Non-esophageal eosinophilic gastrointestinal diseases: a narrative review

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Abstract

Eosinophilic gastrointestinal disorders are a group of rare diseases characterized by the infiltration of eosinophils in the gastrointestinal wall in a greater amount than in homeostatic conditions. ‘Non-esophageal eosinophilic gastrointestinal disorders’ is the umbrella term for all eosinophilic gastrointestinal disorders outside of the well known eosinophilic esophagitis. This includes eosinophilic gastritis, eosinophilic enteritis and eosinophilic colitis. The clinical presentation is atypical and not very different for the three disorders. The depth of infiltration has a bigger influence on the presenting symptoms than the disease location. Although the frequency of diagnosis and research in this subject is increasing over time, non-esophageal eosinophilic disorders are rare and high quality evidence is limited to date. In this narrative review, we provide an overview of the latest insights in the pathophysiology, diagnostic approach and available treatment options. Transcriptome studies have found the pathogenesis to be Th1 helper type 2 driven. Various laboratory findings can be used to trigger raised suspicion and investigation with endoscopy. As the endoscopic appearance of the mucosa is normal in most cases, multiple biopsies in each segment are needed to quantify the amount of eosinophils in the tissue. Eosinophil cut-offs for diagnosis are a controversial topic and a consensus is still lacking. A recently developed tissue based diagnostic platform which measures differentially expressed genes might be available in the future to classify patients with intermediate eosinophilic tissue levels under the cut-off. For the treatment, corticosteroids are still the cornerstone of treatment but promising research suggests a role of biologicals, such as Lirentelimab (anti-siglec 8) in particular. (Acta gastroenterol. belg., 2023, 86, 449-459).

Keywords: Eosinophilic gastrointestinal disorders, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis.

Introduction

Eosinophilic gastrointestinal disorders (EGIDs) are a group of chronic inflammatory conditions characterized by gastrointestinal infiltration of eosinophils without a secondary cause of eosinophilia (1). EGIDs are divided into four separate disorders according to the affected site in the gastrointestinal (GI) tract (1-3). Eosinophilic esophagitis (EOE), in which the eosinophilic infiltration is limited to the esophagus, is the most common and best characterized disease of the esophagus (4). EGIDs distal to the esophagus are a lot less frequent and poorly understood as there is limited literature available (5). Current information is predominantly derived from case reports and single center retrospective studies (6-8). In the last decade there was a heterogeneity in the terminology of non-esophageal eosinophilic EGIDs (non-EoE EGIDs) with ‘eosinophilic gastroenteritis’ often being used as the umbrella term (9). Following recent international consensus recommendations for EGID nomenclature, non-EoE disorders include eosinophilic gastritis (EG), enteritis (EOE) and colitis (EOC) (9). Clinical manifestations of non EoE-EGIDs are non-specific and depend on the affected layer and site of the GI wall (10). Therefore diagnosis is not always easy and requires a high clinical index of suspicion.

Eosinophils are leukocytes located in the lamina propria of the gastrointestinal tract in homeostatic conditions with the exception of the esophagus where there are no eosinophils in normal conditions (11). Eosinophils have a role in host defense. They contribute to tissue homeostasis by selectively protecting against pathogenic parasites and bacteria. Hereby they also modulate the intestinal microbiome (12). Eosinophils originate from pluripotent hematopoietic stem cells and mature in the bone marrow before migrating to the GI tract. Chemotaxis is ensured by the local production of chemoattractants, particularly chemokines with eotaxin-1 (CCL11) being the most selective (12). Cytokines and chemokines regulate the survival of eosinophils. Interleukin 5 (IL-5) is the most potent and selective eosinophil regulator (12). Upon activation, eosinophils degranulate and release toxic substances. This contributes to the inflammatory process in which eosinophils work in synergy by clustering with Th2 lymphocytes (11). When eosinophils are more prominently present than normal, it results in pathology (12). Apart from EGIDs, an elevated number of GI eosinophils can also be present in drug reactions, food hypersensitivities, inflammatory bowel disease, parasitic infections, gastroesophageal reflux disease and hypereosinophilic syndrome among others (13,14).

