

LETTER TO THE EDITOR

Oral immunotherapy in children with persistent food protein-induced enterocolitis syndrome: case series

OIT in children with persistent FPIES

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Key words

Food protein-induced enterocolitis syndrome; oral food challenge; oral immunotherapy.

To the Editor

Acute Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated food allergy (FA), characterized by repetitive vomiting occurring 1-4 hours after ingestion of the culprit food, and sometimes by pallor, lethargy, and diarrhea (1).

The natural history of FPIES and the spontaneous acquisition of tolerance vary according to the trigger food and geographic region (2). In some children, tolerance is not achieved within the expected average time frame. If the average age mentioned above is exceeded by at least one year, we define these patients—as having persistent FPIES.

The treatment of FPIES currently consists of elimination of the trigger food from the patient's diet (1). In contrast, for IgE-mediated FA, oral immunotherapy (OIT) is available (3). However, in 2021, a case report (4) describing a patient with persistent acute FPIES to hen's egg successfully treated with OIT was published.

Here, we present our experience with OIT in a small cohort of patients with persistent FPIES.

Paediatric patients diagnosed with persistent acute FPIES were enrolled. Patients with atypical FPIES and patients who were unable to reach emergency access within 1 hour were excluded. The diagnosis of acute FPIES was made according to the International Consensus Guidelines (ICG) (1) or, if the criteria were

insufficient, based on a failed oral food challenge (OFC). The severity of the episodes was determined according to the ICG (1). Persistent FPIES was defined by the patient having continued reactivity to their food trigger for at least a year beyond the average age at which tolerance is achieved for that food trigger. The average age was established as follows: 24 months for cow's milk (5), 44 months for hen's egg (6), 53 months for fish (7), and 16,5 months for cereals (8).

The last acute FPIES episode, whether reported by history or following a failed OFC, had occurred within 1 month before study inclusion.

OIT was initiated at doses ≤ 30 mg of food protein, with dose escalations of 10% every 2 weeks over approximately 3 months. Thirty mg of protein remain significantly below the lowest threshold dose indicated by the ICG (1) in its summary statement n. 25, which is 150 mg of protein/kg body weight. In the absence of reactions or parental concerns, the rate of dose escalation was increased after patients reached one-third of the planned total OIT dose (see Table 2). Doses were administered at least four times weekly, with no more than two consecutive days missed.

Patient carers were asked to administer all doses of trigger foods, both the first and subsequent ones, at home and to observe the child whilst awake for at least 4 hours. Any interruptions and resumptions of OIT due to intercurrent events were managed via email. If the interruption exceeded 3 days, OIT was resumed at 50% of the last tolerated dose for one week, followed by reinstatement of the full dose. No specific recommendations regarding potential cofactors (e.g. exercise, nonsteroidal anti-inflammatory drugs, fever, etc.) were provided. Patients were provided with oral ondansetron and instructions for its use, providing them with an action plan (9).

Treatment adherence was monitored by sending weekly emails.

"Dietary therapeutic success" was defined as ingestion, without adverse reactions, of a normal age-appropriate serving of the implicated food at the end of the OIT escalation phase.

Once the OIT escalation phase was complete, patients were advised to consume a portion of the suspected food appropriate for their age at least twice a week. The maintenance phase was monitored by sending weekly emails.

The research protocol was approved by the Ethics Committee of the Agostino Gemelli University Polyclinic Foundation IRCCS - Catholic University of the Sacred Heart - Rome (protocol no. 0021260/24, ID: 6563; July 18, 2024). Written informed consent from all parents/legal guardians and assent from all children (when applicable) for all procedures performed and publication were obtained.

Between July 30, 2024 and August 6, 2025 seven patients were enrolled, their characteristics are described in Table 1. The results are summarized in Table 2. In brief: 5 patients successfully completed the the incremental phase of the procedure and are continuing without any adverse effects during the maintenance phase; 1 withdrew due to fear of adverse reactions, a concern shared by the parents (patient no. 3); 1 withdrew due to aversion to the implicated food (patient n. 4); no patient experienced adverse reactions; all patients tolerated the initial dose.

