

Oral and Sublingual Immunotherapy: Potential Causes for Eosinophilic Gastrointestinal Disorders?

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Abstract

Food allergy is a common health problem worldwide, with increasing prevalence during recent decades. The only approved treatments for food allergy are food avoidance and administration of emergency medications in case of accidental exposure, which negatively affects patients' quality of life, so new treatments are highly desirable. Different food immunotherapy modalities have recently been used, with variable success rates in the induction of desensitization and tolerance, and different numbers and types of adverse reactions. Adverse reactions, especially intolerable gastrointestinal symptoms, are the most important causes of immunotherapy withdrawal. Eosinophilic esophagitis has been reported as a complication of milk, egg, and peanut oral immunotherapies and sublingual immunotherapy for respiratory allergies, but not for food allergies. Eosinophilic gastritis and eosinophilic colitis also rarely happened following egg and milk oral immunotherapies. The patients undergoing oral and sublingual immunotherapies should be closely

followed up for a long time, and those with gastrointestinal symptoms should be evaluated by endoscopy of the gastrointestinal tract. These complications are usually reversible after early diagnosis and stopping the immunotherapy protocol.

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Introduction

Food allergy (FA) is an important growing health problem throughout the world. The only approved treatments for FA are food avoidance and administration of emergency medications. Avoidance leads to multiple psychological and nutritional defects, and negatively affects the patients' quality of life; moreover, accidental exposures might be life threatening [1–4]. New therapeutic approaches and different immunotherapy modalities have been investigated recently; among them, oral immunotherapy (OIT) has attracted more attention. Overall, 10–20% of the subjects could not complete their OIT trial [4, 5]. Although some withdrew OIT because of anaphylaxis or other acute reactions, most of them could not continue because of chronic intolerable gastrointestinal symptoms [5]. Here we will review the potential gastrointestinal

complications of OIT in detail. As some of these complications were also reported following sublingual immunotherapy (SLIT), these data will also be reviewed at the end.

Food Allergy

FA is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [1]. This response comprises all types of immune-mediated reactions. The prevalence of FA has increased during the past 2 decades. FA affects up to 8% of young children and 3–6% of the entire US population [1–4, 6]. In developed countries, IgE-associated FA affects 3–8% of children and 1–3% of adults [7]. Moreover, in the EuroPrevall birth cohort study, self-reported adverse reactions to food ranged from 30% in German mothers to 5–8% in mothers from Spain [8].

Adverse reactions to foods, including food intolerances or adverse physiological reactions, are often misclassified as IgE-mediated food reactions. Self-reported FA is more common than proved FA [9], therefore the precise diagnosis of FA and differentiating nonallergic food reactions are necessary to confirm the diagnosis [10]. Recently chip-based assays have provided information about cross-reactivity among different sources of food allergens, and identified disease-causing food allergens [7].

Although more than 170 foods could be triggers of FA, a relatively small number of allergens cause a high proportion of food allergies, such as peanut, tree nuts, fish, shellfish, milk, egg, wheat, soy, and seeds [9, 11]. The type of allergenic foods might be different in some countries and needs local studies [12].

The Course of Natural Tolerance

The rate of allergy resolution varies according to the food, the patient's age, the pathophysiology of the allergy, and some other factors and is not well characterized for most foods [10, 13]. Most children with FA eventually tolerate milk, egg, wheat, and soy [13]. Milk allergy is the most common FA in children. Milk allergy resolves in approximately 80% of patients by the age of 5 years, but other studies have shown that 19% of them resolve at the age of 4 years and 79% by the age of 16 years [1, 10, 14]. Similar findings have been observed for egg allergy [15]. Regarding wheat and soy, resolution rates are slightly more rapid, 29 and 25% by the age of 4 years, respectively, while 65% of wheat allergies resolve by the age of 12 years, and

69% of soy allergies resolve by the age of 10 years [9, 16]. Allergy to peanut and tree nuts persists more often, and the natural resolution rate for peanut allergy is about 15% [17]. It is somehow lower for fish and shellfish allergy [18].

Immunotherapy Modalities in FA

The only currently approved treatment for FA is avoidance and administration of emergency medications for accidental exposure. Despite precautions taken by patients and their families, accidental ingestion of the culprit foods may cause severe reactions [19]. In brief, FA causes significant impairment in the patient's quality of life [20] and can lead to nutritional deficiencies [21]. Due to the growing prevalence of FA and its associated morbidities, safe and effective therapies are highly desirable.

