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The role of biologics in the pathogenesis and treatment of eosinophilic esophagitis

Abstract

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder characterized by inflammation, and intraepithelial infiltration of eosinophils in the esophageal epithelium. It is associated with unbearable symptoms, such as dysphagia, and bolus impaction which affect the nutritional status, and quality of life of the patients. It is diagnosed from a thorough medical history, and confirmed by endoscopy and esophageal biopsy. Traditionally, it has been treated with elimination diet, proton pump inhibitors, and swallowed topical corticosteroids. However, several of the patients with EoE are refractory to the treatment. Eosinophilic esophagitis like eosinophilic asthma is a T helper type 2 lymphocyte (Th2)-mediated allergic disease. During an allergic inflammation Th2 cells secrete cytokines, such as interleukin-5 (IL-5). IL-4, and IL-13 which play a key role in the pathogenesis of EoE. Th2 cytokines promote eosinophilopoiesis, differentiation, proliferation, maturation and activation of eosinophils. Activated eosinophils liberate several cytotoxic cationic proteins, and reactive oxygen species which cause epithelial injury, inflammation, and remodeling, which later progresses to esophageal fibrosis. Dupilumab (dupixent®)is a monoclonal antibody which target the IL-4 receptor (IL-4Rα) which signals for both IL-4 and IL-13. Dupilumab is the only biologic which is effective, and approved for the treatment of EoE in adults and children 12 years and older. Treatment with dupixent® has been shown to improve dysphagia, dilate and relax the gullet, and allow patients to enjoy their cherished dish. Biologics such as dupilumab should be administered early in patients with EoE in order to prevent the menacing complications of the disease, such as esophageal stricture, and esophageal perforation, which necessitate surgical esophageal dilatation, and repair.

Keywords: eosinophilic esophagitis, endoscopic dilatation, pharmacological therapy, straumann dysphagia instrument, esophageal epithelium, chronic rhinosinusitis

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Abbreviations: EoE, eosinophilic esophagitis; CRSwNP, chronic rhinosinusitis and nasal polyps, Th2, T-helper type 2, MBP, major basic protein, ECP, eosinophil cationic protein, EDN, eosinophil-derived neurotoxin

Eosinophilic asthma

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder characterized by inflammation, and intraepithelial infiltration of eosinophils in the esophageal epithelium.[1,2] Eosinophilic esophagitis is a relative new disorder, which was initially described in the early 1990s.[3] The incidence of EoE is about 30-100/100 000 in adult population, and 29-42/100 000 in the children population, and its prevalence is increasing in North America and Europe.[4,5] EoE affects both adults and children, with a peak incidence between 30-50 years. It is more common in males than females,[6] with a male-to-female ratio of 3:1.[7]

The symptoms of of EoE are due to esophageal dysfunction and narrowing, and include dysphagia, bolus impaction, gastroesophageal reflux, vomiting, central chest pain, and epigastric pain.

The pathophysiological mechanisms of EoE are similar to those of the diseases of the "atopic match" which include atopic dermatitis, allergic rhinitis, eosinophilic asthma, and chronic rhinosinusitis and nasal polyps (CRSwNP).[8-10] Eosinophilic esophagitis is the fifth and the last member in the atopic match.[11] Table 1 show the allergic diseases associated with eosinophilic esophagitis.

Eosinophilic esophagitis is an allergic disease due to sensitization to food antigens. It is caused by T-helper type 2 cell (Th2), and innate group 2 lymphocyte (ILC2) responses to food antigens in contact with the esophageal epithelium. Activation of Th2 and ILC2 result in Th2 inflammatory response which leads to secretion of Th2 cytokines, such as interleukin-5 (IL-5), IL-4, and IL-13, chemokines, adhesion molecules, and growth factors.[12,13]. Th2 cytokines are also secreted by haematopoietic, and non-haematopoietic cells, such eosinophils, basophils, mast cells, fibroblasts, and myofibroblasts. The Th2 cytokines lead to eosinophilopoiesis, differentiation, proliferation, maturation, recruitment, and activation of eosinophils in the esophageal mucosa. Additionally, Th2 cytokines prolong eosinophil survival by preventing apoptosis.[14] Chemokines, such as RANTES, MCP-3, MCP-4 and eotaxins stimulates eosinophilic migration to the inflamed esophageal mucosa, amplifying the eosinophilic inflammation.

Table 1 Allergic diseases associated with eosinophilic esophagitis

Food allergy
Allergic dermatitis (eczema)
Allergic rhinitis
Eosinophilic asthma
Chronic rhinosinusitis with nasal polyps
Aspirin exacerbated respiratory disease

Activated eosinophils degranulate and liberate four cytotoxic cationic proteins, such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil-derived peroxide (EDPX)[15] (Table 2). The cytotoxic cations are very injurious and damaging to the esophageal epithelium which results in intense eosinophilic inflammatory, and remodeling,[14] followed by healing and fibrosis.[4,16] Fibrosis causes esophageal lumen narrowing, and the esophagus to be less distensible.

