Schoos et al. World Allergy Organization Journal (2024) 17:100865
http://doi.org/10.1016/j.waojou.2023.100865

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Bypassing the build-up phase for oral immunotherapy in shrimp-allergic children

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ABSTRACT

Background: Oral immunotherapy is an effective treatment for food allergies; however, its use in clinical practice is limited by resources and lack of standardized protocols for foods other than peanut. Previous studies have suggested that shrimp has a higher threshold for reaction than other allergenic foods, suggesting it may be safe to directly administer maintenance doses of immunotherapy.

Methods: Children aged 3–17 years who had 1) skin prick test $\geq$3 mm and/or specific IgE level $\geq$0.35 kU/L and convincing objective IgE-mediated reaction to shrimp, or 2) no ingestion history and specific IgE level $\geq$5 kU/L, underwent a low-dose oral food challenge to 300 mg shrimp protein, with the goal of continuing daily ingestion of the 300 mg maintenance dose as oral immunotherapy.

Results: Between January 2020 and April 2023, 17 children completed the low-dose oral food challenge. Nine (53%) tolerated this amount with no reaction, and 8 (47%) had a mild reaction (isolated oral pruritis or redness on chin). Sixteen (94%) continued maintenance low-dose oral immunotherapy eating 300 mg shrimp protein daily. None of the patients developed anaphylaxis related to the immunotherapy.

Conclusion: Our case series suggests that some shrimp allergic patients being considered for oral immunotherapy should be offered a low-dose oral food challenge, to potentially bypass the build-up phase of immunotherapy.

Keywords: Oral immunotherapy, Food allergy, Shrimp, Children, Eliciting dose, Oral food challenge, Build-up phase

INTRODUCTION

Oral immunotherapy (OIT) is an effective treatment option for children with peanut- and tree-nut allergies.[1,2] OIT typically involves ingesting increasing amounts of the allergenic food(s) over several months under clinical supervision until a maintenance dose is reached. This process is time-consuming and resource-intensive for allergists and families, requiring coordination and flexibility from both parties, as it entails multiple visits at an appropriate facility with trained personnel. While

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http://doi.org/10.1016/j.waojou.2023.100865

Received 28 June 2023; Received in revised from 13 December 2023; Accepted 20 December 2023

studies on OIT for peanut allergy[1,3–5] and tree-nut allergy[2] have been published, OIT to shrimp has only been described in 1 previous report[6] of 3 patients, 2 of which were children (<18 years). Given the high prevalence of shellfish allergy at 1.3% with a low resolution rate,[7,8] there is a need for further investigation of OIT as a treatment option for shellfish allergy. Previous studies have suggested that shrimp has a higher threshold for reaction than other allergenic foods due to a lower content of allergenic protein within the same amount of total food protein.[9,10] We hypothesize that with the higher threshold, it could be safe in patients with mild shrimp allergy to bypass the build-up phase of low-dose OIT and proceed directly to a maintenance dose of 300 mg protein, albeit lower than a typical OIT maintenance dose for shrimp. In patients who are highly sensitized, offering a low-dose OFC could be an option to incorporating small amounts of shrimp into the diet instead of strict avoidance.

Children (<18 years) who were assessed in the Allergy Clinic with 1) skin prick test ≥3 mm and/or specific IgE level ≥0.35 kU/L and convincing objective IgE-mediated reaction to shrimp, or 2) no ingestion history and specific IgE level ≥5 kU/L, were eligible for a low-dose oral food challenge (OFC) to shrimp (Table 1). The low-dose OFC was either performed as a 300 mg protein single dose or incremental doses totaling minimum 300 mg protein (given as 100 mg and 200 mg 15–25 min later), at the discretion of the treating allergist. The OFC was performed within a maximum of 6 months of the allergy testing. Symptoms were graded according to a modified World Allergy Organization (WAO) Subcutaneous Immunotherapy Reaction Grading System,[11] with adaptations specific to allergic reactions in infants, as previously published.[1,2] If patients were able to tolerate the 300 mg dose, they were encouraged to continue maintenance OIT at home by consuming 300 mg of shrimp protein daily (equivalent to 1.3 g of cooked shrimp). Informed consent was obtained from parents prior to initiation of the low-dose OFC. This case series was eligible for a waiver from ethics review since the ethics committee categorized this as a quality improvement project. Prior to starting low-dose OIT, parents received comprehensive education about recognition and management of adverse reactions, such as anaphylaxis, and an epinephrine autoinjector was always available. The children were followed up via ad hoc virtual communications in case of non-emergency situations, such as mild reactions that could be handled by caregivers at home. Parents were advised to record any adverse reactions and to use epinephrine autoinjector and seek immediate medical assessment in the emergency department in case of anaphylaxis.

