Review paper

Eosinophilic gastroenteritis – a manifestation of an allergic disease in the gastrointestinal tract? Part 2. Treatment

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Abstract

Treatment of eosinophilic gastroenteritis (EGE) is mainly empirical and is based on the assessment of symptom severity and the experience of clinicians. Patients with mild disease can be treated symptomatically, while patients with more severe symptoms or malabsorption symptoms require more aggressive therapy. So far, several therapeutic options have been proposed, including the following: dietary treatment, glucocorticosteroids, inhibitors of leukotriene receptors, mast cell stabilizers, immunomodulating drugs, and biological drugs. Unfortunately, there is still a lack of well-designed, prospective. and randomized clinical trials involving large groups of patients with EGE and assessing the effectiveness of individual treatments. More research is needed to compare the efficacy and safety profiles of the various treatments available, and to select the prognostic factors of relapse, which in turn will be extremely important in making decisions about the initial treatment phase and maintenance therapy.

Introduction

Eosinophilic gastroenteritis (EGE) is a rare disease characterized by inflammatory infiltrates of the gastrointestinal wall, mainly composed of acidophilic cells. It is a poorly understood disease. We do not know the exact frequency of the disease or its pathomechanism, there are no diagnostic standards, and even less is known about its effective treatment. The treatment of EGE is mainly empirical and based on assessment of the severity of symptoms and experience of clinicians. Patients with mild disease can be treated symptomatically, while patients with more severe symptoms or malabsorption require more aggressive therapy. Several therapeutic options have been proposed so far including the following: dietary therapy, glucocorticosteroids, leukotriene receptor inhibitors, mast cell stabilizers, immunomodulatory drugs, and biologics. Most therapeutic strategies have been tested only in small groups of patients or single cases, and randomized trials conducted on this topic have only evaluated the efficacy of montelukast in paediatric patients.

Dietetic treatment

Dietary treatment can be presented schematically in the form of 3 staircases, as shown in Figure 1. "Ascending" the successive levels of treatment involves the elimination of successive foods from the patient's diet. This method may be burdensome for the patient and arouse many controversies, but in the case of exhausting other possibilities, it may turn out to be the only alternative to therapeutic helplessness.

The role of dietary therapy in EGE is controversial, and studies often report different results. Lucendo *et al.* investigated the efficacy of dietary therapy in EGE and demonstrated clinical remission in > 75% of patients who followed an elemental diet, and the efficacy of the diet was demonstrated primarily in mucosal EGE [1]. In contrast, a study by Wong *et al.* found that one in 18 patients with EGE had food allergy and clinical improvement after an elimination diet, which was confirmed by follow-up endoscopy showing resolution of eosinophilic infiltration [2]. In contrast, Yamada *et al.*

