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New developments in patients with eosinophilic gastrointestinal diseases presented at the CEGIR/ TIGERS Symposium at the 2018 American Academy of Allergy, Asthma & Immunology Meeting

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Abstract

The Consortium of Eosinophilic Gastrointestinal Diseases and the International Gastrointestinal Eosinophil Researchers organized a day-long symposium at the recent 2018 Annual Meeting of the American Academy of Allergy, Asthma & Immunology, which was coupled for the first time with the World Allergy Organization meeting to create an international platform. The symposium featured experts in many facets of eosinophilic gastrointestinal diseases, including allergy, immunology, gastroenterology, pathology, and nutrition, and was a well-attended event. The basic science, genetics, cellular immunology, and clinical features of the diseases, with a focus on epithelial, eosinophil, and mast cell responses, as well as current and emerging treatment options, were reviewed. Here we briefly review some of the highlights of the material presented at the meeting.

Keywords

Eosinophilic esophagitis; food allergy; treatment; diagnosis

Knowledge related to the epidemiology of eosinophilic gastritis (EG), gastroenteritis, and eosinophilic colitis (EC) remains limited. The prevalence of these conditions ranges from 3.5 to 8.3 per 100,000, with approximately 50,000 cases total estimated in the United States.[1] There does not appear to be a male predominance, but there is an association with atopy.

No etiologic or risk factor studies have been done for EG, eosinophilic gastroenteritis, or EC. The epidemiology of eosinophilic esophagitis (EoE) is far better described.[2] The prevalence is approximately 1 per 2000, with an estimated 150,000 cases in the United States and large burden of disease (>$1 billion annually).[3,4] Both the incidence and prevalence of EoE are increasing rapidly, and there is much research interest in these evolving trends. Although no specific "cause" for this increase has been found, there are a number of potential risk factors, including the decrease in *Helicobacter pylori* infection, low population density, and early-life exposures, such as antibiotic use.[5] Gene-environment

interactions, particularly between breast-feeding and single-nucleotide polymorphisms in calpain 14 (CAPN14), have been identified recently as a predisposing factor.[6] EoE is a highly atopic disease with a high rate of asthma, allergic rhinitis, and IgE-mediated food allergy. For food allergy, it is also known that oral immunotherapy can induce EoE in about 5% of cases.[7]

CONSEQUENCES OF EoE: REMODELING

Unbridled T_H2 eosinophilic esophageal inflammation leads to esophageal rigidity in children and adults through tissue remodeling that includes histologic changes of basal zone hyperplasia, fibrosis, angiogenesis, and smooth muscle hyperplasia with hypertrophy.[8,9] Current data in adults demonstrate that uncontrolled EoE can result in a fibrostenotic state, with resultant strictures in the majority of patients.[10,11] The use of endoscopic functional lumen imaging probe technology provides a novel esophageal readout for compliance and motility.[12,13]

A rigid extracellular matrix has consequences in terms of both esophageal biomechanics and structural cell function.[14,15] Esophageal fibroblasts cultured on a rigid matrix have increased contractility and myofibroblast features, and smooth muscle cells become hypertrophic and have increased expression of contractility and fibrotic genes when cultured in a stiff matrix.[14,15] Therapies that reduce inflammation in children and adults can reverse histologic fibrosis and esophageal rigidity in a subset of subjects.[16,17] A future direction for EoE therapy will be to treat not only inflammation but also the complications of dysfunctional esophageal biomechanics.

RELATIONSHIP BETWEEN EoE AND OTHER FORMS OF ESOPHAGITIS WITH FOCUS ON PROTON PUMP INHIBITOR RESPONSES

The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is addressing a number of key issues in the field of eosinophilic gastrointestinal disorders (EGIDs), including the relationship between EoE and various other forms of esophagitis.[18] EoE and gastroesophageal reflux disease share a complex relationship, and previous assumptions used to dichotomize the 2 might be flawed.[18,19] Proton pump inhibitor (PPI)–responsive esophageal eosinophilia (PPI-REE) describes patients with esophageal eosinophilia; typical EoE symptoms, endoscopic features, and histology; and no evidence of gastroesophageal reflux disease, as determined by using endoscopy, but who exhibit clinical and histologic response to PPIs. There is still controversy surrounding the entity and extent to which it overlaps with or is a subtype of EoE.[20,21] Clinically, a number of conditions can cause esophageal eosinophilia. However, when patients present with typical symptoms of esophageal dysfunction, atopy, endoscopic findings suggestive of EoE and biopsy specimens with marked esophageal eosinophilia, they appear to have EoE. There are now extensive data that suggest the clinical, endoscopic, histologic, immunologic, and molecular features of these patients at baseline (before PPI treatment) are largely indistinguishable between PPI responders (PPI-REE) and nonresponders (classic EoE).[3,20–22] One possible mechanism for PPI-REE is that patients with EoE respond to the anti-inflammatory effects of PPIs unrelated to gastric acid inhibition. PPIs have been documented to induce histologic remission in

