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Impressions and Aspirations from the FDA GREAT VI Workshop on Eosinophilic Gastrointestinal Disorders Beyond Eosinophilic Esophagitis and Perspectives for Progress in the Field

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Abstract

The U.S. Food and Drug Administration (FDA) hosted a workshop on July 21, 2021 to discuss the disease characteristics, natural history, and endpoints to assess treatment benefit in patients with eosinophilic gastrointestinal disorders (EGID) beyond eosinophilic esophagitis (EoE). Notably, EGID beyond EoE, such as eosinophilic gastritis, eosinophilic enteritis, and eosinophilic colitis, herein referred to as non-EoE EGID, are understudied relative to EoE. This workshop provided a forum for open discussion among stakeholders—medical professionals (including their societies and research groups), FDA representatives, an industry representative, and a patient representative—to facilitate drug development. Experts in many disciplines related to EGID, including allergy, immunology, epidemiology, gastroenterology, and pathology, and both adult and pediatric clinicians contributed. Herein, we discuss some of the insights of the material presented at the meeting and present perspectives on moving the field forward towards drug approval.

Keywords

Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR); eosinophilic gastrointestinal disorder; eosinophilic gastritis; eosinophilic gastroenteritis; eosinophilic enteritis; eosinophilic colitis; eosinophilic duodenitis; Food and Drug Administration (FDA); food allergy; treatment; diagnosis

Introduction

Eosinophilic gastrointestinal disorders (EGID) are rare diseases characterized as chronic, immune-mediated conditions that manifest clinically with gastrointestinal symptoms and histologically with pathologic eosinophil-predominant inflammation. Current practices diagnose these conditions on the basis of the location of the eosinophilia within the gastrointestinal tract—eosinophilic esophagitis (EoE); eosinophilic gastritis (EoG); eosinophilic enteritis (EoN, which includes involvement of the duodenum, jejunum, and/or ileum); and/or eosinophilic colitis (EoC). The broad term "eosinophilic gastroenteritis (EGE)" has been used previously to describe disease states that include eosinophilia of the stomach and/or small intestine; however, later clinical observations created the need for further characterization of patients with this type of inflammation with resultant efforts to recategorize disease states based on the primary area of eosinophilia, such as EoG and/or EoN in lieu of EGE (Table 1). For instance, for the first time, work from the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) determined clinical, endoscopic, histologic and molecular features of EoG and distinct and critical differences of EoG compared to non-EoG controls.(1) These findings are supportive of the fact that clinical observations identifying key features of different parts of the gastrointestinal tract affected by EGIDs will be further defined by molecular patterns and likely represent distinct disease entities. Thus, efforts to revise current nomenclature are underway and critical to advance the field.

Ongoing molecular, genetic, and epigenetic studies will establish further parameters by which to understand and classify these conditions individually and their context within the greater spectrum of EGID and allergic diseases. A range of differential diagnoses can complicate the identification of EGIDs, as the well-characterized symptoms for EGIDs are not specific to these conditions. However, clinicians familiar with non-EoE EGID clinical manifestations and appropriate medical workups can recognize and differentiate these diseases for clinical and research purposes. Suitable diagnostic eligibility criteria for clinical research populations may vary from criteria utilized to inform clinical diagnosis to facilitate the detection of potential treatment effects and ensure that observed effects are attributable to the action of a candidate therapy on the condition of interest.

The Food and Drug Administration (FDA) recently organized a meeting entitled Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI) Workshop on Eosinophilic Gastrointestinal Disorders Beyond Eosinophilic Esophagitis. The goal of the GREAT VI workshop was to discuss disease characteristics, natural history, and endpoints to assess treatment benefit in patients with non-EoE EGID and provide a forum for open discussion among stakeholders to facilitate drug development for these disorders. Key stakeholders involved in planning and presenting at the meeting included medical professionals, FDA representatives, an industry representative, and a patient representative. Medical professionals included those from professional societies (American Academy of Allergy, Asthma and Immunology [AAAAI], American College of Gastroenterology [ACG], American Gastroenterological Association [AGA], and North American Society for Pediatric Gastroenterology, Hepatology & Nutrition [NASPGHAN], and Society for Pediatric Pathology) and a key research group, the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) (for the meeting agenda and list of participants, see this article's Online Repository at www.jacionline.org). Herein, we summarize some of the material presented at this meeting and present a number of other thoughts regarding next-step goals for improving lives of patients with these diseases.