Table 2 Eosinophil-derived inflammatory mediators in eosinophilic esophagitis

Cationic proteins
Major basic protein (MBP)
Eosinophil cationic protein (ECP)
Eosinophil-derived neurotoxin (EDN)
Eosinophil-derived peroxide (EDPX)
Reactive oxygen species (superoxide, peroxide, and hypobromite)
Leukotrienes (LTC4, LTD4, LTE4)
Prostaglandins (PGE2)
Cytokines (IL-2, IL-3, IL-4, IL-5, IL-9, IL-13, IL-23, IL-25, IL-33, and TNFα)
Chemokines (CXC-, CC-, CX3C, and XC)
Enzymes (elastase)
Growth factors (TGF-β1, VEGF, and PDGF)

Abbreviations: IL, interleukin; LT, leukotriene; PG, prostaglandin; TGF-α, transforming growth factor-α; TNF-β, tumour necrosis factor-β; VEGF, vascular endothelial growth factor, PDGF, platelet-derived growth factor; CXCL, C-X-C motif chemokine ligand

Diagnosis of EoE is from thorough history of esophageal dysfunction, but esophagogastroscopy is required to obtain biopsies from six different locations of the esophageal lining, in order to confirm the diagnosis. Histologic diagnosis of EoE is based on the presence of at least 15 eosinophils per high-power (eos/hpf) field in the absence of other gastrointestinal diseases associated with esophageal eosinophilia, such as achalasia, gastroesophageal reflux disease, and eosinophilic gastritis.[6]. Other endoscopic changes of EoE demonstrate mucosal oedema, exudates, mucosal rings (tracheolization), linear furrows, and strictures.[17].

Treatment of EoE comprises of dietary restriction, proton pump inhibitors, such as omeprazole, lansoprazole, esomeprazole, and pantoprazole,[1,18,19] and swallowed topical corticosteroids,[20] including viscous budesonide slurry.[21,22], fluticasone from a multi-dose inhaler,[23,24] and mometasone.[25,26] However, this standard of care is not effective in most patients. Severe esophageal is inevitably treated with endoscopic dilatation, in patients with severe dysphagia, bolus impaction, and in those who do not respond to pharmacological therapy.[17]. Table 3 shows the pharmacological and biological treatment of eosinophilic esophagitis.

Table 3 Pharmacological and biologic treatment of eosinophilic esophagitis

Proton pump inhibitors
Omeprazole
Lansoprazole
Esomeprazole
Pantoprazole
Corticosteroids
Budesonide
Fluticasone
Mometasone
Ciclesonide
Biologics
Dupilumab

Treatment of eosinophilic asthma with biologics targeting IL-5, IL-4, and IL-13, and their receptors is well established, and is very effective. Currently, there has been attempts to repurpose some of these biologics for the treatment of eosinophilic asthma to treat EoE. However, targeting IL-5 with mepolizumab and reslizumab, two anti-IL-5 antibodies that block the biological effects of IL-5 did not reach end points in clinical trials. Both biologics in the studies in children and adults with EoE resulted in reduction in esophageal tissue and blood eosinophils, but no significant reduction in esophageal symptoms.[27]

In the MESSINA clinical trial which studied 210 patients with histological active EoE, benralizumab an IL-5R blocking monoclonal antibody (mAb) was associated with significant improvement in the histology of EoE. However, treatment with benralizumab did not improve symptoms of EoE, such as dysphagia.[28]

The duet sister cytokines IL-4 and IL-13 have a 25% homology, and signals through a common IL-4Rα signaling chain, and have similar biological and immunological functions. They play a central role in the pathogenesis of several allergic diseases, such as atopic dermatitis, allergic rhinitis, eosinophilic asthma, and chronic rhinosinusitis with nasal polyps.

Dupilumab (Dupixent®) is a fully humanized IgG4 monoclonal antibody targeting the IL-4Rα, which mediate signalling for both IL-4 and IL-13, thereby inhibiting their biological effects. Clinical trials have shown that treatment subcutaneous dupixent® significantly reduces the (SDI) patient-reported outcome (PRO) score. It has also been demonstrated to reduce the peak esophageal intraepithelial eosinophil count. Furthermore, treatment with dupilumab has been reported to reduce the EoE-histologic scoring system (HSS) severity score, and the endoscopic reference score. Noteworthy, dupilumab has been shown to increase esophageal distensibility, and ameliorate dysphagia.[29] Dupilumab has also been associate with improvement in esophageal symptoms, such as dysphagia when use for the treatment of other allergic diseases.[30] Dupixent® was approved by the Food and Drug Administration for the treatment of moderate-to-severe eosinophilic asthma in adults and children 12 years and older on May 20, 2022.

Dupilumab is a master biologic which is approved for the treatment of eczema, eosinophilic asthma, chronic rhinosinusitis with nasal polyps, and EoE. It is very beneficial in the treatment of patients with severe, uncontrolled eosinophilic asthma with the above comorbid diseases because it effective also in treating the associated diseases.

Conclusion

Eosinophilic esophagitis is a chronic immune-mediated disorder characterized by inflammation, and intraepithelial infiltration of eosinophils in the esophageal epithelium. It is associated with debilitating symptoms, such as dysphagia, and bolus impaction which affect the nutrition, and health related quality of the patients. The standard of care of EoE includes dietary restrictions, proton pump inhibitors, and swallowed topical corticosteroids. However, the disease remains refractory to the SoC in some of the patients. Th2 and ILC2 cytokines, such as IL-5, Il-4, and IL-13 play a key role in the pathogenesis of eosinophilic esophagitis. Attempts to block the immunopathological effects of IL-5 in order to treat EoE have not been successful. Dupilumab is a mAb which target the IL-4 receptor (IL-4Rα) which signals for both IL-4 and IL-13, it is the only biologic which is effective and approved for the treatment of EoE. Treatment with dupixent®is associated with improvement in distressing dysphagia, dilate and relax the gullet, and allow patients to swallow their cherished meals. Patient with eosinophilic esophagitis may benefit from early treatment with biologics, such as dupilumab, in order to prevent the menacing complications of the disease, such as esophageal stricture, and esophageal perforation, which necessitate surgical esophageal dilatation, and repair.

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Conflict of interest

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