The first dose of the culprit food was administered at home in 5/7 patients. In two cases, parents requested that the first dose be administered in hospital. Subsequent dose escalations were always performed at home.

Email-based management was not particularly challenging, except in one case, which was probably due to language comprehension difficulties which were resolved with explanations repeated several times and using simple language. The average response time to caregivers' emails was 4 hours, ranging from 2 to 24 hours.

The treatment of FPIES currently consists of an elimination diet (1). However, OIT is emerging as a potential therapeutic strategy.

The pathophysiology of FPIES is not well understood (10). It has been shown that FPIES reactions are associated with systemic innate immune activation (11). An interleukin-17 (IL-17) inflammatory signature has been demonstrated in acute reactions, in both pediatric (12) and adult (11) populations. Perhaps OIT helps to regulate IL-17 production; specific studies will be needed to confirm this hypothesis.

Two studies on OIT in pediatric patients with FPIES have already been published (13, 14).

Ye et al (13) evaluated the Canadian Egg Ladder in children with mild acute FPIES to hen's egg (lethargy had to be absent), starting with baked egg products and progressively reducing the degree of cooking. The mean age at initiation of the procedure was 10 months (range = 9-11 months). Nineteen (90.5%) patients completed the procedure in 7 months, and 2 were still completing it at the time of publication. Four patients experienced symptoms defined as mild (vomiting, pallor, belching). Considering the young age at initiation, spontaneous acquisition of tolerance cannot be entirely excluded in some enrolled patients. Patients with mild FPIES to hen's egg are few. Therefore, the applicability of this protocol is limited.

Hamada et al (14) evaluated CAFI (continuous allergenic food intake) in 8 patients with FPIES, 5 of whom could be classified as persistent. The foods involved were: egg yolk, cow's milk, wheat, and soy. The mean age at CAFI initiation was 33 months (range 18-44 months). Patients began CAFI at home, with almost daily intake. The dose was gradually increased up to 100-fold in the absence of adverse reactions. Of the 8 enrolled patients, 7 achieved desensitization within 4 months. One patient with persistent FPIES to egg yolk discontinued CAFI due to abdominal pain. The authors emphasized that in FPIES, OIT should start with lower doses than those used for IgE-mediated FAs, but that dose increments may be performed much more rapidly. Indeed, the rate of dose escalation in this study (14) is remarkable.

The limitations of our study, as well as of the 2 similar ones (13, 14), include the absence of an untreated control population and the small sample size. Formally, spontaneous tolerance acquisition during the procedure cannot be excluded for any patient. However, recruitment of patients with persistent FPIES that was clearly active shortly before initiation of the procedure (as required by our protocol and as observed in 5/8 patients in Hamada et al [14]) reduces this bias, although it cannot completely eliminate it.

Conversely, the most relevant finding is the absence of the reported adverse reactions. This allows dose escalation to be performed at home, unlike what occurs in IgE-mediated FA (4). Consequently, waiting list issues may be bypassed, thereby reducing the duration of the procedure and associated costs. However, home-based dose escalation requires careful supervision and may not be generalizable to broader clinical practice.

For example, we believe that patients with atypical FPIES and those who were unable to reach emergency access within 1 hour cannot perform this procedure at home.

We also wish to emphasize that none of our patients experienced adverse reactions following ingestion of the first dose of the implicated food, which was always more than to the ED05 (« eliciting dose 5% », that is the dose capable of causing an allergic reaction in 5% of patients who are allergic to that food) defined in the VITAL 4.0 protocol (15). It is true that the VITAL 4.0 protocol was designed for IgE-mediated FA. However, for example, a patient with cow's milk FPIES who has tolerated our initial dose of 24 mg of cow's milk protein should not have adverse reactions after ingesting a food packaged with PAL (precautionary allergen labeling) for cow's milk, for which the ED05 according to the VITAL 4.0 protocol (15) is more than 10 times lower. In all our patients, the initial dose was at least four times higher than the respective ED05. This finding supports the suggestion contained in the ICG (1): “Do not routinely recommend avoidance of products with precautionary allergen labeling in patients with FPIES.”