Immunotherapy relies on the delivery of increasing doses of specific allergens over a period of weeks or months to develop desensitization and induce tolerance in patients with IgE-mediated food allergies [22]. The exact mechanisms underlying allergen immunotherapy are still not fully understood. Immunotherapy induces an early and transient increase in allergen-specific regulatory T cells, which deviate Th2 responses to Th1 responses. Moreover, it can increase the level of allergen-specific IgG4 antibodies and reduce mast cell and basophil activation and mediator release [4, 23–25]. It has not been clearly established whether the clinical tolerance induced by OIT resembles natural tolerance or not [25].

Immunotherapy has been successfully used to treat asthma, allergic rhinitis, and venom hypersensitivity. Immunotherapy also shows promise in the treatment of FA. In the 1990s, the subcutaneous immunotherapy for peanut allergy caused a high rate of life-threatening side effects and became unacceptable [26]. The first randomized placebo-controlled SLIT for hazelnut allergy was published in 2005 [27]. Subsequent studies focused on alternative routes of allergen delivery to induce tolerance, while at the same time increasing its safety. OIT, SLIT, and epicutaneous immunotherapy as well as other novel approaches are the potential future treatments for patients with persistent FA.

Oral Immunotherapy

Regarding the high prevalence of FAs, the negative effect of food avoidance on the patients' quality of life, and the potential for life-threatening accidental exposures,

OIT seems to be a promising tool in the treatment of FA. In spite of mild to moderate symptoms during the therapy, OIT seems to be effective in inducing desensitization [25].

The OIT methods generally include an initial rapid dose escalation phase, followed by a slower buildup phase to reach the maintenance dose; indeed, they may vary in details [4]. The effectiveness of treatment is evaluated by an oral food challenge test, after a certain period of allergen avoidance. The final oral food challenge is performed to distinguish transient desensitization from the sustained unresponsiveness.

The majority of studies revealed that OIT increases the threshold of reactivity to the causative food. After early case reports of successful peanut OIT [28, 29], several peanut OIT trials showed a significant increase in the threshold of reactivity after OIT [30–34]. Studies on egg OIT also generally showed positive results [35–37]. The majority of studies on milk OIT showed successful desensitization [38–44]. Ebisawa et al. [45] performed OIT to treat food-induced anaphylaxis and enrolled 227 patients with egg, cow's milk and wheat anaphylaxis. This study showed different efficacies among different food antigens [45, 46]. Moreover, patient compliance is an important factor influencing the success rate of OIT [47].

Patient safety is a critical issue for OIT to be successful and acceptable. The frequency of adverse reactions was variable in different studies, but this mainly included mild to moderate reactions. Local symptoms, such as oral pruritus and transient abdominal pain, are the most common and generally require either no treatment or antihistamine alone [4, 25, 48]. Although a recent review [4] has reported a similar rate of adverse reactions in milk, egg, and peanut OITs, in another trial, milk, egg, and wheat had higher adverse reactions [25, 45]. Cofactors, such as infection, exercise, or allergen coexposure, may be associated with an increased risk of reaction [4, 25]. The overall risk associated with the allergen exposure varies with the patients' characteristics. The small number of enrolled patients and the fact of excluding patients with a history of severe reactions or anaphylaxis make it hard to draw conclusions. Eosinophilic gastrointestinal disorders (EGIDs) have been documented in some of the patients undergoing OIT and SLIT. It becomes a matter of concern as an undiagnosed complication of immunotherapy in patients with chronic intolerable gastrointestinal symptoms. Although immunotherapy appears to be effective in the treatment of FA and induces desensitization without major morbidity or mortality, at the present time it is not ready for implementation in clinical practice.

OIT and Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is one of the EGIDs, affecting children and adults. It is a chronic antigen-mediated esophageal disease, characterized by dysphagia and symptoms of food impaction. The diagnosis is made based on the patients' clinical symptoms, histopathological examination demonstrating more than 15 eosinophils/high-power field (HPF) and unresponsiveness to proton pump inhibitors [49]. The prevalence of EoE has increased considerably during the last few decades [50, 51]. EoE is caused by food allergens in a substantial number of children, so the elimination diet is an effective therapeutic approach in childhood, but adults with EoE are mostly sensitized by aeroallergens [52].

EoE has been suggested as one of the complications of food OIT in recent years. Adverse reactions are common in initial doses of OIT, but long-term complications are not sufficiently studied. For the first time, Hofmann et al. [53] reported that among 28 children undergoing OIT for peanut allergy, 1 patient could not complete the OIT protocol and stopped it during maintenance dosing because of the development of EoE, which resolved several weeks after discontinuation of peanut OIT.