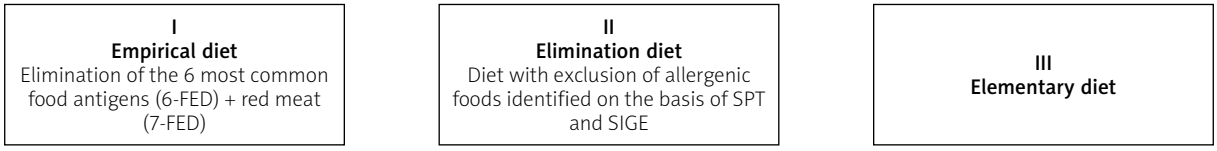

Figure 1. Degrees of dietary treatment in EGE

found that an elemental diet causes rapid resolution of symptoms, but duodenal eosinophilic infiltration persists [3]. However, Katz *et al.* showed that an elimination diet may not prevent relapse [4]. A retrospective study by Ko *et al.* compared different dietary therapies (elemental diet, diet with exclusion of the 6 most allergenic foods and red meat (7-FED), and empirical diet with avoidance of 1 to 3 foods) in 30 children with EGE. A positive clinical response was demonstrated in 82% of patients; however, histological evaluation was not performed for most of them [5]. In 2009, a prospective study was conducted involving adults with histologically confirmed EGE treated for 6 weeks with a diet excluding the 6 most allergenic foods (6-FED) or an elemental diet. Clinical and histological remission was observed in both groups, but the number of patients involved was small and a control group was lacking [6]. A prospective study evaluating the effect of a 6-week elemental diet in adult patients (aged 18–65 years) with EGE with a primary endpoint of histological remission (< 30 eosinophils/HPF) and a secondary endpoint of resolution of symptoms is currently underway; unfortunately, no definitive results are available at this time [7].

The data in the literature are insufficient to recommend dietary treatment in routine management, but initially an elemental diet may be considered as adjunctive treatment, primarily in severe cases. The available literature suggests that the later EGE develops, the less responsive it is to dietary modifications. Finally, it is emphasized that it is difficult to track unequivocally whether the patient tolerates and adheres to the diet, especially when an elimination or elemental diet is used, so future randomized trials are required, which must include assessment of histologic remission to better characterize the phenotypes of patients who respond to dietary treatment [8].

Pharmacological treatment

Corticosteroid therapy (GCS)

Corticosteroid therapy (GCS) is the mainstay of treatment for EGE in both adults and children. Corticosteroids inhibit the transcription of IL-3, IL-4, IL-5, and GM-CSF genes and many chemotactic factors; they reduce both the number of eosinophils and the effects of their toxic products. The duration of steroid therapy is unknown, and relapse of symptoms often means that prolonged treatment is required, which can lead to the development of side effects, and there is a risk of developing steroid resistance. Although evidence to date suggests that GCSs are the most effective therapy for EGE, there are no well-designed scientific studies available to support this statement [9].

Prednisone acts by inducing apoptosis of eosinophils and inhibiting their chemotaxis. It is the GKS of first choice for induction of EGE remission, effective in > 90% of cases. It is usually administered orally at an initial dose of 30–40 mg/day for 6–8 weeks with gradual dose reduction. Remission occurs within 2–3 weeks, manifested by a decrease in eosinophilic infiltrate, eosinophil levels, and eosinophilic ascites. It has been shown that the highest response rate to prednisone occurs in patients with serous type EGE. Because of possible side effects, prednisone is discontinued once remission is achieved. However, relapses may occur, requiring low maintenance doses (1–10 mg/day) or replacement of prednisone with budesonide. If there is an initial lack of improvement with prednisone, the diagnosis and type of EGE should be reassessed or changed to another pharmacological agent (budesonide or steroid-sparing agents) [10, 11].

Budesonide is commonly used in Crohn's disease and ulcerative colitis. It reduces inflammation and capillary permeability in addition to being a topical drug due to its slow-release enteral capsules. It is a very well tolerated agent with few side effects. Treatment of patients with gastrointestinal involvement with enteral budesonide, after crushing the tablet, has been shown to have good results [12]. Budesonide is effective in inducing and maintaining clinical and histopathological remission. It has been shown to induce remission in 61% of patients with EGE. The usual dose used is 9 mg/day and can be reduced to 6 mg/day for long-term use as well as for maintenance treatment. The efficacy and better safety profile of budesonide treatment compared to other GCSs appear to be particularly beneficial in the long-term treatment of EGE [13].

Leukotriene receptor antagonists

Leukotriene receptor antagonists are a class of drugs commonly used in the treatment of asthma and are also used in EGE. Montelukast sodium, as the flagship of this group, is usually administered at a dose of

5–10 mg/day in monotherapy or in combination with low-dose steroids in the induction and maintenance of remission in steroid-dependent or steroid-resistant disease in both adults and children [14, 15]. The first scientific reports created hope for a breakthrough in the treatment of EGE. Positive clinical and histological responses were obtained in most patients within 2–4 weeks of treatment, with remission lasting at least 12 months [16]. One study showed a reduction in eosinophilia after montelukast treatment, but without any relief of symptoms [17]. Unfortunately, the results of 2 further studies showed a complete lack of efficacy of the drug. Due to the lack of unequivocal scientific evidence for the efficacy of leukotriene receptor antagonists, more randomized studies are needed to evaluate the long-term benefits and side effects of this group of substances [17–26].