Currently, there is no standard approach to the diagnosis of non-EoE EGIDs but histological presence of eosinophilia without a secondary cause in multiple biopsies is necessary (6). The optimal number of biopsies and the eosinophilic cut-off required for diagnosis is unclear and an area of active investigation (15,16). First-line treatment consists of dietary therapy and corticosteroids (17). Given the limitations and adverse effects of these treatments, there is increasingly more research in steroid sparing agents (18).
In this narrative review we aim to provide a comprehensive understanding of non-EoE EGIDs and present the most recent insights into diagnosis and treatment.

**Epidemiology**

Non-EoE EGIDs are very rare conditions. A large population-based study in the United States of more than 3 million adults and children reported the prevalence of eosinophilic gastroenteritis and eosinophilic colitis to be respectively 1/20,000 and 1/50,000 (5). Eosinophilic esophagitis is respectively 10 and 25 times more common with a prevalence of around 1/2000 (4). Sensitivity analyses of these studies have shown that when a more restrictive case definition is used to exclude cases with possible confounding factors like secondary eosinophilia, the calculated prevalence remains the same for eosinophilic gastro-enteritis (EGE) but not for EoC (5,19). Nearly 25% of all patients originally considered as EoC were actually patients with inflammatory bowel disease. This reduced the estimated prevalence of EoC to around 1/70,000 (5). In eosinophilic esophagitis there is a known 3 to 2 male predominance (4). The opposite is true for EGE and EoC which is slightly more prevalent in females with an odds ratio of respectively 1.11 and 1.60 (5). Similar to eosinophilic esophagitis, the prevalence of non-EoE EGID in caucasians was higher than in African-Americans and Asians (2,4,5). In terms of age of the patients, the highest prevalence of EGE was found in children (<18 years of age) and decreases with age (5,19). Multiple studies have shown a peak in the age-based prevalence rates in the age group of 10-24 years old (5,19). Therefore, age of onset tends to be younger than EoE which peaks at 30-39 years (4). EoC seems to be following the same trend as it is relatively more common in adults but the differences in prevalence between age groups are less clear for EoC (5,19).

Recently a study by Talley et al. revealed that non-EoE EGIDs may be underdiagnosed as it showed that almost 50% of patients with chronic functional GI symptoms that underwent an endoscopic biopsy, met histologic criteria of EG and/or eosinophilic duodenitis (EoD) (20). In contrast, Hui et al. showed that only 3% of all patients presenting with lower GI symptoms meet histologic criteria for EoN (ileum) or EoC when a colonoscopy with biopsies was performed, followed by a gastroscopy when positive (21). Patients who met the criteria were significantly younger and were more likely to have diarrhea or abdominal pain as a presenting symptom (21).

Lastly, a recent retrospective study has shown that the frequency of diagnosis of non-EoE EGIDs has increased over the past decade (2). This raises the thought that these diseases might not be as rare as traditionally thought.

**Overlap between EGIDs**

The overlap in eosinophilic disease in the stomach and the small intestine is often referred to as ‘eosinophilic gastroenteritis’ (EGE) (9). This overlap in disease is seen very frequently to the extent that they are often described as a distinct diagnosis (2). The overlap in other segments of the gastrointestinal tract is less described (2). In a retrospective study of 376 patients, it was seen that 41% of subjects had multiple sites of eosinophilic inflammation even with EGE being considered as a single diagnosis (2). Overlap in disease was significantly more common in children than in adults (2). Of the patients with multisite involvement, 75% had esophageal involvement (2). It is unclear if these findings are representative of the population as other studies have found different rates of multisite inflammation, varying from 20-88% (22,23).