In 2011, Ridolo et al. [54] reported a case of EoE following OIT for egg allergy. They presented an 11-year old boy, with egg allergy from the age of 1 year. He underwent a 2-month egg OIT protocol when he was 10 years old and developed solid food dysphagia and dyspepsia 5 months after completing the OIT. EoE was diagnosed according to endoscopy and histopathological findings and resolved after 3 months of adhering to an egg-free diet and oral steroid therapy.

In another retrospective study, 3 of 110 patients undergoing OIT for treatment of milk allergy were reported to develop EoE, 3 and 14 months after achievement of the final dose of 200 mL of milk (confirmed by endoscopy and histopathological findings). These patients recovered after a milk-free diet. One of the patients had undergone endoscopy before starting OIT, and no sign of inflammation or eosinophilic infiltration had been observed [55].

In a randomized clinical trial, comparing the efficacy of OIT and elimination diet in the treatment of children with egg allergy, among 40 patients in the OIT group, 1 was withdrawn from the trial because of EoE development [56].

There is also another report of EoE development in a 3-year-old girl during milk OIT, confirmed by endoscopy and histopathology evaluations, which turned to normal

Table 1. The characteristics of all published cases of EoE and EG following OIT

First author [ref.], year	Design	Type of OIT	Number of cases included	Number of cases developing EoE/EG	Timing of start of symptoms	Resolution upon avoidance or OIT discontinuation	Time of symptom resolution after avoidance
Hofmann [53], 2009	Prospective	Peanut	28	1 EoE	During maintenance phase	Yes	Several weeks
Ridolo [54], 2011	Case report	Egg	1	1 EoE	5 months after completing OIT	Yes	3 months after avoidance and treatment with methylprednisolone
Sánchez-García [55], 2012	Retrospective	Milk	110	3 EoE	1: 14 months after completing OIT 2, 3: 3 months after completing OIT	Yes	1, 2: after 3 months of avoidance and 2 months of treatment with omeprazole and oral fluticasone 3: 8 months after avoidance
Fuentes-Aparicio [56], 2012	Randomized clinical trial	Egg	40	1 EoE	During escalation phase	Not mentioned	
Morais Silva [57], 2014	Case report	Milk	1	1 EoE	During escalation phase (3 weeks after starting OIT)	Yes	4 months after avoidance and treatment with oral fluticasone
Semancik [58], 2016	Case series	Peanut	3	3 EoE	1: 2 weeks after starting OIT 2: 2 weeks after changing OIT to whole peanuts 3: 1–2 weeks after changing OIT to whole peanuts	Yes	1: not mentioned; normal endoscopy 4 months after stopping OIT and treatment with lansoprazole 2: not mentioned; normal endoscopy 3 months after stopping OIT 3: not mentioned; normal endoscopy 6 months after stopping OIT, treatment with lansoprazole, and dairy-free diet
Okamoto [76], 2015	Case report	Egg	1	1 EG	During maintenance phase	Not mentioned	
Echeverría-Zudaire [59], 2016	Prospective	Milk and egg	128	6 EoE 2 EG	6 after completing OIT (with a median time of 29 months) 2 in induction phase of OIT	Yes ¹	Not mentioned
Babaie [68], 2017	Prospective	Milk	18	1 EoE	During escalation phase	Yes	Several weeks after stopping OIT

EoE, eosinophilic esophagitis; EG, eosinophilic gastroenteritis; OIT, oral immunotherapy. ¹ OIT was discontinued only in 3 patients, with complete resolution. Among 5 other patients, symptoms resolved without OIT discontinuation in 3 patients (with proton pump inhibitors or corticosteroid therapy).

4 months after treatment with swallowed topical fluticasone and a milk-free diet [57].

Recently, Semancik and Sayej [58] have reported 3 cases of EoE following peanut OIT. The patients had presented EoE symptoms a few weeks after starting or a change in dose of their peanut OIT, with complete or partial improvement after OIT cessation.

Another prospective study, published in 2016, reported a higher prevalence of EoE and eosinophilic gastroenteritis (EG) in 128 children undergoing milk and egg OIT. Among 97 children in the milk OIT group, 7 (7.2%) developed EoE or EG, and among 31 patients in the egg OIT group, 2 (6.4%) developed EoE. OIT was discontinued in both patients with EG and 1 of the patients with EoE,

which was followed by histological remission. Among 5 other patients, 3 achieved histological remission by proton pump inhibitors alone or in combination with swallowed fluticasone, 1 remained histologically active, and 1 refused follow-up endoscopy [59]. Table 1 summarizes the characteristics of all published cases of EoE and EG following OIT.

