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EDITORIAL

Eosinophilic esophagitis: Current state and perspectives in Latin America

Esofagitis eosinofílica. Estado actual y perspectivas en Latinoamérica

Eosinophilic esophagitis (EoE) was initially described in the 1970s. However, the first efforts to establish a clinical definition were not made until 2007.[1] At present, EoE is considered a chronic, progressive, immune-mediated disease, characterized by the presence of eosinophilic infiltration of the esophageal mucosa.[2] It affects both children and adults, and in the latter, generally presents in males, young individuals (between 30 and 40 years of age), and those with a history of allergic conditions (40-60%). The primary symptom is dysphagia, and the disease can frequently progress to esophageal fibrostenosis, leading to severe dysphagia and food impaction. Reports state that this complication can present in up to 70% of patients that have a 20-year history of active disease.[3] EoE is related to allergic diseases (allergic rhinitis, asthma, and atopic dermatitis) because they share similar pathogenic mechanisms, particularly those involved with the Th2 inflammatory pathway.

Its accurate diagnosis necessarily requires the demonstration (in biopsies of the esophageal mucosa obtained through upper endoscopy at distal and proximal levels of the esophagus) of an infiltrate of > 15 eosinophils/high power field (HPF) and the ruling out of other causes of esophageal eosinophilia.[4] Due to the sensitivity of EoE to proton pump inhibitors (PPIs) in approximately 50 to 60% of cases, their suspension is recommended 3 weeks before performing upper gastrointestinal endoscopy (UGIE) with biopsy in patients suspected of having the disease.[5]

Even though the presence of endoscopic abnormalities of the esophageal mucosa (edema, mottling, grooves, rings, strictures) are frequent, they are not considered obligatory criteria for making the definitive diagnosis and only serve to support the diagnosis, or as an additional tool for evaluating treatment response.[6]

The main treatment aim is histologic remission at a level of < 15 eosinophils/HPF in esophageal biopsies, given that higher levels have a greater association with disease progression and the development of stricture and food impaction. However, the improvement of symptoms (mainly dysphagia), quality of life, and endoscopic abnormalities should also be included as treatment goals.[7]

There are 4 medical treatment modalities with proven effectiveness: PPIs, swallowed topical steroids (fluticasone or budesonide), biologic drugs (dupilumab), and dietary therapy.[3] Topical steroids are more effective than PPIs and elimination diets because they induce greater histologic remission, but importantly, each of those treatments has its advantages and disadvantages. Therefore, in addition to therapeutic effectiveness, the factors of availability, administration ease, expected adherence, treatment cost, and patient preferences should be taken into account.[8]

In the global context, EoE is more frequent in Northern Europe, the United States, Canada, and Australia. A recent systematic review and meta-analysis of 40 studies conducted in different countries reported that EoE has a global incidence of 5.3 cases/100,000 inhabitants and a prevalence of 40 cases/100,000 inhabitants. Prevalence has increased significantly from the 1980s to the present, from 8.1 to 74.4 cases/100,000 inhabitants. Low-income countries had a significantly lower incidence than high-income countries.[9]

Incidence and prevalence in Latin America are unknown due to a lack of studies on the general population, given the low frequency of the disease. Prevalence studies carried out on the Latin American subcontinent are few. In Mexico and Brazil, prevalence in patients undergoing UGIE due to esophageal symptoms was 1.7 and 1.0%, respectively.[10,11] Other studies conducted in Mexico reported a 4% prevalence in patients with symptoms of refractory gastroesophageal reflux disease (GERD) and an 11% prevalence in patients with food impaction.[12,13] Said figures are significantly lower than those described in Europe, the United States, and Australia. Whether the differences in incidence between these different regions can be due to genetic, racial, sociocultural, or environmental causes has not been determined. Certain frequent sociocultural factors in low-income countries, such as transvaginal delivery, exclusive breastfeeding, and nonlethal infections in infancy (particularly *Helicobac-*

ter pylori), have been reported to be inversely associated with EoE. Additionally, low diagnostic suspicion due to a lack of knowledge of the disease by physicians cannot be ruled out as a contributing factor.

In this setting, the publication of the study by von Muhlenbrock et al. in the current issue of the *Revista de Gastroenterología de México*[14] is especially relevant, given that it is the study with the largest patient cohort (despite having only 62 patients) yet to be published in Latin America, describing the clinical, endoscopic, and therapeutic characteristics of adult Chilean patients with EoE. A descriptive study on 35 adult patients conducted in Mexico, with similar aims, was previously published in 2022.[15]

Von Muhlenbrock et al. conducted their retrospective study at a university referral center with celiac disease and immune-mediated gastrointestinal disease programs. Nevertheless, the recruitment of patients with EoE from 2008 to 2023 was 62 cases, indirectly reflecting the low incidence of the disease. The clinical and demographic characteristics of the patients were similar to those of the Mexican study and to data reported in the international literature, specifically regarding mean age, predominant sex, and the number of histories of atopy. In the Mexican study, endoscopy was normal in 32% of the cases but was 5% in the study by von Muhlenbrock et al., whereas mean disease duration before diagnosis was similar in the two studies (4 vs 2.1 years, respectively). The short symptom duration could explain the low frequency of food impaction observed in the patients of both studies.

Regarding treatment, 55% of patients received PPIs as monotherapy, 40% received a combination of PPIs and topical steroids (combination therapy), and the remaining 5% received topical steroids or an elimination diet, but the criteria utilized for the type of treatment selected were not reported. Likewise, whether the two drugs in the combination therapy were initially administered simultaneously or sequentially was not described. Importantly, patients treated with PPIs as monotherapy, compared with those that received a combination therapy, had a similar histologic response, defined as < 15 eosinophils/HPF (76.5% vs 80%, respectively), indicating there were no advantages in having received combination therapy over PPI monotherapy.