Nomenclature, Clinical Presentation, and Natural History

As noted above, recent work by CEGIR presented a clear and convincing description of clinical and molecular features of EoG.(1) With increasing clinical experiences, efforts within CEGIR are underway to further develop relevant and meaningful terminology for non-EoE EGIDs. In this regard, and for the purposes of thoughts presented here, more specificity will be used to promote characterization of the small bowel inflammation. For instance, EoN can be further characterized to involve the duodenum (eosinophilic duodenitis [EoD]), jejunum (eosinophilic jejunitis [EoJ]) and ileum (eosinophilic ileitis [EoI]) (Table 1). Notably, the small bowel is heterogeneous in function; therefore, signs and symptoms may vary depending on the part that is involved. Signs and symptoms that currently do not distinguish among the anatomic sites may with further study include signs and symptoms that are more site-specific.Thus, at this stage in disease discovery, detailed inquiries identifying and recognizing signs and symptoms that are most relevant to a particular part of the small bowel could guide decision-making at many levels, including whether to perform upper endoscopy, lower endoscopy, or both. Furthermore, seeking this type of information advances the precision medicine necessary for personalized medicine for patients with

non-EoE EGIDs. In future years and with more knowledge, further descriptions of the colon may be needed as it pertains to its anatomic features. Use of these terms and characterization of their features awaits more study and definition.

Symptoms of EGID vary by organ involvement and the layer of the bowel wall involved. EGID may be classified into subtypes as mucosal, muscular, or serosal, according to the layer involved.(2) The information herein focuses primarily on the mucosal subtype. EoG and EoN can have similar symptoms, which can include abdominal pain, nausea, vomiting, early satiety, bloating, and diarrhea.(3) EoC typically has symptoms of abdominal pain, diarrhea, and gastrointestinal bleeding.(3) Notably, these symptoms are not necessarily specific to the involvement of any gastrointestinal segment; consequently, there is clinical overlap among the various types of EGID. In contrast to EoE, non-EoE EGID are often associated with iron-deficiency anemia.(2) Protein-losing enteropathy can also be present.(2, 4) Atopy seems associated with non-EoE EGIDs, more closely with the EoG and EoN than EoC, but atopy is not universal in any EGID.(3, 5) Non-EoE EGIDs do not show evidence of the male predominance that has been observed for EoE,(3, 5–8) suggesting important differences in disease presentation and pathogenesis.

Patients suspected of having EGID need to undergo endoscopy and biopsy with histologic assessment of mucosal samples. Endoscopic findings in non-EoE EGID may be normal or may include erythema, nodularity, erosions, ulcerations, thickened folds, and pyloric stenosis.(9) Reference systems, such as the EoG endoscopic reference system (EoG-EREFS) are useful in systematically evaluating endoscopic irregularities that can be commonly seen in EoG (e.g., erosions, ulcerations, raised lesion, erythema, granularity, friability, thickened folds).(9) Importantly, many patients with EoG have normal, mild or non-specific endoscopic findings (e.g., erythema, granularity), highlighting the importance of biopsies for histologic assessment even in the absence of overt abnormalities (e.g., ulceration, raised lesions, thickened folds). In biopsies for histology, pathologists may observe areas of dense eosinophilic infiltration, patchiness of eosinophilic infiltration, and non-specific histologic changes in the context of dense eosinophilic infiltration, such as reactive gastropathy in the stomach and villous flattening in the duodenum.(10–12) Importantly, the severity of the EGID presentation can vary widely and is an important factor in individualizing the medical evaluation and treatment plan.

There is a lengthy delay of 4–9 years of symptoms prior to non-EoE EGID diagnosis.(3, 13, 14) Several circumstances can contribute to diagnostic delay, including non-specific symptom presentation, lack of endoscopic assessment, insufficient biopsy sampling, and lack of appropriate histopathologic evaluation (Table 2).(3, 13, 14) Interestingly, the recent use of deep machine learning in quantifying esophageal eosinophilia may be a potential strategy to more comprehensively assess eosinophilia within and between gastrointestinal segments despite the histologic patchiness.(15) Diagnostic delays adversely influence disease burden and quality of life (QOL).(16) Worsening outcomes and complications occur with increased duration of disease for non-EoE EGID,(2, 17, 18) which is similar to EoE.(19) These can include strictures, obstruction, perforation, ulcer formation, motility disturbances, anemia/bleeding, malnutrition, chronic symptoms, decreased QOL, and

financial burden.(2, 20) Currently, no predictors of disease progression nor predictors of complications for non-EoE EGID exist.

Unlike EoE, for which the basic genetic and heritability components have been mapped out, less is known about these components for non-EoE EGID. As noted previously, the EoG transcriptome has been elucidated and shown to partially overlap with the EoE transcriptome, particularly in cardinal type 2 immunity pathways.(1) Biomarker analysis, including elevated circulating thymic stromal lymphopoietin in EoG, support the role of type 2 immunity.(1) In regard to EoC, the similarities and dissimilarities with EoE and the underlying mechanisms are being studied, and the clinicopathologic and molecular characterization and pathogenesis of EoN and EoC are ongoing areas of research through the longitudinal studies of CEGIR as part of the Rare Diseases Clinical Research Network (RDCRN).(21) Rare Mendelian diseases and connective tissue disorders, such as Loeys-Dietz syndrome, have been associated with EGID.(22, 23) However, common genetic variants that may predispose to non-EoE EGID have yet to be identified, in part because the low prevalence of non-EoE EGID tends to restrict studies to cohorts of small size.