Some other reports during 2009–2013, published as abstracts, also described variable but not large numbers of patients developing EoE following milk and peanut OITs [60–67]. In our experience among 18 patients who underwent milk OIT, 1 patient developed EoE. Her symptoms were relieved after stopping OIT and starting a milk-free diet [68].

Putting together about 12 studies published in this field in a systematic review with meta-analysis in 2014, the overall prevalence of EoE after OIT was reported to be as high as 2.7% (95% confidence interval 1.7–4.0%) [69].

Gastrointestinal symptoms are common in patients undergoing OIT, but as diagnosis of EoE is dependent on an invasive procedure like endoscopy and biopsy, the true prevalence of EoE might be higher than reported in the above-mentioned articles. On the other hand, as endoscopy is not done regularly before starting OIT, it cannot be firmly concluded that it is a consequence of OIT or exacerbation of a previous subtle EoE [70]. Although different articles have reported EoE as a complication of OIT, almost all the patients (except 1) improved after discontinuation of OIT.

Changes in cytokine responses, reduced allergen-specific IgE, increased allergen-specific IgG4, diminished Th2 and increased regulatory T cells are reported following OIT, but other contradictory features like increased levels of interleukin-5 and tumor necrosis factor- α and decreased numbers of Foxp3 regulatory T cells, 12 months after OIT, have also been demonstrated, which can be associated with OIT complications [25, 33]. The most recognized immunological mechanism of EoE development following OIT is an increase in food-specific IgG4 and its deposition in the esophagus. Food-specific IgG4 decreases the following dietary elimination of the offending food [71]. Allergen-specific IgG and IgA increase after OIT [72]. Allergen-specific IgG subclasses (1–4) and IgA are able to bind to an allergen, act as an immune complex, and activate eosinophils; hence, they can induce eosinophil activation after SLIT or OIT and probably lead to the development of EoE [73].

It was suggested that the esophageal epithelium can behave as a nonprofessional antigen-presenting cell in the influence of the inflammatory cytokines like interferon- γ . These epithelial cells may contribute to EoE pathogenesis by presenting antigens on the major histocompatibility complex class II molecules. The participation of these numerous populations of cells in the pathogenesis of EoE may explain the higher incidence of EoE after OIT comparing other types of immunotherapy [74].

OIT and EG and Eosinophilic Colitis

EG and eosinophilic colitis (EC) are subgroups of EGIDs, along with EoE. EG is defined as an EGID, with involvement of the stomach and/or small intestine, with variable involvement of the esophagus and large intestine.

EC involves the large intestine alone [75]. Although there have been multiple case reports of EoE during or following OIT, little has been reported of EG, and as far as we know, no reports of EC during or following OIT exist [59, 69, 76].

Symptoms of EG and EC are known to differ according to the part of gastrointestinal tract involved and depth of eosinophilic infiltration [77]. Nonspecific gastrointestinal symptoms such as nausea, vomiting, dyspepsia, abdominal pain, and diarrhea are commonly seen.

Diagnosis is made when gastrointestinal symptoms are accompanied by the presence of marked eosinophilic infiltration of the gastrointestinal tissue on endoscopic biopsy, and other causes of eosinophilic infiltration have been excluded [78]. However, unlike EoE, consensus on the histological criteria for diagnosis of EG and EC has not yet been reached. Blood tests may be useful for the diagnosis of EG since peripheral eosinophilia is reported in 70–90% of confirmed cases, while it seems to be not as useful in the diagnosis of EoE [79–81].

The pathogenesis of EG and EC is not yet fully understood, but unlike EoE, they are considered to be Th2-type inflammatory diseases in which food exposure leads to eosinophilia in the gastrointestinal tract [82, 83]. There are case reports of EG in which a single FA was found to be the cause [84, 85], and a patient placed on an empirical elimination diet was also reported to show improvement of the symptoms [86]. Elemental diets were reported to be effective in a majority of EG patients, which also suggests that exposure to food antigens may be the cause, but the results were questionable due to the lack of objective evaluation of clinical and histological changes [87]. Although more studies are needed, at least a subset of patients with EG and EC seems to be associated with FA.