approximately 50% of patients with symptomatic esophageal eosinophilia, block T_H2 cytokine–induced eotaxin-3 secretion in esophageal (and bronchial) epithelial cells, and reverse an allergic T_H2 inflammatory transcriptome signature.[23] Given the weight of evidence documenting that PPIs reduce esophageal eosinophilia, A Working Group on PPI-REE (AGREE) is putting forth an updated diagnostic algorithm for EoE that includes removal of the PPI trial requirement and suggests that PPIs are better classified as a treatment rather than as a diagnostic criterion for EoE.[19]

EoE THERAPY: DIET VERSUS STEROIDS?

The advantages of using diet therapy over steroid therapy to treat EoE (particularly over the long-term) were reviewed. Diet therapies achieve histologic remission, consistently resolve symptoms, and might mitigate long-term esophageal complications by reversing epithelial hyperplasia and subepithelial fibrosis.[17,24–26] Elimination diet therapies can be a practical treatment for patients of all ages, and with the assistance of dietitians, diet therapies might improve the nutritional quality of patients' diets.[27] In recent years, elimination diets have become easier to follow because food manufacturers have improved the palatability of foods used as substitutes for eliminated foods. Although therapies for EoE should be individualized and based on the patients' lifestyle and clinical needs, diet therapy has become an increasingly feasible treatment option for many patients.

EoE THERAPY: STEROIDS VERSUS DIET?

The advantages of using steroid therapy over diet for patients with EoE were reviewed (Table I). Important points favoring steroid therapy include that use of topical corticosteroids is effective at achieving histologic, endoscopic, and symptomatic end points while preventing complications, such as fibrosis and food impactions.[28–30] This treatment offers good tolerability with minimal effect on quality of life and without the use of multiple endoscopies. Topical corticosteroids have a good side effect profile, and complications are rare. Overall, the right choice on initial therapy is very individualized and patient driven, being based on consideration of the goals of care and what fits best with the subject's lifestyle and needs.

NUTRITIONAL IMPLICATIONS OF EoE

Children with EoE might be at increased nutritional risk. A number of studies have reported poor growth at diagnosis in the pediatric population with EoE.[31,32] Although there appears to be greater risk of stunting and being underweight in children with IgE-mediated food allergy on cow's milk or multiple food elimination diets, studies in children with EoE on elimination diets do not indicate growth consequences when the patient is under the care of a dietitian; receiving adequate energy, protein, and micro-nutrients; and/or using a supplemental formula to support the diet. Feeding difficulties in patients with EoE have also been reported, and data exist that many children with EoE have maladaptive eating behaviors on the basis of a validated behavioral feeding assessment scale. Tools have been developed through an American Academy of Allergy, Asthma & Immunology workgroup

report to assist practitioners in minimizing the nutritional effect of EoE and the associated diet therapies used in disease management.[33]

IgG VERSUS IgE AND DISEASE PATHOGENESIS

The importance of IgE versus IgG_4 in the pathogenesis of EoE was discussed. On the one hand, it was concluded that IgE might not have a major role in EoE for several reasons, including the following: (1) symptoms are typically not temporally related to food triggers, (2)skinprick test resultsand serumIgE levels to foods are only weakly predictive offood triggers,[34,35] and (3) allergy test–based elimination diets (directed by skin prick tests, serum food-specific IgE levels, and IgE measurement of allergenic molecules by using component-resolved diagnostics) are not that effective in inducing EoE remission.[36,37] Furthermore, omalizumab, an antibody targeted against IgE, was not effective in inducing EoE remission in a double-blind, placebo-controlled clinical trial.[38] IgG_4 was thought to potentially have a role in EoE pathogenesis, although the current evidence for this is still preliminary. Serum, plasma, and esophageal tissue IgG_4 levels to common food triggers were shown to be increased in patients with EoE, although the increase was not predictive of food triggers in these patients.[39,40] Therefore it was concluded that higher levels of IgG_4 than IgE are produced in patients with EoE and that evidence to support IgG_4 involvement directly in disease pathogenesis is needed.

