Eosinophilic esophagitis as a side-effect of allergen immunotherapy: protocol for a systematic review and meta-analysis

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ABSTRACT

Background: Sensitization to food and airborne allergens is common in the majority of patients with eosinophilic esophagitis (EoE). Although there is not a direct cause-effect relationship of IgE-mediated allergy with the pathogenesis of EoE, there is a growing evidence that oral desensitization to food and sublingual immunotherapy (SLIT) may induce the development of EoE as an adverse effect. As part of the ‘EoE and Allergen Immunotherapy (AIT)’ Task Force funded by the European Academy of Allergy and Clinical Immunology (EAACI), a systematic approach will be followed to review the evidence from the published scientific literature on the development of EoE in children and adults under any type of AIT.

Methods: This systematic review will be carried out following the PRISMA statement guidelines. Studies will be assessed for inclusion in the review according to the Population-Interventions-Comparators-Outcomes (PICO) criteria.

Results: Expected outcomes will provide evidence on the AIT-EoE development connection.

Conclusion: The findings from this review will be used as a reference to provide useful guidelines for physicians treating patients with EoE and/or are practicing AIT.

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Keywords: eosinophilic esophagitis, allergen immunotherapy, oral desensitization.
Impact Statement

A continuously increasing incidence of eosinophilic esophagitis (EoE) is noticed during the last 2 decades. In the same timeframe, protocols of food desensitization (oral tolerance induction with the use of fresh food and immunotherapy with food extracts) have been developed for patients suffering of food allergy. Many cases of EoE development in patients following food desensitization protocols have been reported in the literature, as well as cases of EoE following sublingual immunotherapy to airborne allergens. A Task Force has been funded by EAACI to examine this association. The present paper, describes the methodology adopted to examine the association and is the first one produced by the relevant TF.

BACKGROUND

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease clinically characterized by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (>15 eosinophils per high power field)(1). Various EoE phenotypes have been proposed, based on response to therapy, atopic status and natural history of the disease, while three different endotypes have also been identified, based on histological, endoscopic and molecular features(2). Although EoE is not etiologically caused by an IgE-mediated pathomechanism, sensitization to airborne and food allergens is common in these patients with an underlying T-helper 2 (Th2) cell-mediated pathophysiology (3,4).

Food allergens are considered common triggers for EoE, and this hypothesis has been sustained by the fact that elimination diets are often an effective treatment option. However, their effectiveness is not noticed in all EoE patients. It appears that EoE is a multifactorial disease caused by a combination of genetic predisposition, epithelial barrier dysfunction, environmental risk factors and allergen sensitization (5).

Airborne allergens have also been implicated in the pathogenesis of EoE, although there is no strong evidence of a cause-effect relationship. EoE has been developed experimentally in a murine model by initial intranasal sensitization to Aspergillus fumigatus, followed by challenging mice with the relative airborne allergen (6). Several single-center clinical observations have also found correlations between the onset or worsening of EoE symptoms with seasonal aeroallergen exposure (7–10). These findings have not been confirmed by other studies and no significant variations in the seasonal distribution of either the diagnosis of EoE or its clinical recrudescence throughout the year was reported by a systematic review and meta-analysis on this topic (11).

Regular contact of the esophageal mucosa with large amounts of food allergens and the minuscule exposure to airborne allergens have been involved in the development of EoE (12). This potential causative relationship poses the question on whether allergen immunotherapy (AIT) administered per os may represent a risk factor for the onset of EoE. There are case reports of biopsy-confirmed EoE developed in patients undergoing sublingual immunotherapy (SLIT) to pollen or house-dust mites, but the incidence rate is unknown (13–17).

The involvement of oral immunotherapy (OIT) to food allergens in the development of EoE has also been described (18,19). OIT has emerged as a promising therapy for patients with IgE-mediated food allergy, with various tolerance induction protocols being developed and a variety of food allergens being addressed. The incidence of confirmed newly developed EoE as a side-effect of OIT has been reported in approximately 2.7-5.3% of patients, with a 5.6% OIT discontinuation rate due to a diagnosis of EoE (or symptoms possibly related to EoE) (18–20). The clinical and histological remission of EoE reported in case-series after the discontinuation of OIT is a further clue of this interaction.
Given the overarching principles of the European Academy of Allergy and Clinical Immunology (EAACI) to promote effective and safe medical care, EAACI created a Task Force (TF) to investigate the causal relationship between EoE and AIT, conducting a systematic review and meta-analysis. Subjects with active EoE would rather rarely undergo SLIT or OIT, so the systematic review aims to evaluate the ab initio manifestation of EoE in patients undergoing such treatments and to provide useful guidelines for physicians treating patients with EoE and/or practicing AIT. The protocol of the systematic review on the development of EoE as a side-effect in patients treated with AIT to airborne and food allergens is presented here.

