



## Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,  
Alergología y Asma Pediátrica

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### ORIGINAL ARTICLE

# Is eosinophilic esophagitis an equivalent of pollen allergic asthma? Analysis of biopsies and therapy guided by component resolved diagnosis

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Received 13 October 2017; accepted 21 November 2017

#### KEYWORDS

Eosinophilic  
esophagitis;  
Allergen  
immunotherapy;  
Component-resolved  
diagnosis;  
Pollen tube;  
Biopsy

#### Abstract

**Background:** Eosinophilic esophagitis (EoE) is characterized by esophageal dysfunction and, histologically, by eosinophilic inflammation. There is not a clear etiologic treatment. Biopsies analysis using plant histology methods may show callose and pollen tubes in the esophageal mucosa. Component-resolved diagnosis (CRD) with microarrays could detect possible allergens involved and indicate an elimination diet and allergen immunotherapy (AIT).

**Methods:** One hundred and twenty-nine patients with EoE were tested for environmental and food allergens. CRD, histological and botanical analysis were performed. Clinical scores and endoscopic biopsy were performed every six months for three years. Fifty healthy patients, 50 asthmatics due to pollen, and 53 celiac disease patients were included as comparison groups. CRD-directed AIT was administered in 91 EoE patients and elimination diet in 140 patients (87 EoE and all 53 CD patients).

**Abbreviations:** IgE, immunoglobulin E; CAP, Immunoassay ImmunoCAP® Allergen; SACYL, Health Department of Castile and Leon Community; CRD, component resolved diagnosis.

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<https://doi.org/10.1016/j.aller.2017.11.001>

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Please cite this article in press as: Armentia A, et al. Is eosinophilic esophagitis an equivalent of pollen allergic asthma? Analysis of biopsies and therapy guided by component resolved diagnosis. Allergol Immunopathol (Madr). 2018. <https://doi.org/10.1016/j.aller.2017.11.001>

**Results:** CRD detected allergen hypersensitivity in 87.6% of patients with EoE. The predominant allergens were grass group 1 (55%), lipid transfer proteins (LTP) of peach and mugwort, hazelnuts and walnuts. Callose from pollen tubes was found in 65.6% of biopsies. After CRD-guided elimination diet and/or AIT, 101 (78.3%) EoE patients showed significant clinical improvement ( $p < 0.017$ ) and 97 (75.2%) were discharged (negative biopsy, no symptoms, no medication) without relapse.

AIT-treated patients had better outcomes (odds ratio 177.3, 95% CI 16.2–1939.0).

**Conclusion:** CRD-directed AIT and/or elimination diet was efficient in treating EoE patients and was well tolerated.

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## Introduction

Eosinophilic esophagitis (EoE) is a chronic atopic disease of unclear etiology with characteristic histology – dense eosinophilic leukocyte infiltration. The estimated prevalence is 0.4% in children and adults,<sup>1</sup> and men are preferentially affected.<sup>1–3</sup> Previously considered a food allergy, genetic, molecular, cellular, animal and translational studies have shown that, in EoE, exposure to allergens leads to a complex, coordinated type 2 inflammatory reaction causing eosinophil influx.<sup>1–6</sup> Mucosal barrier dysfunction due to desmoglein dysregulation,<sup>7</sup> eotaxin-3 disturbance, thymic stromal lymphopoietin (as in rhinitis and allergic asthma),<sup>8</sup> IL13 and filaggrin, and CAPN14, has been reported.<sup>1,2</sup> Persistent EoE may lead to esophageal fibrosis, in which TGF-beta and TNF-alpha are involved.<sup>7,8</sup>

Many EoE patients present rhinoconjunctivitis, atopic dermatitis and associated asthma, in addition to dysphagia and food impaction, and 87% are sensitive to aeroallergens.<sup>5</sup> The phenotype is the same whether or not patients are sensitized to foods, and EoE exacerbations are often seasonal.<sup>3,5,6,9</sup> Children with EoE are more often sensitized to foods<sup>6</sup> and adults to airborne allergens.<sup>1,2,6,9</sup>

The utility of allergy testing in the etiologic diagnosis of EoE is unclear: some reports state they lack utility<sup>10</sup> and others that they are necessary and that component-resolved diagnosis (CRD)-directed elimination diets are effective.<sup>11–13</sup>

In a pilot study of 67 EoE patients, we found CRD-guided diagnosis and allergen immunotherapy (AIT) showed a high percentage of patients were sensitized to environmental allergens, especially pollens, and that after three years of CRD-guided diet restriction and AIT, EoE significantly improved.<sup>13</sup>

We hypothesized that, as the esophageal and bronchial mucosa share the same embryonic origin,<sup>14</sup> they might respond with similar inflammatory mechanisms to environmental and food allergenic stimuli and that asthma due to allergens and esophagitis may have an equivalent response to AIT.

Some reports suggest that so-called “immunotherapy” with food, (in fact, the induction of tolerance, not to be confused with AIT), is not indicated in EoE. Meta-analyses have been based on very few valid studies. Lucendo<sup>15</sup> selected only three of the 118 reports considered due to

their methodology, excluding two good studies in which AIT with aeroallergens improved patients, and concluded that AIT was related to EoE in 2.7% of patients, although the endoscopic study before AIT was not clear. In an EoE patient hypersensitive to a food, the induction of tolerance with the same food could present problems, as may any desensitization technique, albeit controlled.

Most studies have shown that IgE is not important in EoE<sup>16</sup> and that food triggering EoE can only be identified by an elimination diet with subsequent reintroduction controlled by endoscopy and histology, which has limited treatment with specific immunotherapy. However, no study has ruled out a role of allergen-directed specific IgE antibodies, in addition to other inflammatory mechanisms in EoE.

We also hypothesized that the inflammatory response of the esophageal mucosa in patients with high levels of antibodies to pollen allergens and worsening seasonal EoE may be due to swallowing airborne pollen and the intrusion into the esophageal mucosa of pollen tubes emitted after pollen germination that encounter a pH and humidity resembling the stigma at pollination,<sup>17,18</sup> which might be facilitated by desmoglein deficit.<sup>7</sup>

We aimed to fulfill the classical Koch-Henle postulates,<sup>19</sup> which show that a causal agent must be present in each case, must not be found randomly in other diseases or healthy controls, and can be identified in all damaged tissues.

The objectives of this study were: to obtain an accurate etiological diagnosis of EoE using standard allergy tests and CRD; to demonstrate a pathogenic role for environmental allergens in EoE using human and plant histology; and, to evaluate the effectiveness of CRD-guided specific AIT and/or elimination diet.

## Material and methods

### Design

We made an observational, longitudinal study to compare the effectiveness and safety profile of CRD-guided specific AIT and/or elimination diet with usual EoE maintenance therapy over a five-year period of real time analysis (a real world study). All suitable patients with EoE from two hospitals and 21 primary care centers in the autonomous community of Castile and Leon, Spain, were identified from

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