REVIEW ARTICLE

Eosinophilic Esophagitis: update on treatment approaches

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Abstract

Eosinophilic esophagitis (EoE) is a clinical entity with continuously increasing incidence in children and adults. Diet therapy and corticosteroids are the most important therapeutic interventions currently used, while new therapies are being developed, based on the research of the disease mechanisms. In this review we assess the results of the latest clinical trials on management of patients with EoE, and the advances in the development of novel drug therapies. Hippokratia 2012; 16 (3): 200-204

Key words: Eosinophilic esophagitis, topical swallowed steroids, oral systemic steroids, targeted elimination diet, six food elimination diet, elemental diet

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Introduction

During the last decade an important increase in eosinophilic esophagitis (EoE) incidence has occurred among children and adults. The definition of the disease provided recently by the updated EoE consensus recommendations published in 2011[1] suggests that the disease is chronic, immune/antigen mediated, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation[1]. Feeding difficulties are the most common symptoms in infants and toddlers, vomiting and retrosternal pain in children and dysphagia in adolescents. The main histological feature of EoE is striking eosinophilia of esophageal mucosa, usually along with microabcesses and basal zone hyperplasia. Esophageal eosinophilia is not an exclusive feature of EoE. Diseases that are associated with esophageal eosinophilia are gastroesophageal reflux disease (GERD), Crohn's disease, connective tissue disease, infectious esophagitis (herpes, candida), celiac disease, achalasia, graft-versus-host disease, drug hypersensitivity, eosinophilic gastroenteritis and hypereosinophilic syndrome[1-3].

Elimination diet and topical steroids are the most important therapies of EoE. In the present review we assess the therapeutic approaches of EoE, the results of the latest clinical trials and the advances in the development of novel drug therapies.

Dietary treatment

Studies conducted in children suggest that EoE is often related to food allergens. In this population, food elimination has proven to resolve symptoms and improve esophageal histology. Three different approaches/diets have been developed for inducing remission of the disease:

1. Elemental diet (ELED), which is a complete liquid amino-acid based formula, free of allergens,

2. Six food elimination diet (SFED), which excludes from the diet a number of common food allergens that have been associated with EoE (dairy, soy, eggs, wheat, peanuts, fish/shellfish), and

3. Targeted elimination diet (TED), which removes foods that is possible to cause symptoms, based on history and the results of allergy skin prick and patch testing[3].

In children with EoE, ELED has been shown to be extremely effective in resolving symptoms within 7-10 days while, tissue lesion regression follows in 4-6 weeks[4,5]. Disadvantage of this therapy is the high cost and the poor taste, requiring in some patients nasogastric or gastrostomy tube placement in case of non tolerance. Therefore, its use is an option mainly in children with multiple food allergies who have to follow a highly restricted diet.

SFED was reported in an observational study in 35 children with EoE to be associated with significant clinical and histological improvement in 74% of the patients. In the same observational study, ELED was given to 25 patients and was reported to be associated with significant improvement in 88% of the patients[6].

TED has also been shown to be an effective mean. Spergel et al reported that 77% of 146 patients with EoE responded well to TED and only 10% did not respond. Egg, diary and soy were detected as causative factors by skin prick testing while corn, soy and wheat were detected by atopy patch testing[7]. The main disadvantage of TED is that patch testing requires validation and it is not available everywhere.

The decision on the use of a specific diet should be individualized and consider several factors including pa-

tient's lifestyle and family's resources. Nutritional status of the patient should be assessed before and during diet intervention, while the adherence to diet and its nutritional adequacy should be checked by an experienced dietitian.

Following clinical and histological remission of the disease, food reintroduction is recommended, starting from the less allergenic foods[8]. Foods proved to trigger EoE symptoms should be restricted further[1]. By using this approach, patients can go back to an appropriate diet, acceptable to the patient and the family.

Antisecretory drugs

A short term antisecretory therapy is useful for the diagnosis of EoE. Patients with esophageal eosinophilia becoming asymptomatic after a protein pump inhibitor (PPI) trial have either GERD or the yet undefined PPI-responsive esophageal eosinophilia[1]. However, PPI's should not be considered first line therapy but adjunctive therapy for relieving symptoms caused by the coexistencing GERD[1,3]. Sayej et al suggest that high dose PPIs may be used to histologically distinguish EoE from other forms of esophagitis as in patients with EoE, PPIs may lead to improvement of symptoms but not of histological abnormalities[9]. In a prospective randomized trial in 25 adults with EoE, esomeprazole was compared to swallowed fluticasone propionate[10]. It was shown that both medications had similar effectiveness in reducing dysphagia and eosinophil numbers in the esophagus[10] which may be attributed to the entanglement of GERD in EoE mechanisms in adults. Furthermore, in a study in 35 adults with either GERD or EoE symptoms, the histologic response was evaluated after a 2-month trial of rabeprazole. The authors reported significant resolution of eosinophilic infiltration in both groups with 50% of patients with EoE symptoms responding to therapy[11].