A number of variations in the pattern of non-EoE EGID course have been observed (continuous flare, relapsing flare), which suggest disease chronicity; single disease flares that resolve spontaneously and never recur are relatively rare and may suggest a reactive process rather than a “true” EGID.(17, 24) Mucosal and muscular subtypes are more common than the serosal subtype and tend to present with continuous or relapsing flares, (17) further supporting the chronicity of these disorders, similar to the chronicity of EoE.(2, 17, 18, 24, 25) EoC disease course and subtypes are a current area of study.(26, 27) Given the potential overlap and co-occurrence of EGID in multiple locations,(3) clinicians should have a low threshold for screening for EoG and EoN in patients who are undergoing a diagnostic endoscopy with persistent and prominent gastrointestinal symptoms suggestive of EGID. Colonoscopy and push enteroscopy are recommended only if suggestive symptoms are present for lower tract disease or if clinically indicated by other laboratory or radiologic findings.(28) The use of these procedures in research studies should be guided by the likelihood of obtaining key data to drive discovery and innovation on the basis of previous findings or underlying pathogenetic mechanisms.

Treatment of non-EoE EGID is based upon clinical acumen, case reports, and case series and includes dietary, steroid, immunosuppressive, and/or biological agent therapy.(4, 18, 29) Clinical experience and research suggest that EoG and EoN are likely pathogenically similar to the more commonly diagnosed and well-studied EoE.(6) As EoE is associated with atopy, has a type 2 immune–mediated immunological mechanism,(11, 16, 30) and responds to elemental formula,(4, 25, 31) gastric and duodenal EGID also may be food allergy–related diseases. A recent pilot clinical trial of patients with abdominal pain consistent with functional dyspepsia and duodenal eosinophilia treated with budesonide showed no overall efficacy (i.e., no significant difference between active treatment and placebo groups in baseline-to-post-treatment mean change in eosinophil or intraepithelial eosinophil counts) but did show a significant correlation between symptom improvement and a reduction in the combined duodenal eosinophil counts of all subjects.(32) Other recent clinical trials of an elemental diet (ELEMENT(14)) or biological agent (ENGIMA(33), testing anti–SIGLEC 8)

suggest that these therapies have potential clinical benefit and that EoG and/or EoD respond similarly to treatment, hinting at potential overlap in pathogenesis.

Disease Diagnosis and Prevalence

The diagnosis of non-EoE EGID is clinicopathologic, involving synthesis of clinical symptoms and signs and demonstrating pathologically elevated eosinophil counts of the gastrointestinal tract. Estimates of the prevalence of non-EoE EGID from large administrative databases are approximately 6 EoG, 7 EGE, or 3 EoC cases per 100,000 people;(3, 5, 34) currently, EoN prevalence is undetermined as no diagnostic codes exist for these conditions alone. The non-EoE EGID of EoG, EGE, and EoC thus represent <50,000 cases combined in the United States of America. However, the prevalence of these conditions seems to be increasing,(3) potentially suggesting either increased recognition or a true increase in incidence. Similar to EoE, for which the prevalence is approximately 1 in 2000 people in the general population but can be much higher in patients undergoing endoscopy for dysphagia (5–15%) and in patients with food impaction (>50%),(35) emerging data suggest that the prevalence of gastrointestinal eosinophilia may be substantially higher in patients with chronic and unexplained gastrointestinal symptoms, particularly when using a more extensive biopsy protocol (8 gastric and 4 duodenal biopsies) and a moderate-to-severe gastrointestinal symptom threshold (assessed daily by validated patient-reported outcomes [PRO]) as a clinical trial screening tool.(16, 33, 36)

A crucial element of the diagnosis of EGID is the histopathologic examination of gastrointestinal mucosal biopsies. Clinicians must realize that, unless specifically prompted, pathologists outside specialized centers may not describe eosinophils in gastric, duodenal, and colonic biopsies. As the normal density of eosinophils is not agreed upon, pathologists may not report mild to moderate elevations in eosinophils. Significant aggregates of eosinophils tend to elicit searches for parasites, which are difficult to detect and may be underdiagnosed. Only dense, diffuse infiltrates may prompt a pathologist to mention the possibility of an EGID-like condition.

Prior to the mid 2000s, few pathologists counted esophageal eosinophils. Because of the diagnostic concerns for EoE, clinicians began having conversations with pathologists regarding the inclusion of numbers of eosinophils per HPF in esophageal tissue samples. Since seeing the diagnostic benefit, pathologists have routinely followed this practice in patients with suspected EoE. Taking from this experience, it will be helpful for providers to re-engage in dialogue with local pathologists to assess for mucosal eosinophilia if a high degree of suspicion is present for an EGID.

A key aspect of diagnosing non-EoE EGID, similar to diagnosing EoE, is assessing for and excluding alternative etiologies for gastrointestinal mucosal eosinophilia. This can include parasitic or other infections (e.g., *H. pylori*), drug reactions, celiac disease, inflammatory bowel disease (IBD), and hypereosinophilia syndrome (HES).(18, 37, 38) The challenges of addressing diagnostic threshold values for eosinophils is that, in contrast to the esophagus where no eosinophils reside at the baseline, the stomach, small intestine, and colon normally contain resident eosinophils. In addition, establishing thresholds leads to oversimplification of the mucosal immuno-milieu, as there are abnormalities other than excess eosinophils.

