Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 4 Issue 5 May 2021

Review Article

Maintenance Treatment of Eosinophilic Esophagitis

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Received: March 29, 2021

Published: April 15, 2021

Abstract

Eosinophilic Esophagitis is a chronic, immunologically mediated pathology characterized by eosinophil infiltrates in the esophageal mucosa, causing dysfunction of the organ. It can affect any age group, being more common in young people and with other atopics such as asthma, food allergy and allergic rhinitis. The symptoms presented by the patient can range from manifestations of gastroesophageal reflux, abdominal pain, to dysphagia and food impaction. The diagnosis is made through upper digestive endoscopy with biopsies demonstrating eosinophilic infiltrate greater than 15 eosinophils per field. This article has as main theme the treatment of maintenance of eosinophilic esophagitis, aiming to contextualize medical professionals with the therapeutic options used and the impact on clinical improvement and histological remission. Theoretical research started from non-experimental methodology, through literature review on the subject in recent years. The practical guidelines for the therapy of Eosinophilic Esophagitis should involve multidisciplinary follow-up with specialized professionals, such as gastroenterologist, nutritionist and allergist, being based on pharmacological and dietary measures. Dietary treatment consists of the identification of specific food allergens through tests or the empirical elimination diet of potentially more allergenic food groups. Clinical management includes an initial course with proton pump inhibitors. Topical corticosteroids (Fluticasone or Budesonide) are medications capable of reducing the eosinophilic inflammatory response and inducing histological and clinical improvement. Systemic courses of oral corticosteroids, such as Prednisone, may be necessary in patients with significant symptomatology. Endoscopic treatment, through esophageal dilation, is indicated in cases of symptomatic esophageal stricture. The choice of therapy will depend on the clinical picture, the histological analysis and the reported symptoms, as well as the preference of the physician, the patient and the costs.

Keywords: Eosinophilic Esophagitis; Elimination Diet; Corticotherapy; Fluticasone; Budesonide; Esophageal Dilation

Historical review of eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is considered an emerging pathology, reported in recent studies, in the last 20 years [1]. The first description of the disease occurred in 1977, in a patient with asthma with dysphagia and retrosternal pain, with eosinophilic infiltration of the esophageal and intestinal mucosa. In the following year, Landres, Kuster and Strum reported the first case of eosinophilic infiltration in the esophagus in an adult with dysphagia, epigastric and retrosternal pain [2]. This was the first described case of EoE restricted to the esophageal region and at the time it was considered a variant of eosinophilic gastroenteritis, associated with esophageal dysmotility [1].

In a study carried out in 1982, with pediatric patients, it related the infiltration of eosinophils in the esophageal mucosa with reflux esophagitis [1]. Some researchers of the disease have established relationships and similarities in pH monitoring, esophageal manometry, digestive endoscopy and histological findings suggestive of GERD and eosinophilia. Lee presented a series of 11 cases demonstrating that 91% of individuals affected with EoE had associated GERD [2]. Thus, for a long time it was believed that GERD was involved in the pathophysiology of EoE.

The major milestone in the historical evolution of EoE occurred in the early 90s, in a study by Attwood that compared patients with EoE and reflux esophagitis. The study involved a sample of 12 patients submitted to biopsy by endoscopy, pH monitoring, esophageal manometry and esophagogram [3]. The patients were divided into two groups: a group of individuals with a clinical diagnosis of dysphagia, without esophageal obstruction and with normal pHmetry, and the other group with patients with an established clinical condition of GERD [2]. The result of the study demonstrated that in patients without pH change there was a greater expressive increase in eosinophils when compared to patients with GERD [1]. This group had a percentage of 92% of patients with a high degree of eosinophilia with 56 eos/hpf and with unconfirmed pHmetry of GERD. Another relevant fact of the study is that 58% of individuals with a high degree of eosinophilia were allergic compared to another group suggestive of GERD studied that demonstrated a percentage of 48% of patients with eosinophilia at an average of 3.3 eos/hpf and altered pH suggestive of reflux esophagitis. Such an analysis widened the path for more recent research, with the objective of refuting GERD, as the exclusive cause of eosinophilia [4].

