

Cross-sector sponsorship of research in eosinophilic esophagitis: A collaborative model for rational drug development in rare diseases

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Like many rare diseases, eosinophilic esophagitis (EoE) is a poorly understood disorder, and assessment tools to accurately determine disease activity, remission, and natural history have long been inadequate. Clinical outcome end points able to assess the effectiveness of candidate therapeutic agents in clinical trials have been a particular deficiency and are urgently needed. With no approved therapy available to patients and with the prevalence of EoE on the increase, collaborative approaches to drug development are becoming ever more important. We describe a collaborative effort mobilized across institutions, including both the public and private sectors, that was initiated within the past 18 months expressly to address the need for further clinical research into the cause and treatment of EoE. Collaborators include the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition; the International Gastrointestinal Eosinophilic Researchers; and the US Food and Drug Administration. This effort has resulted in the elucidation of several parameters essential for effective EoE registration trials, including the need for clinically meaningful end points that measure changes in clinical symptoms in addition to the assessment of intraepithelial mucosal eosinophilia. The development and use of biomarkers, particularly in early-phase drug development, have become an important focus for investigations that might reduce clinical reliance on serial invasive monitoring. The concerted efforts described here to develop rational therapeutics and drug development paradigms in EoE also appear to provide a model for effective collaboration in the context of drug development for rare diseases and perhaps more generally for public health initiatives. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Clinical outcome assessment, eosinophilic esophagitis, the International Gastrointestinal Eosinophil Researchers, US Food and Drug Administration, Study Endpoints and Labeling Development

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Abbreviations used

COA: Clinical outcome assessment
EoE: Eosinophilic esophagitis
FDA: US Food and Drug Administration
PRO: Patient-reported outcome

Eosinophilic esophagitis (EoE) was initially described as a distinct clinicopathologic entity in adults in 1993.¹ It has been increasingly recognized by the medical community over the past decade,² affecting a significant percentage of the pediatric and adult population³ and presenting with symptoms that vary significantly among different age groups. In infants and toddlers symptoms of EoE usually include feeding difficulties and failure to thrive. School-aged children with the disease are prone to vomiting and abdominal pain, whereas adolescents and adults are most likely to present with dysphagia and food impaction.^{3,4} To date, the tools used to assess EoE activity have included patient- and parent-reported symptoms, as well as direct eosinophil enumeration in the esophageal epithelium. Evolving work to develop a clinical outcome measurement tool has been featured in the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS, version 2.0; Cincinnati Children's Hospital and Dr James P. Franciosi, Cincinnati, Ohio).⁵ Confounding the nonspecific nature of EoE symptoms, symptom frequency can vary from daily flare-ups to 1 every few months in children and adults. Currently, there are no US Food and Drug Administration (FDA)-approved qualified symptom assessment tools for EOE, and no FDA-approved pharmacologic therapies exist to offer effective treatment.

A well-developed symptom measure is urgently needed for use in clinical trials to assess the effects of interventions on EoE and to support drug development. There are ongoing efforts by several groups to develop questionnaires to assess symptoms of pediatric and adult EoE, but psychometrically well-defined and reliable self- or caregiver-reported outcome assessment instruments remain lacking. The development and psychometric validation of patient-, parent-, and physician-reported outcomes for pediatric EoE have faced many challenges. For example, the target population for pilot testing is sparsely distributed, given the rarity of the disease, and there is a lack of appropriate control cohorts. Certain hurdles, which are particularly problematic in the reliability of self-reporting among children, arise from not only the lack of appropriate symptom scales for self-reporting but also inappropriately long recall periods used to assess subjective response.

EoE AS AN EXAMPLE OF DRUG DEVELOPMENT IN RARE DISEASE

EoE illustrates many challenges inherent to the clinical development of candidate therapeutic agents to treat rare disorders.

Although each rare disease poses unique clinical challenges, many medical and epidemiologic issues are common among drug development programs that address rare diseases in general. For example, many rare diseases continue to lack diagnostic criteria that conform to a consistent definition of disease. The lack of a clear disease definition can affect the parameters that describe the disease (eg, laboratory or histology), which disease-modifying interventions are most appropriate, the frequency of clinical follow-up, and the discrepant selection of clinical outcome assessments (COAs) to assess disease activity and treatment response. Because patients with rare disorders are seen infrequently, few physicians and treatment centers might be experienced with their diagnosis and treatment. These factors, among others, often result in an inadequate scientific foundation on which drug development programs might be designed effectively to assess the clinical effectiveness, safety, and benefit/risk profiles of investigational agents.

