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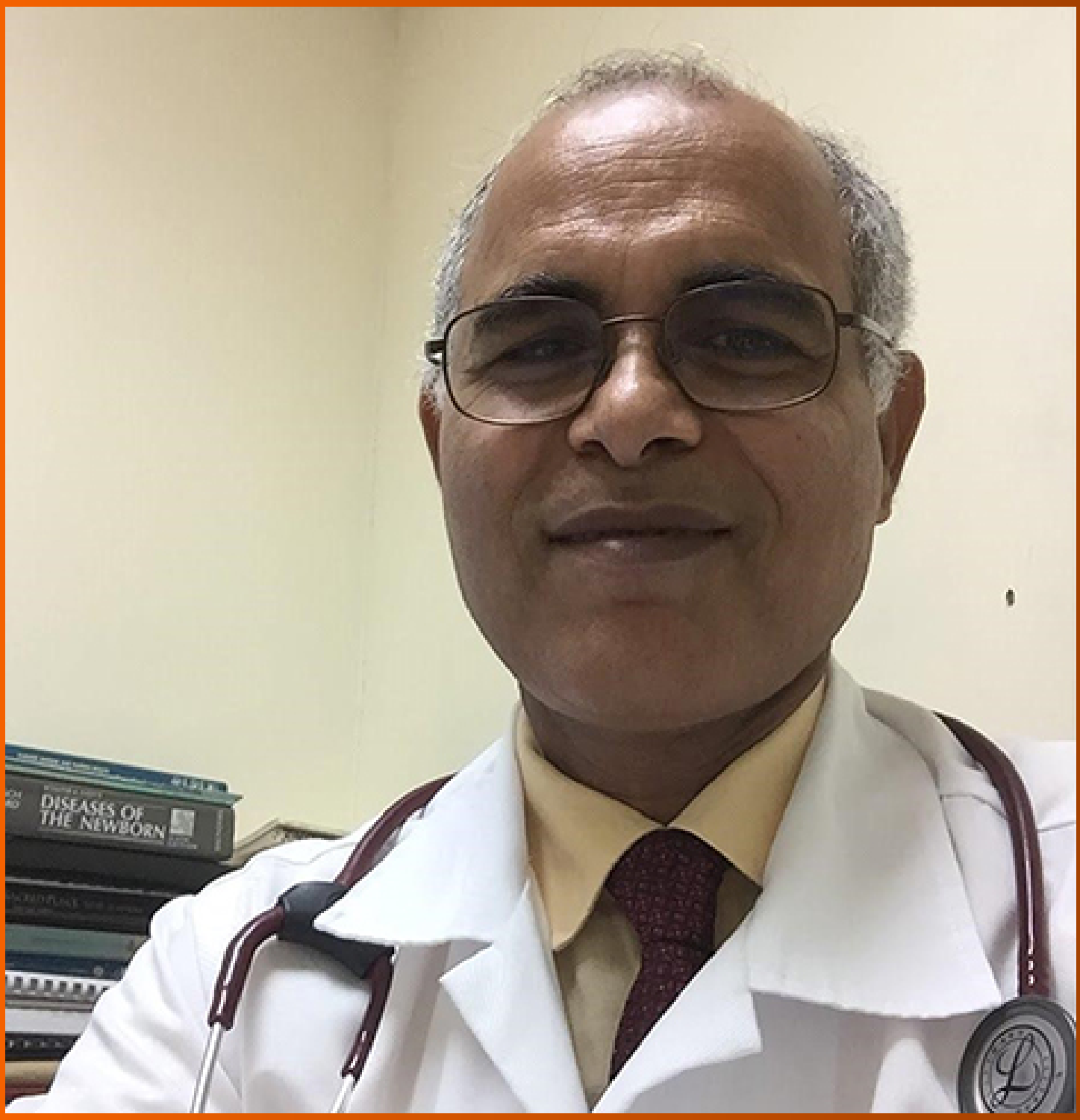

