

LETTER TO THE EDITOR

Induction of tolerance to different types of fish through desensitization with hake

To the Editor:

Food allergy is a health concern causing an important impact in patient's quality of life (1) and on that of their families, due to the continuous monitoring required in order to avoid the allergen and the risk of potentially fatal reactions resulting from the accidental ingestion of the allergenic food. Fish is one of the main causes of food allergies in children (2), and, unlike other infant food allergies such as allergies to cow milk or eggs, fish allergy tends to persist over time (3). Even the inhalation of steam generated while cooking the allergenic food can also trigger allergic reactions, hence affecting the quality of life of these patients (4). There are few cases described in the literature regarding desensitization with fish (5–7). However, there is no evidence of induction of tolerance to other types of fish after specific desensitization. We report a case of oral immunotherapy (OIT) with fish performed in a patient who experienced several allergic reactions to fish due to accidental ingestion and even symptoms after being exposed to steam generated while cooking fish.

We present the case of a 6-year-old female who presented with generalized urticaria after first eating fish (hake) at the age of 9 months and later at the age of 12 months following the reintroduction of small portions of different types of fish (hake and sole). Despite avoidance of fish ingestion, she had four reactions (ranging from contact urticaria to anaphylaxis) with accidental ingestions of fishes (e.g., grouper). One of the reactions that she had was observed after eating a processed pork meal wherein the possibility of fish contamination could not be confirmed by the manufacturer. The patient subsequently tolerated the ingestion of pork. Furthermore, she started suffering facial hives after being exposed to steam generated while cooking tuna at her home since the age of six. She was also diagnosed with atopic dermatitis since the age of four which was well controlled with topical corticosteroids. She had no history of other food allergies, bronchial asthma nor sensitization to aeroallergens.

A complete allergology workup, including skin prick test (SPT) (prick by prick) (data summarized in Table 1) and determination of total and specific IgE (ImmunoCAP, Phadia, ThermoFisher Scientific) was carried out showing total IgE (28.7 kU/l) and specific IgE levels to hake (3.31 kU/l) and carp parvalbumin (4.87 kU/l). Oral food challenge (OFC) was carried out through a specific protocol designed in our department using hake (*Merluccius capensis*). She presented abdominal pain after ingestion of 256 mg of hake. OFC doses and symptoms are described in Table 2 (day 0).

Taking into account the clinical history and the allergologic study, we decided to perform oral immunotherapy (OIT) with this food. Specifically, we selected the fish hake, a white fish which is frequently consumed in our country, because it was the first fish that triggered an allergic reaction and it showed

one of the greater wheals in SPT among all tested fish species. We used individually packaged portions (80 g of hake contains 16.2 g of protein) of ultrafrozen hake loin (Pescanova®, Galicia, Spain), which were crushed with a hand mixer (Braun®, Leonberg, Germany) and lyophilized (lyophilizer Cryodos 50, Telstar) in three different occasions (7.99 g, 4.52 g, and 9.56 g of hake per 1 g of lyophilized hake, respectively). The lyophilized hake (LH) was stored and all doses were weighed using the same scale and handled by an expert laboratory technician. The stability and allergenicity of the fresh hake, defreeze ultrafrozen hake and LH were also confirmed by SPT (11 × 9 mm, 9 × 12 mm, and 12 × 8 mm, respectively). To establish the starting dose, we performed SPT with different concentrations of the LH dissolved in 0.9% sodium chloride (2 mg/ml: 7 × 5 mm, 0.2 mg/ml: 5 × 4 mm, 0.02 mg/ml: 3 × 2 mm). The protocol consisted with an induction phase with increasing doses of LH until reaching tolerance to 12 g and, subsequently, by eating increasing portions of microwave-cooked hake until reaching 40 g. The initial doses were disguised with plain, sweetened yogurt or vegetable puree and administered in the hospital during the build-up or induction phase. Exercise was avoided after ingestion of the dose. The build-up phase of the OIT lasted eleven months. It was started as a rush protocol with 5 mg of cetirizine as premedication. However, due to the onset of recurrent abdominal pain after administering the doses, the protocol was switched to conventional OIT with weekly dose increments without premedication. The patient experienced an anaphylactic reaction (day 216) which was treated with epinephrine, probably related to a concomitant infection (otitis) that showed up the day after, as well as four episodes of moderate abdominal pain that required antihistamines as the sole treatment in two occasions, and antihistamines plus oral corticoids in the other two episodes. During the build-up phase, the patient underwent a tonsillectomy as a result of experiencing recurrent tonsillitis associated with high levels of antistreptolysin antibodies (2700 UI/ml) without incidences, as she was advised to avoid the ingestion of fish the day of the surgery and the following 2 days. After those days, the reintroduction of fish was successfully performed at the hospital, administering the same dose that the patient had tolerated the day before the surgery. Data regarding increasing dosage and clinical manifestations are shown in Table 2. During the maintenance phase, the patient ate 40 g of hake every 2–3 days. Tolerance to increased amounts of hake was confirmed through OFC at the hospital thirteen months (80 g) and eighteen months (160 g) after finishing the induction phase of the OIT. No exacerbation of her known atopic dermatitis was observed during the induction or maintenance phases.