Accordingly, efforts have been made to establish histology scoring systems (HSS) that include both eosinophil numbers and other markers of inflammation that permit histologic staging and grading. Similar to the EoE HSS,(39) current efforts are underway to develop histologic metrics for non-EoE EGID.(1)

There have been concerted efforts to address the lack of standardization of HPF for eosinophil counts and also in developing threshold values for non-EoE EGID; consensus diagnostic criteria and thresholds for non-EoE EGID are being finalized and shared. Importantly, these include the number of biopsies, number of HPF, and threshold of eosinophilia specific to the location of sampling. For example, a clinical trial identified EoG and EGE cases by measuring eosinophilia in 8 gastric and 4 duodenal biopsies.(16) Another clinical trial of eosinophilic inflammation of the duodenum used twice the normal peak value as a potential threshold.(33) Notably, gastric and duodenal biopsy specimens from patients with EGID were also found to have significant increases in mean mast cell counts compared with biopsy specimens from patients without EGID, and work is underway to determine how to incorporate this information into practice.(40) For EoC, the threshold values are complicated by the normal variation in eosinophil density in the colon, with the greatest density occurring in the cecum/right colon and the least in the sigmoid colon/rectum in some but not all studies;(41–44) however, threshold values for EoC are being further refined and are in use.(27) Excess eosinophils could be considered as a multiple of the peak eosinophil count per HPF in normal biopsies (e.g., 2 × normal eosinophils/HPF by location);(27, 45) however, due to the segmental grading of eosinophil load, (41–44) the location of sampling is important to report. Developing communications between clinicians (e.g., gastroenterologists) and pathologists and the specificity in directions from clinician-to-pathologist and results from pathologist-to-clinician would benefit and likely increase the EGID diagnoses.

As more biopsies of the small intestinal tract are being procured, an emerging body of evidence suggests that the duodenum may contain more eosinophils during homeostasis than previously expected and that eosinophil levels have a variable relationship with gastrointestinal dysfunction or pain in children and adults. Pediatric gastroenterologists obtain biopsies from the esophagus, stomach, and duodenum regularly as a part of standard of care during evaluations for upper gastrointestinal tract disease, including abdominal pain; in most of these studies, mucosal eosinophil numbers are not increased on the basis of previously published normative eosinophil values (i.e., eosinophil levels normal despite gastrointestinal disease/pain in children). Recent work in adult patients suggests that duodenal mucosal eosinophil levels (≥30 eosinophils in ≥3 HPF) may be associated with chronic abdominal pain reported in patients thought to have functional dyspepsia, irritable bowel syndrome (IBS), or disorders of brain-gut interaction (DBGI, previously known as functional gastrointestinal disorders [FGID]),(36) even in cases in which the levels fall within the previously identified normal range for duodenal eosinophils (i.e., eosinophil level above an empiric threshold, whether within normal or above-normal range, may correspond with gastrointestinal disease/pain in adults). Tissues from these patients may exhibit increased permeability, altered neuronal structure and function,(46) and correlation of neuronal damage with the inflammatory infiltrate, suggesting that there may be a mechanistic link related to type 2 inflammatory processes.[3–18] Together, these findings

provide speculative intersections of gastrointestinal eosinophilia, gastrointestinal symptoms, and potential underdiagnosis or misdiagnosis of EGID, although more data on this subject are needed.

Defining Clinical Benefit in non-EoE EGID Clinical Trials

The FDA-NIH BEST (Biomarkers, EndpointS, and other Tools) glossary definition of "clinical benefit" is a positive, clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.(47) Meeting the standards of sufficient and substantial evidence for determining clinical benefit requires ≥2 adequate and well-controlled studies, one to affirm and one to confirm and for the study design to be able to differentiate the effect of the tested therapeutic from other factors (e.g., placebo effect, biased observation, spontaneous change).(48, 49) Current challenges to defining clinical benefit for non-EoE EGID include the lack of standardized terms, including PROs, and lack of standardized consensus diagnostic criteria (Table 3), although results from efforts to address both of these issues are forthcoming. Notably, there can be differences in clinical practice and regulatory assessment standards (e.g., histologic thresholds), inclusion/exclusion of comorbid conditions (e.g., clinical trials may include cases with more severe or inflamed non-EoE EGID), and outcome requirements (e.g., eosinophilia reduction or resolution(33)) that should be considered prior to trial initiation to inform design and promote the interpretability of the results.

As non-EoE EGID are clinicopathologic conditions, leveraging clinical outcome assessments (COA), which measure or describe how a patient feels, functions, or survives, as coprimary endpoints may be beneficial to support the assessment of efficacy in clinical trials. COA include PRO, clinician-reported outcome, observer-reported outcome, and performance outcome assessments; these are in development and have been used in clinical trials (e.g., ENIGMA(33)). Further development of the non-EoE EGID PRO and COA should take into consideration that assessments designed for clinical practice may or may not be suitable for regulatory purposes, which have set standards of an assessment being well defined, reliable, and fit for an intended purpose. Additionally, using proxy measures (i.e., where observers report on non-observable symptoms [e.g., pain]) as if they were the patients is not recommended. COA administration schedule should be compatible with the heterogeneity (chronic, intermittent, frequency) of the disease symptoms, which can be challenging due to the variable frequency of the multiple symptoms associated with EGID. Therefore, continuing the dialogue between key stakeholders, including patients, researchers, and FDA and industry representatives, will be key in defining clinical benefit in non-EoE EGID clinical trials.