The premises described in the study by Attwood (1993) point out that the presence of esophageal eosinophilia in individuals with dysphagia and normal pH-metry, suggesting esophageal eosinophilic pathology distinct from GERD [1].

Within this perspective, in 1993, an article was published exposing the clinical and pathological findings of patients with normal esophageal pH monitoring, dysphagia and dense eosinophilic infiltration in the mucosa (> 20 eosinophils/high magnification field), being diagnosed as "esophageal eosinophilia. with dysphagia [2]. On that occasion, the disease was defined as a clinical-pathological entity with eosinophilic infiltration of the esophagus causing dysphagia in adults, in the absence of GERD [5].

Still in the 1990s, another study followed 10 patients with recurrent dysphagia over a 4-year period. The endoscopic examination of these individuals showed slight changes and histology showed high concentrations of eosinophils in the mucosa. This study resulted in the publication of an article by Straumann (1994), which he attributes to the denomination "idiopathic eosinophilic esophagitis", due to the changes found [3].

Following this line of research, Ruchelli and collaborators analyzed the use of anti-reflux medication therapy and observed persistent esophageal eosinophilia, treatment failure in those patients with a history of allergic pathology and a high number of eosinophils found in esophageal biopsies [1].

In 1995, a group of researchers suggested a different case series for the disease during the evaluation of individuals with reflux findings, resistant to conventional therapy, it was observed in biopsy that 31% contained persistent eosinophilia. Of the total of 75 of these patients, 12 decided to continue the prospective elementary diet study for a period of 6 weeks. After that period, 60% completely improved eosinophilia in post-treatment biopsies, and 80% completely resolved the symptoms. Given these findings, the hypothesis was raised that EoE would have its occurrence more linked to food pathogens than to reflux, and that elementary diets could be effective in the treatment of tip symptoms and patients resistant to the treatment dedicated to dysphagia [4].

Since then, several studies have started to analyze allergic reactions as a relevant factor in the pathophysiology of the disease, describing a series of patients with EoE, with allergic symptoms and esophageal narrowing, which when treated with corticosteroids showed good response to treatment [6].

In the early 2000s, a differentiation was established between Reflux Esophagitis and Eosinophilic Esophagitis (EoE), based on the response to acid suppressive treatment, indicating that EoE would need to gain new approaches for a specific treatment [2]. In 2002, another publication established the relevance in the identification of food antigens, through skin exams, in the approach of EoE. At that time, treatment was based on the administration of corticosteroids, acid suppression and food exclusion [1]. In the following year, treatment based on elementary diet gained prominence among publications on the management of patients affected by EoE and refractory to traditional treatments. This finding is close to the study by Markowitz and collaborators, who treated 51 pediatric patients with an elementary diet in the period of 4 weeks. As a result, in 95% of cases, a reduction from 33.7 eos/hpf to 1.0 eos/hpf and improvement of symptoms after 8 days of treatment [4].

It is observed, in the course of historical evolution, that after 1995 there was an increase in the number of cases diagnosed as EoE, as well as the number of publications related to the theme. At the end of the 1990s, the publications related to Eosinophilic Esophagitis indexed therein, numbered three, growing considerably to forty in 2007. And progressively, since then, in the year 2014, more than two thousand publications related to the issue have been observed. The growing number of journals, articles, journals and theses related to pathology contributed to the better dissemination of current knowledge about EoE, reflecting an increase in the diagnosis of this condition, which impacts on the greater incidence and prevalence [1].

Epidemiology

The epidemiology of eosinophilic esophagitis has been better understood over the past decade. The disease is described in any age group, being more prevalent in children, between 5 and 10 years old, and in young adults, between 20 and 40 years old [7].

During a statistical survey of children conducted in the United States of America in 2011, an annual incidence of 12.8 cases was identified for every 100,000 inhabitants and a prevalence of 43 for every 100,000 inhabitants. Another study involving adults identified an annual incidence of 1.7 cases for every 100,000 inhabitants and an EoE prevalence of 30 for every 100,000 inhabitants [8].

