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Review

The treatment of eosinophilic esophagitis - a review from literature

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Abstract. Eosinophilic esophagitis EoE is a chronic, immune-mediated disorder. The diagnostic requires three major criteria: clinical symptoms of esophageal dysfunction, at least 15 eosinophils/field on esophageal biopsy and exclusion of other causes of esophageal eosinophilia, mainly eosinophilia due to gastroesophageal reflux. The EoE pathogenesis is complex, the central role being played by eosinophilic cells. There are two important types of treatment: dietary treatment (exclusion diet) and steroid treatment (both topical and systemic corticosteroids). The aim of this study was to summarize the recent therapeutic trends, after thorough analysis of the most recent international literature.

Key Words: eosinophilic esophagitis, dietary treatment, steroid treatment.

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Introduction

Eosinophilic esophagitis (EoE) is a "chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" (Liacouras et al 2011). The prevalence of EoE continues to increase (Soon et al 2013). The prevalence of EoE reported in different regions is variable, depending on whether the report included, for instance, the Southern Denmark (lower prevalence) or the Ohio State (lower prevalence) (Spergel et al 2011, Dalby et al 2010). The disease is more common in children and in males (Spergel et al 2011). In order to diagnose the EoE, three major criteria are necessary (Liacouras et al 2011):

- clinical symptoms of esophageal dysfunction (children experience abdominal pain, vomiting, difficulties in feeding and dysphagia, which is also present in adults, alongside chest pain, heart burn and food impaction);
- esophageal biopsy (both the proximal and distal esophagus) with eosinophil-predominant inflammation - at least 15 eosinophils/field (additional features: basal layer hyperplasia, eosinophilic microabscesses and extracellular eosinophilic granules);
- exclusion of other causes of esophageal eosinophilia (eosinophilic gastrointestinal diseases, celiac disease, Crohn's disease, hypereosinophilic syndrome, infection, vasculitis, connective tissue diseases and eosinophilia due to gastroesophageal reflux).

The lack of response to high doses of proton-pump inhibitors given for 8 weeks is necessary to confirm EoE in the patients presenting the first two diagnostic criteria and to exclude esophageal eosinophilia due to reflux disease (so-called "proton-pump inhibitor responsive esophageal eosinophilia"- (PPI-REE)) (Liacouras et al 2011; Evan et al 2013). The disease should alleviate under therapy with dietary exclusion, corticosteroids (topical /systemic), or both, but this feature is not necessary for diagnosis (Liacouras et al 2011).

The endoscopic features of EoE include the presence of longitudinal furrowing, white exudates, edema, longitudinal shearing and corrugated or ringed esophagus (Straumann 2013).

Three main categories of factors interact in the pathogenesis of EoE: genetic, environmental and host immune system factors. Normally, the esophagus is devoid of eosinophils (Eo). In EoE the number of eosinophils increases over 15/field in response to a variety of stimuli (allergens). Antigenic proteins, from food and aeroallergens, stimulate T helper-2 lymphocytes (LTh-2) to produce cytokines (interleukin-5, IL-5 and interleukin-13, IL-13). IL-13 subsequently promotes resident cells, such as esophageal epithelial cells, to produce a large set of proteins. IL-5 induces the activation and growth of the eosinophils. The gene that produces eotaxin-3 is very strongly induced; eotaxin-3 recruits eosinophils from the peripheral blood into the tissue (Mishra et al 1999). All these mechanisms result in subepithelial fibrosis with esophageal dysfunction and stenosis.

The treatment has two principal components: dietary treatment (the exclusion diet) and steroid treatment (both topical and systemic corticosteroids). Because it is a chronic disease, long-term therapy and repeated endoscopies are often needed.

Three important consensuses exist for the diagnosis and treatment of EoE: the first consensus was published by Liocouras et colab in 2007, (updated in 2011) (Liacouras et al 2011).