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Contents

Quarterly Volume 13 Number 3 June 20, 2023

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

SYSTEMATIC REVIEWS

World Journal of Methodology

Quarterly Volume 13 Number 3 June 20, 2023

Contents

META-ANALYSIS

World Journal of Methodology

Quarterly Volume 13 Number 3 June 20, 2023

Contents

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MINIREVIEWS

Adult eosinophilic esophagitis and advances in its treatment

Martina Grando, Silvia De Pauli, Giovanni Miotti, Massimiliano Balbi, Marco Zeppieri

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Abstract

Eosinophilic esophagitis (EoE) is a chronic eosinophil inflammation that seems to be T helper type 2 antigen-driven. The disease is one of several eosinophilic gastrointestinal disorders in which there appears to be inflammation of the gastrointestinal tract without any apparent underlying causes. Differential diagnosis needs to be made with gastroesophageal reflux, which is characterized by chronic inflammation due to gastric refluxate from disorders related to motility. EoE, however, is considered a chronic allergic inflammatory disorder related to destructive tissue remodeling. There seems to be a higher prevalence of EoE in Western countries. It is typically found in atopic male individuals. Physiopathological risk factors include atopy, environmental factors, esophageal epithelial barrier dysfunctions, *etc.* EoE can cause several symptoms that include retrosternal burning sensation, dysphagia, food impaction, chronic reflux symptoms, nausea, and vomiting. Early diagnosis, which requires a biopsy to assess for esophageal inflammation, is essential for proper treatment. The aim of our brief overview is to summarize the current literature regarding the characteristics, diagnosis, complications, mechanisms of pathology, clinical features, influence of comorbidities, and treatment in patients with EoE.

Key Words: Eosinophilic esophagitis; Gastroesophageal reflux; Chronic allergic inflammatory disorder; Eosinophil inflammation; T helper 2

Core Tip: Eosinophilic esophagitis (EoE) is a chronic eosinophil inflammation. Differential diagnosis needs to be made with gastroesophageal reflux, which is characterized by chronic inflammation due to gastric refluxate from disorders related to motility. It is of clinical importance to diagnose, manage, and treat individuals with EoE. Patient outcomes, success of therapy, prevention of complications, and management of existing comorbidities depend on proper organ functioning.

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INTRODUCTION

Eosinophilic esophagitis (EoE) can be characterized as a T helper type 2 (Th2) antigen-driven disease that is due to chronic eosinophil inflammation, which causes signs and symptoms of esophageal dysfunction. The disease is part of a spectrum of eosinophilic gastrointestinal disorders that show eosinophilic inflammation of the gastrointestinal tract that can be explained by other causes. The first cases were described in the 1970s. Before 1960, interrogation of the intestinal mucosa was limited to surgical resections or postmortem analyses. An important element in the study of this disease was the advent of luminal fiberoptic endoscopy[1].

Esophageal eosinophilia was believed to be solely a manifestation of reflux esophagitis[2] and EoE was seldom diagnosed. In the mid-1990s, however, several studies described the disease as it is recognized today[3,4]. Since then, the number of publications on EoE has increased dramatically, especially considering that this condition has become more prevalent over the past 20 years as one of the main causes of upper gastrointestinal disorders. With the current diagnostic technology available, it is possible to provide a better diagnosis of gastroesophageal reflux (GERD) and EoE. GERD is characterized by chronic inflammation resulting from exposure to luminal gastric refluxate deriving from a disorder of motility. EoE, however, is defined as a chronic allergic inflammatory pathology characterized by signs, symptoms, and complications which tend to be related to destructive tissue remodeling [1].