Mast cell stabilizers

Mast cell stabilizers are a group of drugs that primarily include cromoglycate and ketotifen. Studies on the efficacy of these substances have been controversial because they have produced contradictory results; however, they are still being considered as an alternative to steroids. The dose of cromoglycate used in the treatment of EGE has typically ranged from 100 to 300 mg 3–4 times daily, with treatment durations ranging from 10 weeks to over a year [16, 27]. Ketotifen is usually used at a dose of 1–2 mg twice daily. This drug has never been used as monotherapy, but mainly as an adjunct to steroids and montelukast for the treatment of refractory EGE in children and adolescents [18]. One study described 6 patients with EGE, who responded clinically and histologically to ketotifen; however, it also described a case in which the drug provided only symptomatic benefit, with immediate relapse after discontinuation of treatment [21, 22].

Immunomodulatory drugs

Immunomodulatory drugs, like azathioprine (AZA) or 6-mercaptopurine, are an alternative for steroid-dependent or steroid-resistant patients. They act by inhibiting purine synthesis and additionally inhibit T and B lymphocyte proliferation. To date, only one study has been published using 6-mercaptopurine in eosinophilic oesophagitis that achieved clinical and histologic remission sustained for > 3 years [23]. The efficacy of azathioprine was observed in patients with steroid-resistant and steroid-dependent EGE when the drug was used at a dose of 50 mg/day. Studies have shown that patients treated with AZA alone experienced complete clinical and histological remission, which persisted for > 3 years, and that the combination of AZA and prednisolone 2 mg/day was more effective than AZA alone [24, 25]. Given the sparse scientific evidence, further randomized trials with larger numbers of patients and comparison of immunomodulators with other EGE therapies are needed to draw more reliable conclusions.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are the primary drugs in eosinophilic oesophagitis. Neutralization of gastric juice acidity with PPIs is thought to be effective in relieving symptoms and reducing eosinophilic infiltration even when gastroesophageal reflux disease is not present. Treatment with lansoprazole (10 mg/day) has been shown to reduce the extent of duodenal eosinophilic infiltration in children and adolescents with EGE by blocking IL-4 and IL-13 activity and by suppressing hydrochloric acid secretion, which may shorten eosinophil viability by increasing pH [26].

Biological treatment

Due to the necessity of high dietary restrictions in the nutritional treatment of patients with EGE, the difficulties in maintaining the diet, the complications of GCS treatment, and the conflicting results of studies on the use of other drugs, other effective and above all safe therapies are being sought, which could be an alternative to the current standards or a new basis for the treatment of EGE. Currently, great hopes are placed on biological drugs, whose action is based on immunological relations and interrelationships, thus increasing hopes not only for effective control of symptoms, but also for elimination of the cause of the disease by interfering in its pathogenetic basis.

Anti-TNF-α treatment

TNF-α is involved in the induction of adhesion molecule expression, which leads to the selective recruitment of eosinophils. The currently used drug to inhibit this mechanism is infliximab. However, there is only one case report showing the use of infliximab in a patient with EGE. In this study, infliximab was effective in inducing remission in a child refractory to standard therapy, but its use was limited by the development of resistance and secondary loss of response [27].

Omalizumab, is an anti-IgE monoclonal antibody that reduces free IgE levels and is a widely recognized effective treatment for allergic asthma and seasonal allergic rhinitis. It is worth noting here that a 16-week open-label clinical trial in 9 patients with EGE did not result in clinical or histopathological improvement. Additionally, no biopsy was performed to document changes in tissue eosinophilia [28].