Moreover, this procedure could potentially also be used for the introduction of new high-risk foods into the diet of children with FPIES, particularly in cases of multiple FPIES.

Our study is a small series of cases. It is certainly not possible to draw definitive conclusions. However, we believe we are on the right track: OIT in children with FPIES appears to be feasible. And indeed, it seems to be easier than OIT for IgE-mediated FA.

Ethics approval statement and patient consent statement

The research protocol was approved by the Ethics Committee of the Agostino Gemelli University Polyclinic Foundation IRCCS - Catholic University of the Sacred Heart - Rome (protocol no. 0021260/24, ID: 6563; July 18, 2024). Written informed consent from all parents/legal guardians and assent from all children (when applicable) for all procedures performed and publication were obtained.

Author Contribution Indication

Stefano Miceli Sopo conceived design of the study. Stefano Miceli Sopo and Francesco Mastellone drafted the article. Giovanni Cosimo Indirli, Lucia Liotti and Giulia Bersani acquired the data and researched the scientific literature, analyzed and commented on it. All authors gave final approval of the version to be published.

Material in the electronic repository

None

Data availability statement

The data are available on request from the corresponding author

Permission to reproduce material from other sources

No material from other sources has been reproduced

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We declare that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Table 1. General characteristics of the patients studied

Number of patients	7
Sex (M/F)	4M - 3F
Age at enrollment mean range	6 years, 5 months 2 years, 10 months - 9 years, 9 months
Diagnosis (number of patients) only medical history medical history and failed OFC	5 2
Single FPIES -----	7 -----
Multiple FPIES	0
Mild FPIES -----	0 -----
Moderate FPIES -----	5 -----
Severe FPIES	2
Typical FPIES -----	7 -----
Atypical FPIES	0
Triggering Food (number of patients)	• Cow's milk: 3 • Hen's egg: 1 • Bony fish: 1 • Wheat: 2
Associated Atopic Markers (number of patients)	• Family history of allergy: 1 • Atopic dermatitis: 2 • IgE-mediated food allergy: 1 • Allergic asthma: 0 • Allergic rhinitis: 0

Legend. FPIES = Food Protein-Induced Enterocolitis Syndrome

Table 2. Characteristics of Oral ImmunoTherapy in the patients studied

Patient	Age Last Reaction	Age OIT Initiation	Triggering Food	First Dose Setting	Initial Dose (food amount / protein amount)	Dose Escalation (%)	Final Dose Achieved# (food amount / protein amount)	OIT Duration (months)	Need for Masking	Number of Emails
1	2 y 9 m	2 y 10 m	Wheat	Hospital	300 mg / 30 mg	10–20%	100 g/13 g	19	Yes	37
2	8 y 1 m	8 y 1 m	Cow's milk	Home	0.5 mL /17 mg	10–20%	200 mL/7 g	19	Yes	127
3	7 y 6 m	7 y 7 m	Sole	Home	140 mg /30 mg	10–40%	10 g/1,7 g	13**	Yes	20
4	6 y 7 m	6 y 7 m	Cow's milk	Home	0.5 mL /17 mg	10–20%	10 mL/0,35 g	10**	No	40
5	5 y 8 m	5 y 9 m	Wheat	Home	200 mg /20 mg	20%	120 g/ 15,6 g	12	No	28
6	4 y 8 m	4 y 9 m	Cow's milk	Hospital	0.5 mL /17 mg	10–40%	200 mL/7 g	21	No	12
7	9 y 8 m	9 y 9 m	Raw egg	Home	0.1 mL /13 mg	10–30%	50 mL/6,5 g (1 egg)	19	Yes	36

Legend. OIT = Oral Immunotherapy; *Ongoing procedure; **Interrupted procedure; #caregiver report via email.