METHODS

Study design

In this systematic review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines will be followed (21,22). The methodology has been reviewed and approved by all authors in a TF meeting held on December 2022.

Search strategy

The electronic search of the literature will be performed in three engines: Pubmed, Scopus, and Embase. Grey literature (e.g., conference abstracts) will also be searched, and the list of references of full-text articles will be screened to identify further relevant studies.

All databases will be searched from inception to March 31st, 2023. The following Medical Subject Heading (MeSH) terms and text words will be used in the queries: "eosinophilic esophagitis" OR "eosinophilic oesophagitis" OR "EoE" combined with ("AND") "Allergen immunotherapy" OR “Specific immunotherapy” OR "desensitization" OR "AIT" OR "Sublingual immunotherapy" OR "SLIT" OR "specific oral tolerance induction" OR "SOTI" OR "oral immunotherapy" OR "OIT" OR "airborne allergen" OR "respiratory allergen" OR "food allergen" OR “Epicutaneous immunotherapy” ("AND") "side effect" OR “adverse effect”.

Eligibility criteria

Studies will be assessed for inclusion in the review according to the Population-Interventions-Comparators-Outcomes (PICO) criteria:

Population

Human studies, without age, gender, or origin limits, will be included.

Intervention(s) / Exposure(s)

Any type of AIT (probably only oral or sublingual) reported to cause or exacerbate, histologically and clinically diagnosed EoE, will be considered. Modalities used for AIT may include any protocol of food desensitization or sublingual AIT and any fresh food or extract used for these purposes.

Comparator(s) / Control(s)

Studies comparing the assessment of EoE before and after AIT will be considered. A comparator can also be a group of AIT-treated patients that have been histologically and clinically assessed for the development of EoE, in parallel with the ones that developed EoE.

Main Outcome(s) / Additional outcome(s)

There are two similar but not identical questions that will be addressed, both regarding the development of EoE after starting AIT. The first is the connection of EoE development after sublingual AIT using extracts of airborne allergens and the second is the
connection of EoE development during oral desensitization to food allergens. The primary outcome for both will be any evidence on AIT-EoE development connection. Indicating AIT and OIT as the causal factor of EoE can be done with certainty only if patients have undergone an endoscopy prior to desensitization. The extended use of the non-invasive technique of sponge test, performed during endoscopy, has started facilitating the diagnostic procedure. Triggering the exacerbation of pre-existing EoE after AIT can be examined as a secondary outcome. Another secondary outcome is the course of EoE after the discontinuation of the culprit AIT, for both branches of the study.

Inclusion criteria
Observational (prospective and retrospective) and interventional studies examining the correlation of AIT with the development of EoE in humans will be included in this systematic review. Any type of AIT, including different protocols of food desensitization and any extract of SLIT, should have been performed in the primary studies. In order to confirm AIT as the trigger of EoE, confirmed histological diagnosis of EoE (>15 eosinophils/high-power field) developed after the start of AIT will be considered. There will be no restrictions in terms of age, sex, and race. No language restrictions of the studies will be imposed.

Exclusion criteria
- Case reports, Case series, Reviews, Opinion articles, Editorial articles
- Studies on laboratory animals
- In vitro – ex vivo studies not directly referring to clinical data (EoE symptoms)
- Studies that do not include AIT as described in the inclusion criteria and refer to other procedures; for example, the use of food supplements or herbal infusions.
- Studies on the use of AIT for the treatment of EoE are subject of another project of our TF.

