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Tanbeena Imam & Sandeep K. Gupta

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EDITORIAL

Topical glucocorticoid vs. diet therapy in eosinophilic esophagitis: the need for better treatment options

Tanbeena Imam  and Sandeep K. Gupta

Riley Hospital for Children, Indiana University Health, Indianapolis, IN, USA

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Eosinophilic esophagitis (EoE) is defined as a chronic, immune-mediated disease of the esophagus characterized by symptoms indicative of both esophageal dysfunction and the presence of eosinophils in the esophageal epithelium, as noted on endoscopically obtained mucosal biopsies [1]. In adults and adolescents, manifestations of disease include dysphagia, food impaction, and gastroesophageal reflux disease symptoms, while in the younger population, symptoms can vary by age. Infants and toddlers with EoE often develop nonspecific symptoms related to feeding difficulties, including vomiting, food refusal, and failure to thrive, while children typically present with abdominal pain or vomiting [2]. Occasionally, disease may be uncovered incidentally during endoscopic evaluation undergone for unrelated reasons. Chronic eosinophilic inflammation that is unrecognized and/or undertreated may be associated with scarring leading to narrowing of the esophageal lumen and esophageal strictures [3]. The chronic nature of EoE commits patients to long-term therapy. The multifaceted nature of EoE with its combination of symptoms, endoscopy, and microscopy makes goals of treatment difficult to define. Typically, goals include a combination of histological remission, symptomatic relief, endoscopic reversal, and resolved fibrosis, but standardized goals of treatment in EoE are not well defined. An important goal of treatment is to improve symptoms; however, symptoms do not always correlate with disease activity in EoE. Untreated or partially treated EoE, even if asymptomatic, can lead to complications as noted above. The ultimate goal in treatment of EoE should be to achieve histological remission, defined as <5 eosinophils/high power field and eventually, deep remission in which esophageal caliber and motility are maintained in sustained disease control. Most importantly, the health-care team including the patient and family should design a plan that maximizes the patient's quality of life.

A subset of patients with EoE will respond to proton pump inhibitor (PPI) therapy. It was previously believed that these patients were separate and the disease state was termed PPI-responsive esophageal eosinophilia (PPI-REE); however, recent evidence shows that PPI-REE may be a continuum of the same process underlying EoE [4]. Present guidelines, however, recommend that patients first undergo an 8-week trial of PPI

before pursuing other treatments [2]. Currently, there is no medication specifically approved by the US FDA for EoE [5]. Existing practice guidelines dictate treatment can include dietary or pharmaceutical therapies, each having benefits and drawbacks [2].

Pharmacological interventions include systemic or topical corticosteroids (TCS); the American College of Gastroenterology recommends TCS (fluticasone or budesonide) as first-line pharmacological treatment [6]. A randomized, double-blind, placebo-controlled study of swallowed fluticasone showed a 50% histologic remission rate [7]. A randomized, placebo-controlled study in children using an oral suspension of budesonide with various doses showed about 53% response rate accounting for both symptomatology and histology with medium-dose and high-dose oral budesonide [8]; the response rate for histological remission was higher at 77% for high-dose oral budesonide. This study also assessed safety of the drug and found it to be generally well-tolerated with rare adverse events. Another recent randomized, double-blind trial of effervescent budesonide tablets showed similar efficacy to oral suspension, and was better tolerated by patients [9]. Systemic corticosteroids have also been shown to be a very effective treatment, but the drawbacks of long-term use outweigh the benefits [10]. This point is further augmented by a study showing similar response, both symptoms and histological, of topical fluticasone to oral prednisone; this study noted no significant difference in time to relapse, but noted substantial differences in adverse effects. In the prednisone group, 40% exhibited adverse systemic effects (weight gain, hyperphagia, and/or cushingoid features), while in the fluticasone group, the only adverse event was esophageal candidal overgrowth, noted in 15% [11]. In summary, these findings all highlight the advantages of TCS treatment: effectiveness, rapidity of response, and generally low risk. Disadvantages of TCS include the required attention to administration (e.g. swallowing an inhalant) and the risk of candidal overgrowth, although this is being seen less frequently with greater attention to drug administration and is easily treated with antifungal therapy. There are other risks of unknown significance, such as long-term adrenal suppression, growth impairment, and reduced bone density with use of corticosteroids. However, although the use of TCS causes potential systemic exposure, the low-potency metabolites

absorbed from the gastrointestinal tract exhibit high first-pass metabolism in the liver causing this exposure to be relatively low [8].