RESULTS AND DISCUSSION

Between January 2020 and April 2023, 17 children (aged 3–17 years, median 9 years) underwent a low-dose OFC to 300 mg shrimp protein in the Allergy Clinic. Baseline characteristics and outcomes are listed in Table 2. Seven children (41%) were included based on convincing sensitization (specific IgE to shrimp ≥5 kU/L), 6 children (35%) had a history of a Grade 1 immediate-type hypersensitivity reaction to shrimp, and 4 (24%) had a history of a Grade 2 reaction. All children completed the low-dose OFC with either no reaction (53%), or mild reaction in the form of oral pruritis or redness on the chin (47%). Sixteen (94%) continued maintenance OIT at home eating 300 mg shrimp protein daily. One child decided not to proceed with OIT due to oral pruritus during the OFC. To date, none of the patients have developed anaphylaxis, required epinephrine, or attended emergency services related to the OIT.

Eligible	Ineligible
1) Objective evidence of shrimp sensitization: • skin prick test (SPT) ≥3 mm AND/OR • Shrimp specific IgE ≥0.35kU/L AND History of Grade 1–2 (11) allergic reactions to shrimp during OFC or reported by caregiver OR 2) Shrimp specific IgE level ≥ 5kU/L	Grade 3–4 (11) severe allergic reaction to shrimp during oral food challenge (OFC) or reported by caregiver OR Significant patient or caregiver anxiety preventing continuation with OIT at home

Table 1. Eligibility criteria allowing children to bypass the build-up phase of low-dose shrimp oral immunotherapy (OIT)

Age at OFC (y, mo)	Other current food allergies	Co-morbidities	HDM mix[a] sIgE/SPT	Pre OIT shrimp reaction, grade, age, and symptoms	Pre-OIT fresh shrimp SPT (vs extract if done)	Pre-OIT shrimp sIgE (kU/L)	Cumulative dose tolerated during OFC	Immediate reactions during OFC and grade	Immediate reactions during OIT and grade	Duration of maintenance
7 y, 5 mo	None	AR, AD, asthma	NA/10 mm	Grade 2, 6 years, oral pruritus and generalized urticaria	13 mm (0 mm)	NA	300 mg	None	None	Since March 11, 2022
16 y, 0 mo	Hazelnut, cashew, walnut, pea, sesame, peanut	Asthma, AD	NA/neg	Grade 2, 7 years, voice change, stridor, vomiting (trigger not 100 % clear)	7 mm	1.27	300 mg	None	None	Since May 30, 2022
14 y, 5 mo	Peanut, tree nuts	Asthma, AD, AR	NA/neg	Grade 1, 6 years, oral pruritus	12 mm	1.43	300 mg	Oral pruritus, grade 1	None	Since June 27, 2022
17 y, 11 mo	Peanut, tree nuts, soy, fish, legumes	AR, AD, Asthma	NA/neg	No exposure	13.5 mm	18.6	300 mg	Oral pruritus, grade 1	None	Since June 27, 2022
10 y, 8 mo	CM, egg, peanut, wheat, tree nuts	Asthma, AR, AD	NA/5 mm	Grade 1, 10 years, oral pruritus	3.5 mm	5.85	300 mg	Oral pruritus, grade 1	None	Since August 29, 2022
9 y, 11mo	Peanut, hazelnut, fish	Asthma, AR, AD	NA/5.5 mm	Grade 2, 4 years, hives, nausea, and vomiting	7 mm (3.5 mm)	NA	300 mg	None	None	Since October 17, 2022
9 y, 8 mo	Cashew, hazelnut, walnut	AD, asthma, AR	NA/9.5 mm	Grade 1, 5 years, oral pruritus (generalized hives to	6 mm	10.1	300 mg	None	None	Since October 17, 2022

(continued)