Assessing Meaningful Benefit in EGID Clinical Practice: Clinician and Patient Perspectives

Clinical assessment depends on the presenting features because patients with non-EoE EGID typically have a variable combination of clinical manifestations.(17, 50) This variability of clinical manifestations (symptoms, endoscopic, biochemical and hematologic abnormalities, and histopathologic findings) for children and adults with non-EoE EGID means that heterogeneity should be considered when assessing meaningful benefit, including evaluating individual pre-therapy and post-therapy symptoms at the subdomain level; current clinical

trials often use the mean across domains and/or patients, which can disguise meaningful benefit of the therapy by homogenizing a heterogeneous presentation. Notably, how to assess responsiveness may differ by symptom domain (e.g., 3 months vs. 12 months required for differences), necessitating compatible clinical trial design. In clinical practice, meaningful benefit can manifest as improvement in hematologic parameters (anemia, peripheral eosinophilia) and biochemical abnormalities (iron deficiency, hypoproteinemia) independent of symptom activity.

Healthcare utilization(50) and disease burden(34) is high in individuals with non-EoE EGID; in a retrospective study of EoG and EGE in children and adults, cases underwent an average of 5 endoscopic procedures per year.(50) Endoscopies, during which a limited number of random biopsy samples are taken, may show histopathologic patchiness or appear to be “normal”.(24, 51) Thus, inadequate sampling and disease heterogeneity can limit a clinician’s ability to diagnosis, interpret treatment response, and determine treatment approach. Furthermore, clinicians need to balance how to treat non-EoE EGID with how to limit side effects in order to optimize patient psychological, social, financial, and physical wellbeing and QOL. When caring for patients, wellbeing and QOL are often individualized and consider not only what is important to the patient’s health in terms of minimizing disease impact and avoiding complications, but also what is most important to the patient (e.g., relief from symptoms, such as nausea, pain, or diarrhea; ability to attend work/school). Symptom assessments, endoscopy, and histopathology may correlate with decreased eosinophilia and histopathology in at least a subset of patients.(26) Disease heterogeneity and healthcare utilization should be considered when assessing meaningful benefit. Developing non-invasive assessments may be helpful in providing reassurance when attempting to minimize invasive testing. Although QOL is an important aspect of patient care, these assessments can have many contributing factors that are not direct reflections of the disease process.

A series of EoG/EGE semi-structured interviews of patients and families with EoG or EGE identified that psychosocial, social, financial, and physical aspects of health-related QOL are important issues.(20) Relative to EoE, non-EoE EGID seem to have more frequent symptoms and a higher frequency of fatigue and isolation(34) and persistent and severe disease.(6) Moreover, patients with non-EoE EGID have a high burden of mental health comorbidities.(52) Less is known about EoC QOL, though longitudinal studies are ongoing through CEGIR. Importantly, the time to diagnosis is long for non-EoE EGID. Studies of other immune-mediated disorders of the gastrointestinal tract suggest that QOL and health-related QOL are dependent on the time to diagnosis and subsequent therapy.(53, 54) These circumstances prompt clinicians and researchers to move forward with what is currently known about non-EoE EGID to develop safe and effective treatments while simultaneously investigating more specifics for patients with non-EoE EGID in order to improve patient QOL by decreasing the time to diagnosis and effective treatment.

Conclusion and Closing Thoughts

The FDA Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI) Workshop on EGID Beyond EoE comprised various stakeholders that

provided valuable expertise and perspective and demonstrated how much we know about non-EoE EGID and how much energy, resources, and expertise are being used to continue enriching that knowledge as we press forward toward FDA-approved therapies. The meeting highlighted current and new information about non-EoE EGID and emphasized areas for further communication and consensus regarding disease diagnosis, etiology, treatment, endpoints, and outcomes (e.g., Table 4). This conference facilitated discussion about how to further advance the field together to address unmet needs for EGIDs beyond EoE and spoke to the need for a better understanding of non-EoE EGID natural history and an FDA-approved therapy for all EGID. Notably, the primary FDA-identified areas for further development and investigation are active areas of steady progress, the primary FDA-identified areas for further development and investigation are active areas of EGID standardized nomenclature and normal values for gastrointestinal eosinophils (tissue-resident vs. infiltrating) and threshold values for non-EoE EGID are at the cusp of being finalized and shared for widespread clinical implementation. In terms of clinical benefit (clinical trial) and meaningful benefit (clinical practice) outcome assessments, several purpose-developed EoG and EoN symptom outcome assessments are in development. In summary, the pressing need for EGID therapy is underscored by the onset of clinical trials in the midst of improving the foundation of understanding and speaks to the unmet need of thousands of patients who have no FDA-approved therapies.

