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Non- and semi- invasive methods to monitor Eosinophilic Esophagitis (EoE)

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Abstract

Background/Aims—Monitoring inflammation associated with EoE relies on the identification of biomarkers that provide an objective measure of disease activity; to date, this metric has been the number of eosinophils in the squamous epithelial tissue. The search for alternative biomarkers as well as alternative methods to capture them has been the topic of much research.

Methods—Based on clinical experiences and review of the literature, the aim of this chapter is to identify potential EoE biomarkers and methods to assess them.

Results—With respect to the biomarkers, a number of candidates have arisen including peripheral blood eosinophils, eosinophil granule proteins, Th2 related cytokines and exhaled nitric oxide. Methods to assess these biomarkers have included peripheral blood, luminal lavages, breath collections.

Conclusions—Future research will identify the best clinical outcome measure for EoE. While mucosal eosinophilia currently serves as the well defined metric of inflammation, newer research studies will continue to address whether this number correlates reliably with other patient reported outcomes, endoscopic findings, molecular analyses or other yet to be defined biomarkers.

Keywords

Eosinophilic Oesophagitis; Esophageal String Test; Endoflip

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Introduction

Rationale for monitoring mucosal eosinophils

Over the course of the last decade, a number of EoE treatments have been developed that lead to symptomatic relief in the majority of children and adults [1]. In addition, the use of swallowed steroid preparations and elimination diets can induce resolution of not only eosinophilia but also associated features of epithelial injury. While both prospective and retrospective studies have utilized a variety of patient reported outcome tools, peak eosinophil counts have remained the histological gold standard for therapeutic trials [2,3]. The primary issue directing this focus are studies demonstrating that activated eosinophil participate in pathological tissue remodeling resulting in end organ dysfunction. With respect to EoE, it is thought that this unbridled inflammation may lead to the two known complications of EoE; food impaction and esophageal stricture.

Benefits and limitations of endoscopic and invasive monitoring

The only method to monitor EoE inflammation is with mucosal pinch biopsies obtained during endoscopy. While the procedures of endoscopy and biopsy are low risk and commonly performed, they are costly, encumber time lost from work and school, require anesthesia and in rare cases, are associated with complications. In addition, this technique is limited in its ability to capture all the inflammation that may be present in the esophagus since it samples a small fraction of the total circumferential and longitudinal mucosa. This is particularly important limitation since EoE is a pan-esophageal disease.

Other metrics have relied on the appearance of the mucosa with respect to the amount exudate and edema and degree of furrowing, ring and stricture formation [4]. In addition, assessments of esophageal wall compliance with Endoflip and contractions with high-resolution manometry have provided real time assessment of esophageal function [5,6]. These represent important steps forward in the analysis of response to treatments but are relatively invasive techniques that require specialized equipment and interpretation.

While the current standard of care dictates that endoscopy and mucosal biopsy, and counting of eosinophils, are the gold standard to monitor inflammation activity, other methods that have sought to improve on this analysis include development of scoring systems based on immunohistochemical staining for eosinophil granule proteins and molecular based panels. Together, they represent excellent metrics to further understand pathogenetic mechanisms and response to treatments but again they require endoscopic procedures [7-9].

Biomarkers and non- / minimally invasive measurement techniques

Based on these concerns and limitations, the search for, and validation of, biomarkers that reflect mucosal inflammation in patients with EoE, that can be captured in a non-/ minimally invasive fashion, continues. Below is a summary of the minimally invasive method and biomarkers used to assess EoE disease activity.

Peripheral blood eosinophils—A number of studies have focused on determining whether patients with EoE also demonstrated evidence of peripheral eosinophilia [10-21].

This was based on the rationale that either patients with EoE may have elevated systemic levels of eosinopoetic or Th2 cytokines or that patients who were experiencing a flare would have elevated peripheral eosinophils that could be captured during their migration from the bone marrow to the esophageal mucosa. Comparisons of these studies are hampered by the fact that threshold levels defining peripheral eosinophilia vary from study to study, subject populations may include atopic patients or not and documentation of medication use that may influence counts is inconsistent. Overall, the majority, but not all, of these studies show that peripheral eosinophil levels can increase during active disease but whether this reflects mucosal inflammation, or other atopic disease activity in general, is less certain. Boldorini 2013, straumann 2010 This has been addressed a number of ways in the following studies. First, investigators attempted to tease apart peripheral eosinophilia from other factors by comparing atopic features in EoE subjects with asthma to another group who only had asthma[22]. Atopic features included peripheral eosinophilia, history of concomitant allergic diseases, family history of eosinophils and gender. They determined that peripheral eosinophilia was the most highly significant feature distinguishing patients with EoE and asthma from those only with asthma. In another study, investigators used logistic regression analysis of clinical features and determined that the combination of peripheral eosinophilia, a history of food impaction and proton pump inhibitor refractory heartburn was able to distinguish EoE from GERD[23]. Another study examined whether phenotypic analysis of eosinophil surface markers could distinguish treated from untreated disease. Elevated levels of surface CD66 intracellular phospho-STAT1, and phosphor-STAT6 were able to differentiate children with active disease from treated and healthy controls[24]. Finally, a prospective study of 47 children revealed that absolute eosinophil count, eosinophil derived neurotoxin and eotaxin-3 levels together correlated with esophageal inflammation[25].