The incidence rates of EoE continue to rise[5]. The prevalence of EoE is increasing rapidly in modern times, with rates approaching the prevalence of inflammatory bowel diseases. The prevalence of EoE follows the rising trend of allergic diseases over the last 50 years[6]. The prevalence estimates of EoE vary in different parts of the world. Studies have demonstrated a high prevalence in Western countries and a low prevalence in Eastern countries[5]. EoE occurs both in the pediatric and adult populations and tends to be more common in atopic male patients. Approximately 75% of all EoE patients tend to be male. This increased gender risk of EoE is supported by a genetic variant in the cytokine receptor-like factor 2 gene that encodes for the thymic stromal lymphopoietin receptor[6].

The aim of our minireview is to briefly assess the current literature regarding the characteristics, diagnosis, complications, mechanisms of pathology, clinical features, influence of comorbidities, and treatment in patients with EoE that have been published in the literature and considered in clinical settings since 2000. We conducted a search of the published literature from January 1, 2000 to March 1, 2023, using PubMed (https://pubmed.ncbi.nlm.nih.gov) and *Reference Citation Analysis* (*RCA*) (https://www.referencecitationanalysis.com). The main topics in this minireview can be found in Table 1.

PHYSIOPATHOLOGY

Atopy

EoE is considered an atopic disease, which is associated with food antigen-driven hypersensitivity. The majority of patients with EoE have an atopic phenotype. Individuals with EoE tend to have higher rates of other allergic conditions such as asthma, atopic dermatitis, allergic rhinitis, or increased IgE to aeroallergens and foods[6,7].

Environmental factors

Studies have shown that certain environmental factors can increase the risk of EoE, which include: Dysbiosis and dysregulation of the microbiome; residence in rural and suburban areas; cesarean birth; exposure to antibiotics; lack of breastfeeding, *etc*[8].

Table 1 Main topics of the minireview

Main topic	
Physiopathology	Atopy
	Environmental factors
	Esophageal epithelial barrier
	Th2
	Eosinophils
Clinical presentation	
Diagnosis	
Treatment	Dietary management
	Pharmacologic therapy
	Esophageal dilatation
	Biologic agents
Conclusions	

Th2: T helper type 2.

Esophageal epithelial barrier

The epithelium plays a central role in the development of EoE. In this condition, the epithelium demonstrates characteristic alteration that includes basal cell hyperplasia, dilated intra-cellular spaces, and impaired barrier function. When the epithelium barrier is broken or disrupted, it can lead to a hypersensitivity immune response to foreign antigens[6]. Several EoE patients can have an altered epithelial barrier when there are no signs of inflammation, which can predispose these individuals to allergic sensitization. Studies have reported the presence of transcriptional alterations in individuals with EoE[1]. There seems to be a downregulation of genes including filaggrin and involucrin. Other junctional proteins like claudin-1 and E-cadherin can also be decreased in EoE. Deoxyspergualin (DSG) (a transmembrane desmosomal cadherin) shows decreased activity in individuals with EoE[6]. Calpain 14 (CAPN14) has been found to be the most highly associated gene with EoE[9,10]. It is overexpressed in the esophageal epithelium in patients with EoE. Induced interleukin (IL)-13 stimulation in the esophageal epithelium can cause overexpression of CAPN14 and impaired barrier functioning. Altered expression of these genes and/or activation by type 2 cytokines such as IL-13 may predispose to barrier dysfunction.

The alteration of the barrier can also be due to peptic or other injuries. This hypothesis is derived from the clinical signs of EoE that can form after epithelial damage from trauma, acid, or infection. In these circumstances, food and other substances in direct contact with the damaged epithelium can sensitize the microenvironment of the esophageal mucosa and lead to activation of the Th2 inflammatory response. Barrier dysfunction can also occur as a self-perpetuating product of inflammation. Once the inflammation starts, the epithelium can become increasingly permissive and allow more allergenic stimulation to penetrate and develop an ongoing allergic cycle[1].

