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Investigational Agents in the Treatment of Eosinophilic Esophagitis

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Abstract

Eosinophilic Esophagitis (EoE) is a chronic, allergic disease of the esophagus that is characterized by increased esophageal eosinophils caused by allergens. If untreated, EoE precipitates esophageal remodeling that can lead to structural esophageal changes and difficulty eating. Although there are currently no FDA approved therapies for the treatment of EoE, therapies approved for other inflammatory conditions such as topical corticosteroids have a strong recommendation in the current guidelines. Dietary strategies are also currently being utilized, but have shown to be unfeasible in clinical experience. Although not yet approved, new treatment options are being developed to enhance the quality of life in patients suffering from EoE. This article features novel therapeutic approaches to treating EoE, including investigational agents RPC4046, dupilumab, antolimab, and benralizumab.

Eosinophilic Esophagitis (EoE) is a chronic, allergic disease of the esophagus that is characterized by esophageal symptoms and eosinophils, a type of white blood cell that causes injury and inflammation.[1-3]If left untreated, EoE can precipitate esophageal remodeling, such as strictures and narrowing that are harmful to the esophagus.[4-6] EoE is known to be triggered by common food allergens which complicate the use of dietary strategies as a form of treatment.[3] At this time, there are no US Food and Drug Administration (FDA) approved therapies for the treatment of EoE.[7] However, commonly used agents include proton pump inhibitors (PPI) and topical corticosteroids to avoid complications of the precipitating allergen.[5,7]

EoE was first described in 1978, but did not receive a formal pathology and phenotype until the early 1990s.[7,8] Since this time, researchers have begun to evaluate the genetic and environmental risk factors of EoE. It has been deemed a disease of both the innate and adaptive immune response and includes many pathways that contribute to its complications. The specific cells that play a predominant role in the pathophysiology of EoE are eosinophils, Th2 cells, thymic stromal lymphopoietin (TSLP), transforming growth factor (TGF)-β1, and interleukin (IL)-13, among others.[5] In previous years, the diagnosis of EoE was determined by an esophageal biopsy showing a peak eosinophil count of 15 or greater intraepithelial eosinophils per high-powered field with at least an eight week PPI trial.[7] In 2017, the need for a PPI trial was removed from the diagnostic criteria due to their recognition as treatment for the disease.[7]

EoE symptoms can develop in all age groups, but it is most common in children and young adults.[3] Some common symptoms include throat pain, dysphagia, choking during meals, food impactions, or not wanting to eat. Patients often learn ways to adapt to their condition by eating slower, eating smaller bites, or drinking an unusually high amount of liquids with meals.[3] In addition to the biopsy criteria, patients must also be showing symptoms of esophageal dysfunction. The final criteria to be diagnosed with EoE involves ruling out other disorders that may cause similar symptoms as EoE. These disorders include GERD, Celiac disease, Crohn's disease, and infection. Many patients who have EoE also have comorbid inflammatory conditions such as allergies, asthma, and dermatitis.[3] Having these diseases increases the chances for someone to develop EoE.[6] Endoscopic examinations, though not necessary for diagnosis, can be useful to establish presence of EoE precipitated abnormalities such as linear furrowing, concentric rings, white exudates, small-calibre esophagus, linear superficial mucosal tears, and Schatzki ring (a circular band of tissue that forms at the bottom of the esophagus which makes it more difficult to swallow).[1]

CURRENT GUIDELINES

The American Gastroenterological Institute and Joint Task Force on Allergy-Immunology Practice Parameters published clinical guidelines in 2020 giving recommendations on the treatment of EoE. Since there is little data studying EoE, the guidelines do not have high quality of evidence for their recommendations.[7] Many of the recommendations have very low quality of evidence or have a conditional recommendation.[7]

NON-PHARMACOLOGIC RECOMMENDATIONS

Notably, the elemental diet, 6-food elimination diet and allergy testing-based elimination diet carry a conditional recommendation.[7] The elemental diet consists of amino acid-based formulas.[4] This treatment option is undesirable to patients due to taste, nutritional concerns, practical implementation, and cost.[7] The elemental diet has considerably harmful consequenses including interference with development of oral motor skills in children, the potential need for gastrostomy tube, and social isolation due to dining restrictions. There is insufficient data regarding the harmful effects of an elemental diet and more research should be conducted.[7]

Additionally, the 6-food elimination diet consists of removing the six most common food allergens from the diet and then reintroducing them gradually over time. These common allergens are dairy, eggs, nuts, soy, wheat and seafood. Extrapolated data from ten studies reported a histologic response rate of 68% of those who were able to adhere to this diet, yet patients who were unable to adhere to this technique were not included in the primary analysis.[7] Practically, eliminating 6 common foods can be challenging for patients, and more data is needed to reflect the desirability of this technique. Furthermore, it can be difficult to determine the presence of relapse as it may be evident in pathology but the patient may not experience symptoms.[7] The allergy testing-based elimination diet is very similar to the 6-food elimination diet but includes allergy testing to help guide the treatment. While there may be a potential role for these dietary treatments, the risk of potential de novo IgE-mediated allergy upon reintroduction of the common food allergen, as well as risks associated with sequential endoscopies are a concern.[7]

PHARMACOLOGIC RECOMMENDATIONS

Proton-pump inhibitors were the mainstay of treatment in EoE for some time.[3] Twenty-three observational studies that evaluated the histologic response to PPIs showed that PPIs failed to induce histologic remission in about two-thirds of patients, compared with more than 85% of patients in the placebo groups. This caused the committee to lower the recommendation to conditional.[7]

The only treatment intervention for EoE that carries a strong recommendation is topical glucocorticosteroids.[7] Two formulations have been studied in