As we move forward in our next steps for FDA-approved therapies for non-EoE EGID (e.g., Table 5), we wish to share the poignant perspective of the patient representative at the conference when asked of her advice to other patients with EGID, advice we believe to be relevant and motivating to everyone involved in a patient's journey: "I would say to never give up hope. I know it is easier said than done, but I know that all of these wonderful doctors are working tirelessly to better understand EGID and how to treat them…Celebrate all the milestones, big and small. Try to look at everything from an optimistic view point because, for me, it has made dealing with my condition more bearable." In this regard, swift and substantial progress has been made in the non-EoE–related EGID, and we hope that the ongoing efforts for scientific advancement in the field and the engagement of investigators and the FDA will bring rapid and meaningful approval of new therapies for patients and families.

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Conflicts of Interest

M.E.R. is a consultant for Pulm One, Spoon Guru, ClostraBio, Serpin Pharm, Allakos, Celldex, Celgene, Astra Zeneca, Adare/Ellodi Pharma, Glaxo Smith Kline, Regeneron/Sanofi, Revolo Biotherapeutics, and Guidepoint and has an equity interest in the first six listed and royalties from reslizumab (Teva Pharmaceuticals), PEESSv2 (Mapi

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Abbreviations

AAAAI	American Academy of Allergy, Asthma and Immunology
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association

APFED	American Partnership for Eosinophilic Disorders
BEST	Biomarkers, EndpointS, and other Tools
ausEE	Australian eosinophilic esophagitis patient advocacy group
CEGIR	Consortium of Eosinophilic Gastrointestinal Disease Researchers
CME	continuing medical education
COA	clinical outcome assessments
CURED	Campaign Urging Research for Eosinophilic Diseases
EFC	Eosinophilic Family Coalition
EGE	eosinophilic gastroenteritis (formerly accepted term for EoG and/or EoN)
EGID	eosinophilic gastrointestinal disorder
EoC	eosinophilic colitis
EoD	eosinophilic duodenitis
EoE	eosinophilic esophagitis
EoG	eosinophilic gastritis
EoI	eosinophilic ileitis
EoJ	eosinophilic jejunitis
EoN	eosinophilic enteritis
EOS Network	British eosinophilic disease patient advocacy group
EREFS	Endoscopic Reference System
EurEoS	European Eosinophil Society
FDA	Food and Drug Administration
DBGI	disorders of brain-gut interaction
FGID	functional gastrointestinal disorders (formerly accepted term for FBGI)
GREAT	IV Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI
HES	hypereosinophilia syndrome
HSS	Histology Scoring System

IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
HPF	high-power microscopic field
MOC	maintaining certification
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology & Nutrition
PRO	patient-reported outcome
QOL	quality of life
RDCRN	Rare Diseases Clinical Research Network
TIGER	The International Gastrointestinal Eosinophil Researchers [TIGER]

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Key Points

- Diagnosis of non–eosinophilic esophagitis (non-EoE) eosinophilic gastrointestinal disorders (EGID) can be challenging, as eosinophils are resident cells during homeostatic healthy conditions in the non-esophageal portions of the gastrointestinal tract. Nevertheless, eosinophil thresholds for diagnosis, especially in patients with eosinophilic inflammation of the stomach and duodenum, and more comprehensive disease manifestation assessments are steadily being refined to permit the assessment of meaningful benefit in clinical practice and in clinical trials.
- Standardized nomenclature for clinical and research purposes for non-EoE EGIDs is fundamental for further progress and is being developed.
- The non-EoE EGID field is expanding, and data related to diagnosis, natural history, and pathogenesis are rapidly emerging and transforming clinical practice.
- As chronic diseases associated with substantial morbidity, health care utilization, and poor quality of life, EGIDs are in desperate need for efficacious and FDA-approved drugs.
- Potential differences in assessment standards, diagnostic and eligibility criteria, and outcome measures between clinical practice and those suitable for regulatory purposes to support drug development should be considered prior to trial initiation to inform design and promote the interpretability of the results to support the assessment of clinical benefit.

Table 1.

Disease abbreviations*

Disease	Abbreviation (Status**)
Eosinophilic gastrointestinal disorders	EGID • collective term for this spectrum of clinicohistopathologic disorders featuring eosinophilia in segments of the gastrointestinal tract (Accepted) • singular term for a case of EGID in which eosinophilia is in multiple segments of the gastrointestinal tract (e.g., "EGID with esophageal and duodenal involvement" instead of "EoE and EoD") (Provisional)
Eosinophilic esophagitis	EoE (Accepted)
Eosinophilic gastritis	EoG (Provisional; currently also abbreviated as "EG")
Eosinophilic enteritis Eosinophilic duodenitis Eosinophilic jejunitis Eosinophilic ileitis	EoN (Provisional) • EoN can be further characterized to involve the duodenum (EoD; Provisional), jejunum (EoJ; Prospective) and ileum (EoI; Prospective)
Eosinophilic colitis	EoC (Provisional; currently also abbreviated as "EC")
Eosinophilic gastroenteritis	EGE (Formerly Accepted; to be de-emphasized) • The broad term EGE has been used to describe disease states that include eosinophilia of the stomach and/or small intestine; however, clinical observations created the need for further characterization of patients with this type of inflammation, resulting in efforts to recategorize disease states on the basis of the primary area of eosinophilia (e.g., EoG, EoN, EoD, EGID with gastric and enteric involvement). This term is used herein primarily to discuss earlier studies that did not differentiate between EoG and/or EoN.