Th2

EoE is also Th2-mediated. The cascade of inflammatory response is similar to that of chronic allergic disease with an aberrant Th2 response. The lymphocytes are cells typically present in the inflammatory infiltrates found in EoE[11]. This immune response is mediated by ILs secreted by Th2, like IL-4, IL-5, and IL-13.

IL-5 is secreted by mast cells, Th2 cells, and eosinophils. This substance influences eosinophil survival and expansion and primes them to respond to activating signals in chronic allergic reactions[6]. IL-13 is one of the most important cytokines involved in EoE pathogenesis. Studies have demonstrated that IL-13 is upregulated in the esophagus of patients with EoE[12]. It can induce remodeling in the esophageal epithelial barrier; it has been shown to downregulate DSG-1, filaggrin, and involucrin[13]. IL-13 also upregulates eosinophil chemotaxis inducing the expression of chemokine ligand 26. Furthermore, it is responsible for epigenetic modification in the expression of CAPN14, an esophageal-specific protease [14]. CAPN14's substrates include signaling molecules, structural proteins, cell adhesion molecules, transcription factors, and inflammatory mediators of allergic responses, like IL-33 and STAT6[12], both of which tend to be pivotal in the development of EoE.

Eosinophils

Under normal conditions, the human esophageal epithelium has little or no eosinophilic leucocytes. The presence of intraepithelial eosinophils in the esophageal lamina propria and submucosa defines EoE [15]. Eosinophils are recruited by local chemotaxis. They have been shown to have effects on tissue damage[16]. Eosinophil also acts as antigen-presenting cells, recruiting T cells, mast cells, and basophils.

CLINICAL PRESENTATION

EoE may present with a wide variety of symptoms, which ranges from retrosternal burning sensation to dysphagia or episodes of food impaction. Some patients complain of chronic reflux symptoms, nausea, and vomiting. The clinical presentation tends to be different between adults and children[17,18]. The most typical signs and symptoms in adults include heartburn, dysphagia, chest pain, and food impaction. About 50% of adult patients initially presenting with food impaction have been shown to have a diagnosis of EoE[19]. In contrast, children present more commonly with vomiting, regurgitation, abdominal pain, and failure to thrive. Numerous patients begin to implement compensatory behaviors, such as eating food cut into small pieces, eating slowly, lubricating items with sauces, chewing carefully, diluting foods with drinking liquids, and avoiding medications and substances that induce dysphagia[8]. Several validated tools are now available to evaluate symptoms. In adults, the Eosinophilic Esophagitis Activity Index has been shown to offer good correlations between symptoms, histology, and patient-reported outcomes[20]. The most serious complication of EoE is the spontaneous rupture of the esophagus after a food impaction or episodes of vomiting (Boerhaave's syndrome). Fortunately, this complication is rare. Other associated complications that can happen in association with EoE include esophageal stricture, perforation, food impaction, and malnutrition[8].

DIAGNOSIS

There is no specific or diagnostic symptom of EoE. Diagnosis normally requires a biopsy to assess for esophageal inflammation. Endoscopic features can be misleading, thus several esophageal biopsies are needed in all individuals with risk or suspicion of EoE independent of endoscopic clinical appearance [21]. The most typical endoscopic signs in adults with EoE include mucosal rings (64%), linear furrows (80%), white plaques and/or exudates (16%), small caliber esophagus (28%), and strictures (12%)[22]. An endoscopic scoring system has recently been developed and validated to assist in the assessment and standardization of EoE signs based on the presence of rings, edema, exudates, strictures, and furrows[23].

The presence of the following criteria is required for the diagnosis based on the American College of Gastroenterology Clinical guidelines and consensus recommendations, which were reported in a review study of EoE by Gomez Torrijos *et al*[24]: (1) Clinical symptoms of esophageal dysfunction; (2) An increased number of eosinophils in the esophageal epithelium, with ≥ 15 eosinophils per high-power field, and the eosinophilia is limited to the esophagus; and (3) Exclusion of other possible causes of esophageal eosinophilia (including eosinophilic gastroenteritis, infection, hypereosinophilic syndrome, *etc*.). Characteristic histological features, which, however, are not pathognomonic, are also eosinophil aggregates or micro-abscesses and eosinophil layering along the surface of the lumen[8].