Furthermore, lansoprazole, in addition to its acid-suppressing effects, was shown to modulate inflammatory status, reduce oxidative stress and ameliorate mucosal injuries[12]. Moreover, in vitro studies demonstrated that PPI's inhibited the increased expression of vascular adhesion molecules, the activation of neutrophils and the production of proinflammatory cytokines, which play a role in the pathophysiology of EoE[13,14]. The recommended dosage of PPI's for children depends on patient and PPI and varies from 1 to 2 mg/kg/day with the maximum dose reaching adult dose[1].

Chromolyn sodium – Leucotriene receptor antagonists

The use of chromolyn sodium has not been studied systematically. In a trial of 14 patients receiving 100 mg x 4 chromolyn for one month period no improvement was reported[15]. Therefore, its use is not recommended in patients with EoE[1].

The use of leucotriene receptor antagonists is not supported by current data[1]. Gupta et al reported that leucotriene levels did not differentiate among children with EoE and healthy ones[16]. In a study in 8 patients with EoE, the use of montelukast for 14 months resolved symptoms. However, 3 weeks after the stop of treatment, symptoms relapsed[17]. Another study showed that 3 out of 8 children with EoE receiving montelukast improved clinically but not histologically[18]. In a recent study in adults with EoE, Lucento et al demonstrated that montelukast was not efficient in maintaining the histological or clinical response achieved by topical steroids[19].

Corticosteroids

The use of oral systemic and topical corticosteroids leads to clinical symptom and histologic lesions resolution. However, the discontinuation of treatment is often followed by relapse[3]. Liacouras et al demonstrated that the use of oral systemic corticosteroids improved symptoms within 1 week and histologic lesions within 4 weeks in 20 out of 21 children with EoE[20]. However, due to the side effects of systemic oral steroids in children, their use is limited in patients requiring immediate relief (patients with severe dysphagia, dehydration, weight loss or esophageal strictures). The effective dose of prednisone for resolving symptoms and histological abnormalities is 1-2 mg/kg/day with maximum dose reaching 60 mg.

Due to significant side effects of long term use of oral systemic steroids, several studies evaluated the efficacy of topical steroids in achieving remission in both adults and children[21-26]. In a randomized trial in adult patients with EoE, comparing systemic oral prednisone with topical use of swallowed fluticasone propionate, both therapies were reported to be effective in achieving histologic lesion regression. Although prednisone per os achieved a greater degree of histologic regression, no statistical difference was found between the two groups regarding symptom resolution, symptom relapse or time of relapse. Symptom relapse was common in both groups and occurred within a mean of 5.8 to 8 weeks following discontinuation of therapy[21].

Similarly, Remedios et al showed in 19 adults with EoE, that a 4-week treatment with swallowed fluticasone propionate (500 mcg twice daily) was associated with significant clinical and histological improvement[22]. The duration of the remission following treatment with topical steroids is not clear. Arora et al reported that 21 adults receiving 220 mcg swallowed fluticasone propionate twice daily for 6 weeks, achieved resolution of the pretreatment referred dysphagia which maintained for at least 12 months[23]. In another retrospective study in 51 adults however, 91% of the patients receiving fluticasone propionate for 6 weeks reported recurrent symptoms after a mean of 8.8 months following therapy completion[27].

In children with EoE, the first randomized double blind study comparing the administration of fluticasone propionate (880 mcg/day for 3 months) to placebo was published in 2006[28]. Adequate histological response was considered in case of the presence of < 1 eos/hpf. Histological improvement was achieved in 50% of children that received fluticasone propionate (n=21) comparing

to only 9% of children receiving placebo (n=15) while, resolution of symptoms achieved 67% compared to 27% of patients respectively[28]. Suggested starting dosages of fluticasone propionate for children range from 88-440 mcg twice to 4 times daily to a maximum adult dose (440-880 mcg twice daily)[1]. The patients are advised to spray the metered dose inhaler in the mouth with leaped sealed around the device and not drink or eat for the next 30 minutes[3].