After 1 month in the maintenance phase without any reported untoward reaction, oral food challenges (OFCs) with

	Build-up phase			Maintenance phase			
	T1	T2	T3	T4	T5	T6	T7
Hake	14 × 10	10 × 6	7 × 5	9 × 6	8 × 5	12 × 10	16 × 8
Conger eel	7 × 6	16 × 8	5 × 3	9 × 5	11 × 6	10 × 9	10 × 6
Salmon	10 × 6	10 × 11	6 × 4	7 × 4	6 × 5	10 × 6	7 × 6
Tuna	9 × 5	5 × 7	3 × 1	3 × 2	Negative	Negative	Negative
Monkfish	10 × 10	8 × 5	3 × 2	3 × 4	8 × 5	Negative	6 × 3
Sea bass	20 × 10	5 × 5	4 × 6	8 × 4	6 × 5	11 × 8	5 × 3
Megrim	12 × 9	11 × 4	4 × 4	4 × 3	12 × 6	7 × 6	7 × 5
Sardine	15 × 14	13 × 10	2 × 4	11 × 6	7 × 6	6 × 5	8 × 6
Red scorpion fish	NP	NP	9 × 5	8 × 5	4 × 6	NP	NP

T1: before OTI; T2: day 246 of build-up phase; T3: end of build-up phase; T4: first month of maintenance phase; T5: fifth month of maintenance phase; T6: 1 year of maintenance phase; T7: eighteenth month of maintenance phase. NP: not performed.

Table 1 Skin prick test (prick by prick) to different types of fish before and during OTI (results are expressed as the measure of the wheal—major diameter and minor diameter measured in millimeters—for each tested fish)

Table 2 Specific oral immunotherapy (OIT) with hake. Increasing doses of LH or cooked hake loin, pre-treatment, adverse effects, and given treatment (in parentheses) during the build-up phase are shown