EoE, including fluticasone or budesonide swallowed from an inhaler and a mixed budesonide slurry composed of nebulizer solution.[4] Topical glucocorticosteroids induced remission in two-thirds of patients compared to less than 15% of patients on placebo from eight double-blind studies that enrolled 437 patients for a duration of 8 weeks. [9]

NOVEL ORAL THERAPIES

Currently, there are three novel corticosteroids that utilize different formulations that are benefical in EoE. In December of 2020, TAK-721, budesonide oral suspension (BOS) received acceptance of its new drug application from the FDA and was granted priority review.[10] BOS was created to avoid the patient burden of mixing the slurry themselves which includes pouring the medication into a cup, adding a sweeter such as Splenda and mixing the solution until it is thickened. This noval oral suspension would eliminate the need for this process. Furthermore, BOS was shown to be safe long term and efficacious with the most common adverse events being respiratory complications, gastrointestinal symptoms, and candidiasis.[11]

Budesonide orodispersible tablet (BOT) was also shown to be safe and effective in a randomized clinical trial.[12] Due to these findings BOT was recently approved by the European Medicines Agency but has not yet been submitted for approval in the U.S.[4] A fluticasone propionate orally disintegrating tablet (APT-1011) is currently undergoing a phase 3 clinical trial and has shown promising results in a randomized clinical trial with no significant difference in adverse events from placebo.[4,13]

NOVEL BIOLOGIC THERAPIES

While these novel treatments are showing promise, investigators have moved towards developing biologic agents for the treatment of EoE. Dupilumab is a fully human monoclonal antibody that targets the alpha subunit of the IL-4 receptor and was granted breakthrough therapy designation from the FDA in late 2020 for EoE.[14] This antibody inhibits signaling of IL-4 and IL-13.[14] Both of these interleukins are crucial for developing Th2 cells that contribute to the inflammatory response in EoE.[5] Dupilumab has already received FDA approval for other atopic inflammatory diseases such as asthma, atopic dermatitis and rhinosinusitis with nasal polyposis.[15,16] In a phase 3 trial, 81 patients aged 12 years and older with EoE received weekly subcutaneous injections, either 300 mg of dupilumab or placebo for a duration of 24-weeks.[17] In the dupilumab group, 64% of patients achieved eosinophilic response compared to 8% in the placebo group.[14] Patients receiving dupilumab had significant signs of improvement including comfortable swallowing as early as 4 weeks that only continued to improve throughout the trial.[14] Investigators found reduced severity of the disease by measuring esophageal tissue changes with grade and stage scores. Dupilumab had scores of 0.761 and 0.753, respectively, compared to 0.001 and 0.012 in the placebo group.[14] Safety was also

evaluated with the overall rate of adverse effects being 86% for dupilumab compared to 82% for placebo.[14] Adverse events reported most often were injection site reactions and upper respiratory tract infections.[14,17]

Similarly, RPC4046 is a humanized monoclonal antibody that targets IL-13 which is overexpressed in EoE that leads to esophageal remodeling. A pilot study of an IL-13 antibody in 23 adults showed a reduction of esophageal eosinophil counts and EoE-related gene expression.[18] This led to a phase 2 trial of RPC4046 that showed 50% of patients achieved histological remission.[18] Adverse events were reported in both the treatment groups and placebo group including mild headache, upper respiratory infection, arthralgias, diarrhea, and nausea.[18,19] A phase 3 trial has not yet begun but will be needed to better show the significance of RPC4046 in the treatment and management of EoE.

Aditionally, Antolimab is an antibody that targets Siglec-8, a receptor resulting in inhibition of mast cells and apoptosis of eosinophils. [20,21] Prior to the research for EOE, antolimab was studied in the ENIGMA trial where antolimab was given to patients with eosinophilic gastritis and gastroenteritis for a duration of four months.[21] In a subgroup analysis, 13 of the 14 patients who also had EoE achieved histological remission. [4] The most common adverse event was an infusion related reaction that occurred more commonly in the first infusion session.[21] Currently, antolimab is in a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 trial including 300 EoE patients. The trial includes two different treatment regimens (1.0 mg/kg monthly or 1.0mg/kg first month then 3.0 mg/kg monthly) as well as a placebo group, for a duration of six months and is estimated for completion by May 2022.[20]

A multicenter, randomized, double-blind, parallel-group, placebo controlled phase 3 trial was launched in December 2020 to investigate benralizumab, a monoclonal antibody that targets IL-5 receptor alpha.[22] By targeting IL-5, the body's antibody-dependent cellular cytotoxicity (ADCC) is intensified to induce apoptosis of eosinophils.[23] Benralizumab has previously been shown effective in the treatment for asthma and platelet-derived growth factor receptor alpha (PDGFRA)-negative hypereosinophilic syndrome.[22,24] In a subgroup analysis of PDGFRA-negative hypereosinophilic syndrome patients, two patients had concomitant EoE. In 24 weeks, biopsies showed no eosinophils in these patients.[22] Although benralizumab has not yet been exclusively studied in EoE, the promising biopsy results of these two patients indicates their potential use and warrants further investigation.

In conclusion, EoE is a chronic condition that, if left untreated, can lead to complications such as esophageal remodeling and abnormalities. Currently, the highest recommended available treatment option included in the guidelines are topical glucocorticosteroids. While topical glucocorticosteroids directly treat the

symptoms and excess of eosinophils present in EoE, new biologic antibodies provide a more targeted approach to therapy. By inhibiting the interleukins IL-4, IL-5, and IL-13, these medications can help prevent complications from the origin of the disease. Similarly, by targeting the inhibitory receptor Siglec-8, apoptosis of eosinophils can be induced even before they make it to the esophagus. Treatment options for EoE continue to be investigated for the goal of receiving an FDA approval for the treatment of EoE.

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