Eosinophil granule proteins were measured pre- and post- anti-IL-5 antibody treatment, demonstrating significant declines in eosinophilic cationic protein and eosinophil derived neurotoxin follow up to 13 weeks of treatment[14]. In contrast, another study determining oral viscous budesonide in adults with EoE found no correlation of serum eosinophilic cationic protein with disease activity[14]. Finally, one study determined that EDN levels provided a sustained decrease following treatment in 66 children with EoE [26]. Thus, while there appears to be a correlation of peripheral eosinophils with active inflammation, the ability for this metric alone to track disease activity is limited.

Cytokines—With the advanced understanding of molecular mechanisms of EoE, a number of studies sought to determine whether EoE related cytokines, including IL-5, -13, -15, CCL5, GM-CSF and others were increased in the peripheral circulation[27-29]. In this regard, it is likely that these cytokines play a role in creation of an immunomicromilieu that is conducive to the development to of mucosal eosinophilia. The question of whether the measurement of peripheral cytokines will be reflective of the esophageal mucosa has lead to a series of studies to assess levels of these potential surrogate markers in EoE patients. These studies have either measured Th2 cytokines in plasma of EoE patients or measured these cytokines in the supernatants of peripheral leukocytes taken from these patients.

With respect to the former studies, peripheral cytokines were measured in 10 EoE adults and 8 normal controls [28]. In this series, most of the EoE subjects were not undergoing

treatment; results showed that IL-2, -3, -5 and RANTEs were greater than controls. Lastly, therapeutic studies targeting IL-5 have revealed lack of consistency in either elevated levels during active disease and or decreased levels following treatment[30-35]. Straumann et al measured eotaxin pre and post treatment anti-IL-5 antibody treatment and identified that levels increased in the treatment group but there was no change in the placebo [14]. In another study, these same investigators measured thymus and activation-regulated chemokine (TARC) levels pre- and post-treatment and found a correlation of these peripheral measurements with mucosal eosinophilia [36]. Mishra et al determined that serum levels of IL-15 were significantly increased in the peripheral blood of actively inflamed EoE patients and that these levels decreased following diet restriction and topical steroid treatment [29]. Other therapeutic studies targeting IL-5 have revealed lack of consistency in either identifying elevated levels during active disease or sustained decrease levels following treatment[30-35]. Finally, cytokine levels from normal (n = 12) and EoE subjects with active inflammation (EoE, n = 13) were quantified using a multiplex assay containing 84 cytokines [37]. Of these, IL-13, IL-4, IL-6, IL-5, CD40L, IL-12p70, and EGF levels were significantly altered in EoE compared with normal. When these results were applied to another group of subjects with active and inactive disease, no correlations were seen. With respect to analyses of peripheral leukocyte stimulation assays, the most recent of these studies demonstrated that invariant natural killer cells stimulated with alpha-galactosylceramide and milk allergens release elevated levels of IL-4 and -13 [38]. While this intriguing result may replicate the *in vivo* microenvironment, these types of studies are hampered by variability in experimental conditions thus preventing translation their results to clinical utility.

Taken together, these results suggest that peripheral cytokine measurements do not consistently characterize the esophageal eosinophil levels or disease activity. In addition, analysis of peripheral cytokines, like measurements of peripheral eosinophil levels, are complicated by the confounding influence of concomitant allergic diseases, identification of validated threshold levels

Exhaled nitric oxide—Fractionated exhaled nitric oxide (FeNO) has been used to assess eosinophil predominant asthma and other atopic disorders. Since EoE is characterized by eosinophilia and basic studies suggest a link to pulmonary eosinophilia FeNO was measured in a prospectively study of 11 non-asthmatic subjects with active esophagitis before and after treatment[39]. Five patients responded histologically to topical steroids; while patients experienced a decline in FeNO, this difference did not reach statistical significance. There was a significant correlation between FeNO and symptom scores in responders. Further work will be needed to fully assess the potential utility of this test in monitoring EoE disease activity.

When to monitor?

This question continues to haunt patients and clinicians alike. Clearly, assessment of mucosal inflammation is necessary to make a diagnosis of EoE. But after this initial assessment, the rationale for continuing to monitor still lies in the identification of meaningful subclinical inflammation and complications such as strictures. While

malignancy has not been reported in patients with EoE, some concerns about transformation of chronic inflammation to Barrett's esophagus still exist.

In this light, it is our practice to perform a mucosal biopsy after symptoms have improved and following 8-12 weeks of medical or diet treatment has been instituted. Following this second endoscopy, a number of approaches toward following disease activity have been promoted. With respect to diet therapy, some advocate mucosal biopsy after each food has been added to the diet, some will perform a biopsy after several foods and some will not perform another if the patient is doing well. Since symptoms do not always match esophageal inflammation, a case can be made for any of these scenarios but risks and benefits of each option need to be carefully discussed with the patient and family.

“Surveillance” of the esophageal mucosa in patients with EoE following establishment of a histopathological remission is even more filled with controversy. After an effective diet is determined or medical treatment defined, some will perform yearly assessments of the mucosal to insure the continued success of treatment and / or determine if complications may have developed. Another approach is to not perform another endoscopy if the patient is asymptomatic and treatments are well tolerated. This approach may encumber some risk of not documenting the natural history of the disease.

Lastly, assessment of the mucosa may be dictated when a previously stable patient becomes symptomatic somewhat acutely. The differential diagnosis includes recurrent EoE due to encountering an allergen, viral / fungal infection, lack of adherence to treatment or concomitant reflux disease. If these are addressed, or patients remain symptomatic, monitoring of the mucosa may be indicated.

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