

RESEARCH LETTER

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Long-term medical treatment efficacy in patients with eosinophilic oesophagitis and oral food immunotherapy

To the Editor,

Oral immunotherapy (OIT) may be regarded as an alternative to elimination diet in patients with IgE-mediated allergy. Multiple studies show OIT can induce desensitization or even sustained unresponsiveness. However, the process does not come without risks. Prolonged maintenance treatment is required, and adverse reactions may occur.¹

The onset of eosinophilic oesophagitis (EoE) after OIT has been described. However, the relation between them has not yet been fully assessed. The prevalence of EoE in general population is estimated at 50/100000 but may be as high as 4.7% in allergic children.^{2,3}

A meta-analysis by Lucendo et al. reported a prevalence of EoE after OIT of 2.7%.⁴ A prospective study of our group showed EoE was diagnosed in 4.6% of the patients subjected to OIT.⁵

Nowadays, there is no consensus regarding management of EoE developed in the context of OIT, and many authors point out the risk

of severe allergic reactions after removing the previously tolerated food.

The aim of our study was to determine the prevalence of EoE in a cohort of patients with IgE-mediated allergy who have been subjected to OIT to milk or egg, as well as its management and long-term evolution.

A prospective observational study was conducted including children with cow's milk and egg IgE-mediated allergy who have undergone OIT in the last 15 years in the Paediatric Allergy Department.

They were treated with OIT due to persistent allergy demonstrated by clinical findings, prick testing, specific IgE quantification and a positive open oral food challenge.

Strict monitoring of gastrointestinal signs was carried out during and after OIT, performing a detailed medical history and physical examination on every consultation. None of the patients presented digestive symptoms prior to OIT. If suspected, patients were referred