Due to the proposed association between FA and EG and EC, the initial treatment is usually dietary intervention but when it is not effective, use of oral corticosteroids has been most frequently reported [79, 88–90].

A case report from Japan reports a 9-year-old boy, who presented with vomiting, abdominal pain, and weight loss soon after the rush phase of OIT for hen's egg in which the child had become able to consume a maintenance dose of 1 boiled egg. Blood tests showed a remarkable increase in peripheral blood eosinophil count, and endoscopic biopsy of the upper gastrointestinal tract revealed diffuse eosinophilic infiltration from the esophagus to the duodenum, confirming the diagnosis of EG with concurrent involvement of the esophagus [76]. A recent article has also reported 2 cases of EG following milk OIT [59].

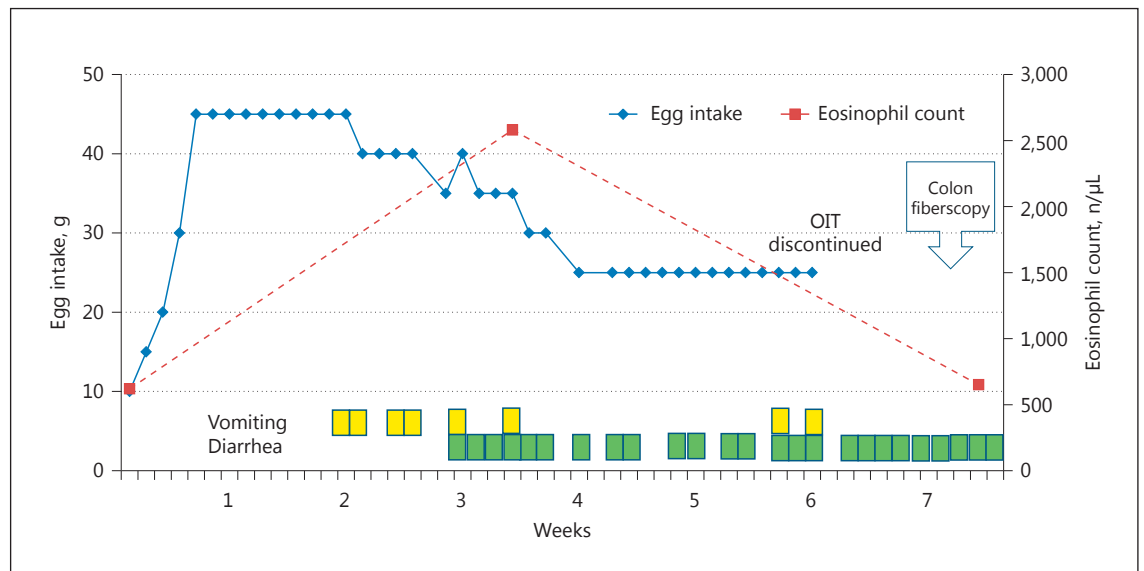


Fig. 1. Clinical course of EC during egg OIT in 1 patient. The full blue line (colors in the online version) represents egg intake (in grams), and the dashed red line indicates the eosinophil count in the patient's peripheral blood (per microliter). Yellow squares are representative of vomiting episodes and green squares of diarrhea episodes.

We experienced 2 cases of EC during OIT at our hospital (Sagamihara National Hospital, Sagamihara, Japan). One case was a 10-year-old boy, who underwent OIT for hen's egg. He presented with vomiting and abdominal pain 1 week after the rush phase of OIT for hen's egg in which he had become able to consume a maintenance dose of 1 cooked egg. The amount of egg ingested was decreased according to the OIT protocol, but after 2 weeks, he started to experience recurrent diarrhea and abdominal pain. An increase in peripheral blood eosinophil count was seen, and the diagnosis of EC was confirmed with endoscopic biopsy, which revealed eosinophilic infiltration throughout the entire colon. A 3-week period of hen's egg elimination did not lead to resolution of symptoms, and treatment with oral corticosteroids was required. The clinical course of this patient is summarized in Figure 1. We also experienced another case in a 13-year-old boy, who had undergone OIT for cow's milk (unpublished data).

OIT and Acute Pancreatitis

There are no reports concerning acute pancreatitis during OIT, but the possibility should be kept in mind. EG involving the duodenum was reported to induce acute

pancreatitis due to obstruction of the pancreatic duct caused by eosinophilic inflammation of the papillary region [84, 85, 91–94]. There is also a report of 2 patients with acute pancreatitis after an oral food challenge, which was possibly due to edema of the papillary region caused by an allergic reaction to the challenged food [95]. When severe abdominal pain is seen in patients undergoing OIT, screening for the possibility of acute pancreatitis by measuring pancreatic enzymes should be considered.