Recently, the combination of omalizumab and mepolizumab (antibody anti-IL-5) was studied and demonstrated symptom relief in a patient with severe asthma and coexisting EGE. However, as in the previous study, no tissue biopsies were performed to assess resolution of tissue lesions [29].

Anti-IL-5 therapy

IL-5 is a key mediator in the activation of acidophilic eosinophils. Antibodies against IL-5 (reslizumab), are designed to reduce eosinophil levels in peripheral blood and tissues. A pilot study with reslizumab (SCH55700) given as a single intravenous dose at 1 mg/kg intravenously in 4 patients with EGE showed that 3 of them had a reduction in eosinophilia in both tissues and peripheral blood, but without any effect on symptoms [30]. In contrast, another study showed that treatment with reslizumab reduced eosinophilia and clinical symptoms in 6 out of 8 patients with hypereosinophilic syndrome or EGE [31]. Another form of anti-IL-5 therapy is treatment with benralizumab, an antibody that blocks the IL-5Rαsubunit for IL5. In studies, this drug normalized gastrointestinal eosinophilia in hypereosinophilic syndrome. A randomized trial (NCT03473977) evaluating the efficacy and safety of benralizumab administered at a dose of 30 mg every 3 months in EoE and EGE is currently ongoing [32].

Anti-IL-4 and IL-13 therapy

Dupilumab is an antibody that antagonizes both IL-4 and IL-13 because its target is the α subunit of the receptor for IL-4, which in turn is shared by both IL-13 and IL-4 receptors. Twelve-week treatment with dupilumab in EoE has shown significant clinical, endoscopic, and histologic improvement. A phase 2 trial (NCT03678545) is currently underway evaluating the efficacy of dupilumab administered at an initial dose of 600 mg 1× followed by 300 mg every 2 weeks (6 injections in total), followed by an open-label phase for treatment response. No results from the study are currently available [28].

Sialic acid-binding immunoglobulin-like protein (Siglec-8)

Sialic acid-binding immunoglobulin-like protein (Siglec-8) is associated with eosinophil apoptosis. In a mouse model, anti-Siglec-8 treatment resulted in a reduction of IL-5-induced eosinophilia. A phase II trial (ENIGMA) of anti-Siglec-8 antibody (AK002-Antolimab) in patients with eosinophilic gastroenteritis has recently been completed, demonstrating a reduction in gastrointestinal tissue eosinophils (95% reduction in eosinophilia) and a reduction in symptoms (in 69% of patients). A phase 3 study is currently underway, but data are not yet available [33].

α4/β7 integrin

α4/β7 integrin is involved in the passage of lymphocytes to the site of inflammatory reaction. Vedolizumab, an antibody against α4/β7 integrin, inhibits the adhesion of eosinophils and their passage to the site of inflammatory reaction. It has been shown to have anti-eosinophilic effects in 2 EGE case series. Of the 5 patients with steroid-resistant EGE who received vedolizumab infusion, 2 showed significant improvement - one patient significantly reduced steroid doses, the other was able to discontinue them [34]. In 3 out of 4 patients with steroid-resistant EGE, administration of vedolizumab resulted in significant clinical improvement. An evaluation of the effect of vedolizumab on tissue eosinophilic infiltration in these patients should also be available soon [35].

Alternative treatment

Among other therapeutic options, the efficacy of gut microbiota transplantation in a patient with severe EGE, manifested by frequent intestinal obstruction and diarrhoea, has also been described. As an adjunctive therapy, it was able to significantly reduce the frequency of diarrhoea, even before the administration of prednisone [36]. Surgical treatment is avoided whenever possible; however, it is necessary in cases of severe EGE complicated by perforation, intussusception, or obstruction, or for full thickness biopsy of the bowel to establish the diagnosis. It has been reported that about 40% of patients with EGE may require surgery during the course of the disease, and about half of them may experience recurrence, even after previous surgical treatment [37].