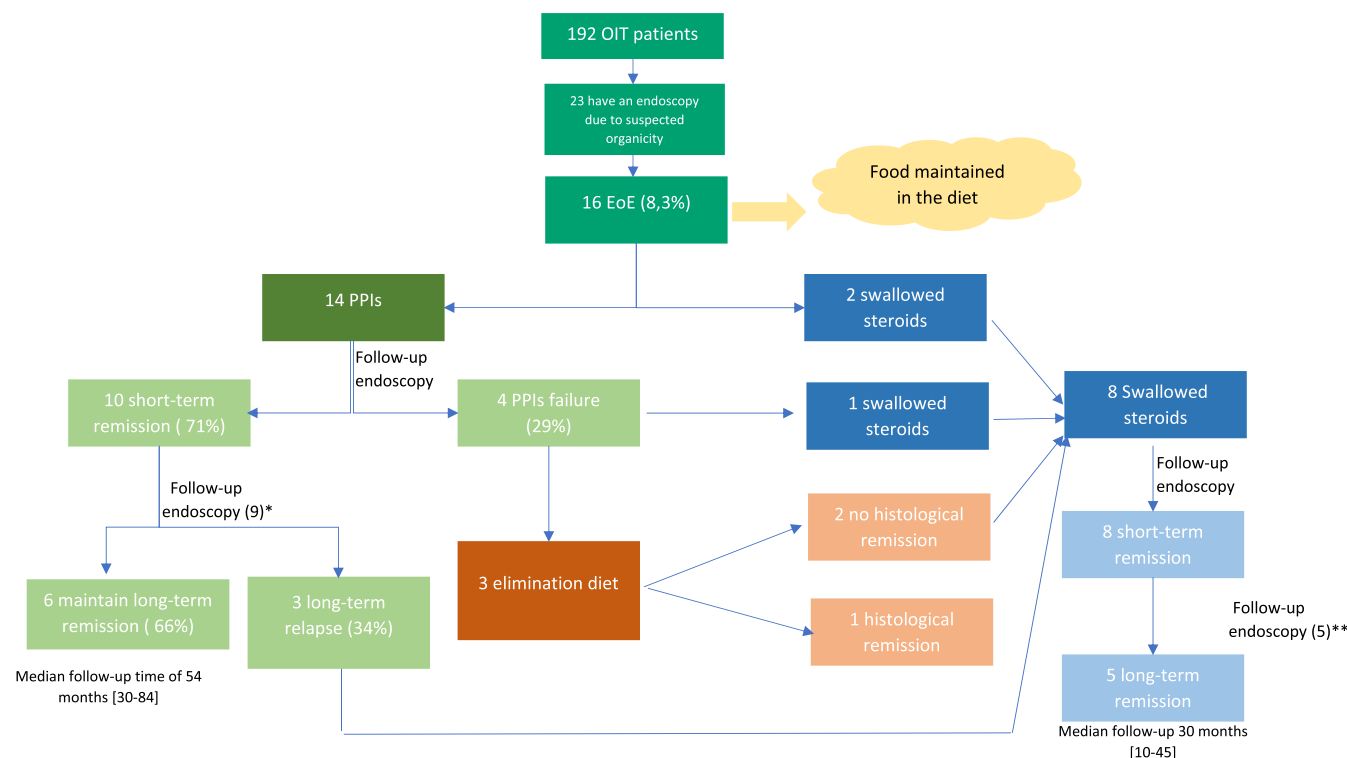


FIGURE 1 Evolution of 16 patients with eosinophilic oesophagitis after oral food immunotherapy. OIT, oral immunotherapy; EoE, eosinophilic oesophagitis; PPIs, proton pump inhibitors. *1 patient no time criteria reached to perform the endoscopy. **3 patients no time criteria reached to perform the endoscopy

to the Paediatric Gastroenterology Unit for evaluation. In cases with suspected organicity, an endoscopy was performed.

These procedures were carried out within the usual clinical practice and were approved by the Clinical Research Ethics Committee of Severo Ochoa University Hospital, and written informed consent was obtained from all patients' guardians.

The diagnosis of EoE was made following European guidelines: symptoms of oesophageal dysfunction in combination with eosinophil-predominant infiltration on oesophageal biopsy of ≥ 15 eosinophils per high power field (eos/hpf).⁶ Response to treatment was defined as less than 15 eos/hpf in all oesophageal biopsies upon repeat endoscopy done 8–12 weeks after baseline endoscopy. Long-term remission was established with a follow-up period of at least 6 months.

Children were excluded if they presented digestive symptoms prior to OIT or if duodenal or gastric eosinophilia were found.

Data collected included EoE characteristics, response to different therapeutic options and long-term evolution.

From 2006 to 2021, 192 children were subjected to OIT (149 with cow's milk and 43 with egg). Twenty-three had an endoscopy due to suspected organicity. Sixteen developed histologically proven EoE (8.3%). The remaining patients were asymptomatic and did not undergo endoscopy.

Most were males (68%) between the ages of 3 and 18 years old. All had a history of atopy (asthma, dermatitis, rhinoconjunctivitis, etc.), and 10 suffered from multiple IgE-mediated food allergies. Eleven were receiving milk OIT (69%), four were receiving egg OIT, and one was receiving both. EoE was diagnosed in only two cases during induction phase, due to persistent vomiting. The others were in maintenance phase after a median time of 46 months (24–78). Abdominal pain was the most frequent symptom (56%), followed by dysphagia (50%) and vomiting (31%). One was diagnosed as a result of an upper gastrointestinal bleeding due to food impaction.

Medical treatment was established as first therapeutic option in all patients, without food removal. Fourteen patients were treated with high-dose proton pump inhibitors (PPIs), and 10 achieved short-term remission (71%). After long-term follow-up, an endoscopy has been performed in nine patients, six of them maintaining remission (66%), with a median time of monitoring of 54 months (30–84). Eight patients were treated with swallowed steroids (six without short- or long-term remission with PPIs and two as first-line treatment), all of them achieving short-term remission. Five of these patients had a long-term follow-up maintaining remission, with a median period of 30 months (10–45).