Study selection and Risk of Bias assessment strategy
Two investigators will independently scrutinize the eligibility of the identified titles and abstracts based on the elements of the “EoE as a side-effect of SLIT with airborne allergens” question. A third author will help resolve disagreements between the first two authors and reach consensus. Two investigators will also work on the identified search results on “EoE due to the specific oral tolerance induction / food immunotherapy” question, with a third investigator helping as a referee. The Rayyan QCRI web tool will be used to assist in the study selection (23). Data extraction will be done twice. Excluded papers will be published as an online supplementary Appendix.

Detailed information on the included studies will be provided in a table describing study participants (number and age groups), research designs, interventions (allergy testing), comparators, and outcomes. The sources of funding for the studies included in the review will be reported.

Two investigators will carry out an independent quality assessment on each eligible study of the final list. AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) will be used to assess the quality of all studies that will be extracted from the literature research, offering an accurate and comprehensive summary of the results (21,22). Moreover, different assessment tools will be used for different study designs. The risk of bias (RoB) of the included randomized controlled trials will be
evaluated using the Cochrane Collaboration RoB Tool (24). To assess the quality of evidence in non-randomised interventions, ROBINS-I will be used (25). Two investigators will review the results.

**Data extraction, analysis and synthesis**

Separate analyses for each one of the outcomes will be undertaken. When possible, subgroup analyses by age group, food allergens, airborne extracts, study design and risk of bias will be performed to investigate potentially different effects on risk.

The heterogeneity of pooled results will be examined using the Cochran’s Q test, with a 0.10 level of significance and the $I^2$ statistic, which describes the percentage variation across studies due to heterogeneity rather than chance (26,27). A narrative synthesis of the data will also be done.

**DISCUSSION**

There are still unmet needs regarding the development of EoE as a side-effect of AIT; age as a risk factor, the implication of each of the two different food desensitization modalities (sublingual and oral) to the development of EoE, the possibility that the practice of spitting (not swallowing) the allergen during SLIT is a safer (still efficacious) option, whether preliminary anamnestic of symptoms posing the suspicion of EoE is enough or whether endoscopy should be performed before the start of desensitization protocols and if the treatment protocols of EoE in the cases related to AIT should be the same with the already followed ones.

In a meta-analysis regarding patients undergoing OIT the overall rates per patient for symptoms possibly related to EoE were 34% for general gastrointestinal symptoms, including 32% of reported symptoms related to abdominal pain and 12% of reported vomiting. The overall rate of OIT discontinuation was 14%, with 4.7% of these reporting symptoms potentially attributable to EoE (19). In general, EoE clinically and histologically resolves after food OIT discontinuation. Food desensitization protocols are proposed in cases of IgE-mediated food allergy, mainly to patients that have a history of anaphylaxis, so it is clear that a decision to stop OIT has to be followed by an updated anaphylaxis action plan.

It is certainly important to offer evidence-based guidelines on whether EoE related to AIT prohibits any future effort to desensitization, either to food or to airborne allergen, using the oral route. Although it appears apparently irrelevant, it should be clear whether desensitization can be performed using other AIT routes for the same patients.

In this paper, we describe the protocol of the systematic review that has been planned. This systematic review will mainly focus on existing evidence i) on whether the severity and frequency of EoE presented during AIT is similar to a comparator population without AIT and ii) how cessation or prolongation of AIT affects the clinical course of EoE. The described option to treat EoE (with proton pump inhibitors and swallowed corticosteroids) and continue the desensitization protocol will be also assessed (20).

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**ETHICS**

Ethical approval and consent were not required as this study was based on publicly available data.

**CONTRIBUTIONS OF EACH AUTHOR**

This protocol was conceptualized by CP, CMR, IT AC and the search strategy was developed by GKN. The initial draft was prepared by EA and CP and initially revised following critical review by
CONFLICT OF INTERESTS
CP, CMR, IT, EH, MV, AA-P, AB, EA, DA-A, GKN, GNK and AC have no conflict of interest to declare relative to this project. OP reports grants and/or personal fees from ALK-Abelló, Allergopharma, Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, ASIT Biotech Tools S.A., Laboratorios LETI/LETI Pharma, GlaxoSmithKline, ROXALL Medizin, Novartis, Sanofi-Aventis and Sanofi-Genzyme, Med Update Europe GmbH, Pohl-Boskamp, Immunotek S.L., John Wiley and Sons, AS, Paul-Martini-Stiftung (PMS), Regeneron Pharmaceuticals Inc., RG Aerztefortbildung.

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