Another study with a large database of more than 2500 subjects reported that only 4.9% of patients had more than 1 disorder (19). A recent study with EoE patients has shown limited yield of gastric and duodenal biopsies in EoE patients, with less than 5% of the patients showing histologic features of EG or EoD (24).

**Pathophysiology**

In contrast to the reasonably well understood pathogenesis of EoE, the exact pathophysiology of non-EoE EGIDs is much less elucidated (25). The pathophysiology is thought to be multifactorial. It is a combination of a pure IgE-mediated allergy and a delayed cellular-mediated response (Fig. 1) (26). Like in EoE, an allergic component has been suggested as total IgE and food-specific IgE serum levels were shown to be elevated in EGE patients and 40-60% of EGE patients were found to have a history of atopic conditions (5,19,25-27). However, any sign of atopy is absent in some EGID patients suggesting there has to be another driving factor behind the eosinophilia. Like EoE, the other EGIDs are T helper type 2 (Th2) driven inflammatory diseases (28,29). Caldwell et al. examined the genome-wide transcript profile of EG patients and compared this with the transcriptome of control patients (28). One hundred transcripts were found to be altered in EG patients. Pathways key to the pathogenesis were identified (IL-13 driven Th2 immunity, IL-17, ErbB-, and Wnt-dependent pathways). Th2 cytokines (IL-4, IL-5, IL-13) and eosinophil-related chemokine eotaxin-3 (CCL26) were expressed significantly more in EG patient’s gastric tissue compared to the gastric tissue of control patients (28). IL-5 is the most selective cytokine for the proliferation of eosinophils and their subsequent release from the bone marrow (26). IL-4 and IL-13 regulate eosinophil accumulation by promoting adhesion to the endothelium. They ensure chemotaxis along with eotaxin-3 and chemoattractant receptors expressed on Th2 cells (28,29). IL-4 and IL-13 also help to activate mast cells and basophils but their exact role in EGIDs is unclear (29). Homing of eosinophils to the GI tract is ensured by integrins. Subsequently, sialic acid-binding immunoglobulin-type lectins (Siglecs) contribute to the binding of eosinophils to the mucosal surfaces (29).
When activated, eosinophils degranulate and release cytotoxic granule proteins (e.g. eosinophil cationic protein, eosinophil peroxidase, major basic protein and eosinophil derived neurotoxin) (11,26). These proteins result in a cytotoxic effect on epithelium, the creation of toxic pores into transmembrane channels which facilitates the entry of toxic molecules and the dysfunction of vagal muscarinic M2 receptors which increases smooth muscle cell reactivity (11,26).

**Clinical manifestations**

The presenting symptoms of non-EoE EGIDS are variable (2,6,10). Firstly, they depend on the site of maximal GI involvement but more importantly on the layer of the GI wall that is predominantly affected (Table 1) (6,10). Klein et al. were the first to make a classification of the three main patterns of clinical manifestations in non-EoE EGIDs: the mucosal, the muscular and serosal pattern (10). Mucosal disease is defined as the infiltration of eosinophils in the mucosa and/or evidence of mucosal edema on imaging without presence of ascites or GI obstruction (10,30). The mucosal variant most frequently presents with abdominal pain, vomiting, nausea, diarrhea, malabsorption and protein-losing enteropathy (6,10). Muscular layer disease presents with obstructive symptoms due to thickening and rigidity of the gut (6,10). Lastly, predominant serosal disease usually leads to eosinophilic ascites and peritonitis (6,10). The share of patients with each variant has shown a shift toward the mucosal variant the last decades (30). In a cohort of 40 patients in 1990, 58% of patients presented with mucosal disease, 30% with muscular disease and 12% with serosal disease (6). A more recent report from Chang et al. found that mucosal disease was even more predominant. The distribution in his 59 patient cohort was 88% mucosal, 5% muscular and 7% serosal disease (30). Chang et al. hypothesized that it is due to increased use of upper GI tract endoscopy in people presenting with GI symptoms and the evolution of the disease, starting in the mucosa and progressing deeper into the GI wall (30). Evidently, the diagnosis of isolated muscular and serosal disease is much more challenging than in case of mucosa involvement. In terms of the effect of the site of obstruction.
maximal GI involvement, multiple studies have reported similar symptoms for EG, EGE and EoC (2,5,19). For EG, nausea/vomiting (54%) and abdominal pain (48%) were the most common presenting symptoms. Patients with EGE have similar presenting symptoms but diarrhea is more frequent (32%). Lastly, EC was reported to more frequently present with abdominal pain (60%) and diarrhea (52%) but less with nausea and vomiting (38%) (2). Another study reported that patients with EG were more likely to have throat or chest pain and patients with EC were more likely to present with GI bleeding (19).

