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LETTER TO THE EDITOR

WILEY

Shrimp-allergic patients in a multi-food oral immunotherapy trial

To the Editor,

Shellfish allergy is one of the most common food allergies in the United States, accounting for approximately 25% of adulthood and 20% of childhood food allergies (FA).[1,2] Of the different types of shellfish, shrimp is a common culprit of food allergy. The prevalence of shellfish allergy in children is substantial at 1.3% and may result in a greater prevalence in the adult population (3%) given that shellfish allergies have a low rate of spontaneous resolution.[2,3]

Shrimp allergy (SA) is a leading cause of severe allergic reactions and results in high rates of healthcare usage.[4] Nearly 50% of patients with SA experience at least one lifetime food allergy-related emergency department visit, yet only 42% of adults and 61% of children with SA reported having a physician-confirmed diagnosis.[1,2] The lack of physician confirmation of SA is concerning given the potentially life-threatening consequences of accidental exposure.[5] Currently, there is no cure and the only management strategies are avoidance of and treatment for severe reactions with adrenaline.[6] However, avoidance can be difficult and requires strict dietary limitations.

Oral immunotherapy (OIT) has emerged as a promising treatment for FA. In OIT, patients ingest increasing doses of the allergenic food with the goal of achieving desensitization so that reactions are less severe. Once a maintenance dose is achieved, the allergen needs to be regularly ingested to preserve the desensitized state. Although OIT has been recently approved by the FDA for peanut allergies, there have been little data in shrimp-allergic patients. In this case series, we discuss a subset of three patients who received shrimp OIT as part of a phase II, multi-food, omalizumab-facilitated OIT clinical trial.

Multi-food-allergic patients were recruited to a multi-site clinical trial between January 1 and November 30, 2016. Full details of trial

TABLE 1 Baseline patient characteristics of shrimp-allergic patients treated with shrimp oral immunotherapy

	Patient A	Patient B	Patient C
Age (years)	5	10	21
Sex	Male	Female	Male
Comorbid conditions	Asthma, allergic rhinitis, and atopic dermatitis	Asthma, allergic rhinitis, and atopic dermatitis	Asthma, allergic rhinitis, and atopic dermatitis
Other food allergies	Egg, milk, peanut, and wheat	Cashew, pecan, peanut, walnut, and pistachio	Cashew, oat, pecan, peanut, and walnut
Total IgE	1072	707	676
Shrimp-specific IgE**	58.2	<0.35*	7.78
SPT wheal (mm)	9	7	11
DBPCFC screening reaction dose (mg)	175	25	175
Adverse events during DBPCFC	Mouth itching, vomiting, conjunctivitis, cough, urticarial, and nasal congestion	Urticaria and sneezing	Urticaria, wheezing, abdominal pain, mouth itching, throat itching, tongue itching, nausea, change in affect (sitting and not engaged), cough, diarrhea, sneezing, pruritus, rhinorrhea, chest itching, ears itching, and nose itching

*Patient B had shrimp-specific IgE performed at an outside facility where it was negative and was not re-performed.

**Tested through the CLIA-approved laboratory at The Johns Hopkins University.

design, inclusion criteria, and exclusion criteria have been previously reported.[7] Patients initially underwent testing with skin prick testing (SPT), specific IgE testing, and double-blind placebo-controlled food challenge (DBPCFC) to confirm their allergy to their culprit foods. To be included, patients were required to have a positive SPT of ≥6 mm wheal diameter, specific IgE ≥0.35 kU/L, a total IgE <2,000 kU/L, and a clinical reaction with DBPCFCs at ≤125 mg dose (Table S1).

Patients enrolled in this clinical trial received 0.016 mg/kg (IU/ml) omalizumab per month or 0.008 mg/kg (IU/ml) every two weeks (based on asthma dosing guidelines)[7] from Weeks 1–16. At Week 8, multi-food OIT was started and escalated under an investigator-supervised multi-OIT up-dosing regimen (Table S2) to reach a maintenance dose of ≥1g of each allergen. Participants who reached maintenance by Weeks 28–29 were randomized and received Week 30 DBPCFC to assess desensitization to the allergenic foods. Patients were then randomized to one of the three arms: high-dose maintenance (1,000 mg), low-dose maintenance (300 mg), or placebo (0 mg). This randomized dose was dispensed at the last Week 30 DBPCFC and consumed until Week 36. At Week 36, DBPCFC was repeated to assess sustained unresponsiveness with differing daily doses of protein.

A total of 70 patients were enrolled, with three found to have SA. Their demographic data and baseline characteristics are detailed in Table 1. All three patients also had asthma, allergic rhinitis, and atopic dermatitis. Each had a convincing clinical history, elevated total IgE, and positive SPT to a mixture of white, brown, and pink shrimp extract from Greer. The diagnosis was confirmed by a reaction during DBPCFC with *Litopenaeus setiferus* shrimp (also known as Northern white shrimp) flour that was manufactured at a Good Manufacturing Practice facility at Stanford University. This flour demonstrated stability over the course of the study and was approved by the FDA for use in the trial. (IND #14831).

Clinical outcomes and adverse events are detailed in Table 2. All 3 patients tolerated dose escalation without serious adverse events or adrenaline requirement, were able to achieve maintenance dose, and did not have an allergic reaction at the Week 30 DBPCFC. Patient A was randomized to the placebo treatment arm while the other two patients were randomized to the 300 mg maintenance OIT arm. At Week 36, Patient A and Patient B had sustained unresponsiveness to 12,000 mg of shrimp protein. Patient C did not follow up for assessment.