The second one is the consensus of the American College of Gastroenterology (Dellon et al 2013), and the third, that of the ESPGHAN (Papadopoulou et al 2014).
In this review we propose an update on the treatment of EoE based on the latest data in the literature.

Treatment of eosinophilic esophagitis

The ideal goals of treatment should be the induction and, subsequently, the maintenance of mucosal healing (histologic remission) in order to prevent chronic complications. This target is, however, difficult to obtain in practice. There is still controversy on whether the final goal of treatment should be histologic remission or clinical improvement, with most of the studies considering that less than 15 eosinophils/field may be a reasonable endpoint (Dellon et al 2013).
Effective treatment has been shown to reverse subepithelial fibrosis and thus to potentially prevent complications such as remodeling and strictures (Kagalwalla et al 2012; Lieberman et al 2012).
The main lines of treatment are: dietary manipulation and corticosteroids (topical and systemic). Other treatment options but which have not fully proven their efficacy are: cromolyn sodium, leukotriene receptor antagonists and biologics (mainly anti-IgE and anti-IL-5 monoclonal antibodies). For patients with esophageal strictures the treatment of choice is endoscopic dilatation.

Dietary Treatment

EoE patients have evidence of both food and aeroallergen hypersensitivity (Slack et al 2013) and, therefore, a dietary manipulation is the first basis of treatment options. It is of the utmost importance, however, that a registered dietitian supervises the diets (both the elemental and elimination diets) (Santangelo et al 2009).
Three types of diet can be used in the treatment of EoE: (1) amino acid-based formula (AAF); (2) targeted elimination diet (TED); and (3) empiric elimination diet (EED).
1. Amino acid-based formula (AAF) is an elemental diet completely devoid of allergens administered either orally or by nasogastric tube. The elemental diet approach has been shown to be an effective treatment (clinical response in up to 96% of patients and histological response between 72-96% of cases) (Peterson et al 2013; Henderson et al 2012; Gonzalez-Cervera et al 2012; Liacouras et al 2005; Markowitz et al 2003). In various studies, the resolution of symptoms has been reported to occur in a time interval between 8 days (Markowitz et al 2003) and two weeks (Henderson et al 2012; Byrne et al 2010) after the introduction of the diet, while histological resolution was achieved in 4 weeks (Markowitz, et al 2003; Henderson et al 2012; Byrne at al 2010).
The main disadvantages of this approach are the high cost of the elemental formula and the low adherence to therapy because placing a nasogastric tube or even a gastrostomy is required in these patients. In young children, using the elemental formula for a long time can delay the development of the oromotor function. In older children and adults this type of diet may affect the quality of life (Joshua et al 2014). At the present time, only patients who reject a restricted diet and young infants with several food allergies are the indications for an AAF.
In practice, after a period of 4 weeks of exclusive elemental formula the patient is assessed clinically and endoscopically. At that time, if the patient has clinical and histologic remission, an attempt is made to reintroduce different foods on the basis of their allergenic potential. Foods known to be the least allergenic (carrots, potatoes, green beans, cauliflower, broccoli, peaches, apricots, apples, pears, raisins, tomatoes, cucumbers, onions, garlic) are tried initially and, if tolerated, those with medium allergenic potential (citrus fruits, bananas, kiwis, mangos, melons, rice) and those with high allergenic potential (white and red beans, oats, barley, rye, meat - chicken, pork, turkey) can be tried next. One single foodstuff is introduced per week with continued clinical evaluation; an endoscopy is scheduled after one month from the moment of established tolerance to 3-4 foods (Johua B et al 2014). The most allergenic foods (milk, eggs, wheat, soy, peanuts, fish and shellfish) are better avoided or will be introduced with very great caution and under strict clinical and endoscopic follow-up.
2.Targeted elimination diet (TED) consists in removal of the food allergen following a thorough assessment of the personal history of food triggers in combination with the results of allergy testing (skin prick test - SPT or allergen patch tests – APT). The skin prick tests (SPT) and allergen patch tests (APT) include milk protein, egg, soy, grains (wheat, rice, corn, rye, oats, and barley), peanuts, meats (beef, pork, chicken and turkey), fish and shellfish. The tests have variable sensitivity and specificity, ranging between 18–88 and 82–97%, respectively. Therefore, SPT exclude rather then confirm the relation to specific foods (Spergel et al 2012). The efficacy of TED in inducing remission has been reported in different studies as being moderate (Lamba et al 2011). Some studies, however, showed no benefit at all (Teitelbaum et al 2002) or, conversely, showed high results (Spergel et al 2012 - significant improvement in 77% of cases after 1-2 months of treatment, Henderson et al 2012 - 63% of cases exhibited histologic remission after 4 months of treatment). In some EoE patients, the skin tests do not identify the presence of intolerance to multiple food antigens, which can explain the modest results of TED found by the majority of studies.
The study of Spergel et al. from 2007 suggests that elimination diets based on elimination of foods found positive on APT and SPT together with milk elimination can prevent the need for an elemental diet in a majority of children with EoE.
3. Empiric elimination diet (EED) or the six-food elimination diet (SFED) implies the removal of allergens known to be strongly correlated with EoE, regardless of sensitization: milk, soy, eggs, wheat, peanuts, fish and shellfish. The approach is based on the observation that 90% of all food allergy reactions are caused by these six foodstuffs. In adults with EoE the most allergenic foods are milk – 55-62%, wheat – 29-60%, nuts - 33%, eggs-26% and fish and shellfish - 11% (Lucendo et al 2013, Gonsalves et al 2011); milk was reported as the most frequent allergenic food in children, followed by wheat, soy, and eggs (Spergel et al 2012).
The principle of introducing the SFED is to eliminate the 6 foods from the very beginning and, after the occurrence of remission, to reintroduce one food at a time at 4-6 week intervals, under clinical and histological follow-up. If there is a recurrence of symptoms that particular food is considered allergenic and will