Multiple studies have reported the association of non-EoE EGIDS with allergy/atopy (2,5,19). This association was reported in 30-60% of the patients with food allergy, rhinitis and asthma being the most prevalent. But also the odds ratio of drug allergy, sinusitis, dermatitis, eczema and urticaria in non-EoE EGID patients to controls is high ranging from 3 to 5 (19).

Very few complications of non-EoE EGIDs have been reported and these reports are limited to single case reports and small case series (Table 1) (31-39).

**Diagnosis**

Currently there is no golden standard in the diagnosis of non-EoE EGIDs like in the diagnosis of EoE (40). It is a hard diagnosis to make as the presenting symptoms are nonspecific (2). Therefore symptoms are not reliable to differentiate between disorders and a high index of suspicion is key to avoid a diagnostic delay (2). Factors that should raise suspicion are refractory unexplained chronic GI symptoms, a history of allergy/atopy and a young age of onset (2,4,5). A wide variety of diagnostic approaches have been proposed but the one most widely used until this day is the approach proposed by Talley in 1990 (6,41). He proposed 3 criteria, i.e. gastrointestinal symptoms, histological presence of eosinophils in the GI wall or eosinophilia in the ascites fluid (serosal disease) and exclusion of other causes of peripheral or tissue

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**Figure 2.** — The endoscopic view of the colon in a patient diagnosed with eosinophilic colitis. Raised nodular lesions are seen on the surface of the colon wall (black arrows).

**Figure 3.** — Suggested diagnostic algorithm for non-esophageal eosinophilic gastrointestinal diseases.

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In most patients the appearance of the mucosa is normal. This underscores the importance of taking biopsies regardless of the endoscopic appearance (15,21,22,43). A retrospective study of 373 patients found that 62% of the subjects had a normal appearance of the mucosa. The most common abnormal endoscopic findings were erythema (24%), ulceration (8%), nodularity (8%), and mucosal friability (6%) (15). This study reported endoscopic abnormalities in the duodenum to be associated with a higher amount of eosinophil infiltration. This association was not found in the stomach and colon (15). The abnormalities were also found to be non-specific and rarely led to histological confirmation in another study (48) (Fig. 2).

A recent study by Hirano et al. (49) prospectively assessed the presence and severity of endoscopically identified gastric abnormalities in a cohort of patients with EG of which most were actively in medical or diet therapy. In this cohort, 92% of patients exhibited one or more abnormalities in the mucosa appearance which is notably higher than most other studies even though most patients were actively treated (15, 22, 43). This study used a new classification and grading system for mucosal abnormalities, EG Endoscopic Reference System (EG-REFS) which was developed by gastroenterologists with expertise in EGIDs, specifically for the endoscopic evaluation of EG. It includes features of erosion/ulceration, granularity, raised lesions, erythema, friability, fold thickness, and pyloric stenosis. (49) The EG-REFS shows great promise for the use in clinical studies as it allows standardization and can be used as a disease metric to complement symptom and histologic features. The EG-REFS showed a strong correlation with physician global assessment of endoscopic activity which confirms its validity. (49)