Remission with medical treatment has been proven to be long term in 11 patients (68.7%), both histological and clinical (with symptoms resolution). In short-term follow-up endoscopies, the mean number of eos/hpf was 0.87 in distal oesophageal biopsies and 1.1 in proximal ones, and in long-term endoscopies 4.6 and 3.7, respectively.

Elimination diet was implemented, by their families' will, in three patients who did not respond to PPIs. Histological remission was achieved in one case only, but OIT could not be reintroduced in another patient who, despite not having achieved histological

Key messages

- An increase in cases of eosinophilic oesophagitis has been described among patients undergoing oral immunotherapy.
- Close monitoring is crucial to detect the appearance of digestive symptoms, requiring a long-term follow-up.
- Medical treatment for EoE can be effective without the need to withdraw the food involved.

remission, referred symptoms with the food intake (Figure 1, Table 1). Additional information about study methods and findings are available in the following repository <https://zenodo.org/record/6885326#.YtrTltJBm8>.

In our study, we have found a high prevalence of EoE among patients undergoing OIT (8.3%).

Although the development of eosinophilic gastrointestinal disorders following OIT has been described, the relationship between these entities remains controversial. Despite only a few studies have been published on this topic, the most studied mechanism of EoE pathophysiology during OIT is the increase in food-specific IgG4 and the formation of immunocomplexes, along with its subsequent deposition in the oesophagus.⁷ The epithelial barrier dysfunction predisposes to an increased antigen exposure, followed by a Th2 inflammatory reaction with an eosinophil chemotactic effect.

Lucendo et al. published a meta-analysis demonstrating a prevalence of EoE after OIT (for egg, milk, peanut or wheat) of 2.7% (95% CI 1.7%–4%).⁴ However, the high prevalence obtained in our study could be explained by the close long-term monitoring in the follow-up phase, which included a detailed medical history and physical examination on each visit. Such thorough long-term monitoring is undoubtedly one of the strengths of the study.

Concerning the diagnosis of EoE, there are neither pathognomonic signs/symptoms nor targeted laboratory tests available, besides the lack of correlation between the clinical and histological findings.

Gastrointestinal symptoms are generally reported during the desensitization schedule. In fact, in 30%–40% of the cases, immunotherapy is actually withdrawn because of this symptomatology. On the contrary, a histologically confirmed diagnosis of EoE is provided in a much lower percentage. However, this probably occurs as a result of an underestimate, since subjects with gastrointestinal symptoms do not routinely undergo endoscopy for confirmation. In such a light, a thorough evaluation at baseline, during symptom flares and in the remission phase, should be performed to fully enable a prime diagnosis of the disease.

In our series, only two of the cases of EoE were diagnosed during the induction phase. In the rest of the cases the time between OIT and the diagnosis was very variable, so being up to 10 years after the induction.

Regarding the relationship between EoE and allergy, it can be postulated that the introduction of food in our patients was not the

TABLE 1 Case summary

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Sex/Age (years)	Male, 5	Male, 7	Female, 9	Female, 11	Male, 3	Male, 9	Male, 11	Female, 18
Personal history	Asthma, multiple food allergies	Asthma	Asthma, multiple food allergies, celiac disease, AD, RCJ	Asthma, AD, RCJ	Asthma, multiple food allergies	Asthma, multiple food allergies, RCJ	Asthma, multiple food allergies, AD, RCJ	Asthma, RCJ
OIT food	Milk	Milk	Milk	Milk	Milk	Milk and egg	Egg	Milk
Time to EoE diagnosis after OIT	8 months	24 months	24 months	47 months	Induction phase	24 months	46 months	120 months
Clinical characteristics	Vomiting Abdominal pain	Food impaction Dysphagia Vomiting Abdominal pain	Abdominal pain	Vomiting Abdominal pain	Dysphagia Vomiting Abdominal pain	Dysphagia	Food impaction Dysphagia	Food impaction Dysphagia
Treatment	Food removal without remission. Long-term remission with topical steroids (3 years)	Long-term remission with PPIs (3 years)	Long-term remission with topical steroids (4 years)	Long-term remission with topical steroids (6 years)	Food removal without remission. Long-term remission with topical steroids (2 years)	Long-term remission with PPIs (5 years)	Long-term remission with PPIs (4 years)	Long-term remission with PPIs (4 years)