It is encouraging that all 3 shrimp-allergic patients in this multi-food OIT clinical trial were able to reach maintenance dose OIT (≥1g), and 2 out of 3 had no reaction with the 12 g DBPCFC dose at Week 30. Tolerating 12,000 mg of shrimp protein is equivalent to approximately 3 medium-sized white prawns. These results suggest that OIT is a potentially efficacious treatment for SA and warrants further study. There are little data on the optimal shrimp allergen product, dose-escalation regimen, and adjunct therapies such as omalizumab to achieve desensitization.

There are several known target allergens that contribute to SA. The first major allergen is tropomyosin, a heat-stable, actin-binding protein found in both muscle and non-muscle cells. Tropomyosin has been implicated as the source of significant cross-reactivity between species of mollusks, crustaceans, and non-shellfish such as

TABLE 2 Clinical outcomes and adverse events of shrimp-allergic patients treated with shrimp oral immunotherapy

	Patient A	Patient B	Patient C
Omalizumab dose (mg)	225	300	600
Omalizumab doses per month for 2 months	2	2	2
Omalizumab dose per month (mg)	450	600	1,200
Standardized omalizumab dose (mg/kg/IU)	0.023	0.025	0.021
DBPCFC Week 30 tolerated dose (mg)	12,000	12,000	4,000
Treatment arm	Placebo	300 mg maintenance OIT	300 mg maintenance OIT
Week 36 tolerated dose (mg)	12,000	12,000	ND
Serious adverse events	None	None	None
Adverse events during OIT	Throat itching, abdominal pain, vomiting, and asthma exacerbation	Facial edema, mouth itching, abdominal pain, nasal congestion, and gas	Abdominal pain, hiccups, tongue itching, throat itching, mouth itching, malaise, pruritus, nausea, throat tightness, and cough
Adrenaline use during dose escalation	No	No	No

Abbreviation: ND, not performed due to non-availability of patient.

cockroaches and mites.[8,9] Other shrimp allergens that have been identified include arginine kinase, myosin light chain, sarcoplasmic calcium-binding protein, hemocyanin, and troponin C.[8,9] There may also be shrimp species-specific allergens, as there have been clinical reports of individuals who react to one species but not the other.[10] It is possible that patients with allergies to different shrimp components may have varied responses to OIT, and thus, additional research is necessary to determine which patient subgroups are most likely to benefit from shrimp OIT. In addition, commercial shrimp extracts are heterogeneous with variable allergen representation.[11] The differing allergens may result in varied responses in SPT and IgE results, which may explain Patient B's apparent negative shrimp IgE test.

Our case series is limited by small sample size, with only three patients receiving shrimp OIT and two following up at Week 36. The lack of immune profiling at endpoint visits, including shrimp IgE, IgG_4, and SPT, is an additional limitation. Although all patients appeared to develop short-term tolerance by Week 30, it is unclear how durable this response would be with a long-term follow-up. Furthermore, there are risks associated with OIT.

Shrimp allergy is a common and serious food allergy that is underdiagnosed and often lifelong. There are currently no effective treatments other than strict avoidance, which can be difficult to achieve and lead to poor quality of life. Our case series presents initial evidence, suggesting that shrimp OIT may be an effective strategy of addressing grave reactions faced by SA patients. Larger studies need to be performed to validate these findings.

KEYWORDS

anaphylaxis, desensitization, food allergen, food allergy, omalizumab, oral immunotherapy, shellfish allergy, shrimp allergy, sustained unresponsiveness

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REFERENCES

1. Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open*. 2019;2:e185630.
2. Wang HT, Warren CM, Gupta RS, Davis CM. Prevalence and characteristics of shellfish allergy in the pediatric population of the United States. *J Allergy Clin Immunol Pract*. 2020;8:1359-1370.e2.
3. Zotova V, Clarke AE, Chan ES, et al. Low resolution rates of seafood allergy. *J Allergy Clin Immunol Pract*. 2019;7:690-692.
4. Ross MP, Ferguson M, Street D, Klontz K, Schroeder T, Luccioli S. Analysis of food-allergic and anaphylactic events in the National electronic injury surveillance system. *J Allergy Clin Immunol*. 2008;121:166-171.
5. Tuano KTS, Anvari S, Hanson IC, et al. Improved diagnostic clarity in shrimp allergic non-dust-mite sensitized patients. *Allergy Asthma Proc*. 2018;39:377-383.
6. Davis CM, Gupta RS, Aktas ON, Diaz V, Kamath SD, Lopata AL. Clinical management of seafood allergy. *J Allergy Clin Immunol Pract*. 2020;8(1):37-44.
7. Andorf S, Purington N, Kumar D, et al. A phase 2 randomized controlled multisite study using omalizumab-facilitated rapid desensitization to test continued discontinued dosing in multifood allergic individuals. *EClinicalMedicine*. 2019;7:27-38.

8. Faber MA, Pascal M, El Kharbouchi O, et al. Shellfish allergens: tropomyosin and beyond. *Allergy*. 2017;72:842-848.
9. Ruethers T, Taki AC, Johnston EB, et al. Seafood allergy: a comprehensive review of fish and shellfish allergens. *Mol Immunol*. 2018;100:28-57.
10. Karnaneedi S, Huerlimann R, Johnston EB, et al. Novel allergen discovery through comprehensive de novo transcriptomic analyses of five shrimp species. *Int J Mol Sci*. 2021;22(1):32. 10.3390/ijms22010032
11. Asero R, Scala E, Villalta D, et al. shrimp allergy: analysis of commercially available extracts for in vivo diagnosis. *J Investig Allergol Clin Immunol*. 2017;27(3):175-182. 10.18176/jiaci.0127

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