However, biopsies are still needed regardless of the endoscopic appearance as histologic presence of eosinophils is a criterion for diagnosis (6). Because of the patchy nature of the disease, multiple biopsies are required in each segment (15,46). There is however no consensus on the optimal number and location of biopsies needed for the diagnosis of non-EoE EGIDs (16). Recently, 6–8 biopsies per site was proposed as guidance (15). Moreover, the eosinophilic cut-offs for diagnosis is a controversial topic. The most commonly used cut-offs are ≥30 eosinophils/HPF in ≥5 HPF for EG, ≥30 eosinophils/HPF in ≥3 duodenal HPFs and ≥60 eosinophils/HPF in the colon (15,50). However, higher cut-offs have been suggested as a distinct transcriptome was only seen when the duodenal eosinophilia peak was ≥50/60/HPF in patients with duodenal eosinophilia (51). A consensus is currently still lacking.

In a recent study, Shoda et al. developed a tissue based diagnostic platform (EGDP18 score) for EG based on differentially expressed genes in gastric tissue (47). A score system was made using the changes in 18
significant and reproducible differentially expressed genes. The EGDP18 score was able to diagnose EG with a sensitivity 88-95% and specificity of 100%. Patients with intermediate tissue levels (1-4 HPFs with ≥30 eosinophils) can possibly be classified with the EGDP18 score system in the future. In the study cohort, 68% of patients with intermediate tissue levels were classified as active EG (47).

Imaging

Current information about imaging of EGIDs is scarce and limited to case reports (52-54). The diagnostic yield of abdominal imaging is low as it often shows non-specific features. The most common features include bowel wall thickening, layering of the bowel wall and diffuse mucosal fold thickening (52). There are two signs that have been reported in several case studies that can aid in the diagnosis (52,53,55). Firstly, the “araneid-limb-like” sign which is a spider leg appearance of contrast within the mucosal sinuses which results from mucosal thickening (53). Secondly, an “halo-sign” is the layering of the bowel wall due to submucosal edema (52). These signs are characteristic of inflammatory pathology and thus can help to differentiate EGIDs from neoplastic pathology such as lymphoma or carcinoma (52,53,55).

Differential diagnosis

When the first 2 criteria for the diagnosis of non-EoE EGID are fulfilled, i.e. having gastrointestinal symptoms and histological presence of eosinophils in the GI wall or eosinophilia in the ascites fluid (serosal disease), secondary intestinal eosinophilia has to be ruled out to obtain a definitive diagnosis (6). The main differential diagnosis to keep in mind are inflammatory bowel disease, eosinophilia secondary to the use of medication (NSAIDs, antibiotics, chemotherapy, choliclimes) and parasitosis (41,56). Other diseases with intestinal eosinophilia include celiac disease, food hypersensitivity and Helicobacter pylori gastritis. Lastly, systemic disorders like Churg-Strauss vasculitis, hypereosinophilic syndrome and malignancies (lymphoma or carcinoma) can also present with eosinophilic infiltration in the bowel (41,56).

The red outlined boxes are newly developed diagnostic techniques with a proven potential in experimental studies but are not readily available to use in daily practice yet. WBC, white blood cells; IgE, immunoglobulin E; IL, interleukin; CCL, C-C motif chemokine ligand; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin; UGIT, upper gastrointestinal tract; LGIT, lower gastrointestinal tract; EC, eosinophilic gastritis; EoD, eosinophilic duodenitis; ED, eosinophilic colitis; DD, differential diagnosis; HPF, high power field; EGDP, eosinophilic gastritis diagnostic panel; Non-EoE EGID, non-esophageal eosinophilic gastrointestinal disease; GI, gastrointestinal.

