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Treatment with proton pump inhibitors as a cofactor in adverse reactions of patients undergoing oral food immunotherapy

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Abstract

Background and objectives: Based on previous studies revealing acid-suppression medication as a risk factor for food allergy tolerance induction, we aimed to establish the importance of those findings in patients undergoing oral immunotherapy (OIT).

Materials and methods, results: We describe a case series of four patients who underwent milk OIT with a concomitant use of proton pump inhibitor (PPI) medication and who developed anaphylaxis after a known, previously tolerated dose of milk.

Conclusions: PPIs may act as a cofactor in patients undergoing OIT, triggering adverse reactions, irrespective of the PPI used or the dosage. It would be necessary to separate the administration of drug from food intake.

Since OIT is a new form of treatment, long-term adverse events arising from PPI treatment and other possible triggers are still uncertain. Consequently, monitoring of patient must be prolonged over time. Additional investigations on the influence of different drugs in OIT maintenance phase are required.

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Introduction and objectives

Oral immunotherapy (OIT) with cow's milk may be regarded as an alternative to elimination diet. Multiple studies have demonstrated that OIT could induce desensitization or even sustained unresponsiveness. However, the process is not risk-free. Prolonged maintenance treatment is required, and adverse reactions may occur. Some of these reactions are triggered by known cofactors such as infections, exercise, and nonsteroidal anti-inflammatory drugs.¹

In addition, the onset of eosinophilic esophagitis (EoE) after OIT has been described, although the relation between them has not been fully assessed. The prevalence of EoE in the general population is estimated at 1.1% but this increases to 8.3% in allergic children.^{2,3} A meta-analysis done by Lucendo et al. reported an EoE prevalence of 2.7% after OIT.⁴ Another prospective study has demonstrated that primary eosinophilic gastrointestinal disorders were diagnosed in 6.25% of the patients subjected to OIT.⁵

Provided that gastrointestinal symptoms, such as reflux or development of EoE, could occur in the context of OIT, patients would require treatment with proton pump inhibitors (PPIs). PPIs alter the processing of food allergens by activation of conformational changes in food proteins, which could favor their recognition by specific immunoglobulins (Igs). Elevation in the gastric pH leads to reduced pepsin activation, enabling persistence of ingested epitopes and their uptake in the intestines, resulting in eosinophilic inflammation and allergic symptoms. In addition, the increased gastric pH results in the persistence of otherwise digestion-labile proteins, which remain stable, and their conformation intact enhances the possibility for *de novo* sensitization and formation of antigen-specific Ig.⁶

Based on previous studies revealing acid-suppression medication as a risk factor for food allergy tolerance induction, we aimed to establish the importance of those findings in patients undergoing OIT.

Patients

Our case series includes four patients, aged between 7 and 12 years, who were in the maintenance phase of milk OIT for at least 2 years. They were treated with OIT due to persistent allergy demonstrated by clinical findings, prick testing, specific Ig (i.e., Ig-E), and a positive oral food challenge.

This study was approved by the Clinical Research Ethics Committee of Severo Ochoa University Hospital, Madrid, Spain, and written informed consent was obtained from all patients.

Three of the four patients were diagnosed with EoE and the fourth one suffered from non-eosinophilic gastritis. Diagnosis was made following European guidelines on EoE: symptoms of esophageal dysfunction in combination with eosinophil-predominant infiltration on esophageal biopsy of ≥ 15 eosinophils per high power field.⁷

Although EoE development in the context of OIT could be a reason to discontinue OIT, there is no consensus regarding management of such patients. In our case, all the patients were initially treated with PPIs because they had been in the OIT maintenance phase for a long time, so a possible causal relationship between OIT and EoE was difficult to establish.

Besides, we were not able to confirm its previous existence since endoscopic study before OIT was not indicated. Moreover, PPI treatment seems to have proved its effectiveness in these patients, reaching rates of success similar to those in EoE patients without OIT history. Finally, we considered the importance of making treatment decisions based on family and patient consensus. Clinical practice established that most of these patients were usually reluctant to elimination diet once OIT is successfully carried out.

Results

Oral immunotherapy was maintained and treatment with PPIs implemented, including omeprazole, esomeprazole, and lansoprazole, using standard or high doses depending on the underlying medical condition. The first drug administration took place between 1 and 4 h after the daily milk intake. In the following 15 min, patients presented urticaria, angioedema, and respiratory distress.