* These abbreviations represent the current trends in changing terminology in the field; clinical observations identifying key features of different parts of the gastrointestinal tract affected by EGIDs will be further defined by molecular patterns, resulting in further efforts to revise current nomenclature to advance the field.

** Abbreviation status herein is Formerly Accepted, Accepted, Provisional, or Prospective use of the indicated abbreviation

Table 2.

Circumstances and solutions to diagnostic delay of EGID*

Contributing Circumstances	Solutions
Non-specific symptoms and lack of considering of EGID as diagnostic possibilities	Consider EGID as part of the differential diagnosis in patients with chronic gastrointestinal symptoms, and obtain an adequate number of biopsy samples at endoscopy. There remains a need to raise clinician awareness; this is occurring through symposia at national meetings (e.g., Digestive Diseases Week, American Academy of Allergy, Asthma & Immunology Annual Meeting, James W. Freston Single Topic Conference of the American Gastroenterological Association). Develop continuing medical education (CME) and maintaining certification (MOC) programs tailored to clinicians, including primary care clinicians, to understand disease (e.g., North American Society of Pediatric Gastroenterology, Hepatology and Nutrition [NASPGHAN] https://learnonline.naspghan.org/products/the-abcs-of-egids).
Delayed referral to gastroenterologist	Seek the attention of gastroenterologists early in the workup of refractory symptoms.
Alternative diagnosis with nonspecific gastrointestinal condition (e.g., IBS, functional dyspepsia)	Consider EGID in patients with idiopathic diagnoses who have persistent severe symptoms and/or are not responding to empiric treatments as expected.
Lack of thorough diagnostic evaluation	Consider EGID as part of the differential diagnosis in patients with chronic gastrointestinal symptoms and/or idiopathic diagnoses. Use a low threshold for detailed workup, including endoscopy and multiple biopsies.
No collection of endoscopic biopsies	Consider EGID as part of the differential diagnosis in patients with chronic gastrointestinal symptoms and/or idiopathic diagnoses. Multiple biopsies are required for diagnosis, even in patients without endoscopic findings.
Number and location of biopsies being insufficient to detect eosinophilia due to its patchiness	Follow consensus recommendations (now in development), which will include biopsy number for non-EoE gastrointestinal sites; multiple biopsies from each gastrointestinal segment increase the sensitivity of diagnosis.
Endoscopic biopsy samples sent to the pathologist without adequate communication about suspicion for an EGID	Clinicians (e.g., gastroenterologist) should communicate with pathologists, especially to alert them to quantify eosinophil levels, and state EGID suspicion in clinical information sent to the pathologist.
No histopathologic quantification of eosinophils nor description of associated pathologic changes	Quantify gastrointestinal eosinophil levels more routinely. The clinician (e.g., gastroenterologist) should request histopathologic quantification of eosinophils and description of associated pathologic changes with comment that these will aid diagnosis and treatment decisions. Notably, experience with EoE has taught us that peak eosinophil counts have become more prevalent in pathology reports largely because of clinician insistence and less so because of pathology recommendations. Pathologists generally respond favorably to clinician requests when the clinician makes it clear that the information is not “nice to know” but instead will be used in clinical decision-making; therefore, we believe that pathologists will respond to clinician requests concerning non-EoE EGID pathology reports more favorably than they would to standardizing assessment schemas composed by other pathologists.

*This is a representative rather than exhaustive list of circumstances

Table 3.

Challenges and progress to defining clinical benefit in non-EoE EGID*

Challenges	Progress
Lack of clinical consensus diagnostic criteria	Consensus criteria are currently being developed for non-EoE EGID (CEGIR initiative).
Heterogeneous nomenclature	Harmonized nomenclature is currently being developed (CEGIR initiative).
Differences in clinical practice and regulatory assessment standards and outcome requirements	An integrated approach is recommended.
Lack of regulatory or drug development precedent	Collaboration of key stakeholders and open dialogue, such as this FDA GREAT VI Workshop, are essential.
Rare diseases with few patients available to participate (although disease recognition is increasing)	Collaborative research involving multiple sites and partnering with patient advocacy groups helps identify, recruit, and maintain patients in research (practices adopted by CEGIR).
Multi-center, multi-country trials required to enroll sufficient patients	Open dialogue, collaboration, registries, and meetings across diverse geographic, demographic, racial, and ethnical groups are underway (e.g., patient advocacy groups, European Eosinophil Society [EurEoS], The International Gastrointestinal Eosinophil Researchers [TIGER]).
Pediatric-specific considerations	It is important to realize that children and adults can require unique considerations, which are discussed through collaborative research endeavors and networks that include both adult and pediatric clinicians and researchers, such as CEGIR (involvement of patient advocacy groups; e.g., American Partnership for Eosinophilic Disorders [APFED], Campaign Urging Research for Eosinophilic Diseases [CURED], Eosinophilic Family Coalition [EFC], ausEE, EOS Network)

*This is a representative rather than exhaustive list of challenges

Table 4.