The prevalence of patients diagnosed with EoE during the performance of upper gastrointestinal endoscopy (EDA) for various reasons is approximately 6.5%, being even higher when the exam

is indicated for the investigation of dysphagia or food impaction, with EoE being identified in up to 63% of cases [7].

As for gender, another relevant factor is the higher prevalence of the disease in men, being about 4 to 5 times more frequent in men than women. The cause for this difference is still unknown. As for race, studies show a higher prevalence in white patients, of Caucasian ethnicity, when compared with other ethnicities and races. One factor that can justify this racial difference is that most studies involving this condition are carried out in countries in North America, Europe and the western hemisphere [1].

There is evidence of genetic factors related to the development of EoE, which can identify cases in the family in a percentage that reaches up to 10% of patients. According to more recent studies, it has been possible to prove that most patients with EoE have a family and personal history of atopy, with hypersensitivity to food and aeroallergens [9].

Eosinophilic esophagitis is more common in patients with other atopies such as asthma, food allergy and allergic rhinitis. However, to date, there are no epidemiological studies that compare the prevalence of EoE in atopic patients with the prevalence in the general population [10].

In addition to immunoallergic diseases, other conditions may be associated, such as celiac disease. Different studies also demonstrate the association of EoE in patients previously diagnosed with gastroesophageal reflux disease (GERD). In 2000, Liacouras and Cols analyzed 1809 children with gastroesophageal reflux disease (GERD). Of these, 214 underwent upper gastrointestinal endoscopy with esophageal biopsies, with EoE being diagnosed in 9.3% of them. It was observed that most patients in this subgroup did not respond to conventional treatment for gastroesophageal reflux disease. The association with GERD can be demonstrated in up to 40% of cases of EoE [10].

Despite being a disease that can affect any age group, sex and race, we must always be aware of the peculiarities of greater relevance in certain clinical contexts, such as young, white, male patients and with a history of atopy, dysphagia and food impaction [6].

Pathogenesis

The pathogenesis of eosinophilic esophagitis is still not completely understood, however, studies point to the interaction between environmental factors and genetic predisposition, with a probable association with immuno-allergic conditions [6].

Esophageal eosinophilia in many cases is triggered as a result of hypersensitivity to certain foods, such as milk, rye, eggs, wheat and seafood, in genetically susceptible patients. Activation of the immune response occurs, triggering a reaction mediated by Th2 lymphocytes, with the production of interleukins (IL-5 and IL-13). In these patients, there is an increase in CD4 + T lymphocytes in the peripheral circulation and high levels of IL-5, when compared with non-atopic individuals [11].

The response to allergens and food antigens leads to the infiltration of eosinophils into the esophageal mucosa, causing epithelial damage (Figure 1).

Figure 1: Histological section showing eosinophils in the esophageal epithelium.

Source: Adapted from Ferreira, 2017, p.51 [3].

The hypothesis that the pathogenesis of EoE is triggered by immediate (IgE) and late (non-IgE) hypersensitivity reactions to food antigens is based on the prevalence of atopy among patients with EoE, which can reach up to 81% of cases. Couto and collaborators identified, through skin allergy tests, sensitization to allergens in up to 50% of patients and specific IgE dosage for at least one food allergen in up to 82% of cases [8]. There is an even greater prevalence of rhinoconjunctivitis and recurrent wheezing when compared to the general population [7].

Although allergens are considered to be the main triggers of the inflammatory process in EoE, the factors that continue inflammation are not fully explained. It is known that eosinophils, once activated, contribute to the recruitment of effector cells from the secretion of extracellular products. The release of granules known as extracellular eosinophil traps (TSEs) trigger the production of IL-5 and the activation of lipopolysaccharide and thymic lympho-

poietin (TSLP) molecules, which create a network of inflammatory mediators that perpetuate the inflammatory process in the esophagus [10]. An infiltration of eosinophils, T lymphocytes, dendritic cells and mast cells occurs in the esophageal mucosa, causing an increase in the levels of interleukins, especially IL-5 and IL-13, which maintain the inflammatory process [8].

