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Reviewer's code: 00044980
SPECIFIC COMMENTS TO AUTHORS
This review article is well written, however, I have a comment as follow. 1. Authors mention about monoclonal antibodies. Please mention the data of each drug in detail.

Answer:

Acordding to your recommendation, we had the following: paragraph:
Monoclonal antibodies against IL-5 (mepolizumab, reslizumab) have been evaluated in 5 studies in children and adults and they have shown evidence of decreased esophageal eosinophilia, symptomatic improvement, and increased quality of life, with an acceptable safety profile. The most frequent adverse events were headache, cough, nasal congestion and upper respiratory tract infections (87-91). Monoclonal antibodies against IL-13 (QAX576, RPC4046) were evaluated in 2 studies in adults that showed a tendency toward improvement of symptoms (mainly dysphagia), endoscopic and histological improvement, improvement in the expression of esophageal transcripts including eotaxin-3, periostin, and mast cell markers, and improved barrier function; the most frequent adverse events were headache and upper respiratory tract infections (92,93). In a pilot study evaluating omalizumab (antibody against immunoglobulin E) , complete remission was found in only 33% of patients (94). Straumann et al. conducted a pilot study in which they evaluated 3 patients with EoE who were treated with an antibody against tumor necrosis factor-alpha (TNF-a) (infliximab) and found no resolution of esophageal eosinophilic infiltration or reduction of symptoms (95).

Reviewer's code: 00008160
SPECIFIC COMMENTS TO AUTHORS
The manuscript submitted by Gomez-Aldana and colleagues provides a review of the current management of eosinophilic esophagitis. General Comments: 1. A formal systematic review and meta-analysis, using AGREE II and GRADE criteria (UEG J

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2017;5(3):335-358), would provide a more rigorous appraisal of the relevant literature. Specific Comments:

1. Abstract: in contrast to the assertion of the authors, dysphagia is much more common in eosinophilic esophagitis than it is a manifestation of underlying peptic esophagitis and esophageal dysmotility due to gastroesophageal reflux disease.

Eosinophilic esophagitis is an immune-allergic pathology of multifactorial etiology (genetic and environmental) that affects both pediatric and adult patients. Its symptoms, which include heartburn, regurgitation, and esophageal stenosis (with dysphagia being more frequent in eosinophilic esophagitis in young adults and children), are similar to those of gastroesophageal reflux disease, causing delays in diagnosis and treatment. Although endoscopic findings such as furrows, esophageal mucosa trachealization, and whitish exudates may suggest its presence, this diagnosis should be confirmed histologically based on the presence of more than 15 eosinophils per high-power field and the exclusion of other causes of eosinophilia (parasitic infections, hypereosinophilic inflammatory bowel disease, among others) for which treatment could be initiated. Currently, the 3 “D”s ("Drugs, Diet, and Dilation") are considered the fundamental components of treatment. The first 2 components, which involve the use of corticosteroids, immunosuppressants and empirical diets or guided food elimination based on allergy tests, are more useful in the initial phases, whereas endoscopic dilation is reserved for esophageal strictures. Herein, the most important aspects of eosinophilic esophagitis pathophysiology will be reviewed, in addition to evidence for the various treatments.

2. Introduction: higher incidence and prevalence rates of pediatric eosinophilic esophagitis were recently reported in a population-based study conducted in the

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western United States (Clin Gastroenterol Hepatol 2019;17:107-114).

Eosinophilic esophagitis (EoE) is a pathology that has emerged only recently. The first report in the literature dates from 1978 (1), and as an emerging disease, EoE has gradually increased in frequency. As a pathological entity, it was recognized in the literature between 1993 and 1994 with the reports by Atwood and Straumann (2,3) that identified an exaggerated response of the immune system to contact with allergens**.** In the last decade, awareness of this pathology has increased, and the incidence and prevalence have increased (4). A recent meta-analysis found that the incidence rate was 6.6/100,000 person-years in children and 7.7/100,000 person-years in adults and that the prevalence was 34 cases per 100,000 children and 42.2 cases per 100,000 adults (4). It is more common in men, with a male to female ratio of 3:1 (5). More than 65% of cases occur during childhood and there is a peak between 30 and 44 years of age (6). In population studies, a higher prevalence of EoE has been found in Europe and North America, whereas there is a low prevalence in Eastern countries, suggesting that it is associated with environmental and immune factors (6). EoE is more common in rural areas with low population densities, which can be explained by vegetation, pollution, and other environmental factors (7), and it varies according to climate zone and season, with more frequent diagnoses during summer (8).

3. Pathophysiology, Immunogenetic factors: the low sensitivity of IgG4 immunostaining of esophageal biopsies in establishing a diagnosis of eosinophilic esophagitis should be noted (JPGN 2019;68:689-694).

In clinical practice, immunostaining for IgG4 in esophageal biopsies has not been effective in diagnosing EoE, as it has a low sensitivity of 48% (28).

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4. Diagnosis: ACG guidelines (reference number 33 cited by the authors) could be complemented by considering and citing more current published experiences (JPGN 209;68:552-558) clinical practice guidelines.

The diagnosis of EoE depends on the clinical manifestations and endoscopic and histological findings in esophageal mucosa biopsies (34-36).

34. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA; American College of Gastroenterology. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108: 679-692. [PMID: 23567357 DOI: 10.1038/ajg.2013.71]

35. Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Amil Dias J, Bove M, Gonzalez Cervera J, Larsson H, Mehike, Papadopolou A, Rodríguez Sánchez J, Ravelli A, Ronkainen J, Santander C, Schoepfer AM; Sotrr MA, Terrejorst I, Straummann A, Attwood SE: Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5: 335-358. [PMID: 28507746 PMCID: PMC5415218 DOI: 10.1177/2050640616689255]

36. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM; Zevit N, Spechler SJ, Attwood SE, Straumann A, Aceves SS, Alexander JA, Atkins D, Arva NC, Blanchard C, Bonis PA, Book WM, Capocelli KE, Chehade M, Cheng E, Collis MH, Davis CM, Dias JA, Di Lorenzo C, Dohil R, Dupont C, Falk GW, Ferreira CT, Fox A, Gonsalves NP, Gupta SK, Katzka DA; Kinoshita Y, Menard- Katcher C, Kodroff E, Metz DC; Miehlke S, Muir AB; Mukkada VA, Murch S, Nurk S, Othsuka Y, Orel R, Papadopoulou A, Peterson KA, Phipott H, Putnam PE, Ricther JE, Rosen R, Rothenberg ME, Schoepfer A, Scott MM, Shah N, Sheikh J, Souza RF, Strobel MJ, Talley NJ, Vaeiz MF, Vandenplas Y,

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Vieira MC, Walker MM, Wechsler JB, Wershil BK, Wen T, Yang GY, Hirano I, Bredenoord A. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology 2018; 155:1022-1033. [PMID: 30009819 PMCID: PMC6174113 DOI: 10.1053/j.gastro.2018.07.009]

5. Diagnosis: the accuracy of a endoscopic reference score based on five endoscopic findings should be considered (Clin Gastroenterol Hepatol 2018;16:1056-1063). Trachealization of the esophagus in the setting of eosinophilic esophagitis could be added as an illustration (NEJM 2019;380:177).

The trachealization picture was added from our own library

6. Diagnosis: the concept of endotypes based on transcriptomic analysis of esophageal biopsies should be addressed (Lancet Gastroenterol Hepatol 2018;3:477-488

Based on the analysis of patients with active EoE the EDP identified three groups associated with different endotypes, named EoEe1-3. The **EoEe1 endotype was associated with a normal-appearing esophagus ([RR] 3·27, 95% CI 1·04–10·27; p=0·0443), and inversely correlated with a history of esophageal dilation (0·27, 0·09–0·82; p=0·0105) and mild molecular, endoscopic and histological changes. EoEe2 patients had an inflammatory and steroid-refractory phenotype (2·77, 95% CI 1·11–6·95; p=0·0376) and the highest expression of inflammatory cytokines. The EoEe3 endotype was associated with a narrow-gauge esophagus (RR 2·77, 95% CI 1·11–6·95; p=0·0376) beginning in adulthood (2·22, 1·19–4·12; p=0·0155), and these patients had the highest degree of endoscopic and histological severity (51). Patients with GERD and EoE exhibit dilation of intercellular spaces between esophageal epithelial cells. The degree of dilation of the intercellular spaces is inversely correlated with the measured**

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mucosal impedance (MI). Direct measurement of the esophageal epithelium's integrity by measuring MI can potentially obviate the need for endoscopies and repeated biopsies in EoE and reduce the pH monitoring time in GERD. A recent prospective study of 69 patients evaluated the performance of a balloon catheter system that measures MI in a long segment of the esophagus in the diagnosis of esophageal disorders including GERD and EoE. In this study, patients were classified into three groups: GERD, EoE and non-GERD, according to the endoscopic, histological and ambulatory pH monitoring results. The pattern of MI along the esophagus was different in the three groups.

7. Diagnosis: the value of esophageal mucosal impedance in distinguishing eosinophilic esophagitis from erosive esophagitis and normal esophageal mucosa might be considered (Gastroenterology 2019;156:1617-1626).

Patients without GERD had the highest MI values in all segments. In patients with GERD, the mucosal impedance (MI) values were low in the distal esophagus and normal in the proximal esophagus. In EoE patients, MI measurements were low in all segments of the esophagus. The increase in MI per distance from the squamocolumnar junction identified patients with GERD with an AUC of 0.67, patients with EoE with an AUC of 0.84 and non-GERD patients with an AUC of 0.83 (52).

8. Treatment: reference number 75 cited should be updated to a more current publication by the same group (Clin Gastroenterol Hepatol 2019;17:419-428).

A recent study that included 229 patients with a median follow-up of 5 years found that patients were taking the topical corticoid by swallowing it in 41.0% of visits; these patients had a higher frequency of clinical remission (31.0% vs 4.5%), endoscopic remission (48.8% Vs 17.8%), histological remission (44.8% vs 10.1%) and complete remission (16.1% Vs 1.3%) compared with patients who were not

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swallowing the topical corticoid (78).

78. Greuter T, Safroneeva E, Bussmann C, Biedermann L, Vavricka SR, Katzka DA, Schoepfer AM, Straumann A. Maintenance treatment of eosinophilic esophagitis with swallowed topical steroids alters disease course over a 5-year follow-up period in adult patients. Clin Gastroenterol Hepatol 2019; 17: 419-428.e6 [PMID: 29902648 DOI: 10.1016/j.cgh.2018.05.045]