Outstanding questions and progress in the non-EoE EGID field

Question	Progress
How do we interpret eosinophil number in tissues that have eosinophils during homeostasis? How can we improve diagnosis for non-EoE EGID?	Consensus criteria are being established in a consensus process led by CEGIR.
Is the number of eosinophils a relevant parameter or, for instance, may localization of the eosinophilia or other histologic or molecular findings be more informative for disease assessment and outcomes and/or therapeutic endpoint assessment?	Histology Scoring Systems (HSS) that take into account a number of parameters in addition to eosinophils are being developed. Likewise, endoscopic scoring systems have been (e.g., EoG-EREFS) and are being developed. Molecular and cellular dissection of disease pathogenesis is developing a framework for disease biomarkers. Furthermore, patient-reported outcome (PRO) metrics are being developed and have been used in EoG/EoD clinical trials; their coimplementation with clinical care is a focus area.
Why do non-EoE EGID have lower prevalence than EoE? Are they underdiagnosed?	Prevalence studies are ongoing and have suggested that a combination of factors, including increased disease recognition and the allergy epidemic, are contributing to increased diagnosis of non-EoE EGID.
How do non-EoE EGIDs, IBS, DBGI (formerly FGID) relate? What does this mean for our understanding of non-EoE EGID?	A detailed analysis of eosinophil levels and type 2 immunity is currently underway; disease overlap may be present in some patients.
Why are some tissues affected and not others?	This is a cardinal question, and detailed studies of EoE suggest that tissue-specific, genetically defined pathways and susceptibility are involved.
Are there differences between resident and infiltrating eosinophils and their role in disease initiation, perpetuation, resolution, and/or recurrence?	Fundamental studies about eosinophil heterogeneity are revealing multiple populations of eosinophils, some with potential helpful properties (e.g., regulatory eosinophils). The role of eosinophil heterogeneity in EGID is an outstanding question.
Do the affected areas represent distinct diseases in a continuum or a spectrum?	Evidence is emerging that distinct tissue involvement in non-EoE EGID may represent a disease continuum, but this is a debated topic.
How do we separate functional dyspepsia, DBGI (e.g., IBS), and EGID?	In most clinical cases, a thorough histologic and pathologic evaluation will lead to the diagnosis of EGID. Moreover, clinicians with familiarity with non-EoE EGID clinical manifestation and appropriate medical workup are able to recognize and differentiate these diseases for clinical and research purposes. Detailed cellular, molecular, and neuro-immunologic characterization of these diseases will likely facilitate future diagnosis and patient phenotyping and endotyping.
What is the EoC disease course and does it differ from gastric and enteric EGID disease courses? What underlies EoC's lower association with atopy relative to other non-EoE EGID?	Preliminary studies suggest a distinct etiology and disease course for EoC; more studies are needed.
What are appropriate endpoints to assess a treatment's clinical benefit for each non-EoE EGID?	A series of broad outcome metrics spanning histologic, endoscopic, molecular, and clinical features are being developed. This is a focus area of CEGIR.
How can the development of approaches and assessments for "clinical benefit" for clinical trials and "meaningful benefit" for clinical practice be complementary?	Increasing dialogue between key stakeholders, including patients, researchers, and FDA and industry representatives, will be key in this regard.
What are appropriate endpoints to assess a treatment's clinical benefit for each non-EoE EGID? How can non-invasive and QOL assessments be developed and/or validated for meaningful benefit for clinical practice?	A series of validated endpoints involving clinical, endoscopic, histologic, and molecular features are being developed and will likely prove to be valuable.

Table 5.

Recommendations for next steps in the non-EoE EGID field

Finalize and implement clinical consensus nomenclature and diagnostic criteria (e.g., histopathologic criteria and thresholds) and further characterize the natural history for these diseases
Develop curriculum for medical and other health professional schools, continuing medical education (CME), and maintaining certification (MOC) programs tailored to clinicians to understand EGID.
Define clinical benefit in clinical trials through collaborations with patients, patient advocates, researchers, clinicians, industry, regulatory agencies, and other stakeholders
Incorporate frequent and early interaction with the FDA for drug development and the prospective design and use of anchor-based analyses to promote the detection and characterization of clinically meaningful change and facilitate interpretation of results across drug development programs from even the early stages of drug development
Develop consensus clinical trial endpoint assessment criteria that are complementary to diagnostic criteria and clinical presentation for each non-EoE EGID to facilitate design and generalizability of findings for clinical trials
Develop FDA-approved drugs for EGID indications; current EGID treatments are limited to off-label uses or clinical trials