Diagnosis

The diagnosis of EoE is based on the association of clinical symptoms of esophageal disorders, especially dysphagia, with or without a history of associated atopy, along with endoscopic and histological changes [6].

The patient with suspected EoE may present several nonspecific clinical manifestations, with symptoms similar to gastroesophageal reflux disease (GERD), such as regurgitation, vomiting, food refusal, abdominal pain, epigastric pain, even dysphagia and food impaction [3].

In view of the clinical suspicion of EoE, it is essential to perform upper gastrointestinal endoscopy with biopsies to confirm the diagnosis. Endoscopic changes suggestive of EoE can often be noted, such as the presence of concentric rings (felinization/trachealization), longitudinal linear streaks, "crepe paper" mucosa, presence of whitish punctate exudate and luminal narrowing [8]. The presence of these endoscopic changes in patients with food impaction or dysphagia raises a strong suspicion of EoE and should be confirmed with biopsies. However, in up to 30% of cases of eosinophilic esophagitis, endoscopic changes are not detected, which should emphasize the importance of performing biopsies, regardless of the findings of the endoscopic examination [12].

Confirming the diagnosis of eosinophilic esophagitis always requires esophageal biopsies. It is advised that biopsies should be performed in proximal and distal segments of the esophagus, regardless of macroscopic changes and a recommended number of six samples should be performed [8].

2 to 4 biopsies of the distal and proximal esophagus must be obtained [6]. The sensitivity is higher the greater the number of fragments analyzed. It is important to perform biopsies in different esophageal segments, since EoE can present in a heterogeneous way [12].

The histological diagnosis is confirmed by counting 15 or more eosinophils per field of wide increase in esophageal biopsies. Other findings that support the diagnosis of eosinophilic esophagitis (EoE) are inflammation and fibrosis of the lamina propria and muscle of the mucosa, presence of degranulated eosinophils, microabscesses, hyperplasia of the basal zone and elongation of the vascular papillae. There may also be an eosinophilic infiltrate in the mucosa of the stomach and duodenum, configuring the diagnosis of eosinophilic gastroenteritis [6].

Other esophageal inflammatory conditions can lead to eosinophilic infiltration of the mucosa, such as GERD. Thus, the performance of the acid suppression test is of fundamental importance for the differential diagnosis of EoE and GERD, through the use of a proton pump inhibitor in a therapeutic dose [8].

Some pathological clinical findings, such as the presence of mast cells in reflux esophagitis (GERD), can help to differentiate the two pathologies. For this, it is necessary to apply a specific staining technique since the mast cells cannot be identified with the usual hematoxylin-eosin stain [6]. Another characteristic that can serve to differentiate between the two entities is that distal esophageal eosinophilia is often found in patients with GERD and, in these cases, the count of eosinophils present in the proximal esophagus helps to distinguish GERD from EoE [6,13].

In some studies conducted with 23 adult patients with EoE and compared with another 20 patients with GERD, the cases with EoE and the number of eosinophils in the proximal esophagus were at high levels of (39.4 vs 0.6 eosinophils) and in the distal (35.6 vs 1.9 eosinophils/cga) and that according to the researchers this feature of conferences of more than 15 eosinophils/cga found in the proximal esophagus occurred only in individuals with EoE in a total of (83% vs 0%) of the cases. This characteristic finding refers to the understanding that EoE also includes the proximal esophagus, distinct from GERD [13].

Some authors have recently demonstrated that patients with EoE show peculiar immunological profiles in peripheral mononuclear cells, in plasma and in esophageal tissue, when compared to patients with healthy controls, GERD, Crohn and ulcerative colitis, indicating that EoE is not manifested only as a local esophageal disease, but rather a systemic condition that can also be detected in plasma [6].

Another way to differentiate these conditions is through fibroblast growth factors, which are relevant in the pathophysiology of eosinophilic esophagitis and which can be components of a con-

jugate of immune markers that could distinguish EoE from GERD. However, additional studies are needed to better define the usefulness of using these markers in the complementary diagnosis [3].