Day	Product	Product amount	Pre-treatment	Events (treatment)	Hake dose
0 (Open food challenge)	Lyophilized hake 1 (7.99 g hake/g lyophilized)	1 mg			8 mg
		2 mg			16 mg
		3 mg			24 mg
		4 mg			32 mg
		8 mg			64 mg
		16 mg			128 mg
		32 mg		Self-limited, AP	256 mg
1		16 mg	Cetirizine 5 mg		130 mg
		32 mg	Cetirizine 5 mg	Mild AP (antihistamine)	260 mg
2		16 mg	Cetirizine 5 mg	Self-limited, AP	130 mg
3	Lyophilized hake 2 (4.52 g hake/g lyophilized)	16 mg	Cetirizine 5 mg		130 mg
		32 mg	Cetirizine 5 mg		260 mg
		64 mg	Cetirizine 5 mg		510 mg
4		64 mg	Cetirizine 5 mg	Mild, self-limited AP	510 mg
9		50 mg	Cetirizine 5 mg	Self-limited, AP	400 mg
10		40 mg	Cetirizine 5 mg	Mild, self-limited AP	320 mg
15		16 mg	Cetirizine 5 mg		130 mg
22		24 mg	Cetirizine 5 mg		190 mg
25		24 mg			190 mg
29		36 mg			290 mg
36		54 mg		Mild, self-limited AP and flushing	430 mg
53		85 mg		Self-limited peribuccal urticaria	680 mg
57		125 mg			1.00 g
65		250 mg			2.00 g
79		500 mg		Vomits and AP (antihistamine)	4.00 g
80		375 mg			3.00 g
86		500 mg		Moderate AP (antihistamine, corticoid)	4.00 g
87		375 mg			3.00 g
93		350 mg			3.35 g
100		430 mg			4.11 g
107		490 mg			4.68 g
114		560 mg			5.35 g
121		640 mg		Mild, self-limited AP	6.12 g
135		730 mg			6.98 g
142		830 mg			7.93 g

Table 2. (Continued).

Day	Product	Product amount	Pre-treatment	Events (treatment)	Hake dose
149		950 mg			9.08 g
156	Lyophilized hake 3 (9.56 g hake/g lyophilized)	2000 mg			9.02 g
163		2300 mg			10.37 g
170		2660 mg			12 g
175	Microwave-cooked hake loin	12 g			12 g
177		14 g			14 g
185		16 g			16 g
192		18 g			18 g
198		20 g			20 g
205		23 g			23 g
212		26 g			26 g
216		26 g		Anaphylaxis (epinephrine)	26 g
217		23 g			23 g
219		25 g			25 g
226		27 g		Moderate AP (corticoids and antihistamine)	27 g
227		25 g			25 g
247		27 g			27 g
254		29 g		Self-limited mild AP	29 g
261		30 g			30 g
270		32 g			32 g
275		34 g			34 g
282		35 g			35 g
294		No dose		Surgical intervention	No dose
295		No dose			No dose
296		35 g			35 g
310		37 g			37 g
317		39 g			39 g
324		40 g			40 g

AP: abdominal pain. Intervals of time of 30 min between doses were awaited when several doses were administered in a single day.

a single dose of other types of fish (50 g of bass, 50 g of tuna, and 50 g of monkfish, respectively) were successfully performed in the hospital. Three months later, the patient tolerated 40 g of sole (single dose) and 50 g conger eel (single dose) at month 18 of the maintenance phase by OFC at hospital. During the maintenance phase, the patient alternated hake ingestion two to three times per week with other types of fish on a weekly basis (bass, tuna, sole, or monkfish) but always eating hake three times per week. Between the 5th month and 12th month of maintenance phase, the patient presented with mild, self-limited abdominal pain immediately after ingesting bass at her home, which resolved by decreasing its dose for 2–3 months and subsequently achieving tolerance to higher doses until reaching tolerance to a dose of 40 g of the fish. Likewise, she reported occasional self-limited oral allergy syndrome after eating hake at home during those months. She remained asymptomatic during exposure to cooking steam of different types of fish. At present, the patient consumes 80 g of hake three times per week, alternating this intake with 50 g of tuna, monkfish, bass, sole, or conger eel 2 days per week, without experiencing adverse symptoms.