Natural history/prognosis

A prospective long-term follow-up study by Pineton de Chambrun et al. with 43 non-EoE EGID cases reported a spontaneous remission without any treatment in 40% of the patients (31). These patients also had a significantly lower risk of relapse than patients who needed treatment at diagnosis. Relapse was seen in 33% of all cases during the median 13.1 years follow-up. The percentage of patients with clinical relapse was higher (60%) in patients treated with corticosteroids as initial treatment. Also hypereosinophilia at diagnosis and predominant mucosal disease involving the duodenum or multiple localizations were found to be associated with a higher rate of relapse. There was no association found between history of allergy and relapse rate (31). There were 3 different disease patterns observed in the study, namely a single flare of disease without any relapse after (42%), recurring disease of at least 2 flares with remission in between (37%) and lastly continuous disease without any period of remission (21%) (31). The continuous group were almost solely patients with mucosal disease. The single flare and recurring group were predominantly represented by mucosal and subserosal disease. Most patients with muscular disease had a recurring disease course (31). These data suggest that in most patients no long-term treatment is needed. Altogether, the available literature has shown that the prognosis of non-EoE EGIDs is good, with no increased risk for malignancy (41).

Treatment

There is high variability in the treatment approach of non-EoE EGIDs between different centers (2). This is likely based on the absence of clear treatment guidelines due to a lack of high-level evidence. The management approach is therefore based on the experience of practitioners (2). The different therapeutics will be reviewed below. In general, the evidence for the individual treatments in non-EoE EGIDs is poor and treatment is still mainly based on experience and expert opinion.

Wait and see

As described above, the strategy of watchful waiting is legitimate as 40% of patients in the study by Pineton de Chambrun went into spontaneous remission (31). To our knowledge, there have been no other prospective follow-up studies confirming this finding. A small retrospective case series of 7 EC patients reported that EC is mild and self-limiting in most cases without a need for therapy (71%) (57). Moreover, based on clinical expertise and the observed natural history of non-EoE EGIDs, most patients do not need continuous therapy in contrast to EoE.
Corticosteroids

Corticosteroids (CS) have been a cornerstone in the management of non-EoE EGIDs for the past decades (2, 58). They have been shown to be effective with clinical response ranging from 80-100% in multiple case series but there have not been any randomized clinical trials (RCTs) to date. (8,30,58). Therefore CS-use remains off-label based on physician’s experience and the type, duration and dosage show great variability (8,17). Also, evidence on histologic remission is limited. Most centers use prednisolone as the first-choice corticosteroid for induction of remission of non-EoE EGIDs. This is likely due to the fact that the vast majority of studies treating EGE with CS have used prednisolone and reported rapid clinical improvement(7,30). Prednisolone is usually given at an initial dose of 30-40mg/d which usually induces remission within 2 weeks. Thereafter, most centers taper the dosage over a 6-8 week period (41,59). However, relapses occur and sometimes require maintenance dose of prednisolone for a longer time (8,58). Patients treated with CS as initial therapy have been shown to have a higher risk of clinical relapse which may be linked to the severity of disease at presentation necessitating steroids (31).

A case report by Hartranfit et al. reported successful treatment of olmesartan-induced enteropathy with “Triple Phase” Enteric-coated (EC) budesonide capsules (60). Budesonide ensures more local activity in the GI tract and less systemic effects because of the low bioavailability (21% in healthy controls). “Triple phase” stands for three capsules of EC budesonide capsules that need to be taken, each in a different manner. The first capsule has to be opened, the EC pellets inside crushed and swallowed with apple sauce to exert an effect in the stomach and proximal small intestine. The second capsule is opened and the EC pellets are swallowed as a whole. The enteric coating dissolves at pH >5.5 so that the timed release starts after passage of the upper small intestine to target the lower part of the small intestine and proximal colon. The third capsule is swallowed intact, with the outer gelatin capsule theorized to ensure release in the more distal colon. EC-budesonide with the normal intake is used for the treatment of Crohn’s disease involving the ileum or ascending colon with good effect (61). As systemic impact is limited in comparison to prednisolone due to the high first pass metabolism and therefore corticosteroid-related adverse effects are significantly less frequent (60,61). As the author of the case report suggests, triple phase EC budesonide can be used in treatment of EGIDs (60). The manner of intake should be adapted to which site in the GI tract is predominantly affected. In some areas budesonide immediate-release tablets are available as well for treatment of proximal inflammatory disorders (41,60). There have been multiple case reports and case series of non-EoE EGID patients successfully treated with budesonid (62-64). Some case reports even reported histological remission.(41,64,65).