Esophageal pH monitoring for the diagnosis of GERD, as a gold standard method, can be used in the differential diagnosis of EoE. However, the most appropriate approach to differentiate these two conditions is to carry out the 8-week therapeutic test with PPI and repeat the endoscopy with biopsies after this period. Recent studies have demonstrated the usefulness of the therapeutic test with PPI not only as a differentiation mechanism between EoE and GERD, but also in the treatment of EoE due to its anti-inflammatory properties [6].

However, according to the most recent studies, the inflammatory changes demonstrated in esophageal biopsies cannot predict the therapeutic response with PPIs to GERD and EoE, they can coexist and the distinction between the two conditions in clinical practice is not always simple [6].

Treatment and maintenance of eosinophilic esophagitis (EOE)

EoE is a chronic condition, with periods of remission and recurrence of symptoms, and should be conducted by a multidisciplinary team involving a gastroenterologist and allergist, in addition to a nutritionist [6]. Treatment is based on the elimination of food and aeroallergenic allergens, when possible, and on the pharmacological control of the eosinophilic inflammatory response. Endoscopic treatment, through esophageal dilation, is indicated in cases of symptomatic esophageal stricture [3].

The choice of therapy will depend on the clinical picture, histological analysis and reported symptoms, as well as the preference of the doctor, the patient and the costs [14]. Patients who present typical symptoms of GERD with histology showing an increase in the number of eosinophils in the esophageal biopsy can be managed with proton pump inhibitors IBP (from the English Proton Pump Inhibitor) [6].

Proton pump inhibitors (IBP)

The current recommendation is that, after histological confirmation of the increase in the number of eosinophils in the esophageal mucosa (> 15 per high-magnitude field), the therapeutic test with full dose PPI is performed for 8 weeks. This measure is essential for the differential diagnosis with GERD, since the persistent increase in the number of eosinophils after treatment with PPI points to the diagnosis of EoE [3].

Proton pump inhibitors (PPIs) should be analyzed as first-line therapeutic agents for the treatment of EoE. The dose used is 1 to 2 mg/Kg dose in the period of 12/12 hours. In general, 1 mg/kg/dose of 12/12 hours is used for 8 to 12 weeks. After this period, it is recommended to do a new endoscopy with biopsies. If the result of the biopsy of the control endoscopy shows a reduction in the number of eosinophils below 15eos/cga, the patient will be able to continue the use of PPI and the dose reduction will be gradually attempted. However, if the patient does not respond to PPI therapy associated with the persistence of esophageal eosinophilia, therapy with corticosteroids and dietary modification should be associated [7].

The use of PPI contributes to the improvement of symptoms by reducing acid reflux, however, it is not able to completely revert to the esophageal histological alteration. Thus, after treatment with PPI, patients should be monitored, since the response to these medications can be a transient phenomenon [15]. A recent database showed that individuals who had a primary histological improvement on PPI monotherapy, after a certain period, had recurrence of esophageal eosinophilia [6].

Following up, the use of PPIs can modulate inflammatory activity by inhibiting cytokines and Th2 lymphocytes, restoring the epithelial integrity of the esophagus. Proton pump inhibitors are able to reduce and even prevent the recruitment of new eosinophils to the esophageal mucosa by blocking the action of cytokines IL-4 and IL-13 [12].

Thus, the use of PPIs is considered the first step in the treatment of patients with EoE, since they reduce the production of acid by the parietal cells, are useful in excluding GERD as a cause of esophageal eosinophilia and provide improvement of symptoms and reduction of expression of inflammatory cytokines, which may have a role in the pathogenesis of EoE [14]. After treatment with PPI has been instituted, if the patient shows clinical and histological improvements, the control endoscopy should be repeated to monitor the response. If there is no response to the use of PPIs, other therapeutic options must be instituted [6].