Age at OFC (y, mo)	Other current food allergies	Co-morbidities	HDM mix[a] sIgE/SPT	Pre OIT shrimp reaction, grade, age, and symptoms	Pre-OIT fresh shrimp SPT (vs extract if done)	Pre-OIT shrimp sIgE (kU/L)	Cumulative dose tolerated during OFC	Immediate reactions during OFC and grade	Immediate reactions during OIT and grade	Duration of maintenance
				aerosol shrimp)						
6 y, 1 mo	Peanut, tree nuts, egg, CM	AD, AR	NA/14 mm	No exposure (2 years old, lobster sauce on skin - > hives)	NA	88.8	300 mg	None	None	Since Oct 21, 2022
11 y, 3 mo	Peanut, tree nuts, fish	AR, asthma, AD	NA/neg	No exposure	6.5 mm	31.1	300 mg	None	None	Since November 14, 2022
3 y, 10 mo	Peanut, almond, hazelnut, egg, milk	AD	NA/neg	Grade 1, 1 year, hives	8.5 mm (7 mm)	NA	430 mg	Redness on chin, grade 1	None	Since April 14, 2023
12 y, 2 mo	Mollusks	AD, asthma, AR	NA/pos	Grade 2, 3 years, angioedema and oral pruritus	12 mm	19.7	300 mg	Oral pruritus, grade 1	Itchy throat, grade 1	Since July 29, 2022
5 y, 4 mo	None	AD, asthma	NA/NA	Grade 1, 7 mo, angioedema of lips and possible perioral urticaria	12.5 mm (7 mm)	NA	300 mg	Oral pruritus, grade 1	None	Since April 26, 2023
9y, 7 mo	Peanut, tree nuts, sesame	AR, AD	-/pos	Grade 1, 8mo, perioral non-urticarial rash to lobster	11 mm	35.8	300 mg	None	None	Since September 14, 2022

(continued)

15 y, 6 mo	Walnut, pecan	AR, AD	-/pos	No reaction to very small piece of shrimp at 15 years	10 mm	7.05	430 mg	Oral pruritus, grade 1	Itchy throat so significant he did want to do OIT	Since May 25, 2022
6 y, 9 mo	Egg, peanut, cashew, hazelnut	Asthma, AD	-/neg	No exposure	9 mm	88.0	300 mg (scaled)	None	None	Since January 31, 2020
13 y, 3 mo	Peanut, tree nuts, lentils, peas	AR, Asthma, AD	-/pos	Grade 1, 3 years, oral pruritus	6.5 mm	24.6	300 mg (scaled)	Oral pruritus, grade 1	None	Since December 2, 2022
4 y, 10 mo	Egg	AD	NA/neg	No exposure	(18 mm)	13.7	346 mg	None	None	Since April 11, 2023

Table 2. Baseline characteristics and outcomes. *OFC = oral food challenge, sIgE = specific IgE, SPT = skin prick test. NA = not available. CM = cow's milk. AR = allergic rhinitis. AD = atopic dermatitis. a. HDM = house dust mite, HDM mix contains: House Dust (Hollister-Stier Labs),* Dermatophagoides pteronyssinus, Dermatophagoides farinae, *and Cockroach (German)*

Our case series suggests that patients with a history of a Grade 1–2 reaction to shrimp or high levels of sensitization and no previous exposure can be offered a low-dose OFC of 300 mg shrimp protein, safely bypassing the build-up phase of low-dose OIT. One previous report described successful shrimp OIT in 2 children, but this report was part of a larger multi-food OIT study where patients enrolled had a history of a clinical reaction to ≤175 mg of shrimp protein and they received omalizumab concurrently with OIT.[6] The results are therefore not comparable to ours.

The success of bypassing up-dosing of low-dose OIT to shrimp and proceeding directly to 300 mg protein maintenance dosing is explained by a recent study combining data from 91 clinical trials of OFCs to 14 priority allergenic foods, which demonstrated a significantly higher eliciting dose (ED) to shrimp compared to the other allergenic foods.[10] For example, the cumulative ED that induced objective allergic symptoms in 10% of the allergic population (ED10) ranged from 1.3 mg (mustard) to 61.6 mg (soy), with an evident gap to shrimp with an ED10 of 1265 mg protein. Accordingly, the percentage of patients reacting to 300 mg of shrimp protein was only 4% (ED04 = 301 mg of shrimp protein).

Our study had some limitations; first, 9 children (56 %) had concurrent sensitization to house dust mite. The tropomyosin component of *Dermatophagoides pteronyssinus*, Der p 10, may be responsible for cross-reactivity to shrimp in these patients explaining some of the milder reactions reported,[12,13] which may be a form of oral allergy syndrome ("mite shrimp allergy syndrome or MSAS"). We did not measure Der p 10 and/or did high-dose OFCs to confirm or rebut this, which is a limitation of our study, although in the real world, allergists do not typically offer high-dose OFCs to children with a history of reaction and positive testing to rule out oral allergy syndrome; instead, they simply diagnose all of them with shrimp allergy. Also, OIT could be an option even for patients with confirmed oral allergy syndrome. Second, there might be selection bias assuming the families were psychosocially more resourceful as many of the patients already had experience with OIT to other foods and they were motivated to undergo OIT at home. All but 1 child had skin prick test (SPT) done with fresh, cooked

