ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Proton Pump Inhibitor–Responsive Esophageal Eosinophilia

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G&H What are the current guidelines for the diagnosis of eosinophilic esophagitis?

ED There have been several iterations of diagnostic guidelines for eosinophilic esophagitis (EoE), the most recent of which were released in 2013. To diagnose EoE, the first required component is the presence of symptoms of esophageal dysfunction (typically, dysphagia, chest pain, or heartburn). Symptoms may be more nonspecific in children (eg, abdominal pain, regurgitation, poor growth, feeding intolerance, and failure to thrive). The second component required for EoE diagnosis is a biopsy demonstrating eosinophilic infiltration of the esophagus, specifically at least 15 eosinophils per high-power field (eos/hpf). However, the presence of these 2 components alone is not enough to establish a diagnosis of EoE. It is also necessary to evaluate for other potential causes of the patient's symptoms and esophageal eosinophilia, the most common of which are gastroesophageal reflux disease (GERD) and proton pump inhibitor–responsive esophageal eosinophilia (PPI-REE). Therefore, the formal diagnosis of EoE requires the presence of high levels of esophageal eosinophils (≥15 eos/hpf) and persistent symptoms after a high-dose PPI trial, usually prescribed for 8 weeks.

G&H When was PPI-REE first described?

ED The first report came in 2006 in a case series of 3 children who had typical symptoms of EoE and high eosinophil counts but who improved completely—in both symptoms and biopsy findings—when treated with a PPI. Thus, the authors questioned if these children had peptic or allergic esophagitis. Prior to this time, the thinking was that if a patient responded to PPI therapy, he or she had a manifestation of GERD, and if the patient did not respond, then he or she had EoE.

Then, in 2011, Dr Molina-Infante and colleagues published the results of the first prospective study on this issue. They found that 74% of patients with esophageal eosinophilia responded to a high-dose PPI trial, and the term *proton pump inhibitor–responsive esophageal eosinophilia* was subsequently adopted in the 2011 guidelines for EoE management. Subsequently, a number of studies conducted in both children and adults have shown very consistently that at least one-third of all patients with esophageal eosinophilia respond to PPI therapy. Interestingly, many of these patients did not clinically appear to have GERD; they were experiencing symptoms such as dysphagia or food impaction in the setting of concomitant allergic diseases rather than heartburn, regurgitation, or reflux.

In my own practice, I diagnose a patient with PPI-REE if, after a PPI trial, the patient has a significant drop in the eosinophil count—typically lower than 15 eos/hpf—and also a clinical response with improved symptoms. If the patient's eosinophil count drops but he or she does not have a clinical response, then there may be another cause of his or her symptoms that needs to be evaluated. Alternatively, if the patient's eosinophil count does not drop and his or her symptoms persist, the patient can be categorized as having EoE.

G&H What are the suspected mechanisms of PPI response in patients with PPI-REE?

ED Three potential mechanisms have recently been identified, but it is not known which mechanism is the primary one, whether all of the mechanisms act together, or if there may be other mechanisms yet to be identified. The group at the University of Texas Southwestern examined esophageal cell culture systems from patients with EoE and found that omeprazole blocked the esophageal endothelium from secreting eotaxin-3 after being stimulated by allergic cytokines such as interleukin (IL)-4 or -13. The interesting aspect of this finding was that these systems did not have any acid at all; thus, in an acid-free cell culture system, just the addition of a PPI could block secretion of eotaxin-3, which is a key chemokine in the pathogenesis of EoE. This finding showed that PPIs have an anti-inflammatory/antieosinophilic effect. This research group has also reported the same finding with other PPIs.

Another possible mechanism involves the effect of PPIs on esophageal barrier function. Recent research from the Netherlands has shown that, in patients with PPI-REE, the administration of PPIs improved barrier function and made the esophageal barrier less leaky, whereas the same effect was not seen in EoE. The researchers speculated that this stronger barrier would prevent allergens that would drive an eosinophilic response from entering the esophageal mucosa.

The third possibility is that, in some people, the esophageal eosinophilia that responds to PPIs is actually due to acid reflux, and by eliminating the acid, the PPIs decrease injury to the esophagus and allow the eosinophilia to resolve. Since this is a very active area of research, it is likely that additional mechanisms of PPI response will also come to light.

G&H Is it possible to predict which patients with esophageal eosinophilia will experience a PPI response?

ED To date, no clinical, histologic, or endoscopic factors allow us to predict which patients with esophageal eosinophilia will have a PPI response, and this has been shown in both retrospective and prospective studies of both adults and children. Before undergoing a PPI trial, the vast majority of patients with PPI-REE appear to have EoE clinically yet respond to the medication. The level of eosinophils in the esophagus does not appear to make a difference in terms of PPI response, so it is very difficult to predict, on a clinical basis, which patients will have a response. Additionally, the ancillary tests that may be performed in these patients, for example pH studies, are not very helpful for predicting response. It would seem logical that a pH study would at least identify patients with pathologic acid reflux that might respond, but these tools have not been found to be predictive in studies. Since it is not possible to predict PPI response, gastroenterologists should always conduct a full PPI trial followed by another endoscopy in patients with esophageal eosinophilia to differentiate between EoE and PPI-REE.

G&H How often should patients be reevaluated to confirm continuing PPI response?

ED Since there are not many data addressing this question, it comes down to the preference of the practitioner. In my own practice, if a patient has had a good symptomatic and histologic response, I typically will follow the patient clinically and see him or her in clinic once or twice a year, but I do not necessarily perform a surveillance endoscopy unless the patient becomes symptomatic again. If the patient does become symptomatic, I perform an endoscopy and obtain esophageal biopsies to determine whether the patient has truly lost PPI response and also ask the patient whether there have been any treatment changes. For example, is the patient still taking PPIs? Is he or she taking a lower dose? Has the formulation changed?

