Eosinophilic Esophagitis

Emerging Therapies and Future Perspectives

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KEYWORDS

• CRTH2 antagonists • Disease monitoring • Eosinophilic esophagitis
• Esophageal distensibility • Esophageal string test • IL-4 antagonist
• IL-13 antagonist

KEY POINTS

- Twenty years have passed since eosinophilic esophagitis was first recognized as a new and distinct entity; this time span has been long enough for research to ascertain several fundamental principles, and also long enough to pose certain critical questions regarding the diagnosis, therapy, and long-term management of this disease.
- In eosinophilic esophagitis, several therapeutic modalities are available but all have important limitations; there is thus an urgent need for alternative treatment options.
- With respect to medications, second-generation CRTH2 antagonists and biologicals targeting IL-13 and/or IL-4 are promising candidates.
- As for dietary treatment, there is hope that a simplified induction regimen, more accurate allergy tests to identify causative food antigens, as well as an individualized maintenance diet will increase the utilization of the dietary approach.

INTRODUCTION

Somewhat more than 20 years have passed since eosinophilic esophagitis (EoE) was first recognized as a new and distinct entity.[1,2] In the early days, the discussion was often dictated by the question, "Do you believe in eosinophilic esophagitis?" This question illustrates the broadly held skepticism that occurs when a disturbing factor invades an established concept which, at that time, was that EoE indicates gastroesophageal reflux. Twenty years later, this question and the initial skepticism have clearly disappeared and gastroenterologists are informed about, and are familiar with, this immune-mediated esophageal disease. Huge educational efforts, including establishing well-defined diagnostic criteria and therapeutic algorithms,[3–5] combined with personal clinical experience coming from their own EoE patients, have led to this

Conflict of Interest: The author has no conflicts to declare regarding this article.

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Gastroenterol Clin N Am 43 (2014) 385–394
http://dx.doi.org/10.1016/j.gtc.2014.02.005 **gastro.theclinics.com**
0889-8553/14/$ – see front matter

change among practitioners. Nevertheless, EoE is still a relatively new disease and one may ask the question, quo vadit? In this article, the focus is on promising therapeutic developments and subsequently on more general perspectives.

EMERGING TREATMENT MODALITIES FOR EoE

EoE is defined as a chronic, mainly Th2-type inflammatory disorder of the esophagus, characterized clinically by symptoms reflecting esophageal dysfunction and, histologically, by an eosinophil-predominant infiltration of the esophageal mucosa.[3–5] Adults and adolescents with EoE usually cope for years with their swallowing disturbances until a food impaction forces them to seek medical attention.[5] This behavior by those affected raised the question of whether EoE patients should continue with their coping strategy or be actively encouraged to seek treatment. Today, the results of several natural history studies suggest that there are at least 3 reasons to treat patients suffering from active EoE: First, dysphagia has a markedly negative impact on the quality of life and this handicap can be precluded by proper treatment.[3–5] Second, untreated EoE patients are at risk for experiencing long-lasting food impactions with the danger of suffering severe esophageal injury.[5] Third, treatment should be sought to prevent esophageal damage caused by tissue remodeling due to uncontrolled eosinophilic inflammation.[4,5] All of the above-mentioned reasons for treatment are valid for both children and adults.[5] Physicians caring for EoE patients are therefore encouraged to inform their patients comprehensively and to offer effective treatment options.

LIMITATIONS OF ESTABLISHED TREATMENT MODALITIES

Currently, the treatment modalities for EoE include the 3 Ds: drugs, allergen avoidance by elimination or elemental diets and, finally, esophageal dilation.[3–5] Furthermore, each of these 3 modalities encompasses several particular options: for instance, at least 10 different drugs are recommended for medical treatment; 3 different dietary regimens are available for allergen avoidance strategy; and 2 types of dilation are currently used. With respect to the long list of available therapeutic modalities, one could ask the question of whether there is actually a need for developing further therapies.

Drugs have the limitation that only corticosteroids have a proven efficacy; indeed, most other compounds have shown only limited or even no effect.[3–5] Swallowed topical corticosteroids (TCS) have undergone the most investigation; they achieve successful remission in up to 80% of patients with active EoE symptoms and inflammation.[6–11] Some 10% of EoE patients require higher doses of TCS to achieve this goal and, with the higher dose, there is an increased risk of systemic side effects.[5] In another 10% of patients, symptoms and inflammation are refractory to TCS treatment.[6–11] Moreover, swallowed TCS have only a limited efficacy in sustaining EoE in clinical and histologic remission over a longer period of time.[12] Systemically administered corticosteroids or immunosuppressants are alternatives,[6] but according to the literature, not superior to TCS[8] and, in addition, their efficacy has not yet been adequately evaluated.[3–5] In several controlled, randomized clinical trials, specific eosinophil-targeted drugs, such as the 2 anti-IL-5 antibodies, mepolizumab and reslizumab, have demonstrated rather disappointing results with persistence of symptoms and endoscopic abnormalities, despite a significant reduction in eosinophils in esophageal tissue and peripheral blood.[13–15] A new approach using the prostaglandin pathway to treat Th2-type inflammations was recently evaluated in EoE: an 8-week blockade of the so-called CRTH2 receptor with the orally available small molecule, OC000459, led to a significant reduction in the eosinophilic inflammation in esophageal tissue, and to a moderate resolution of symptoms and endoscopic abnormalities.