shrimp, and of these, 4 were additionally tested with shrimp extract showing a remarkably lower reaction to the extract (13 mm vs 0 mm, 7 mm vs 3.5 mm, 8.5 mm vs 7 mm, and 12.5 mm vs 7 mm respectively), cautioning against false negative results when using the extract. Even if some of the children in our case series have not been exposed to shrimp previously (the ones with high levels of sensitization), functionally there is no practical way to rule out allergy in these patients because many parents and allergists are hesitant to challenge a patient with very high levels of sIgE due to a fear of reaction, and the families default to 100% avoidance. Our case series demonstrates a feasibility for low-dose OFC in patients who are either highly sensitized, or who have had symptoms in the past with positive skin- and/or specific-IgE- testing. After the OFC, it is advisable to ingest small amounts regularly to induce tolerance.[14] We would label this regular intake of a small amount of shrimp "OIT" to underline that it should go on continuously. Some of these patients may not need OIT, but in real-world clinical practice it is very hard to distinguish the ones who need it from the ones who do not. For this smaller subset with high levels of sensitization and no prior history of ingestion, another way to describe their experience could be "a prolonged daily low-dose period to increase confidence prior to full-dose OFC". The average specific IgE is 26.6 kU/L and average skin test size of our cohort is 9.2 mm. Most allergists would not feel comfortable to challenge patients with these biomarkers to full-dose OFC. The low-dose OFC could be an alternative to avoidance. Patients who tolerate the low-dose OFC could be advised not to worry about trace contamination at restaurants and can ingest "may contain products" which may provide quality of life benefits.

To our knowledge, this is the first case series demonstrating that bypassing the build-up phase for low-dose OIT and proceeding directly to maintenance dosing of 300 mg shrimp protein is safe. Typically, home-based OIT is reserved for children with low levels of sensitization and an OFC showing they are low-dose tolerant.[15] We propose challenging children with allergist-diagnosed shrimp allergy to a low dose of 300 mg of shrimp protein, not just to confirm the high threshold, but to initiate the maintenance phase of low-dose OIT.

Usually, OIT protocols feature frequent in-person clinic visits for up-dosing, which are costly and time-consuming for both clinical staff and families. In contrast, this novel approach of bypassing the build-up phase in shrimp allergic children similar to the reported population could reduce healthcare costs of OIT and some of the inconvenience for families, increasing access especially in areas where shrimp allergy is the most common food allergy (eg, Taiwan, Thailand, Singapore, Vietnam, Hong Kong, etc).[16] Furthermore, it will minimize delays in commencing OIT. The significantly higher threshold for reaction to shrimp compared to other foods[10] indicates that the initial exposure to 300 mg shrimp protein may even be safe to do at home, if more data confirm our findings.

Abbreviations

OIT, Oral Immunotherapy; SPT, Skin Prick Test; OFC, Oral Food Challenge; ED, Eliciting Dose; MSAS, Mite Shrimp Allergy Syndrome.

Funding

BC Children's Hospital Foundation.

Availability of data

All data included in this study are available in Table 2.

Authors contributions and consent for publication

The guarantor of the study is ESC, from conception and design to conduct of the study and acquisition of data, data analysis, and interpretation of data. AMS has written the first draft of the manuscript. All co-authors have provided important intellectual input and contributed considerably to the analyses and interpretation of the data. All authors guarantee that the accuracy and integrity of any part of the work have been appropriately investigated and resolved and all have approved the final version of the manuscript and given consent for publication. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication. No honorarium, grant, or other form of payment was given to any of the authors to produce this manuscript.

Ethics statement

This case series was eligible for a waiver from ethics review since the University of British Columbia ethics committee categorized this as a quality improvement project. Written

informed consent was obtained from the parents before each challenge.

Declaration of competing interest

The funding agency did not have any role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript. No pharmaceutical company was involved in the study.
AMS has been a member of an advisory board for ALK and has received speaker honorarium for ThermoFisher Scientific.
ESC has received research support from DBV Technologies; has been a member of advisory boards for Pfizer, Miravo, Medexus, Leo Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme, Bausch Health, Avir Pharma, AstraZeneca, and ALK; and was co-lead of the CSACI oral immunotherapy guidelines.
TW has been a member of advisory boards for Leo Pharma, Sanofi, Pediapharm, Aralez Pharmaceuticals, Medexus and has received honoraria from Medexus, Covis Pharma, L'Oreal, Pfizer, and Stallergenes Greer for speaking engagements.
RM has been a member of advisory boards for ALK, Novartis, Sanofi, Medexus, Valeo, and Pfizer. He has received speaker honoraria from Amgen, Astra Zeneca, Novartis, CSL Behring, and Pediapharm.
SCE has been a member of an advisory board for ALK and has received honoraria from La Roche Posay. She has received research support from Pfizer and Avir Pharma.
AC and LS have no conflicts of interest to declare.

Acknowledgements

None.

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