Diet

Among current therapeutic options presented for the treatment of EoE, dietary management has been one of the pillars for disease control. For the effectiveness of the treatment, it is essential to eliminate “suspicious” antigens from the diet. Allergic tests (prick

and patch tests) can be used as a guide to identify possible IgE and non-IgE mediated allergies [3]. The performance of allergic tests to identify specific antigens is important, since the patient may not be able to identify foods related to the disease and the antigenicity in EoE is related to the delayed hypersensitivity response, with the symptoms starting days to weeks after the intake of related food [12]. Dietary treatment should be recommended for all patients with EoE, with follow-up with a nutritionist indicated so that restrictions do not interfere with good development and growth [2].

The therapeutic approach based on the use of elementary amino acid formulas requires multidisciplinary monitoring, with an allergist and nutrologist, in order to define the adequate supply of calories, fluids and other nutritional elements, such as minerals and vitamins [12]. This therapeutic modality had a satisfactory response in up to 98% of patients, mainly in the pediatric population with a history of multiple allergies and growth retardation [1]. There is an improvement in symptoms and endoscopic findings, reaching histological remission in up to 90% of cases [12]. The great limitation of this therapy is related to the high cost and little palatability, not being well tolerated by the oral route, often requiring enteral support by tube or gastrotomy for adequate caloric intake [7]. It is added that in addition to the compromised quality of life with the use of this diet, there is a recurrence of symptoms on the return to the polymeric diet [3].

Another dietary alternative is food restriction through the empirical elimination of four to six groups of allergenic foods (egg, peanuts, soy, cow's milk, wheat and seafood), reducing the inflammatory stimulus. It is a more accessible and palatable option than the elementary diet [15] and which has been shown to be efficient in symptomatic improvement and in the reduction of eosinophilic infiltrate in the esophagus in 70% of adults and 74% of children. Allergy to one food was identified in 36% of cases, to two foods in 31% and to three or more foods in 33%, with cow's milk being the most commonly related food antigen, involved in 62% of identified food allergy cases [12].

The elimination of food groups is recommended for a period of 4 to 12 weeks. Eight weeks after starting the diet, it is recommended to perform upper gastrointestinal endoscopy to assess endoscopic and histological remission. If there is remission and a significant improvement in symptoms, food can be gradually reintroduced, with periodic reevaluation after the introduction of each food group [7]. The order of reintroduction of food is relevant in order to identify which allergen may be responsible for the inflammatory process [12]. So, first we must reintroduce the least allergenic foods, with fruits and vegetables, followed by meat, fish, grains, soy, seafood, nuts and dairy products, obeying the interval of 5 to 7 days and, with the recurrence of symptoms with one or more foods, these should be excluded from the diet. One of the disadvantages of this dietary management is the high number of endoscopies performed during the reintroduction of food groups [14].

An alternative to the elimination diet of the six elements would be the elimination of four food groups, with similar results [7] and advantages such as better patient adherence, reduction of the total time needed for the reintroduction of food and the need endoscopy after the reintroduction of each food group [12].

Pharmacological treatment

Currently, therapeutic options in EoE consist of the use of proton pump inhibitors, as previously reported; Topical (Fluticasone or Budesonide) or systemic corticosteroids; Mast cell stabilizers (sodium chromoglycate); Leukotriene receptor antagonist (Montelukast); Anti-IgE monoclonal antibody (Omalizumab) and anti-interleukin-5 monoclonal antibody (Mepolizumab) [3]. Topical corticosteroids are considered effective in the treatment of EoE [6].

Topical corticotherapy

Treatment with topical corticosteroids consists of using Fluticasone or Budesonide, which are inhaled medications, but which must be administered orally (swallowed). These drugs are capable of inducing clinical, endoscopic and histological improvement, both in children and in adults. For several authors, it is an effective and safe treatment option, even if the application method may cause some initial technical difficulty [3]. Treatment with topical steroids is first-line pharmacological therapy [6].

Fluticasone, at a dose of 440 to 880 mcg/day for children and from 880 to 1,760 mcg/day for adults [6] should be administered as follows: two puffs, orally, without spacer, two times a day, and should be swallowed instead of inhaled [12]. After swallowing the mouth is rinsed under running water in order to prevent the appearance of oral candidiasis, which can occur in 5 - 30% of cases [14].