A rare disease (also known as an orphan disease), according to the Orphan Drug Act,⁶ is a disorder that affects fewer than 200,000 persons in the United States. There are an estimated 7,000 different rare diseases,⁷ most of which are poorly understood and lack diagnostic criteria, pathophysiologic markers, and clinical outcome measurements. In 2010, the Institute of Medicine report on rare diseases and orphan products identified several gaps in our understanding of rare disease that hinder the clinical development of effective therapies. The institute particularly noted a lack of “natural history studies to characterize disease process” and advocated for the development of “well-defined questions, validated biomarkers and appropriate surrogate endpoints.”⁸ A thorough understanding of the natural history of a disease is essential for the identification of clinically meaningful outcome measures and their use in drug development. The natural history of a disease is defined as “the natural course of a disease from the time immediately prior to its inception, progressing through its presymptomatic phase and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead without external intervention.”⁹ Although the essential elements to be described in a disease’s natural history are expected to vary depending on the disease, in most cases these should include an assessment of (1) genotypes, phenotypes, and the full range of disease manifestations within the different phenotypes; (2) demographic, environmental, and other variables that correlate with disease outcomes; and (3) major organ system involvement, important morbidities, mortality (if applicable), and time course. Natural history studies can also be used to identify and develop potential biomarkers and clinical outcome measures for assessing disease activity, to recognize gaps in disease knowledge, and to survey and define current standards of care across treatment centers.

Inherently problematic to the rare and new disease is the fact that biomarker development is in its early stages. In addition, the natural history of EoE is difficult to define, and this definition is still in its early stages. In a first natural history study by Straumann et al,¹⁰ it was identified early that EoE leads to persistent dysphagia and structural esophageal alterations but does not affect the nutritional state. Additional study has made it even more clear that EoE has not only an increasing prevalence but also a truly increasing incidence.¹¹ However, additional work on further defining the full spectrum of the disease is needed and is recommended as a focus of future study.

In this article we present a distinctively collaborative approach to building a scientific foundation for EoE research that might lead to clinical programs of drug development. This collaboration was initiated by the FDA after the recognition of the need for a more unified approach to developing an EoE disease definition, its natural history, and COA tools to support drug development. A primary goal in this collaborative approach was to better define the disease and to identify constellations of symptoms that might vary between younger and older patients. This goal is essential to the ultimate development of reliable COAs, meaningful end points, and adequate and well-controlled clinical trials.

COA MEASURES

EoE is characterized by histologic findings and clinical symptoms, but the elucidation of a clinically meaningful end point through which therapeutic efficacy could be established has been challenging. The intraindividual and interindividual variability of EoE symptoms and the variable course of the disease are highly problematic. Furthermore, symptoms of EoE not only change through the natural progression of the disease over time but are also responsive to compensatory behaviors (eg, food avoidance) and off-label medical interventions. The presentation of EoE in young children is particularly challenging because of their limited ability to describe salient symptoms. In all of these respects, the development of COAs to support claims of treatment benefit (including patient-, clinician- and caregiver-reported outcomes) depends on the ability to quantify those symptoms that are most relevant to the individual patient.

The lack of an accepted COA for EoE has been a barrier to the design of adequate clinical trials to investigate new treatments. However, great efforts to standardize the endoscopic assessment of EoE¹² and histologic examinations¹³ have already been undertaken.