never be reintroduced in the diet (Lucendo et al 2013). Most patients (about 60%) are sensitive to wheat and milk.
Studies showed that SFED induced improvement in symptoms in a smaller proportion than AAT; the resolution of symptoms was noted in 78% of cases treated with SFED, with endoscopic and histological improvement in only 56% of cases (Wolf et al 2015). Gonsalves et al and Kagalwalla et al showed better results in their studies and reported a significant clinical improvement in 94-97%% of cases and histological improvement in 70-74% of cases after 6 weeks of diet (Gonsalves et al 2012, Kagalwalla et al 2006). Henderson et al (Henderson et al 2012) found higher efficacy of SFED than that of TED (histological remission in 81% of cases after 18 weeks vs histological remission in 63% of cases after 16 weeks, respectively), but lower than that of AAF (histologic remission in 96% of cases after 18 weeks).
The lower effectiveness of SFED as compared to that of AAT may be explained by the cross reactivity of aeroallergens with food antigens. The presence of seasonal variations in esophageal eosinophils and in symptoms of EoE supports this hypothesis, the most common aeroallergens being: tree, grass and weed pollen (Rezende et al 2014).
Thus, as a conclusion, the most effective diet is AAF, followed by SFED, and then TED. This is also supported by a systematic review and meta-analysis of 33 studies of different dietary treatments that included 1317 patients with EoE (1128 children and 189 adults). The final conclusion was that elemental diets were effective in 90.8% of cases, SFED in 72.1% and allergy test result-directed food elimination in 45.5% of cases. In addition, the dietary therapy provided symptom relief to the majority of patients and resulted in a substantial albeit not complete decrease in eosinophil counts (Arias et al 2014).
The follow-up of EoE patients involves performing repeat endoscopies at certain intervals, depending on the diet of choice: 4 weeks in case of AAF, since symptoms resolve earlier, or 8-12 weeks after initiating TED or EED, where symptoms take longer to resolve. Upon ascertaining histological remission, the least allergenic foods are first considered for reintroduction (Spergel et al 2005). If certain foods trigger EoE symptoms during food reintroduction, the physician may consider restricting them indefinitely (Liacouras et al 2011).
Frequent relapses are reported if the diet is discontinued, which stresses the importance of continuing the optimal diet throughout the patient's life.
Atopic children with EoE benefit most from dietary treatment; patients without atopy, however, may require drug therapy, due to some degree of refractivity to treatment (Noel et al 2004).
A summary of the effectiveness of the dietary approach was provided by a meta-analysis, which reported 66.3% efficacy (Arias et al 2014).