Budesonide, 1 mg/day for children and 2 mg/day for adults, should be divided into 2 to 4 daily doses [6]. It can be administered

in the form of vaporized nebulization or swallowed in the form of viscous paste (mixture of Budesonide, 2 ml, with 3 - 5 mg of sucralose), which has the best result due to the longer time of contact with the esophageal mucosa. These formulations are an adaptation for use in EoE therapy, since they are originally used in the treatment of allergic respiratory pathologies [7].

It is recommended that the patient administer these medications after meals and do not take liquids or food orally for a period of 30 to 60 minutes after using the medication, to increase and favor contact with the esophageal mucosa. Treatment should be continued for 6 to 8 weeks [12].

The use of topical corticosteroids demonstrates a clinical and histological improvement of approximately 50% to 95% with 1 to 3 months of treatment. The symptomatic and endoscopic improvement is also considerable [6]. Treatment with fluticasone reduces the number of CD8 + T lymphocytes and mast cells in the proximal and distal esophagus, being efficient in inducing histological remission in EoE and with less adverse effects than systemic corticosteroid therapy [3].

The use of topical corticosteroids reverses esophageal fibrotic remodeling, especially with the administration of Budesonide in pediatric patients. In adults with EoE, there was no reduction in collagen deposition in the lamina propria after 1 year of treatment, despite the disappearance of gene expression related to pro-fibrogenic cytokines. The cause would be the limited capacity of these topically acting drugs to penetrate the deeper esophageal layers and act on the infiltrate in this area [12].

Some authors argue that topical corticosteroids should be maintained for an indefinite period, however, this position is controversial, especially due to the potential side effects and the lack of data on long-term use. An acceptable alternative, until more studies are available, would be to gradually reduce the dose of the medication to maintain the lowest dose necessary to keep the disease in remission [6]. In cases of recurrence of symptoms after discontinuation of medication, the most recent guidance is the continuity and maintenance of treatment, especially in patients with severe manifestations such as food impaction, history of esophageal perforation and strictures that require dilation. For patients with EoE refractory to topical corticosteroid therapy, we can associate empirical food elimination diets, diets guided by allergic tests and/or esophageal dilatation by endoscopy. The rate of non-response to the use of budesonide is 13% to 36% whereas that of fluticasone is 38% to 50% [12].

Systemic corticotherapy

Among the drug options for EoE therapy, the administration of corticosteroids relieves symptoms and reduces the inflammatory process [3]. Topical corticosteroid therapy is as effective in the treatment of EoE as the systemic and should be preferred due to the lower rate of adverse events. Systemic corticosteroids have limited indication for long-term side effects [6]. They are recommended in individuals with EoE who need immediate symptom relief, such as major dysphagia and food impaction [1]. This is the preferred therapy in cases of severe initial systemic impairment, such as esophageal stricture with intense inflammation, the dilation of which could cause mucosal laceration or esophageal perforation [14].

Methylprednisolone orally at a dose of 1.5 mg/kg/day or Prednisone at a dose of 1 - 2 mg/kg/day, with a maximum dose of 60 mg/day, for a period of four weeks, for patients who did not respond to administration of topical corticosteroids. After the indicated treatment time, the dose should be gradually reduced [3].

Another drugs

Another medication that has been administered for the treatment of EoE is Ciclesonide, an inhaled corticosteroid already used in the treatment of allergic rhinitis and asthma. It is a prodrug that is activated after being converted by esophageal epithelial cell stearases and binds to glucocorticoid receptors in a percentage 100 times greater than Fluticasone and Budesonide and with less systemic bioavailability, due to its high rate of metabolism in the primary passage through the liver. This characteristic provides potential benefits in terms of greater pharmacological efficacy and lesser adverse and systemic side effects [12].

Montelukast is a leukotriene inhibitor and has been evaluated in individuals with EoE in a series of cases. The use of this medication in high doses, in adults with EoE, showed symptomatic but not histological improvement, not being effective to maintain sustained steroid-induced remission [6].