SLIT and EoE

SLIT was approved by the World Health Organization as a treatment for allergic disorders in adults in 1998 and for children in 2001 [96]. Since then, it has been progressively applied as a treatment for food and pollen allergies in adults and children [97]. EoE has been repeatedly reported as an adverse reaction following OIT with milk, egg, and peanut, but it has also been reported to happen following SLIT in some cases.

For the first time, Miehlke et al. [97] presented a 44-year-old woman, who demonstrated the clinical symptoms of EoE following SLIT. She was receiving SLIT with a combination of hazelnut, birch, and alder extracts for the treatment of her allergic rhinitis and asthma and

developed dysphagia 4 weeks after starting SLIT. The presence of more than 164 eosinophils/HPF in an esophageal biopsy specimen confirmed the diagnosis of EoE. Clinical and histological findings resolved 4 weeks after withdrawal of SLIT.

Bauer et al. [98] also reported a 9-year-old autistic boy with a history of allergic rhinoconjunctivitis, asthma, and severe feeding disturbance. Esophageal tissue biopsy showed more than 57 eosinophils/HPF, with no response to an elemental diet and local corticosteroids. Further evaluations demonstrated that he had been undergoing SLIT (grass, tree, and dust mite) for about 1 year previously. SLIT and topical corticosteroids were discontinued, and the elemental diet was restarted. Esophageal eosinophilia was resolved in the follow-up endoscopy 1 year later [98].

In another similar report, Patel and Menon [99] described an 11-year-old boy, who developed burning epigastric pain, dysphagia and odynophagia several months after grass SLIT, which was unresponsive to proton pump inhibitors. Esophageal biopsy showed more than 37 eosinophils/HPF, and the symptoms resolved after cessation of SLIT.

A 10-year-old girl with asthma and allergic rhinitis was also reported to develop EoE following SLIT with standardized *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extracts. Six weeks after starting SLIT, she was admitted to an emergency department because of vomiting, retrosternal chest discomfort, and weight loss. Endoscopy was performed, and esophageal histopathological findings were in favor of EoE. Hence, SLIT was discontinued. Endoscopy and biopsy after 3 months revealed complete resolution of EoE [100].

In addition to respiratory allergies, SLIT was been used for the treatment of FA [27, 30, 38, 101–103], but to our knowledge, EoE and other EGIDs have not been reported so far as a complication of SLIT with foods. OIT was more successful than SLIT in the treatment of FA but induced more adverse reactions [30, 38]. In all the cases of EoE following SLIT, EoE regressed once the SLIT was discontinued. This fact may indicate the causal relationship between SLIT and EoE.

The mechanism engaged in esophageal inflammation following SLIT might be related to chronic antigenic exposure in an atopic patient. The gradual entrance of the culprit allergen, while attenuating the immediate-type hypersensitivity reactions, can cause a chronic stimulation of the immune system [97]. It is believed that food and aeroallergens play an important role in the development of EoE. Continuous exposure to food and aeroal-

lergens during SLIT while decreasing allergen-specific IgE, which attenuates mast cell release, can induce interleukin-10, interleukin-5, and Foxp3-expressing T cells. Consequently, the eosinophils are activated as the key players and cause tissue damage and fibrotic changes, characteristic of EoE [100, 104, 105].

The real incidence rate of EoE following SLIT might be underestimated due to different reasons. Most SLIT trials were performed in adults, though the EoE symptoms in adults are usually subclinical. The latency between the entrance of allergen and the beginning of the EoE symptoms might be long. Exclusion of the patients with severe and anaphylactic reactions from SLIT trials may also lead to underestimation. The need for an invasive procedure like endoscopy to confirm the diagnosis and insufficient size and depth of the biopsies are other important reasons.

Conclusion

EoE is neither a common nor a rare adverse event after OIT, but EG and EC are rare complications. When recurrent gastrointestinal symptoms are seen during OIT, the possibility of the development of EoE, EG, and EC should be considered, and the patient should be evaluated by endoscopy of the gastrointestinal tract, especially when a remarkable increase in the peripheral eosinophil count is seen. Fortunately, these complications are reversible by early diagnosis and cessation of OIT. We recommend a strict and prolonged follow-up of the patients undergoing OIT to detect the adverse events.

Disclosure Statement

The authors declare that they have no conflict of interest.

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