Summary

Eosinophilic gastroenteritis is not a common disease, but it should be considered in the diagnosis of gastrointestinal disorders. Because EGE is rare and difficult to diagnose, it often goes unrecognized. It seems that good communication between clinicians, endoscopists, and pathologists may help to reduce the percentage of undetected cases. Unfortunately, well-designed, prospective, randomized clinical trials evaluating the efficacy of all forms of treatment for this disease are still lacking. Further studies are needed to compare the efficacy and safety profiles of the various treatments available, as well as to select predictors of recurrence, which in turn will be extremely important in making decisions regarding initial treatment and maintenance therapy.

Conflict of interest

The authors declare no conflict of interest.

References

1. Lucendo A, Serrano-Montalbán B, Arias Á, et al. Efficacy of dietary treatment for inducing disease remission in eosinophilic gastroenteritis. J Pediatr Gastroenterol Nutr 2015; 61: 56-64.
2. Wong G, Lim K, Wan W, et al. Eosinophilic gastroenteritis: Clinical profiles and treatment outcomes, a retrospective study of 18 adult patients in a Singapore Tertiary Hospital. Med J Malaysia 2015; 70: 232-7.
3. Yamada Y, Toki F, Yamamoto H, et al. Proton pump inhibitor treatment decreased duodenal and esophageal eosinophilia in a case of eosinophilic gastroenteritis. Allergol Int 2015; 64 Suppl: S83-5.
4. Katz A, Twarog F, Zeiger R, et al. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. J Allergy Clin Immunol 1984; 74: 72-8.
5. Ko H, Morotti R, Yershov O, et al. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. Am J Gastroenterol 2014; 109: 1277-85.
6. Gonsalves N, Yang G, Doerfler B, et al. A prospective clinical trial of six food elimination diet and reintroduction of causative agents in adults with eosinophilic esophagitis (EE). Gastroenterology 2008; 4: A-104.
7. CEGIR 7809: effect of elemental diet on adult patients with eosinophilic gastroenteritis. https://www.clinicaltrials.gov/ct2/show/NCT03320369?recrs=abdf&cond=Eosinophilic+Gastritis&draw=2&rank=35. Accessed May 14, 2019.
8. Pineton de Chambrun G, Gonzalez F, Canva J, et al. Natural history of eosinophilic gastroenteritis. Clin Gastroenterol Hepatol 2011; 9: 950-6.
9. Chang J, Choung R, Lee R, et al. A shift in the clinical spectrum of eosinophilic gastroenteritis toward the mucosal disease type. Clin Gastroenterol Hepatol 2010; 8: 669-75.
10. Zhang L, Duan L, Ding S, et al. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics, a retrospective study of 42 patients. Scand J Gastroenterol 2011; 46: 1074-80.
11. Lombardi C, Salmi A, Passalacqua G. An adult case of eosinophilic pyloric stenosis maintained on remission with oral budesonide. Eur Ann Allergy Clin Immunol 2011; 43: 29-30.
12. Aceves S, Bastian J, Newbury R, et al. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol 2007; 102: 2271-9.
13. Reed C, Woosley J, Dellon E. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. Dig Liver Dis 2015; 47: 197-201.
14. Wong G, Lim K, Wan W, et al. Eosinophilic gastroenteritis: clinical profiles and treatment outcomes, a retrospective study of 18 adult patients in a Singapore Tertiary Hospital. Med J Malaysia 2015; 70: 232-7.
15. Müller M, Keller K, Stallmann S. Clinicopathologic findings in eosinophilic gastroenteritis: a German case series. J Genet Syndr Gene Ther 2014; 5: 2-6.
16. Rached A, El Hajj W. Eosinophilic gastroenteritis: approach to diagnosis and management. World J Gastrointest Pharmacol Ther 2016; 7: 513-23.