Other drugs have been studied in the treatment of EoE, but have not shown concise results. Sodium chromogligate was administered over 4 weeks in 14 patients and showed no histological or symptomatic improvement. Immunomodulators such as 6-mer-

captopurine and Azathioprine have shown histological and symptomatic remission in steroid-dependent patients, but due to side effects and insufficient data and sampling, they are not indicated for continuous use [6].

Mepolizumab, an anti-IL-5 monoclonal antibody, was used in two experiments, one on adults and one on children. In both groups, medication reduced the eosinophil count in most patients, but complete histological resolution occurred in a small percentage, in addition to showing no change in symptoms in adults. Reslizumab was studied in a clinical trial and demonstrated a significant reduction in esophageal eosinophilia in a patient with EoE, without serious adverse effects, however, the improvement in symptoms did not differ from placebo. Omalizumab, an anti-IgE antibody, has been evaluated in a series of cases and has not shown effectiveness [3,6].

The clinical response of these agents is not yet fully proven and further studies using these drugs are needed to define their role in EoE [6].

Endoscopic dilation

Endoscopic dilation is one of the therapeutic modalities for symptomatic esophageal strictures, especially in those that do not respond to other treatments [1]. Esophageal dilation sessions should be gradual and performed with caution, in order to avoid complications such as laceration and esophageal rupture [15].

Endoscopic treatment can be performed using a Savary probe or a hydrostatic balloon. It is a mechanical procedure aimed at relieving dysphagia, but does not interfere with the pathophysiology of the disease [12]. Thus, even after dilation, maintenance treatment with topical corticosteroids should be continued.

Regarding the dilation technique, there are few studies to define which method is preferable. The hydrostatic balloon dilator has the theoretical advantage of preventing damage by shear stress and allows the analysis of the underlying esophageal mucosa between the series of dilations, without the need to reintroduce the endoscope. Savary's dilation candle, on the other hand, uses a guide wire that offers the ability to dilate several points of stenosis in an esophagus diffusely narrowed by EoE [6]. Most authors indicate dilation with progressively larger diameters in several sessions, as it allows the assessment of the esophageal mucosa after each dilation. This treatment is effective in relieving dysphagia in most patients with EoE and has an average duration of response greater than one year [6,7,12].

Immediately after dilation, an endoscopic review is indicated to analyze possible immediate complications such as fissure, laceration and perforation, resulting from the mucosa's rigidity and inelasticity [12]. The procedure can cause chest pain in up to 75% of cases, lasting for a few days.

In general, endoscopic dilation therapy is indicated after assessing the lack of response to dietary and drug treatment, with topical or systemic corticosteroids. However, if significant upper stenosis or food impaction is identified during upper digestive endoscopy, dilation can be performed before other therapies [6]. This therapeutic modality is contraindicated in individuals with EoE who have complications such as deep lacerations and perforations of the esophageal mucosa. The performance of dilation in initial EoE monotherapy is still controversial and should be individualized until more studies and data are available [12,16].

Methodology

To carry out this systematic review, the literature of the last 4 years on the Maintenance Treatment of Eosinophilic Esophagitis (EoE) was consulted in the main search bases: Pubmed and Cochrane databases, using the following subject descriptors: Eosinophilic Esophagitis, EoE Treatment, Diseases related to the Esophagus, Eosinophil Infiltrates in the Esophagus, Eosinophilic Inflammation, Esophageal Dysfunction.

Conclusion

Despite the progressive increase in the number of publications on EoE, the evidence regarding the therapeutic modalities of long-term maintenance is still scarce, regarding the choice of drugs and the ideal dietary approach. The biggest obstacle facing to treat EoE occurs in patients with little symptomatic pathology, whose benefits of therapy over the side effects of medications are still unclear.

The ideal treatment is aimed at relieving symptoms, especially dysphagia and food impaction and preventing esophageal remodeling resulting from chronic inflammation, providing better quality of life for patients.

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