Data regarding the size of the wheal observed with the SPT with hake and other fish performed at different times of the OIT are shown in Table 1. Specific IgEs to hake and carp

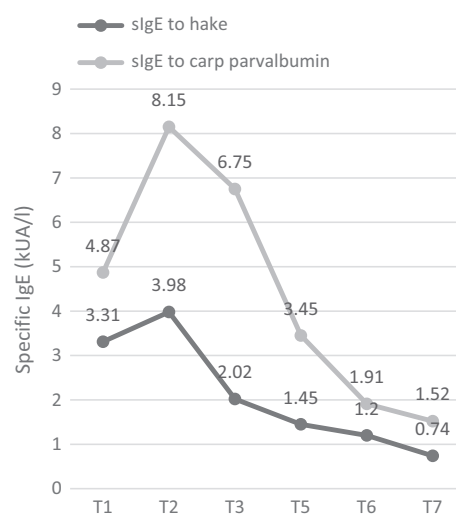


Figure 1 Specific IgE levels against hake and carp parvalbumin determined before and during OIT. T1: before OIT; T2: day 246 of build-up phase; T3: end of build-up phase; T5: fifth month of maintenance phase; T6: 1 year of maintenance phase; T7: eighteenth month of maintenance phase.

parvalbumin were measured at different times (Fig. 1) showing a decreased during the OIT. Specific IgG4/IgE against hake (T2: 1330, T3: 8086, T5: 7270, T6: 5347, T7: 13401) and carp parvalbumin (T2: 649, T3: 2272, T5: 2911, T6: 2465, T7: 5373) were also measured in different times. Unfortunately, sIgG4 basal level was not available. It is of note that hake SPT wheals started decreasing during hake immunotherapy until the fifth month of the maintenance phase (T5) and then increased reaching pre-treatment size at 12 months of the maintenance phase (T6), whereas IgE values decreased progressively from the second part of the build-up phase (T2). Interestingly, patient showed oral allergy symptoms with hake that coincides with low sIgE levels and high SPT to hake (T5–T6). Furthermore, after 1 year of the maintenance phase (T6), a significant increase in parvalbumin specific IgG4/IgE ratio was observed in parallel with hake tolerance in the OFC, even when SPT showed large wheal.

In this case, the patient tolerate other types of fish after performing OIT with hake, which enabled our patient to eat a complete portion of the fish, as well as of other types of fish such as tuna, monkfish, sole, and conger eel. However, it is true that tolerance to different fishes other than hake was not evaluated before the treatment because of ethical issues. We hypothesize that the induction of tolerance to other fish besides hake could be due to the wide cross-reactivity to the major allergen parvalbumin (8, 9), to which our patient showed sensitization. Hence, our experience suggests that sIgE to hake cross-reacts with other species such as tuna, monkfish, bass, sole, and conger eel, probably through parvalbumin, and also that immunologic changes beside sIgE can be

induced in order to tolerate different fishes using hake. In our opinion, this case is interesting as immunotherapy has not always been successful in treating allergy to molecules with wide cross-reactivity (i.e., different mammals' caseins) (10), because cross-reactivity between two allergens is not always similar in both senses. Large samples of fish-allergic patients treated with oral immunotherapy to a certain fish should be studied to assess whether tolerance to different species is always achievable or not. Furthermore, the performance of OIT in this case also enabled the patient to tolerate the exposure to fish cooking steam as it has been previously reported by Casimir et al. (7).

The patient's follow-up during 18 months after the desensitization build-up phase supports the efficacy of the treatment and the maintenance of the acquired tolerance. Further studies are needed to evaluate the efficacy and safety of performing OIT with fish in allergic patients and their clinical and immunologic evolution over the years.

We would like to thank Alberto Delgado, Sonia Ariz, and Maria Angeles Salgado for their helpful collaboration in the processes of lyophilization and measurement of the doses of LH during the OIT.

C. D'Amelio; G. Gastaminza; O. Vega; A. Bernad;
R. C. Madamba; R. Martínez-Aranguren; M. Ferrer & M. J. Goikoetxea
Department of Allergology and Clinical Immunology, Clínica Universidad de
Navarra, Pamplona, Spain
E-mail: migoiko@unav.es
DOI:10.1111/pai.12662

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