Current strategies to establish treatment benefit depend on esophageal biopsy, primarily targeting reduction in eosinophil counts as a biomarker of disease activity. However, emerging data indicate that histologic evaluation of eosinophil counts cannot be relied on as a surrogate end point in clinical trials for EoE, primarily because eosinophil counts do not appear to correlate meaningfully to clinical symptoms. To provide one example, mepolizumab, an antibody against IL-5, has been found to reduce both esophageal intraepithelial eosinophil counts and esophageal inflammation in children with EoE¹⁴; however, these responses to mepolizumab in children correlated neither with patient-reported symptom profiles nor with any clinically clear symptomatic improvement. These and other conflicting results underscore the need for additional studies to define the disease and establish clinical end points.¹⁵ Other studies in adults and children corroborate a clear change in the putative biomarker of eosinophil counts but with variable results in improvement of clinical signs and symptoms of the disease. Conversely, Spergel et al,¹⁶ for example, noted that reslizumab improved symptoms in all treatment groups, but these improvements were not associated with changes in esophageal eosinophil counts.^{14,16,17} Interestingly, a recent report by Gonsalves et al¹⁸ has shown that a 6-food elimination diet used in adults with EoE led to decreased dysphagia symptom scores in both frequency and intensity, but this was assessed with a nonvalidated instrument for dysphagia after the 6-food elimination diet.

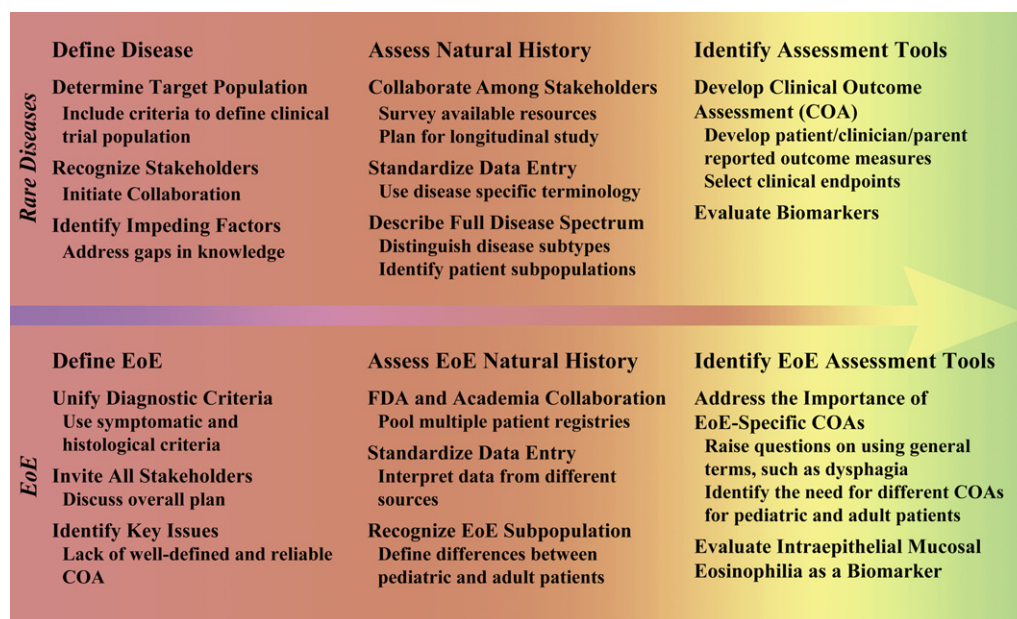


FIG 1. An evolving partnership model for rational drug development.

PARTNERSHIPS AND COLLABORATION

The need for a well-defined biomarker for EoE has been urgently recognized by stakeholders from industry, academia, patient advocacy associations, and government. Collaborative efforts from among these sectors culminated in a topic conference sponsored by the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition, at which the FDA engaged with the International Gastrointestinal Eosinophil Researchers with the expressed goal of developing useful COAs. The FDA's role in this collaboration was built on the agency's initiative in the Division of Gastroenterology and Inborn Errors Products and Study End points and Labeling Development group within the Center for Drug Evaluation and Research. Initial efforts among collaborators have focused on developing a standardized definition for EoE, which is crucial for identifying patients with EoE and establishing a patient population in which the development of clinically meaningful end points could be pursued. The FDA has also encouraged academic researchers to submit their COA tools to the FDA's Drug Development Tool qualification process,¹⁹ as described elsewhere. Additionally, there is a need to standardize endoscopic assessment of EoE¹² and histologic examinations. Efforts toward endoscopic and histologic examination standardization have been undertaken and are currently underway.¹³

