Oral Immunotherapy to Hake in 8 Pediatric Patients

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Increased consumption of fish because of its high nutritional value and role in a healthy diet has led to more common reporting of adverse reactions, including IgE-mediated reactions [1]. In countries where fish intake is high (eg, Spain), fish allergy is one of the most common food allergies in children, together with milk and egg allergy. In a recent systematic review and meta-analysis, the overall pooled estimate (all age groups) of self-reported lifetime prevalence of fish allergy in Europe was 2.2%; the prevalence of food challenge–confirmed fish allergy was 0.1% [2].

Fish allergy often develops early in life and can be an important cause of severe acute hypersensitivity reactions, including life-threatening anaphylaxis. Furthermore, although children can develop tolerance to the most common food allergens, the potential for persistence of fish allergy should be considered when counseling families regarding the expected clinical course [1].

To date, the only method for treating food allergy is avoidance of the offending food in conjunction with rescue medication in case of accidental exposure. Oral immunotherapy (OIT) for several foods (milk, egg, peanut) has proven effective in most treated patients [3], although few cases involving desensitization with fish have been reported in the literature [4-6]. An important limitation of fish OIT is the difficulty adapting the fish product for administration of the necessary doses.

The primary objective of this pilot study was to evaluate the efficacy of achieving desensitization of IgE-mediated hake allergy with an OIT protocol using a well-characterized and lyophilized hake extract (LHE). The secondary objective was to evaluate the safety of this protocol.

We performed a multicenter, prospective, open, noncontrolled study in the pediatric allergology units of various Spanish Hospitals after ethics committee approval. Patients were recruited consecutively according to the following criteria: age 4 to 14 years; history of acute clinical reactions after ingestion of hake; hake IgE >0.7 kU/L (Immuno-CAP, Thermo Fisher Scientific); hake skin prick test wheal at least 3 mm greater than the negative control (1250 µg protein/mL [LETIPharma S.L.]); and a positive result for LHE in a double-blind placebo-controlled challenge test (DBPCFC). For ethical reasons, DBPCFC was not deemed necessary in patients with high levels of sIgE (>20 kU/L: 95% positive predictive value of positive challenge [7]).

We obtained informed consent from the legal guardians of the participating children and informed assent from those aged 12 and older.

LHE was manufactured under conditions of Good Manufacturing Practice according to internal procedures (LETIPharma S.L.) (Supplementary Appendix). A personalized kit was prepared for each patient. The kit consisted of individual vials containing the exact milligram amount of LHE for each dose and was stored refrigerated and under vacuum conditions. Each vial was dissolved in orange juice at the time of administration. Vials for DBPCFC were manufactured under the same conditions but with a single vial of 250 mg for the different dilutions.

The OIT protocol included an initial escalation phase followed by a dose build-up phase (Table S1 in the Supplementary Appendix). The initial escalation phase was conducted over 2 days using rapid up titration, which starts with 0.006 mg of LHE, and doubling of the doses every 60 minutes to a maximum dose of 0.111 mg on the first day and 1.8 mg on the second day. In the build-up phase, the dose was escalated incrementally every week for the following 16 weeks, from 1.8 mg to the target dose of 225 mg. At day 7, after finishing the build-up phase, all patients underwent the DBPCFC with LHE (cumulative dose, 450 mg; equivalent to 150 g of hake), and at day 14, patients underwent an open challenge with 150 g of cooked hake. LHE was diluted in orange juice. All initial dose increases were administered under supervision at hospital; if the dose was tolerated, it was then given daily at home. Instructions for treatment and modification of the dosing schedules according to severity of adverse reactions are in accordance with Spanish guidelines on OIT [8-9].

A total of 8 children were recruited (aged 4-14 years; 87.5% males) (Table). All 8 patients completed the study and reached the target dose of 225 mg (equivalent to 75 g of hake) with good tolerance and continued this dose daily for 2 weeks.

Table. Patient Demographic Data and Allergic and Clinical Characteristics

Patient	Age, y	Symptoms With Prior Hake Exposure[a]	Hake Skin Test Wheal, mm	Endpoint SPT Titration, µg Protein/mL[b]	Hake sIgE, kU/L	rGad C 1- sIgE, kU/L[c]	OFC, Maximal Tolerated Dose (Lyophilized Hake), mg
1	14	Urticarial rash, vomiting, bronchospasm	11	12.5	5.15	-	7
2	13	Urticarial rash, facial angioedema	15	12.5	4.11	2.81	58
3	11	Urticarial rash, facial angioedema	12	1.25	59.2	43.1	ND
4	5	Urticarial rash, facial angioedema abdominal pain	9	12.5	17.5	12.4	58
5	4	Urticarial rash	8	12.5	1.6	0.11	58
6	9	Urticarial rash	12	12.5	25.9	22.6	ND
7	11	Oral pruritus, conjunctivitis, abdominal pain	10	12.5	5.8	4.93	58
8	9	Urticarial rash, facial angioedema, vomiting	16	1.25	30.9	11.4	ND

Abbreviations: ND, not done (hake-specific IgE >20 kU/L); OFC, oral food challenge; SPT, skin prick test.
[a]Symptoms with initial hake ingestion based on reported histories.
[b]Endpoint SPT titration technique with dilutions of hake extract: 1250, 125, 12.5, and 1.25 µg protein/mL.
[c]rGad c 1 sIgE: Immuno-CAP Thermo Fisher Scientific.

At day 7, all patients underwent the DBPCFC with LHE (cumulative dose, 450 mg; equivalent to 150 g of hake), and at day 14, patients underwent an open challenge with 150 g of cooked hake (maintenance dose), with appropriate tolerance and no symptoms. Patients were instructed to continue with a maintenance dose of 150 g of cooked hake once daily for 3 days a week.

Adverse reactions were recorded during the OIT process, both in the hospital and at home. The severity of the reactions was classified as previously reported [10], ie, mild, moderate, and severe (Supplementary Appendix). The frequency of total reactions reported by week 18 was 1.7% (18 reactions/1032 doses, 1.5% mild and 0.2% moderate reactions) (Table S2 in the Supplementary Appendix).

In 2003 and 2007, Patriarca et al [4-5] published the results of fish OIT in 16 fish-allergic children using boiled cod. Treatment was completed successfully in 5 to 10 months in all cases. Patients experienced some mild adverse effects, which were easily controlled by the oral administration of antihistamines or cromolyn sodium.

Other than these studies, the only available results are from a 2017 study on OIT with fish [6]. The authors reported a case of OIT in a 6-year-old girl with fish allergy (hake IgE, 3.31 kU/L). The protocol consisted of a build-up phase with increasing doses of lyophilized hake until 12 g was tolerated and subsequently by eating increasing portions of microwave-cooked hake up to 40 g. The build-up phase of the OIT lasted 11 months. The patient experienced an anaphylactic reaction (dose, 26 g), which was treated with epinephrine, as well as 4 episodes of moderate abdominal pain that required antihistamines with or without oral corticosteroids.

We propose a new and original protocol based on OIT with a known concentration of protein content and parvalbumin consisting of a quick build-up phase and with a target dose equivalent to a typical portion of fish. Our target dose was higher than in any previously published protocols.

Further studies, including studies on maintenance treatment, are warranted. In addition, larger study samples are necessary to complete investigations. Inclusion of immunological parameters may also complement and confirm the efficacy of these treatments in food-allergic patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

This paper was presented at the SEAIC Symposium 2017, 26-28 October, Murcia, Spain and at the 42nd SEICAP Congress 2018, 10-12 May, Málaga, Spain.

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