Steroid therapy

The second treatment regimen for EoE is the topical and systemic steroid treatment. The steroid treatment improves both clinical symptoms and histological changes.

Topical glucocorticoids

Swallowed steroid therapy was found to be more effective when compared with dietary therapies, with complete remission in a significant number of patients, demonstrated by histological evidences (a decrease in eosinophil counts < 15 eosinophils/field) (Noel et al 2004; Remedios et al 2006; Konikoff et al 2006; Alexander et al 2012).
The treatment with topical steroids was proven to improve fibrosis especially in children (Lieberman et al 2012). This could be explained by the fact that the treatment with swallowed glucocorticoids produces a down-regulation of profibrogenic cytokine gene expression (Lucendo et al 2011). But, despite this mechanism, in patients with stenosis, which required endoscopic dilatation, the results were very poor, possibly due to advanced fibrosis (Wolf et al 2014).
Topical steroids may also be recommended, as prophylaxis, to patients who experience seasonal exacerbations (Moawad et al 2010).
The main topical glucocorticoids used are Fluticasone and Budesonide (Arora et al 2003). In addition, a few studies have investigated the use of Ciclesonide. The substances are sprayed into the mouth (Fluticasone, Budesonide, Ciclesonide) or administered in the form of oral viscous liquid (Budesonide). The patient must swallow the amount of substance delivered into the mouth and not drink or eat for at least 30 minutes afterwards.
Fluticasone propionate it should be administered in doses of 440–880 mcg BID in adults, and 2 to 4 daily doses of 88-440 mcg in children (Dellon et al 2013, Remedios et al 2006). If the patients do not respond to lower doses of Fluticasone an increase in dosage may be tried, or may switch to treatment with Budesonide in the form of viscous solution.
Budesonide can be used as a spray or a viscous solution. The dose used for induction of remission is 1mg/day under the age of 10 and 2 mg/day above this age. The viscous Budesonide solution is more effective than when used as a spray because it ensures a greater concentration in the esophagus. (Dellon et al 2012). One study in which the viscous solution was used reported symptom and histological resolution in 72% of adolescents and 87% of children (Straumann et al 2010).
One small study used Ciclosenide in doses of 80 or 160 mcg BID for two months, achieving remission in all four patients in the study (Schroeder et al 2012). The advantage of Ciclosenide compared to Fluticasone is that the former has less systemic absorption than Fluticasone (Stoeck et al 2004).
Clinical improvement occurs in most patients after a few days to a week after the onset of topical therapy (Liacouras et al 1998). The response is much better in children than in adults (complete response in 50% of cases, partial in 91% of cases - Konikoff et al 2006; Schaefer et al 2008). The histological remission occurs after 4 weeks (Liacouras et al 1998). In another study, Wolf et al showed the fact that after the treatment with topical steroids, 79% of patients had symptomatic improvement, 71% had endoscopic improvement, and only 57% had histologic response (Wolf et al 2015).
The induction therapy should be continued for at least 8 weeks. The effect may last up to several months after therapy, but unfortunately some of the patients may relapse (between 14-91% (Remedios et al 2006), in an interval between 4 and 8.8 months (Dohil et al 2010, Helou et al 2008). Maintenance therapy will have to be considered in these patients. While a consensus has not yet been reached regarding the optimal dose (Dellon et al 2013), the recommended doses for adults are 880 mcg/day BID for Fluticasone, and 1 mg/day for Budesonide,

preferably as viscous solution (Dellon et al 2013). In another study, Budesonide was used as maintenance therapy at a dose of 0.25 mg BID (Straumann et al 2011). As a conclusion, the maintenance treatment will be done with the lowest dose that maintains remission, with periodical clinical and histological follow-up (Papadopoulou et al 2014).