An important aspect of EoE therapy has been reported to be oral viscous budesonide. Its first use was reported in 2005 in 2 children with EoE, in which other treatment had failed to achieve remission. Oral viscous budesonide was prepared by mixing liquid solution of budesonide (0,5 mg/ 2 ml of the preparation used for inhalations) and 5 gr of sucralose. The administration of this preparation in those 2 children was associated with resolution of symptoms and endoscopic lesions[29]. In a retrospective study in 20 children with EoE, the effect of oral viscous budesonide was evaluated and proved to be effective in 80% of the patients achieving both clinical and histological response[30]. The first randomized double-blind controlled trial which compared oral viscous budesonide (administered for 3 months) to placebo was performed in 24 children with EoE[31]. Both groups received lansoprazole at the same time. Symptoms improved in 87% of children receiving oral viscous budesonide but in none of the placebo group[31]. In a double-blind randomized trial in adolescents and adults with EoE, the effect of budesonide (1 mg of twice daily for 2 weeks) was compared to placebo. The authors reported regression of dysphagia and histologic abnormalities in patients receiving budesonide compared to placebo. No significant adverse effects were reported[32]. Finally, in a more recent randomized, double-blind, placebo-controlled, 50-week trial, Straumann et al evaluated the efficacy of a low-dose swallowed budesonide to maintain quiescent disease in remission in 28 adult patients with EoE. This study showed that low-dose budesonide was more effective than placebo in maintaining histologic and clinical remission, while the signs of esophageal remodeling showed a trend toward normalization[33].

The recommended dosage of budesonide as a viscous suspension is 1 mg daily for children < 10 years and 2 mg daily for older children and adults[1].

Immunomodulators and biologics

Corticosteroids are very effective in treating EoE, however after drug discontinuation disease often relapses. This is the main reason for the development of novel therapies.

Azathioprine and 6-mercaptopurine in a study of 3 patients with EoE resistant to corticosteroids proved to be effective, leading to symptom resolution. Currently, there are no adequate studies on the effectiveness of this particular therapy[34].

Antibodies against IL-5 do not allow the development of EoE in experimental animals[35,36]. The first double blind randomized trial comparing the use of anti – IL-5 (mepolizumab) to placebo, was performed in 11 adults with EoE. The patients (n=5) who received mepolizumab (doses of 750 mg in the beginning of the study and 1 week later and 2 additional doses of 1500 mg each in case of inadequate response), achieved reduction in the number of eosinophils in the esophagus compared to the control group, without, however, achieving reduction of the inflammatory infiltration of the esophagus or symptom resolution[37]. This study comes in opposition to a previous one suggesting that anti-IL-5 usage was effective for symptom resolution[38]. Additionally, the reported increased levels of IL-5 after mepolizumab use[39], as well as of reactive eosinophilia[40], make doubtful the use of this agent in patients with EoE. In a recent study, reslizumab, an anti-IL-5 antibody[41], was shown to reduce esophageal eosinophilia in children and adolescents with EoE compared to placebo[42]. It should be noted however, that symptoms improved in both groups irrespective of histological changes[42].

The entanglement of food allergens in the pathogenesis of eosinophilic gastroenteropathy, led to the use of omalizumab, an anti - IgE monoclonal antibody in 8 patients for 16 weeks. This resulted in reduction of eosinophils in peripheral blood, stomach and duodenum but not in the esophagus[43]. A recent report in two children with EoE and multiple food allergies showed that omalizumab was effective in improving food tolerance and reversing symptoms but not in improving endoscopic and histological abnormalities[44].

One potential therapeutic target could be TNF-α expressed in the epithelium of patients with active EoE. However, the use of etanercept in a pilot study did not result in the reduction of esophageal eosinophils[45].

Finally, other factors that influence the physiology of eosinophils and could be potential therapeutic targets for the future are antibodies against IL-13[46] and IL-5 receptor, eotaxin receptor antagonists (CCL26, CCL11, CCL24), α4β7 antagonists, monoclonal antibodies anti-CD 25 and interferon-α[46] or pitrakinra which is a recombinant adhesive molecule of a subtype of IL-4 that antagonizes the activation of IL-4 and IL-13 pathway and is being tested in stage II studies in patients with asthma[47,48].

Conclusion

In recent years, there has been a significant increase in clinical experience and in the number of publications on EoE. The management of the disease is accomplished by dietary and pharmaceutical means, each with its own advantages and drawbacks. Further studies defining better the disease phenotype and developing biomarkers will allow to guide more precisely the management of the disease.

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