

Working with the US Food and Drug Administration: Progress and timelines in understanding and treating patients with eosinophilic esophagitis

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The article by Fiorentino et al¹ 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 US 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), academicians, researchers, and the pharmaceutical industry, all of whom 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 (PROs).³ The lack of these questionnaires is described as currently hindering key progress in understanding and effectively treating this emerging disease. We agree that such tools would likely advance the field.

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 use 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

Although limitations continue to exist in the basic, translational, and clinical investigation of EoE, we wish to highlight the progress that has been made (Table I) and the imperative need to move ahead with clinical intervention studies in parallel with multifaceted 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

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TABLE I. Progress in EoE

Topic	Progress		
	Low	Medium	High
Molecular understanding			X
Genetics		X	
Preclinical modeling		X	
Controlled clinical trials		X	
Assessment tools			
Histology		X	
Endoscopic assessment	X		
Clinical outcome tools	X		
Molecular markers		X	
FDA-approved drugs	X		
FDA-approved dietary treatment	X		

an International Classification of Diseases–ninth revision code (2008) through the efforts of an advocacy group (American Partnership for Eosinophilic Diseases, <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 2 comprehensive consensus recommendation reports developed by a multidisciplinary group of clinician investigators that have presented a consistent and functional disease definition, describing EoE as a clinicopathologic disease.² The diagnosis rests on symptoms referable to esophageal dysfunction, the presence of esophageal eosinophils above a threshold (peak number >15 eosinophils/high-powered field), and the exclusion of other causes for esophageal eosinophilia. Although the first controlled clinical trial was reported in 2006,⁴ there have now been 29 controlled clinical trials reported, and the US government's clinical trials Web site (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 (<http://www.regid.org>) and the Eosinophilic Esophagitis Swiss Activity Index, 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 and reslizumab) and IL-13 (QAX576); and dietary intervention trials. In nearly every published interventional trial, there has been a remarkably positive effect, typically measured based on improvement in tissue pathology, the hallmark feature of the disease, and variable improvement in 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 T_H2-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 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; the International Group of Eosinophilic Disease Researchers; Thrasher Foundation; Buckeye Foundation; American Gastroenterological Association; North American Society of Pediatric Gastroenterology, Hepatology and Nutrition; American Academy of Allergy, Asthma & Immunology; and others), industry, and advocacy groups (Campaign Urging Research for Eosinophilic Disease, <http://www.curedfoundation.org>, Bunning Family Foundation, and American Partnership for Eosinophilic Diseases), 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 2 meetings and numerous teleconferences over the course of the last 18 months to discuss the topics presented here.

TIMELINES AND HURDLES

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 clinicopathologic disease, and as such, symptoms and histology need to be considered in any estimation of a therapeutic trial. The authors correctly identify the confounding dissociation between histologic 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 control subjects. Future studies (eg, those by the Registry for Eosinophilic Gastrointestinal Disorders) 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

Fiorentino et al¹ suggest that perhaps monitoring esophageal eosinophil numbers should not be considered sufficient as a trial primary end point or even as the standard for disease definition. They propose the key use of COAs, such as PROs, as coprimary end points. As noted by Fiorentino et al,¹ 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.

Although 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 experience, have identified a correlation between symptoms and histologic evidence of remission.⁶ On the basis of decades of collective clinical experience and review of the last 5 years of the scientific literature, the reliance on histology and eosinophil counts in the esophageal epithelia has been shown to reflect the inflammatory activity of the disease, has proved interobserver and intraobserver 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 decreased esophageal eosinophilia and lack of improvement of clinical symptoms in patients receiving active drug or of the persistent esophageal eosinophilia but improved clinical symptoms in the placebo arm observed in some clinical trials might be explained by any 1 or several of the following: (1) the study intervention did not decrease esophageal eosinophil counts or their activation state to less than the necessary threshold; (2) the use of non-disease-specific, nonvalidated 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-mediated responses, eosinophil-mediated responses, or both) and fibrostenotic consequences of the disease; (4) the ability of subjects to adapt to or cope with their disease and modify behaviors, thus leading to “masking” of symptoms; (5) the unknown effect of the emotional and psychological status of the patient and family unit on the sense of well-being in reporting disease outcomes; and (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 use 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 because of developmental status. Clinical trials of well-recognized disorders that have been intensively investigated for several decades, such as inflammatory bowel disease, cystic fibrosis, heart failure, and asthma, still struggle to establish appropriate COA/PRO tools. Nearly

simultaneous with the EoE/COA discussions, assessment paradigms for inflammatory bowel disease 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 patients with 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 building partnerships among patients, families, industry, physicians, researchers, and lay persons, and we look forward to advancing the understanding of EoE and bringing safe, approved treatments to patients with EoE, 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 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 waiting patients and families.

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