tree nut OIT has been successful^{4,5}, but is burdened by frequent sensitization, as assessed by positive specific IgE (sIgE) or skin prick tests (SPT) to multiple nuts, often without a prior exposure history. Although allergy to each nut could be confirmed or refuted by an oral food challenge (OFC) and OIT performed to each reactive nut, such an approach is not only onerous for patients but each challenge carries the risk of a serious reaction. While simultaneous treatment with multiple nuts has been successful⁴, each nut added to the treatment increases the complexity for patients and for treating allergists. Additionally, increasing the number of nuts treated increases the maintenance dose, further increasing the burden for patients. Cashew and pistachio nuts are known to be cross-reactive as are walnuts and pecans, and walnut OIT has been shown to partially or fully desensitize some patients to other nuts^{5,6,7}.

We performed a retrospective record review (approved by the North Texas IRB) of patients receiving tree nut OIT at two OIT centers. OIT was administered according to a previously reported protocol adapted to each nut⁸. After reaching their primary nut target dose (3-6 grams of nut protein at clinic A and 0.8-1 grams at clinic B, an average cashew has 0.28 grams of protein and an average walnut 0.6 grams), each patient who received OIT to only one member of a cross-reactive dyad and was subsequently challenged with the other nut is included. Open challenges to cross-reactive nuts were performed using methods adapted from published guidelines⁹ at least one month after the patients had reached the OIT nut target dose. The OFC challenge final dose was 3-6 grams of nut protein at clinic A and 1 gram at clinic B. Patients who were eating the cross-reactive nut at the initiation of OIT were excluded. Because this was a retrospective data collection, some of the data sets are incomplete, but all available data is included. Table 1 provides the demographics, reaction history and diagnostic testing to the nuts as well as the outcomes of cross-reactive nut challenges. Patients/parents of those who had never been exposed to the

nut were encouraged, but not required, to undergo OFC's as one of the many considerations in the shared-decision making process of considering OIT.³

Twenty of 36 (56%) of those for whom information is available had a history of reaction to the cross-reactive nut. All cashew-allergic patients tested positive to pistachio and all but one walnut-allergic patient was sensitive to pecan. The large majority of patients had never been exposed to the cross-reactive nut, having chosen avoidance due to awareness of allergy to the dominant nut. Pre-OIT OFC's to the cross-reactive nut were rarely performed, the hypothesis of this report being they are not necessary when electing OIT to the dominant nut. Ninety-four percent (83/88) of cashew treated patients passed a pistachio challenge including a patient who independently began 105-210 mg/day of pistachio protein one month before the 6000 mg challenge. One cashew treated patient who failed a 6000 mg pistachio protein challenge but subsequently tolerated smaller amounts of pistachio is included in the challenge failure group. Ninety-seven percent (30/31) of walnut treated patients passed pecan challenges. The median eliciting dose of the six challenge failures was 1000 mg of protein, with all but one significantly above the trace exposure level. Pre-challenge sIgE to pistachio and pecan were available for 81/87 and 31/32 patients respectively. For the cashew/pistachio and the walnut/pecan dyads, the likelihood of passing the OFC to the cross-reactive nut was significantly inversely correlated with the pre-treatment IgE of both the treatment nut and the cross-reactive nut (Table I). This observation may be partially explained by the possibility that some mildly sensitized patients were not truly allergic. The durations of escalation, maintenance, and total OIT exposure did not correlate with tolerating the cross-reactive nut. The outcomes for those treated with multi-food OIT did not differ significantly from those treated with a single nut.

These observations confirm and extend the walnut OIT results of Elizur, et al^{5,7}. The benefits of desensitizing to a single member of a cross-reactive nut dyad include decreasing the number of pre-OIT challenges, simplifying multi-nut OIT for both patients and providers by decreasing the number of actively treated nuts, increasing the number of nuts that can be desensitized during a single course of OIT and decreasing the risk of reaction to the cross-reactive nut by delaying challenges until after desensitization to the primary nut. Cashew and walnut were selected as the dominant nuts for OIT since it is rare for a patient allergic to pistachio or pecan to tolerate cashew or walnut, respectively, whereas the opposite is observed more often.¹⁰ Therefore, desensitization to pistachio or pecan should not be presumed to desensitize to cashew or walnut.

