



Pro/Con Debates

Minimally symptomatic patients with eosinophilic esophagitis should still be actively treated-CON



Jay Adam Lieberman, MD

Division of Allergy and Immunology, The University of Tennessee Health Science Center, LeBonheur Children's Hospital, Memphis, Tennessee

ARTICLE INFO

Article history:

Received for publication June 21, 2018.

Received in revised form November 8, 2018.

Accepted for publication November 19, 2018.

To frame the reader's mind on the topic discussed in this article, I would like to start by presenting a hypothetical (or not so hypothetical) patient case. A 12-year-old boy presents with abdominal pain and nausea and occasional vomiting for the past year. He is seen by a gastroenterology specialist, who performs an upper endoscopy that reveals linear furrowing of the esophagus and 50 eosinophils per high-power field in the proximal esophagus and 40 eosinophils per high-power field in the distal esophagus. He begins treatment with omeprazole, 1 mg/kg daily, and an additional upper endoscopy 3 months later reveals 40 eosinophils per high-power field in the proximal and distal esophagus. At a follow-up visit after the endoscopy, the patient is asymptomatic and has continued to take his proton pump inhibitor (PPI). The patient and family are happy with the symptom relief provided by the PPI.

If you take care of patients with eosinophilic esophagitis (EoE), then I imagine that this case is not all that unfamiliar. Although updated consensus guideline gives us support that histologic response to PPI does not rule out EoE, there are no guidelines (mainly because of lack of evidence) for patients who respond symptomatically to a PPI but continue to have esophageal eosinophilia.¹ In fact, the new diagnostic guidelines offer no thoughts on treatment of the patient in this case, and older guidelines would still recommend treatment with either respiratory preparations of corticosteroids that are swallowed or some form of an elimination diet.

However, I would like to play the devil's advocate and suggest that sometimes less can be more as long as we understand what we are doing. When we decide to initiate therapy, we must understand what we are treating. In this case, the argument to add therapy is as follows: this patient has esophageal eosinophilia that is not

responsive to current treatment (PPI). This eosinophilia, if left unchecked, will not resolve on its own. Thus, in time, this patient, even if asymptomatic currently, will develop fibrosis and/or stenosis and strictures that will one day cause symptoms of dysphagia and food impaction. So is this true? What is the natural history of EoE?

Let me start by saying 2 things. First, we do not truly know what the natural history of this disease is. Second, there has never been a reported case of EoE that evolved or transformed into a malignancy. Several single-institution studies have attempted to define the natural history of EoE.^{2–7} From these reports, a few themes are apparent. First, EoE rarely spontaneously resolves. Second, most patients develop symptoms in the future. Third, EoE does not transform into any other disease or malignant condition.

One must understand the flaws of these studies and how they may not be applicable to the specific question posed, however. Most of these studies are from tertiary referral centers; thus, introducing a selection bias into the studies (there are likely many patients with a milder phenotype who are not referred and not studied). More importantly, almost all these studies examine symptomatic patients, which is not the question in this case. I would not disagree with the statement that “symptomatic patients with esophageal eosinophilia despite PPI therapy should be treated.” What of asymptomatic patients, though?

For these patients, the question the physician should ask is, “What am I treating?” If the assumption remains that I am treating to prevent future symptoms, then can we find literature to help us understand what asymptomatic esophageal eosinophilia (untreated by corticosteroid or diet) causes? Unfortunately, as stated, few studies are available. However, one report best answers this question. Levine et al⁸ retrospectively examined 38 pediatric patients, aged 1 to 12 years, with confirmed EoE who were treated with PPI therapy only. The patients were followed up for a mean of 3 years, receiving a mean of 3.7 endoscopies over that time. At time of follow-up, 26 patients (68%) were asymptomatic and 12 (32%) reported symptom improvement, whereas none reported no

Reprints: Jay Adam Lieberman, MD, Division of Allergy and Immunology, The University of Tennessee Health Science Center, LeBonheur Children's Hospital, 51 North Dunlap, Ste 400, Memphis, TN 38105; E-mail: jlieber1@uthsc.edu.

Disclosures: Dr Lieberman reported serving on the advisory board for DBV Technologies, ALK Abello, and Aimmune Therapeutics and receiving funding from Aimmune.

improvement or worsening of symptoms. Of the 26 patients who reported that their symptoms had resolved, 20 continued to have eosinophilic inflammation with greater than 15 eosinophils per high-power field. No complications of stricture or food impaction were seen in any patient in the report.