Abbreviations: AD, atopic dermatitis; PPIs, proton pump inhibitors; RCJ, rhinoconjunctivitis.

only possible cause involved. Given that an endoscopy is not indicated in asymptomatic patients prior to OIT, we cannot confirm if patients already had pre-existing subclinical disease or if the disease was newly developed after OIT. Furthermore, significant oesophageal eosinophilia has been reported in allergic patients prior to the beginning of OIT.⁸ Eosinophilia is usually transient and not associated with clinical symptoms. The long-term effects of asymptomatic eosinophilia are not established, but progression to structural disease that will cause symptomatic disease is possible.

Although EoE development in the context of OIT could be a reason to discontinue OIT,⁴ there is no consensus regarding management of such patients. Therefore, some issues may warrant discussions about treatment. A recent study describes persistent EoE despite OIT discontinuation, so the disease could be driven not only by the food antigen but also by other allergens.⁹ Immediate IgE-mediated hypersensitivity in patients with eosinophilic gastrointestinal disorders with prolonged food avoidance has been described, in some cases including severe anaphylaxis with food reintroduction.¹⁰ Perhaps the severity of the allergic reaction should help to assess the management decision.

Food avoidance significantly impacts the patient's quality of life, as well as compromising the growth and nutritional status.

In our study, OIT was maintained in most of the patients while PPI or swallowed steroids therapy was initiated, always taking into consideration the importance of making treatment decisions based on family and patient consensus. Clinical practice shows that most of these patients are usually reluctant to elimination diet once OIT

is successfully carried out. Medical treatment seems to have proved its effectiveness without need for elimination diets, similar to those without OIT history.

Strict monitoring is crucial to detect new digestive signs and symptoms not only during the induction phase but also requiring long-term follow-up. Treatment options should be handled on an individual basis and trying to maintain oral immunotherapy in order to improve their quality of life and to avoid allergic reactions due to the food removal. Further studies are needed to help assess the risks and benefits of maintaining OIT.

AUTHOR CONTRIBUTIONS

Marta García Vega participated in the study design, analysis and interpretation of data and drafting of the manuscript. Sonia Fernández-Fernández and Luis Echeverría Zudaire participated in the study design, data collection and revising the manuscript. Teresa Bracamonte Bermejo, Beatriz Cano del Águila, Pilar Vega Hernández and Estefanía Ortega Sánchez participated in the data collection and patients' recruitment. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

None of the authors have a conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
Male, 7	Female, 12	Male, 15	Male, 9	Male, 14	Male, 3	Male, 12	Female, 15
Asthma, multiple food allergies, AD, RCJ	Asthma, RCJ	Asthma, AD	Asthma, multiple food allergies, AD	Multiple food allergies, AD, RCJ	Asthma, multiple food allergies, RCJ	Asthma, RCJ	Asthma, multiple food allergies
Egg	Milk	Egg	Milk	Egg	Milk	Milk	Milk
46 months	60 months	Induction phase	36 months	96 months	2 months	96 months	132 months
Dysphagia Pyrosis	Dysphagia Abdominal pain	Vomiting Abdominal pain	Chest pain	Food impaction Gastrointestinal bleeding	Abdominal pain Dysphagia	Abdominal pain	Nausea Reflux
Long-term remission with PPIs (7 years)	Short-term remission with topical steroids	Long-term remission with topical steroids (6 months)	Long-term remission with PPIs (1 year)	Short-term remission with topical steroids	Short-term remission with topical steroids	PPIs failure Food removal	Long-term remission with PPIs (6 months)

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