TREATMENT

The goals of the therapy of EoE are to induce histological remission, improve clinical symptoms, and prevent disease progression and complications. The management of EoE includes dietary, pharmacologic, and endoscopic interventions[8]. Commonly used treatments include an elimination diet, acid suppression with proton-pump inhibitors (PPIs), topical steroids, and, in the case of strictures, esophageal dilatation. New therapeutic options include monoclonal antibodies that are tailored to stop the underlying inflammatory processes. Increasing evidence suggests that type 2 cytokines may play key roles in EoE[25].

Dietary management

Diet therapy may prove to be very effective and can directly assist in the underlying pathological allergic mechanism. This method can also assist to identify the various food antigens that are responsible for the inflammatory response[8]. In patients with EoE, allergy tests to identify food allergens that can contribute to the pathogenesis of the disease can be useful to initiate a specific elimination diet. The main methods for testing food allergies are the skin prick test (SPT), *in vitro* specific IgE testing, and patch test (used to identify non-delayed allergic reactions). When an allergy test identifies a specific food allergy, the initial treatment is a testing-directed elimination diet. Studies in

adults and children have shown that direct diets based upon *in vitro* specific immunoglobulin E testing and SPT/patch testing can be successful to varying extents, although further studies are needed before routine use of serum-based testing can be recommended[26,27]. The patient should be referred to an allergology specialist to evaluate the prescription of epinephrine for anaphylaxis self-treatment.

Other dietary approaches are the empiric elimination diet which consists in educating the patient to avoid foods that are most likely to be allergenic (*i.e.*, SFED or the six-food elimination diet which is based on eliminating egg, cow milk, wheat, soy, fish/ shellfish, and peanuts/tree nuts). An elemental diet is an amino acid-based formula with the exclusion of all solid foods[28].

All these diets last normally for several weeks (at least eight weeks). The clinician must then check symptoms and confirm histologic improvement with esophageal biopsies. Problem foods are then slowly reintroduced one at a time, with a periodic evaluation to determine if they are tolerated.

Several prospective adult studies based on an elemental diet showed a lower histologic response in about 3 of 4 cases; however, these trials were limited by a short treatment duration of 4 wk and relatively high dropout and nonadherence due to palatability[28]. A meta-analysis, however, reported better clinical outcomes with the elemental diet when compared with specific food elimination diets [29]. Nonadherence to an elemental diet is due to limited meal variety, taste, lack of insurance coverage, and numerous endoscopies needed during food reintroduction to identify specific triggers[30].

Pharmacologic therapy

PPIs: PPIs are the first-line treatment options with dietary modification and topical glucocorticoids. *In vitro*, studies have shown that PPIs decrease cytokine secretion from the esophageal epithelium, which leads to the idea that PPIs can give an anti-inflammatory benefit[31]. The reported response rates to PPI therapy in patients with EoE can vary widely, ranging from 30%-70%[21]. There is no specific element that can predict the patient's response to these drugs. PPIs may benefit EoE patients by reducing acid production in patients with coexistent GERD. Individuals with well-established EoE can also have symptoms of GERD that are responsive to PPI treatment, where GERD can contribute to the development of EoE[8].

Topical glucocorticoids: Current steroid formulations used in the treatment of EoE are designed for airway delivery. There are various formulations, which include suspensions, puffs from inhalers, viscous slurry, or orodispersible tablets. Fluticasone given orally in the form of a spray from a metered-dose inhaler and liquid budesonide as a viscous preparation are the typical pharmacologic therapies used for EoE[32,33]. Fluticasone (440-880 μg twice daily) or budesonide (1-2 mg twice daily) for 8 wk can be used to induce remission[34]. In 2020, the European Medicines Agency approved an orodispersible budesonide tablet formulation for adults with EoE[21,22].

