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Editorial: Working with the FDA – Progress and Timelines in Understanding and Treating Patients with Eosinophilic Esophagitis

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The article by Fiorentino et al. (1) summarizes recent progress in the development of therapeutics for the emerging allergic disorder eosinophilic esophagitis (EoE) (2). The authors present an encouraging picture of an ongoing partnership between the Food and Drug Administration (FDA) and a number of stakeholders, including patients, families, advocacy organizations, a network of physician investigators (The International Group of Eosinophilic Disease Researchers [TIGERS]), academicians, researchers and the pharmaceutical industry who all focus on EoE. A basic premise of the article is the urgent need to develop validated and meaningful Clinical Outcome Assessment (COA) tools such as Patient Related Outcomes (PRO)(3). The lack of these questionnaires are described as currently hindering key progress in understanding and effectively treating this emerging disease. We agree that such tools would likely advance the field.

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The authors suggest that we are in the early stages of understanding EoE disease pathogenesis and clinical description, but we would like to touch on the tremendous progress that has actually been made over the past decade, including effective clinical trials that have been carried out despite the limitations in currently available COA and PRO tools. We present the concern that the search for a COA tool and its eventual employment have the potential to slow drug development; thus, caution is warranted so as not to become solely focused on COA tools for regulatory product approval.

Rapid and significant progress in a new disease

While limitations continue to exist in the basic, translational, and clinical investigation of EoE, we wish to highlight the progress that has been made (Table 1) and the imperative need to move ahead with clinical intervention studies, in parallel with multi-faceted COA/PRO research, in an effort to refine the tools available for measuring disease progression and improvement. It is notable that since EoE was first described (1992) and received an ICD-9 code (2008) through the efforts of an advocacy group (American Partnership For Eosinophilic Diseases [APFED, http://www.apfed.org]), there has been a rapid growth in the number of publications concerning clinical and basic aspects of EoE: 10 in 2001, 70 in 2006, and 161 in 2011. These articles include two comprehensive consensus recommendation reports, developed by a multi-disciplinary group of clinician investigators, that have presented a consistent and functional disease definition describing EoE as a clinico-pathological disease (2). The diagnosis rests on symptoms referable to esophageal dysfunction, presence of esophageal eosinophils above a threshold (peak number >15 eosinophils/high-powered field), and the exclusion of other causes for esophageal eosinophilia. While the first controlled clinical trial was reported in 2006 (4), there have now been 29 controlled clinical trials reported, and the U. S. government's clinical trial website (clinicaltrials. gov) currently lists 47 active clinical studies concerning EoE. Validated pediatric and adult PRO tools are under development at the Registry for Eosinophilic Gastrointestinal Disorders (REGID, http://www.regid.org) and the Eosinophilic Esophagitis Swiss Activity Index (EEsAI), respectively. Treatments reported include off-label indications of currently approved drugs such as fluticasone, budesonide, and ciclesonide; new biological agents such as humanized antibodies against IL-5 (mepolizumab, reslizumab) and IL-13 (QAX576); and dietary intervention trials. In nearly every published interventional trial, there has been a remarkably positive effect, typically measured by improvement in tissue pathology, the hallmark feature of the disease, and variable improvement of clinical outcomes.

Considerable progress has also been made in understanding the pathogenic steps involved in EoE. Collectively, several recent studies have defined the disease as a complex interplay of environmental and genetic factors, resulting in polysensitization to multiple foods; the development of Th2-polarized adaptive immune responses, resulting in activation of local epithelial-inflammatory cell responses, including IL-13-elicited eotaxin-3-dependent eosinophilia and associated mastocytosis and activation; and the potential role of other inflammatory mediators and cells on disease complications (5). These and other studies have established paradigms that represent worthwhile strategic targets for therapeutic intervention and refinement of disease definition and activity at the molecular level.

Thus, in a relatively short time period and with the research support from a variety of different sources, including but not limited to the National Institutes of Health, foundations (Food Allergy Initiative; Food Allergy Project; Food Allergy and Anaphylaxis Network; Swiss National Science Foundation; TIGERs; Thrasher Foundation; Buckeye Foundation; American Gastroenterological Association; North American Society of Pediatric Gastroenterology; Hepatology and Nutrition; American Academy of Allergy, Asthma and

Immunology; and others), industry, and advocacy (Campaign Urging Research for Eosinophilic Disease [CURED, http://www..org], Bunning Family Foundation, and APFED), tremendous progress has been made in research; this recent partnership described by the FDA, between the various EoE stakeholders, represents another remarkable chapter in this disease's brief history. Importantly, these stakeholders have participated in two meetings and numerous teleconferences over the course of the last 18 months to discuss the topics presented here.

Timelines and hurdles

But collectively, how can we bring safe and effective treatment in a more timely fashion to our patients? All stakeholders share this common goal, but the necessary metrics, processes, tools, finances, and timelines to reach this goal vary significantly for each group involved. As the gatekeeper for safe and effective drug development, the FDA sets these metrics for approval. Their present engagement with a number of stakeholders to identify these metrics is commendable, but several hurdles need to be overcome.

Natural history difficult to define

EoE is a clinico-pathological disease and, as such, symptoms and histology need to be considered in any estimation of therapeutic trial. The authors correctly identify the confounding dissociation between histological improvement (reduction in esophageal eosinophil counts) and objective measures of clinical improvement in several therapeutic trials and the necessity of defining natural history. However, none of these studies has been long enough to observe the development of long-term complications in subjects after treatment is stopped or in untreated controls; future studies (such as those by REGID) addressing these potential complications will take years to complete and thus do not meet the immediate need of patients with EoE.