They received treatment with antihistamines, oral corticosteroids, and bronchodilators with a good and quick response. One of them required intramuscular adrenaline. Symptoms disappeared within the first 24 h. The existence of other known triggering factors was ruled out. Prick tests for PPIs were negative, and oral challenge for the involved drug was performed without immediate or delayed symptoms (Table 1).

Conclusions

This finding suggests that PPIs could have a role as a cofactor of adverse reactions in patients undergoing OIT.

However, the findings of this study must be seen in the light of some limitations, since it is an observational study with a limited sample size and without a control group.

Oral immunotherapy is a novel form of treatment, and long-term safety is poorly reported, so long-term adverse effects remain unknown, and the possible cofactors and underlying mechanisms are unclear.

Previous studies have revealed that acid-suppression treatment interferes with the digestion of proteins, leading to IgE induction and food allergy. This enhances the possibility for *de novo* sensitization and formation of antigen-specific Igs, which leads to the promotion of T-helper 2 immune milieu, generating structural changes in the intestinal epithelium.^{6,8}

The small intestine is considered the main organ of intolerance development and food allergy induction. Selective intestinal permeability is essential for the uptake of nutrients and oral tolerance. A dysfunctional gastrointestinal barrier has an essential contribution to food allergic reactions. Hypoacidity of the stomach is associated with modified composition of intestinal microbiota. A recent meta-analysis revealed that PPIs have a more prominent effect on microbiota composition than antibiotics.⁹

A study has demonstrated that children with a previous history of taking antacid medication had a greater prevalence of food allergy (57% vs 32%, $P = 0.008$).¹⁰

Table 1 Clinical characteristics of the study population

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Female	Female	Male
Age (years)	7	8	12	10 years
Maintenance phase of cow milk OIT	2 years	2 years	6 years	3 years
Disease	Eosinophilic esophagitis	Gastritis	Eosinophilic esophagitis	Eosinophilic esophagitis
PPI	Lansoprazole	Omeprazole	Esomeprazole	Esomeprazole
Adverse reaction	Angioedema + Respiratory symptoms	Urticaria + Angioedema + Respiratory symptoms	Urticaria + Respiratory symptoms	Urticaria + Respiratory symptoms
Treatment of adverse reaction	Antihistamines + Corticosteroids + Bronchodilators	Antihistamines + Corticosteroids + Bronchodilators + Epinephrine	Antihistamines + Corticosteroids + Bronchodilators	Antihistamines + Bronchodilators
Time to clinical resolution	<24 hours	<24 hours	<24 hours	<24 hours
Time after first dose drug administration	1 hour	4 hour	2 hour	1 hour
Time after cow milk intake	5 minutes	15 minutes	15 minutes	20 minutes
Trigger factor (exercise, NSAIDs...)	No	No	No	No
Prick test for PPIs	Negative	Negative	Negative	Not performed.
Oral challenge for the PPI involved	Negative	Negative	Negative	Not performed. Still under treatment.

OIT: oral immunotherapy; NSAIDs: nonsteroidal anti-inflammatory drugs (NSAIDs); PPI: proton pump inhibitor

In another observational cohort study of 152 patients (none of them with previous history of allergy or atopy), anti-acid drugs were given for 3 months. IgE sensitization to food allergens was compared before and after the treatment. The relative risk to develop food-specific IgE after treatment was 10.5. The long-term effect was evaluated 5 months after the therapy. Food-specific IgE could still be found in 6% of the patients as well as elevated serum concentrations of an IL-33 receptor (ST2), a Th2-specific marker.¹¹

In mouse models, gavage of digestion-labile food allergens together with antacids resulted in formation of allergen-specific IgE antibodies, positive skin tests, a drop in core body temperature, and mast cell mediator release, which all are associated with anaphylactic reactions.¹²

In conclusion, the role of PPIs as a cofactor of adverse reactions in patients undergoing OIT is a finding of considerable interest and could have significant implications for clinical practice.

These drugs may be considered as a cofactor, irrespective of the PPI used or the dosage. It would be necessary to separate the administration of the drug from food intake.

Since OIT is a new form of treatment, long-term adverse events arising from PPI treatment and other possible triggers are still uncertain. Consequently, patient monitoring must be prolonged over time.

Additional investigations on the influence of different drugs in OIT maintenance phase are required.

Declarations of interest

None.

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