Long-term topical glucocorticoid therapy is indicated in EoE due to frequent recurrence with tetracycline antibiotics removal. Maintenance therapy with topical steroids and dietary restriction should be considered, especially in patients with severe symptoms (*i.e.*, dysphagia, food impaction, and weight loss), anatomical complications (high-grade esophageal strictures), and rapid relapse after initial therapy[19]. Clinicians must pay close attention to side effects, such as esophageal candidiasis.

Esophageal dilatation

This treatment is reserved for patients with EoE that do not benefit from conservative therapy or for patients with EoE that show high-grade strictures. Endoscopic dilation can provide immediate symptomatology improvement in 95% of patients with EoE that have narrow caliber esophagus or strictures [34]. Since dilation has only a mechanical effect and does not stop the inflammation of the underlying eosinophil, repeated treatments are normally required to keep symptoms under control. The association of medical therapy is recommended in these individuals[34].

Biologic agents

Current evidence suggests that type 2 cytokines play a key role in EoE[25]. Monoclonal antibodies are used in other Th2-mediated allergic diseases and have the potential of modifying the natural history of the disease. Treatments that block the underlying inflammatory processes and prevent disease progression can be useful.

IL-13 has been implicated as an important cytokine in the pathogenesis of EoE. *The New England Journal of Medicine* has recently published the results of a three-part, randomized, double-blind, placebo-controlled trial based on dupilumab, a fully human monoclonal antibody that blocks IL-13 and IL-4 signaling[35]. Eligible patients were aged 12 years or older and had a diagnosis of EoE by endoscopic biopsy despite 8 wk of high-dose PPI therapy. The two primary endpoints after 24 wk included histologic remission (≤ 6 eosinophils using a high-power field) and the decrease from baseline in the Dysphagia Symptom Questionnaire score. The study demonstrated that dupilumab at a weekly dose of 300 mg led to reductions in symptoms of EoE and enhancements in histologic outcomes amongst adolescents and adults[35]. The most frequently reported adverse event throughout the period of treatment with dupilumab was an injection-site reaction. Other common adverse reactions were respiratory tract infections, arthralgia, and herpes viral infections. Dupixent (dupilumab) was approved by the Food and Drug Administration in May of 2022 for the treatment of EoE in patients 12 years and

older weighing at least 40 kg[36].

Another biological agent that has been considered in the treatment of EoE is mepolizumab. This agent is a humanized monoclonal antibody against IL-5, a cytokine that is crucial for the recruitment of eosinophils. Studies regarding mepolizumab, however, have shown variable results[37,38]. Other biologics such as cendakimab (a monoclonal antibody inhibiting IL-13 receptor binding), lirentelimab (a monoclonal antibody to sialic acid-binding immunoglobulin-like lectin 8, a CD33 receptor present on the surface of mast cells and eosinophils), and bevacizumab (a monoclonal antibody directed against the membrane-bound IL-5 receptor α chain present on eosinophils) are in various stages of clinical trials [39]. Some of these drugs have been approved for other atopic conditions, and thus appear as potentially promising treatment options for EoE and other eosinophilic gastrointestinal diseases. Further studies are needed to determine the long-term treatment outcomes for each of these drugs[39].

CONCLUSION

EoE remains to be one of the most frequent eosinophilic gastrointestinal diseases. Standard treatments with diet modifications, PPIs, and topical corticosteroid preparations have variable rates of response. Current studies in the literature have been enriching the understanding of the mechanisms and pathogenesis involved in EoE disease, which can help find potential disease-modifying biologic therapies, such as dupilumab, as an effective treatment option. Further studies are needed to determine the long-term outcomes of these drugs. The use of these agents in EoE offers a potentially promising option for patients with severe symptoms and complications.

FOOTNOTES

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