To address the problem of incomplete data to describe the natural history of EoE, the FDA has collaborated with the University of Florida Pharmacometric College to sponsor 2 master's degree students on short-term research fellowships exploring these issues. These students have provided valuable insight into the state of natural history data and COA development available across research centers. These research center collaborations have included Drs Alex Straumann and Alain Schoepfer of the Swiss EoE Research Group, Glenn Furuta of the University of Colorado School of Medicine, and Jim Franciosis of the Cincinnati Children's Hospital Medical Center. Significantly, student sponsorship has already resulted in the identification of key areas in which improvements in data collection can be made

and has prompted several provocative insights (Fig 1). First, it has become clear that there is a general lack of coordination among researchers collecting symptomatology data and tracking the natural history of EoE. This problem has been exacerbated by a lack of standardized methods of data collection, which encumbers the pooling of data from various sources. EoE symptomatology has historically been defined in terms that are nonspecific (eg, "dysphagia") and frequently vague. A clear opportunity for improvement would be provided through the standardization of symptom terminology in EoE datasets (eg, preferred terms).

The collaborative short-term research initiative has also furthered understanding into the relationship between clinical manifestations of EoE and intraepithelial eosinophil counts obtained through endoscopic biopsy. However, ongoing research to identify and develop noninvasively assessed biomarkers could obviate the need for invasive procedures to monitor disease activity and intervention, particularly in early-phase drug development.

Finally, the need for a reliable and well-defined patient-reported outcome (PRO) instrument for EoE, which could discriminate changes attributable to pharmacologic intervention, remains paramount. A PRO that has been properly defined and accepted psychometrically and clinically is particularly critical for the development of new therapies for pediatric and adult patients with this rare disease. Challenges in the development of a PRO instrument include the variability in symptoms experienced between patients, as well as among the different age groups of children. These complexities do not exist for the development of PROs in adults; attempts at developing PROs in adults are ongoing and being developed by Straumann et al (personal communication, January 2012), including, for example, assessments of dysphagia. These challenges will only be approachable through the identification of appropriate control cohorts and assessment of age-related abilities to communicate and recall symptoms. An appropriate response scale for self-report of symptoms in young children and adolescents with EoE is key.

CONCLUSIONS

Like a multitude of other rare diseases affecting children, EoE research relies on a critical collaboration between all stakeholders. Thus the EoE collaborative model presented here presents a new opportunity for defining coordinated scientific programs for leveraging expertise and experience across stakeholder groups, with the ultimate goal of expediting the development of solutions for complex problems that underlie drug development for rare diseases (Fig 1). Collaboration among the International Gastrointestinal Eosinophilic Researchers, other professional societies, patients and their advocates, and all other stakeholders, including the pharmaceutical industry, to identify pathways for the development of end points that are mutually beneficial is the important overall goal of this effort. For EoE registration trials, we believe that the priority should be focused on directly evaluating an appropriate clinically meaningful end point that should include improvement in clinical symptoms, as well as assessment of intraepithelial mucosal eosinophilia. As illustrated with the collaborative initiative in EoE research, many rare diseases lack an adequate scientific foundation, including such fundamental elements as disease definition and the understanding of disease natural history. These elements further demand an adequate description of the full range of disease manifestations. The urgent need for clinical development and adequate assessment of potential therapies can only be met by addressing such deficits in understanding. Thus it is imperative that all stakeholders involved in drug development, including academia, industry, patient advocates, and regulatory agencies, work collaboratively and proactively for the benefit of public health and to promote efficient and scientifically sound clinical development.

Involvement of patients and disease advocates and the academic and treatment communities are especially important for rare diseases, and efforts to obtain representation from the entire disease stakeholder community in early phases of research (eg, translational phases) are recommended. Ideally, collaborations should be formed before initiating clinical trials so as to maximally benefit from foundational scientific information because the opportunity for study of candidate therapeutics in a small patient population will be limited. Establishment of public-private collaborations, such as this EoE example, can be initiated and successfully steered by any of the interested parties (ie, academia, industry, government, and advocacy) and will likely depend on existing support and funding for these efforts. In recent years, disease advocacy groups have become more prominent in establishing these collaborations, including providing financial support, participating in multiple aspects of research and recruitment, and data collection, among others.²⁰ Because advocacy groups have a special interest in the long-term viability and success of rare disease research, support and partnership for advocacy group efforts by other stakeholders in the rare disease community is encouraged.

We believe that the collaborative model for EoE research, as outlined here, demonstrates that this progress is possible when

disease problems are addressed concertedly from multiple directions. We hope that this model will be of encouragement to other collaborations to combat rare disease.

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