Dietary intervention as a therapy for EoE is an attractive option both in pediatric and in adult patients, but more so in young children whose diets are easier to control. The idea of diet therapy was first introduced by a landmark study in 1995 by Kelly et al. [12] showing that 10 children with EoE showed improvement in symptoms and complete resolution of histological findings after exclusively taking amino acid formula for 6 weeks. Since then, elimination diets for EoE have evolved into three main strategies. The elemental diet, which involves exclusively amino acid formula, eliminates nearly all potential food allergens. Although this method has been consistently shown to be the most efficacious, it is the hardest to follow. One study in adults demonstrated efficacy but noted that the diet was expensive (\$980 for the 4-week duration of the study), not palatable (resulting in high dropout and noncompliance rate), and associated with marked weight loss [13]. As expected, this method is better tolerated in infants, and used only in special situations such as children with multiple food allergies, failure to thrive, or severe disease [2]. The second method, the targeted elimination diet, is based upon skin prick testing or atopy patch testing. Foods associated with positive allergy testing are avoided. Advantages over the elemental diet include better tolerability; however, these allergy tests often do not detect food antigens accurately, thereby questioning the role of immunoglobulin E in the pathophysiology of EoE. In the third approach, empiric elimination, the most common allergenic foods are avoided: cow's milk, wheat, egg, soy, peanuts/treenuts, and seafood (fish/shellfish). Some studies suggest milk elimination only is quite effective.

The first study to compare effectiveness of the three different dietary therapies showed the elemental diet to be superior in inducing remission [14]. This report also demonstrated no significant difference between empiric elimination and targeted elimination. A meta-analysis studying the efficacy of dietary interventions quoted an overall remission rate of >90% for elemental diet, compared to 72% for empiric elimination and <50% for targeted elimination [15]. No randomized control trial of any diet therapy for the treatment of EoE has been reported.

In all three groups of diets, after remission is documented, individual foods are gradually reintroduced. Beginning with foods less likely to be allergens, a stepwise fashion is employed while recurrence is closely monitored. Some suggest repeat endoscopy (with attendant risk) with each new food reintroduced [16] especially with those that are more likely to be allergenic. Otherwise endoscopic evaluation may be performed after introducing three to four low-allergic foods in a stepwise manner, though this may be confounding. There is yet to be a large prospective study validating the utility of these dietary therapy methods. Some form of long-term dietary modification is often required to maintain clinical remission. Although the main advantage of diet therapy, drug-free remission, seems attractive, there are limitations. These include reduced compliance due to severity of the diet, especially in the elemental diet. Even with the targeted and empiric elimination diets, patients often require formula

supplementation to maintain nutrition. Since insurance generally does not cover diet therapy, the expense can make this modality unfeasible as well. A multidisciplinary approach is vital in these patients to maintain quality of life, so resources must be available as well.

Overall, there are relatively few high-quality randomized controlled trials that have evaluated pharmacological or dietary treatments for EoE. More large prospective studies are needed. Even fewer studies have assessed the efficacy or consequences of the medications in the long term, though there is data that suggests dose reduction by 50% maintains remission in 73–93% [17]. The only available long-term study of budesonide from 2011 does show efficacy over 50 weeks, but again larger, longer-term studies are needed [18]. One recent study striving to assess the consequences of long-term TCS showed the adrenal insufficiency rate in a selective cohort of patients on chronic high-dose fluticasone therapy to be 10% [19]. It is imperative to elucidate the long-term consequences of current and future therapies for this chronic disease.

In summary, the urgent need for establishing standard of care for induction and maintenance of remission in EoE continue to be unmet. None of the currently available strategies for treating EoE is ideal for this increasingly prevalent disease. This is further emphasized by the high noncompliance rates of 30% and 33%, respectively, for medication and diet therapies [20]. In addition, the current literature has not adequately addressed patient-reported outcomes, patient preferences, or quality-of-life indices. We look forward to the changing landscapes of EoE research in the foreseeable future, especially as consortia and multicenter studies are established. Additionally, as improved understanding of the pathophysiology of this disease becomes available, whether it is the microbiome derangements, immunological environment, or natural history of the disease, these will provide insight into more effective use of current therapies as well as development of newer treatment options.

Declaration of interest

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ORCID

Tanbeena Imam  <http://orcid.org/0000-0002-5247-5927>

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 - of considerable interest

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