Complexities in understanding relationships between symptoms and histology

The authors suggest that perhaps monitoring esophageal eosinophil number should not be considered sufficient as a trial primary endpoint or even as the standard for disease definition. They propose the key usage of COAs, such as PROs, as co-primary endpoints. As noted by the authors, several of the major intervention studies showed clinical improvements with the study medication; however, these improvements were not substantially different from the response to the placebo, highlighting the complexity of incorporating COA tools for this disease.

While we recognize the limitations of using eosinophil counts as a biomarker, a number of adult and pediatric prospective, controlled and retrospective, uncontrolled studies studying topical corticosteroids and diet, as well as extensive clinical experiences, have identified a correlation between symptoms and histological evidence of remission (6). On the basis of decades of collective clinical experience and review of the last five years of the scientific literature, the reliance on histology and number of eosinophils in the esophageal epithelia has been shown to reflect the inflammatory activity of the disease, has proven inter- and intra-observer stability, and is associated with the development of chronic sequelae such as esophageal strictures. Performance of prospective studies to confirm this finding, as well as to identify better biomarkers that more definitively diagnose and monitor disease activity, are critical to maintaining progress in providing state-of-the-art care and increasing our understanding of disease pathogenesis, but we cannot wait for results from these studies to make timely decisions for therapeutics that are urgently needed.

Potential explanations for lack of correlation between symptoms and histology

Possible explanations for the apparent dissociation of the (a) decreased esophageal eosinophilia and lack of improvement of clinical symptoms in patients receiving active drug or (b) persistent esophageal eosinophilia but improved clinical symptoms in placebo arm observed in some clinical trials may be explained by any one or several of the following: (1) the study intervention did not lower esophageal eosinophils or their activation state below the necessary threshold; (2) the employment of non-disease specific, non-validated COA tools, such as those that do not capture data relating to growth parameters, which are a major concern for pediatric patients; (3) the potential differential effects of available therapeutics on inflammatory (mast cell and/or eosinophil-mediated responses) and fibrostenotic consequences of the disease; (4) the ability of subjects to adapt to / cope with their disease and modify behaviors, thus leading to “masking” of symptoms; (5) the unknown impact of the emotional and psychological status of the patient and family unit on the sense of well-being in reporting disease outcomes; (6) the known limitations of PROs, in common diseases such as hypertension and in rare diseases, for which patients and their family members are desperately longing for the first approved therapy (7). Again, these issues require further study with considerable input from all stakeholders to help meet the metrics necessary for FDA-approved EoE treatments.

Need for more than PROs in EoE assessments

We appreciate the rigor and attention to safety that the FDA has provided in many randomized, controlled trials using validated instruments that demonstrate significant improvement over placebo and seek to understand the regulatory and scientific complexities that surround the decision-making process to bring safe treatments to our patients. The usage of valuable COA tools such as PROs is a desirable goal (3), but we wish to point out that achieving this standard is not an easy pathway (8), particularly in pediatrics wherein a substantial proportion of patients are unable to provide a personal account of their symptoms due to developmental status. Clinical trials of well-recognized disorders that have been intensively investigated for several decades, such as inflammatory bowel disease (IBD), cystic fibrosis, heart failure, and asthma, still struggle to establish appropriate COA/PRO tools. Nearly simultaneous with the EoE/COA discussions, assessment paradigms for IBD are beginning to shift from only PROs to now include assessment of gross and microscopic pathology. Drugs such as nesiritide, which was FDA approved initially on the symptom PRO of dyspnea in heart failure but was eventually shown to be less effective on the functional primary outcome variable of heart failure, emphasize the difficulties in using symptoms as an adequate reflection of disease activity. Despite these challenges, effective, FDA-approved drugs for these diseases are available. Similar to asthma, evaluations of EoE therapeutics will need to be judged on both PROs and biomarkers (9).

Next steps forward

We applaud the FDA for their approach to build partnerships between patients, families, industry, physicians, researchers, and lay individuals, and we look forward to advancing the understanding of EoE and bringing safe, approved treatments to EoE patients, especially in view of EoE as an orphan disease with a growing unmet need. In these early stages of EoE's history, we need to continue to perform the much-needed research that will support or refute the many aspects of what our clinical experiences have taught us and identify new methods to provide us the best measures of disease activity. During this time period, we hope that the FDA will exercise flexibility in its assessment of new investigational therapies for this disease as it has with other orphan diseases (10), including not using solely the important

COAs but also using histology and, when available, other relevant biomarkers, to make critical decisions about product approval. We think that using an integrated approach for the assessment of therapeutic efficacy will bring rapid and meaningful approval of new treatments for our anxiously awaiting patients and families.

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Table 1

Progress in Eosinophilic Esophagitis

TOPIC	PROGRESS		
	LOW	MEDIUM	HIGH
Molecular Understanding			X
Genetics		X	
Pre-clinical Modeling		X	
Controlled Clinical Trials		X	
Assessment Tools			
Histology		X	
Endoscopic Assessment	X		
Clinical Outcome Tools	X	X	
Molecular Markers			
FDA-approved Drugs	X		
FDA-approved Dietary Treatment	X		