In addition, maintenance therapy must be recommended to patients with a history of stenosis, severe dysphagia and dilatation, regardless of the initial response to treatment. Maintenance therapy is required also in patients who do not wish to follow an exclusion diet or in those in whom the allergens responsible for EoE could not be identified (Dellon et al 2013).

The main side effect of the topical steroid treatment is oral and esophageal candidiasis (Noel et al 2004). Xerostomia is another less frequent side effects observed (Arora et al 2003). A case of herpes esophagitis was reported in one study (Lindberg et al 2008).

Systemic steroids

Systemic steroids are less used in the treatment of EoE. Generally they are used in patients with severe disease requiring a rapid improvement of symptoms or who have not responded to topical treatment (Dellon et al 2013; Papadopoulou et al 2014). The recommended doses of Prednisone are 1-2 mg/kg/day.

Regarding the differences between the systemic and topical therapy, a comparative study between Fluticasone and Prednisone administration showed no significant differences in terms of remission of clinical symptoms, Prednisone proving its superiority only in terms of histologic improvement. Regardless of the therapy chosen, relapse after treatment occurred in the same proportion (45% of patients had relapses in each group) and after the same period (24 weeks). And, as expected, adverse effects were more significant in patients treated with Prednisone (systemic effects in 40% of patients), while in the patients treated with Fluticasone the only recorded side effect was esophageal candidiasis in 15% of cases (Schaefer et al 2008).

Other types of drug therapy

Antileukotriene therapy

Montelukast is a leukotriene inhibitor (a leukotriene D receptor, cysLT1 receptor,- antagonist) but it has not proven effective in the treatment of EoE, clinical trials showing only clinical, but no histological improvement (Attwood et al 2003; Lucendo et al 2011).

Anti-interleukin-5 (IL-5) and anti-interleukin-13 (IL-13) therapy

Two drugs which inhibit IL-5: mepolizumab and resalizumab, are available at present. They are humanized anti-IL-5 antibody and they act by inhibition of eosinophil activation, and by reducing the eosinophil load in the blood and the wall of esophagus. Despite the initial hope, they have not shown real effectiveness (Straumann et al 2010, Spergel et al 2012). Only children experienced resolution of symptoms, and histologic resolution was only found in a small proportion of the cases, with relapse of symptoms after treatment discontinuation.

Anti-IL-13 neutralizing antibody is another pharmacological agent (Niranjan et al 2013) whose use has not yet entered into clinical practice.

Other therapies tested in EoE, based on its pathophysiology, but which have not been proven their efficacy, were biological remedies - infliximab (anti –TNF therapy), anti-Ig E antibody, purine analogues, prostaglandin D2 receptor antagonist and neutralizing antibodies of invariant natural killer-cells (humanized anti-CD1d and anti-Vα24Jα18 antibodies) (Straumann et al 2008, Rocha et al 2011, Netzer et al 2007, Straumann et al 2013, Rayapudi et al 2014).

Endoscopic treatment

The endoscopic treatment consists in esophageal dilatation and it is recommended to patients with severe esophageal stricture and dysphagia. Generally, these patients have severe disease, and they do not respond to other medical therapies. The main complication after dilatation is perforation, but the prevalence was low in several studies (<1%) (Moawad et al 2013, Bohm et al 2010, Shoepfer et al 2014, Jacobs et al 2010, Dellon et al 2010). One of the major problem is the recurrence of the stenosis which may occur in 3 month up to 2 year.

Conclusion

In conclusion, the treatment of EoE is very complex and requires a multidisciplinary team consisting of a clinician, dietician, endoscopist and pathologist. The treatment should be individualized and the patients must be followed-up very closely.

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