17. Tien F, Wu J, Jeng Y, et al. Clinical features and treatment responses of children with eosinophilic gastroenteritis. Pediatr Neonatol 2011; 52: 272-8.
18. Daikh B, Ryan C, Schwartz R. Montelukast reduces peripheral blood eosinophilia but not tissue eosinophilia or symptoms in a patient with eosinophilic gastroenteritis and esophageal stricture. Ann Allergy Asthma Immunol 2003; 90: 23-7.
19. Lu E, Ballas Z. Immuno-modulation in the treatment of eosinophilic gastroenteritis. J Allergy Clin Immunol 2003; 111: S262.
20. Sheikh R, Prindiville T, Pecha R, et al. Unusual presentations of eosinophilic gastroenteritis: case series and review of literature. World J Gastroenterol 2009; 15: 2156-61.
21. Melamed I, Feanny S, Sherman P, et al. Benefit of ketotifen in patients with eosinophilic gastroenteritis. Am J Med 1991; 90: 310-4.
22. Freeman H. Longstanding eosinophilic gastroenteritis of more than 20 years. Can J Gastroenterol 2009; 23: 632-4.
23. Netzer P, Gschossmann J, Straumann A, et al. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. Eur J Gastroenterol Hepatol 2007; 19: 865-9.
24. Redondo-Cerezo E, Cabello M, González Y, et al. Eosinophilic gastroenteritis: our recent experience: one-year experience of atypical onset of an uncommon disease. Scand J Gastroenterol 2001; 36: 1358-60.
25. Copeland B, Aramide O, Wehbe S, et al. Eosinophilia in a patient with cyclical vomiting: a case report. Clin Mol Allergy 2004; 2: 7.
26. Yamada Y, Toki F, Yamamoto H, et al. Proton pump inhibitor treatment decreased duodenal and esophageal eosinophilia in a case of eosinophilic gastroenteritis. Allergol Int 2015; 64 Suppl: S83-5.
27. Turner D, Wolters V, Russell R, et al. Anti-TNF, infliximab, and adalimumab can be effective in eosinophilic bowel disease. J Pediatr Gastroenterol Nutr 2013; 56: 492-7.
28. Lucendo A, López-Sánchez P. Targeted therapies for eosinophilic gastrointestinal disorders. BioDrugs 2020; 34: 477-93.
29. Han D, Lee J. Severe asthma with eosinophilic gastroenteritis effectively managed by mepolizumab and omalizumab. Ann Allergy Asthma Immunol 2018; 121: 742-3.
30. Prussin C, James S, Huber M, et al. Pilot study of anti-IL-5 in eosinophilic gastroenteritis. J Allergy Clin Immunol 2003; 111: S275.
31. Kim Y, Prussin C, Martin B, et al. Rebound eosinophilia after treatment of hypereosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700. J Allergy Clin Immunol 2004; 114: 1449-55.
32. Kuang F, Legrand F, Makiya M, et al. Benralizumab for PDGFRA-negative hypereosinophilic syndrome. N Engl J Med 2019; 380: 1336-46.
33. Dellon E, Peterson K, Murray J, et al. Efficacy and safety of AK002 in adult patients with active eosinophilic gastritis and/or gastroenteritis: primary results from a randomized, double-blind, placebo-controlled phase 2 trial (ENIGMA study). United Eur Gastroenterol J 2019; 8 (Suppl): 1419-20.

34. Kim H, Reed C, Herfarth H, et al. Vedolizumab treatment may reduce steroid burden and improve histology in patients with eosinophilic gastroenteritis. Clin Gastroenterol Hepatol 2018; 16: 1992-4.
35. Grandinetti T, Biedermann L, Bussmann C, et al. Eosinophilic gastroenteritis: clinical manifestation, natural course, and evaluation of treatment with corticosteroids and vedolizumab. Dig Dis Sci 2019; 64: 2231-41.
36. Dai Y, Shi C, Cui B, et al. Fecal microbiota transplantation and prednisone for severe eosinophilic gastroenteritis. World J Gastroenterol 2014; 20: 16368-71.
37. Amruthesh T, Kini D, Yachha S, et al. Eosinophilic gastroenteritis: clinical characteristics and management. Indian J Gastroenterol 2021; 40: 338-43.

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