There are 2 take-home points from this report. First, it appears that some patients with esophageal eosinophilia that does not respond to PPI will be asymptomatic while taking the PPI and that at least some of these patients do not progress during a period of a few years to develop further complications. Second, 6 patients had esophageal eosinophilia despite PPI treatment on their initial post-PPI endoscopy, who later did not have eosinophilia even though they were only treated with PPI monotherapy. Thus, some patients may require a longer trial of PPIs to resolve eosinophilia (or perhaps some have eosinophilia that will resolve without intervention). On the basis of these findings, it seems reasonable to suggest that pediatric patients with EoE who are asymptomatic while receiving PPI therapy alone can be treated with this monotherapy and observed, at least for a few years.

Now, one might argue that the changes may occur later and that the fibrostenotic phenotype is more apt to present in adolescence and adulthood, and thus by not treating the eosinophilia these patients will likely develop a food impaction later in life. I would agree with that assessment. However, even if this happens, this is the worst case-scenario. On the basis of everything we know of EoE, we are not setting up this patient for a life-threatening complication. In addition, studies have found that both corticosteroids and diet can reverse fibrosis.^{9,10} Thus, even if the patient treated with PPI alone later develops dysphagia and even food impaction, the eosinophilia and fibrosis are still amenable to the other therapies, which can be started at any time if deemed necessary.

One final point to make in this argument is that we no longer live in the “take 2 of these and call me in the morning” era of medicine. Shared decision making is an important topic in today’s, medicine and therapies should always be discussed with patients and families. In my experience, many families are hesitant to initiate swallowed corticosteroids, especially without an end point in mind. Whether long-term effects of these corticosteroids, taken in the studied preparations, warrant that concern is debatable. However, one should not discount the family’s concern. In addition, dietary therapies can be difficult to adhere to and may decrease a patient’s quality of life, depending on what quality-of-life domain one examines,¹¹ especially in an asymptomatic patient whose quality of life is not likely affected by EoE if not having symptoms. Balancing these issues is the concern of long-term PPI use (a concern frequently brought to my attention by parents). Although numerous concerns have been reported in medical literature and in the lay media regarding this topic, the current Best Practice Advice

report on this topic from the American Gastrointestinal Association reports that the evidence supporting all complications attributable to PPIs (eg, dementia, bone fracture, myocardial infarction) have low to very low evidence levels to support these claims.¹² Thus, all these factors should be taken into account when deciding whether it is worth adding one of these therapies to an asymptomatic patient.

In conclusion, when examining decisions on whether to treat asymptomatic esophageal eosinophilia (despite PPI therapy), one must take many factors into account. Understanding the limitations in our knowledge of long-term outcomes of EoE and the limited data available on the risk-benefit ratio of the long-term use of the currently available treatments, it seems reasonable to monitor asymptomatic patients taking PPIs, as long as patients and their families understand the possible risk in doing so—uncontrolled inflammation that could lead to fibrosis and future symptoms.

References

1. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: proceedings of the AGREE Conference. *Gastroenterology*. 2018;155:1022–1033, e1010.
2. Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology*. 2003;125:1660–1669.
3. DeBrosse CW, Franciosi JP, King EC, et al. Long-term outcomes in pediatric-onset esophageal eosinophilia. *J Allergy Clin Immunol*. 2011;128:132–138.
4. Menard-Katcher P, Marks KL, Liacouras CA, Spergel JM, Yang YX, Falk GW. The natural history of eosinophilic oesophagitis in the transition from childhood to adulthood. *Aliment Pharmacol Ther*. 2013;37:114–121.
5. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc*. 2014;79:577–585, e574.
6. Bohm M, Jacobs Jr JW, Gupta A, Gupta S, Wo JM. Most children with eosinophilic esophagitis have a favorable outcome as young adults. *Dis Esophagus*. 2017;30:1–6.
7. Lipka S, Keshishian J, Boyce HW, Estores D, Richter JE. The natural history of steroid-naïve eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years. *Gastrointest Endosc*. 2014;80:592–598.
8. Levine J, Lai J, Edelman M, Schuval SJ. Conservative long-term treatment of children with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2012;108:363–366.
9. Aceves SS, Newbury RO, Chen D, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy*. 2010;65:109–116.
10. Lieberman JA, Morotti RA, Konstantinou GN, Yershov O, Chehade M. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy*. 2012;67:1299–1307.
11. Mukkada V, Falk GW, Eichinger CS, King D, Todorova L, Shaheen NJ. Health-related quality of life and costs associated with eosinophilic esophagitis: a systematic review. *Clin Gastroenterol Hepatol*. 2018;16:495–503, e498.
12. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology*. 2017;152:706–715.