ROLE OF T CELLS IN EoE PATHOGENESIS

There is evidence of a T_H2 phenotype in blood and biopsy specimens, indicating that T-cell function might play a key role in disease pathogenesis.[41] Patients with active EoE have local T_H2 inflammation characterized by high levels of IL-13, IL-4, IL-5, and thymic stromal lymphopoietin, chemokines that attract eosinophils (eg, eotaxins), lymphocytes, mast cells, basophils, and invariant natural killer T (iNKT) cells.[41–43] T_H2 polarization can be favored by genetic background in patients with EoE with higher production of epithelial factors, such as thymic stromal lymphopoietin, thereby promoting differentiation of naive $CD4^1$ T cells into T 2 cells.[44] Accumulating evidence suggests that both innate (ie, iNKTs) and conventional T cells are able to recognize and mount a T_H2 response against food antigens in patients with EoE. Mouse models have demonstrated that T, but not B, cells are essential for EoE development.[45] iNKT numbers are increased at the site of inflammation and have a T_H2 pheno-type in patients with EoE.[46,47] Milk-derived lipid antigens are able to specifically activate iNKT cells and induce a T_H2 response in patients with EoE.[46,48]

In addition, patients with active EoE disease triggered by milk consumption have a significant increase in numbers of activated peripheral blood $CD4^1$ T cells expressing T_H2 cytokines compared with those seen in healthy control subjects or patients with inactive EoE.[41] This $CD4^1$ T-cell population is capable of *in vitro* milk-specific antigen responses.[41,49] These data confirm that both innate and adaptive T cells could have a central role in antigen recognition and initiation of T_H2 inflammation.

MAST CELL INVOLVEMENT

Mast cells are increased in patients with active EoE, and their counts correlate with eosinophil levels and decrease with treatment in a majority of patients with EoE.[50] Mast cells can have a role in symptoms through esophageal nerve activation and smooth muscle contraction, and the mast cell transcriptome correlates with dysphagia scores. Mast cells have a potential role in fibrosis and esophageal remodeling, and their esophageal density correlates with endoscopic furrows.

LESS INVASIVE TESTING

Less invasive testing for evaluating the esophagus is a rapidly growing area of clinical medicine and inquiry. Such testing includes methods that replace endoscopy or complement endos-copy with or without sedation. Most of these modalities are generally not currently available, except for the endoscopic functional lumen imaging probe (EndoFLIP), unsedated trans-nasal endoscopy (TNE), and the EoE Diagnostic Panel (EDP). Other technologies will likely becoming more clinically available soon, such as the esophageal string test, mucosal impedance, and cytosponge, which are currently only available in research settings. These technologies have the potential to enable improved monitoring of the esophagus with lower cost but have tradeoffs compared with a more complete, biopsy-centric mucosal examination with sedated endoscopy. Other complementary technologies might offer additional information regarding esophageal compliance or more rapid assessment of mucosa compared with mucosal pathology, but the usefulness of such testing is debated.

PATIENT ADVOCACY

The positions of patient advocacy groups were presented. In particular, the many challenges of rare diseases were discussed, from obtaining a correct diagnosis to limited treatment options to finding a knowledgeable physician.[51] Patients with EGIDs have limited treatment options for a lifelong disease that significantly affects quality of life. Patient advocacy groups, such as the American Partnership for Eosinophilic Disorders and the Campaign Urging Research for Eosinophilic Diseases (CURED), can help physicians by assisting patients in finding support, lay friendly educational materials, patient conferences, and practical tools for everything needed to live life to the fullest.

PILOT STUDIES WITH POTENTIAL TO AFFECT EGIDs

The CEGIR Pilot Study Program examines novel areas with the potential to create or change diagnostic and therapeutic paradigms concerning EoE, EG, and EC.[18] Currently, 4 pilot studies have been funded and are active: (1) a microbiome initiative examining the gastrointestinal mucosal and fecal bacterial genomes in patients with EoE, EG, and EC; (2) a prospective clinical trial of losartan in patients with EoE; (3) a prospective trial of elemental diet in adults with EG; and (4) a prospective study examining the utility of TNE in children with EoE. Characterization of dysbiosis of the intestinal tract should provide fundamental insight into the pathogenesis of EGIDs. The losartan and elemental diet trials are the first prospective evaluations of such treatments in patients with the indicated diseases. Finally,

evaluation of TNE can reduce the necessity of anesthesia during endoscopy during food reintroduction, a major limitation of the elimination diet approach in patients with EoE.