There are limitations to this report in addition to its retrospective nature. Not all data elements are available for each patient. The most significant limitation is that few patients underwent challenges to the cross-reactive nut before OIT. Therefore, the data presented may overstate the rate of cross-desensitization, but it is noteworthy that four of the six patients who reacted at the post-OIT cross reactive OFC were from the group that had never been exposed to the nut prior to OIT.

If the goal of OIT is not just to reduce the risk of a reaction, but to make the lives of patients and families more normal, each food that is suspected to pose a risk must be addressed. Exploiting the high degree of clinical cross-reactivity between cashew and pistachio nuts and between walnuts and pecans simplifies pre-OIT testing, reduces the complexity of multi-nut OIT, and decreases the risk of reaction to the untreated nut.

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Table 1

Characteristics of Cashew and Walnut Treated Patients and the Outcomes of Cross-Reactive Nut Challenges.

	Cashew OIT/Pass- ed Pistachio Challenge	Cashew OIT/Fail- ed Pistachio Challenge	Signifi- cance	Walnut OIT/ Passed Pecan Challenge	Walnut OIT/Fail- ed Pecan Challenge	Signific- ance
Number of patients	87	5		32	1	
Age (SD)	8.71 (4.13)	9.30 (3.11)		7.76 (3.65)	7.24	
Male/Female	50/37	3/2		20/12	0/1	
Single food OIT/multi-food OIT	36/51	2/3	P=0.992	3/29	0/1	P=0.975
Reaction*¹ history to the OIT nut (number of patients):						
Oral food challenge						
Recall $\geq$ grade 2	13	0		3	0	
Recall < grade 2	25	2		7	0	
Never exposed	22	1		8	1	
	27	2		13	0	
Reaction history to the cross- reactive nut (number of patients)						
Oral food challenge						
Recall $\geq$ grade 2	7	0		0	0	
Recall < grade 2	12	1		3	0	

grade 2	14	0		5	1	
Never exposed	54	4		24	0	
Pre-Treatment Specific IgE						
Treatment nut IgE², mean (SD)	19.83 (29.47)	54.49 (44.23)	p=0.015	17.58 (19.01)	3.7	p<0.001
Treatment nut IgE median (range) (IQR)³	4.85 (0.15 -100) (17.43)	46 (3.07-100)		7.73 (0.78-37.3) (19.35)	3.7	
Treatment nut IgE/total IgE (SD)	0.041 (0.048)	0.091 (0.139)	p=0.053	0.059 (0.075)	0.007	p<0.001
Cross-reactive nut IgE⁴, mean (SD)	17.21 (26.90)	56.59 (42.41)	P<0.003	7.05 (10.42)	0.9	P<0.002
Cross-reactive nut IgE median (range)(IQR)	5.72 (0.23-100) (18.0)	44.4 (3.57-100)		2.77 (0-51) (8.6)	0.9	
Passed the cross-reactive nut challenge - yes/no	87/5	-		32/1	-	
Passed the 1 gram protein cross-reactive nut challenge - yes/no	50/4			14/0		
Passed the 6 gram protein cross-reactive nut challenge - yes/no	37/1			17/1		
Cross-reactive nut challenge at office/home	81/6	5/0		26/6	1/0	
Eliciting doses for failed challenges		3360mg, 560mg, 1000mg, 1000mg, 70mg			2100mg	

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187 ^{1.} Reactions were graded according to routine criteria.

188 ^{2.} Pre-OIT sIgE's were available for 90/92 cashew treated and all walnut treated patients.

189 3. IRQ=interquartile range

190 4. Cross-reactive nut SIgE was available for 85/92 cashew treated and 32/33 walnut treated
191 patients.