In our Latin American countries, for pragmatic reasons, the use of sequential therapy objectively demonstrating the histologic response of each of the treatments is recommended. Different factors should be taken into account when selecting the initial medical treatment: disease severity and treatment availability, costs, administration ease, and adverse effects. The acceptance of the patient to cooperate with the therapy is another important factor to evaluate. PPI monotherapy is generally recommended as initial treatment. The use of swallowed topical steroids is indicated after treatment with a PPI has failed; they can also be used as initial therapy when there is esophageal fibrostenosis or severe esophageal inflammation.[16] Regarding dietary treatment, the 6-food elimination diet (the most widely studied at present) is difficult to implement, given a lack of motivation, low adherence, and the need for multiple endoscopies, increasing risks and costs. A way to simplify dietary treatment is to go from fewer to more, i.e., initially eliminating only the food considered the most allergenic (dairy products) and then gradually increasing the number of restricted foods to be evaluated.[17]

Biologics are the most recently introduced drugs, and dupilumab has been the most widely evaluated. The drug is a fully human IgG4 monoclonal antibody that targets the IL-4 and IL-13 receptors. It has recently been approved by the FDA for cases that are refractory to other treatments or cases of EoE and severe comorbid atopic conditions.[18] There is little opportunity to use dupilumab in Latin America due to its excessive cost and low availability.

An important omission in the study by von Muhlenbrock et al. was not having evaluated the symptom response to treatment, especially dysphagia. Dysphagia is the primary symptom of EoE and is associated with the deterioration of quality of life and imminence of food impaction. Even though reports have stated that there may be no association between the severity of dysphagia and the grade of histologic activity, the improvement of dysphagia is accepted as an important goal in the therapeutic evaluation of EoE. Patients that persist with dysphagia despite having a histologic response often present with mild-to-moderate esophageal fibrostenosis, which can be treated with esophageal dilatations. Changes in the intensity of dysphagia that patients manifest should be interpreted with caution, given that there can be a false ''improvement'' resulting from the modification of the consistency of the ingested foods. Semiquantitative evaluation methods, such as the Dysphagia Symptom Questionnaire, EoE Activity Index, and the Pediatric EoE Symptom Severity module, assess the frequency and intensity of dysphagia episodes and have been validated as clinical evaluation measures for patients with EoE.[19]

Strikingly, no patient had food impaction as an initial symptom in the study described herein, nor did any patient require endoscopic esophageal dilatation or present with food impaction in the follow-up period, suggesting an early diagnosis of EoE (the symptomatic period prior to diagnosis was reported as a mean 2.1 years, which effectively can be considered short). The question must also be raised of whether patient follow-up was carried out uniformly and carefully. On the other hand, the fact that the phenotype of the disease in the Latin American population could also be more benign than in other regions may also be suggested.[20] In that context, in a Mexican study that included 4,700 patients that underwent UGIE, EoE was the cause of food impaction in 11% of the cases,[13] contrasting with the elevated incidence of food impaction (40 to 60%) reported in other regions of the world.[4]

Finally, although it was not a study aim, von Muhlenbrock et al. reported an increase in the frequency of the diagnosis of the disease in the last 8 years of the 17-year period the study encompassed (8 cases from 2008 to 2016 to 54 cases from 2017 to 2024), representing a 7.7-fold increase. This increase is most certainly due to a greater referral of patients to the specialized center where the study was conducted, as well as to a more intense search for the disease by the medical team interested in the disease, applying effective diagnostic strategies. However, that does not rule out the contribution to said increase of immunoallergic susceptibility modifications in the population and environmental risk factors.

In conclusion, the major limitations of the study by von Muhlenbrock et al. can be considered the low number of patients making up the cohort and the lack of a clear and uniform strategy in the treatment of the patients. However, it is the result of an effort worth taking into account, for the reasons discussed above. It leaves us with challenges for addressing the problem of EoE in our region: carrying out multicenter and multinational Latin American studies on a large number of patients, in which the clinical profile of the patients in our region can be better profiled; knowing the short-term and long-term outcomes and defining an adequate treatment strategy based on the local clinical characteristics of the disease; the resources available in the environment; and the Latin American idiosyncrasy. This study also puts forth the need to fine tune the diagnostic strategies through greater diffusion, for the purpose of increasing the detection of underdiagnosed cases in our region.

The number of patients diagnosed with EoE will most certainly be increasingly higher in our region in the near future, as a result of a better and more intense search for the disease, a modification of the socioeconomic conditions of our countries, and the change in populational risk factors. Time will catch up with us.

Ethical considerations

The present manuscript is a reflection of the author's opinion about a specific theme, thus requires no authorization by an ethics committee.

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Conflict of interest

The author declares there is no conflict of interest related to the theme.

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D. García-Compeán*
Servicio de Gastroenterología, Hospital Universitario ''Dr. José Eleuterio González'', Facultad de Medicina Universidad Autónoma de Nuevo León Monterrey, Nuevo León, Mexico

* Correspondence to: Servicio de Gastroenterología, Departamento de Medicina Interna, Hospital Universitario y Facultad de Medicina, Universidad Autónoma de Nuevo León, Avenida Madero y Gonzalitos S/N, Col. Mitras Centro, C.P. 64460 Monterrey, Mexico. Tel.: +52-81-83487315; Fax: ++52 81 89891381.
E-mail address: digarciacompean@prodigy.net.mx