G&H Has there been any long-term research on patients with PPI-REE to see whether their condition changes?

ED There has been only a little research on this issue. The first paper, which came from Drs Dohil and Aceves of the University of California San Diego pediatric gastroenterology and allergy groups, described 4 patients who were maintained on PPIs and who, after having a documented response, started to experience recurring symptoms and esophageal eosinophilia. This meant that these patients now met the diagnostic criteria for EoE even though they previously had had a PPI response. The authors looked at factors that may have influenced the change in these patients, such as dietary changes, seasonality with environmental allergies, and PPI compliance, but these factors did not appear to explain the observations. Although this is a small case series, it does support the concept of following these patients clinically over time.

More recently, Dr Molina-Infante and colleagues have started to compile data from multiple centers on the loss of PPI response over time. To date, they have data on approximately 50 patients, and approximately 20% to 30% have lost PPI response. In general, most of these patients lost response when they lowered their PPI dose, and almost all of the patients regained response when their PPI dose was increased. In my practice, loss of response to PPIs is rare.

G&H Is it possible that PPI use could actually cause EoE?

ED This is a very interesting question. As far as I know, there are no documented cases in which a PPI was implicated as the cause of EoE. Having said this, there are some theoretic possibilities about this potential relationship. The first is what is called an ecologic relationship. EoE has exploded in frequency over the past 2 decades, and one thing that has also increased tremendously over the past several decades is the availability and use of PPIs. Thus, there is a temporal relationship between EoE and PPIs that makes it intriguing to even ask this question. Some recent research has even shown that PPIs can be associated with the development of new food sensitivities. The exact mechanism of this development is not known. However, we do know that PPIs can make the stomach and small-bowel mucosa a bit more permeable, which could theoretically allow exposure to allergens or antigens, which could then trigger an allergic response. This is a theoretic possibility that merits more research, particularly since PPIs are being used more often in young children. However, it should be pointed out that, in general, most people have some type of symptoms before they start a PPI, so conceptually, there is a bit of a disconnect there. This issue is also interesting because it involves a bit of a paradox. Could a PPI cause EoE and then also be used to treat esophageal eosinophilia? This could be possible because 2 different mechanisms may be involved.

G&H Could you discuss the recent research on the use of genetic profiling and tissue biomarkers for distinguishing PPI-REE from EoE?

ED Since the usual clinical, endoscopic, histologic, and pH testing parameters cannot distinguish between these conditions, the natural next question is what else could be used, such as novel biomarkers or genetic profiling. Recently, there has been some work looking at tissue biomarkers of eosinophil activation and inflammation, such as major basic protein, eotaxin-3, and tryptase (a mast cell marker). These markers have been shown to very nicely distinguish patients with EoE from those with GERD. However, all of these markers show equally elevated levels in esophageal biopsy tissue specimens before a PPI trial in both PPI-REE and EoE patients. The similarities in their immunologic profiles may support the theory that PPI-REE is actually a subtype of EoE.

In addition, preliminary data have shown that the levels of cytokines such as IL-13 and -5 are quite similar between PPI-REE and EoE patients. This is important because these cytokines are integral to the pathogenesis of EoE. They can be measured either with esophageal sampling techniques or in the blood, but they do not appear to distinguish between the 2 conditions.

Most recently, there has been gene profile analysis of patients with EoE and PPI-REE showing that the gene expression between these 2 groups is very similar and notably distinct from that of patients with GERD or normal esophageal biopsy findings. Because the expression in EoE and PPI-REE is so similar, it is not yet clear whether this approach may help distinguish between the 2 conditions, although it does provide more evidence that these conditions are more similar than different. The recent study of gene expression analysis, which consisted of a multicenter group pooling specimens of patients with PPI-REE, found that a subset of up to 10 genes might differ between the 2 conditions; however, more research is needed in a much larger set of patients to determine whether those genes are truly discriminative.

Dr Dellon has no relevant conflicts of interest to disclose.

Suggested Reading

Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut*. 2013;62(6):824-832.

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(5):679-692.

Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. *Am J Gastroenterol*. 2013;108(12):1854-1860.

Dellon ES, Speck O, Woodward K, et al. Markers of eosinophilic inflammation for diagnosis of eosinophilic esophagitis and proton pump inhibitor-responsive esophageal eosinophilia: a prospective study [published online June 30, 2014]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2014.06.019.

Dohil R, Newbury RO, Aceves S. Transient PPI responsive esophageal eosinophilia may be a clinical sub-phenotype of pediatric eosinophilic esophagitis. *Dig Dis Sci*. 2012;57(5):1413-1419.

Dranove JE, Horn DS, Davis MA, Kernek KM, Gupta SK. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *J Pediatr*. 2009;154(1):96-100.

Francis DL, Foxx-Orenstein A, Arora AS, et al. Results of ambulatory pH monitoring do not reliably predict response to therapy in patients with eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2012;35(2):300-307.

Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6.

Molina-Infante J, Katzka DA. Proton-pump inhibitor-responsive esophageal eosinophilia. *Curr Opin Gastroenterol*. 2014;30(4):428-433.

Molina-Infante J, Rivas MD, Hernandez-Alonso M, et al. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. *Aliment Pharmacol Ther*. 2014;40(8):955-965.

Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus—peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol*. 2006;101(7):1666-1670.

Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol*. 2007;102(6):1301-1306.

Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SA, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals PPI-reversible allergic inflammation. *J Allergy Clin Immunol*. In press.