ENDOTYPES IN PATIENTS WITH EoE

Three EoE endotypes have been identified based on probing esophageal biopsy specimens from pediatric and adult patients with EoE across sites associated with CEGIR by using the EDP, a set of 96 informative transcripts.[52] Of histologic features, basal zone hyperplasia correlated relatively strongly with the EDP, and of different endoscopic features, furrows correlated relatively strongly with the EDP.

The EDP identified 3 clusters associated with distinct endo-types (termed EoE endotype 1 [EoEe1] to EoE endotype 3 [EoEe3]) despite similar eosinophil levels. EoEe1 was strongly associated with a normal-appearing esophagus and showed relatively mild histologic, endoscopic, and molecular changes. EoEe2 demonstrated an inflammatory and steroid-refractory phenotype and showed the greatest expression of cytokines and steroid-responding genes. EoEe3 was associated strongly with a narrow-caliber esophagus and showed the highest degree of endoscopic and histologic severity and the lowest expression of epithelial differentiation genes. These endotypes have potential to allow tailoring of EoE-specific therapy, as well as prognostic predictions.

PREDICTING THE FUTURE IN EGIDs

The potential needs for patients, researchers, and physicians were discussed for the immediate future and the next 10 years (Table II). The major developments will be availability of US Food and Drug Administration–approved medications for patients with EoE and less invasive biomarkers for diagnosis. In the more distant future, personalized medicine based on genetics and genomics on esophageal biopsy specimens, as well as disease endotypes, is likely to advance patient care and understanding.

Abbreviations used

CEGIR:	Consortium of Eosinophilic Gastrointestinal Disease Researchers
EC:	Eosinophilic colitis
EDP:	EoE Diagnostic Panel
EG:	Eosinophilic gastritis
EGID:	Eosinophilic gastrointestinal disorder
EoE:	Eosinophilic esophagitis
EoEe1:	EoE endotype 1 (EDP identified)
EoEe2:	EoE endotype 2 (EDP identified)
EoEe3:	EoE endotype 3 (EDP identified)

iNKT:	Invariant natural killer T
PPI:	Proton pump inhibitor
PPI-REE:	Proton pump inhibitor–responsive esophageal eosinophilia
TNE:	Transnasal endoscopy

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TABLE I.

Pros and cons of diet versus steroids

Diet therapy		Swallowed steroids	
Pro	**Con**	**Pro**	**Con**
"Natural"	Lower quality of life to adjust to dietary restrictions and poor palatability in case of elemental diet	Ease of use	Side effect: esophageal candidiasis (5% to 10%)
Removing upstream trigger of disease	Grocery cost of restricted diet	Not approved by FDA	Theoretic adrenal and growth suppression
Highest response rate with elemental diet	Multiple endoscopies	Improved quality of life	Cost of unapproved medication
Reverse fibrosis		Reverse fibrosis in children	
Reduce symptoms		Reduce symptoms and, in adults, improve complication of food impactions	
Decrease eosinophil count and improve histologic pathology		Decrease eosinophil count and improve histologic pathology	

FDA, US Food and Drug Administration.

TABLE II.

Future needs in EGID

Need	Near future	Far future
Drug approval	Topical esophageal corticosteroid (adults)	Biologics for disease modification: anti–IL-13; anti–IL-4Ra; eosinophil-depleting antibodies and drugs Small-molecule inhibitors for mast cell, eosinophil, T-cell, and/or epithelial cell function and/or modification
Personalized medicine	Endotype-based therapy based on esophageal transcriptome profiling (eg, EDP) PPI-responsive patients	Genetic SNP-based therapy
Inflammation-dependent and independent remodeling therapy	Biologics (eg, anti–IL-13 in adults)	Inflammation-independent antifibrotic therapy
Understanding long-term complications and long-term response to therapy	Increased Multicenter Trials, across the United States (via CEGIR)	Genotype-phenotype variability Natural history in large cohorts of children
Less invasive or noninvasive biomarkers	Esophageal string test TNE Sponge test	Peripheral blood markers/panels
Improved diet therapy	One-food elimination (eg, milk elimination diets)	Induction of food tolerance

SNP, Single nucleotide polymorphism.