A recent case series reported 100% clinical and histologic success in 8 children treated with the triphasic EC budesonide therapy. The administration regimens were modified for each patient to treat the endoscopy-determined target areas of EGID. (64) The usual initial dose is 9mg/day, this can be tapered to 6mg/d and even 3mg/day for use as maintenance therapy. The duration of therapy needs to be individualized, but in most patient therapy can be stopped after 3-6 months. Altogether, the similar efficacy but better safety profile of budesonide makes it the preferred CS for long term therapy of steroid dependent disease though high level evidence is needed.

Dietary therapy

Dietary therapy has been shown to be effective in small case series and case reports (66,67). However most studies do not objectively measure the change in symptoms and have no evidence of histologic remission (66). Most evidence gathered is with amino acid-based elemental diet therapy (EDT) which is a hypoallergenic artificial formula. A systematic review by Lucendo et al reported a clinical improvement of over 75% in non-EoE EGID patients. Histologic follow up was done for a small fraction of the patients of which 83% reached histologic remission (66). Recently, Gonsalves et al. performed the first prospective dietary trial in EG/EGE. The study showed histologic remission in 100% of the patients who completed the 6 week trial with EDT (68). The most commonly used dietary therapies are empiric elimination diets with 6-FED and 7-FED being the most common, which respectively includes the elimination of wheat, egg, seafood (shellfish, finfish), soy, cow’s milk, hen’s egg and the former along with red meat (17,66). Symptomatic improvement was reported in most cases but evidence on histologic evolution is scarce (66). Elimination of food based on allergy testing has not been proven effective and cannot be reliably used, similar to EoE where allergy testing can also not be used to guide dietary exclusion. At this point in time, there is no test able to identify the triggering foods that need to be eliminated. (29,66). Successfully determining the causative foods by serial reintroduction of foods after a period of an elimination diet has been reported in small case reports and case series. (67,69).

Proton pump inhibitors

Even though PPIs were the most commonly used medications for non-EoE EGIDs, literature on PPIs in non-EoE EGIDs is scarce (2). Most evidence on the potential effect of PPIs in EGIDs is for EoE in which PPIs are a cornerstone in disease management (41). PPIs have anti-inflammatory effects apart from the effect on acid secretion (70,71). PPIs were shown to inhibit eotaxin-3 expression (stimulated by IL-4) in esophageal cells of EoE patients by reducing STAT6- and RNA polymerase binding to the eotaxin-3 promoter (71). Moreover, in
functional dyspepsia, PPIs have also been shown to reduce duodenal eosinophilia thereby reducing symptoms (72). Multiple case reports/case series have reported PPIs to be effective in EG and EoD with significant clinical and histologic remission (2,69,73). High level evidence is lacking as the available studies are retrospective and have a small sample size with even lower numbers with histologic follow up (2).

**Leukotriene-Receptor Antagonists (LRA)**

Montelukast is a potent selective antagonist at the cysteinyl leukotriene D4 receptor (cysLT1) (74). CysLT1 plays a role in eosinophil recruitment while LTC4, LTD4 and LTE4 are released by eosinophils and mast cells in the inflammatory process (17). Montelukast is a selective inhibitor of cysteinyl leukotriene D4 (LTD4) with a usual dose of 5-10mg once daily. Montelukast has been reported effective as monotherapy but also in combination with other therapeutics (8,44,75,76). Most reports describe a single case with clinical remission. Only a few case reports show histologic remission (76). The likelihood of reporting bias is high as very few reports of failure to response have been reported (77). More randomized trials are needed to determine the benefits of LRA in the treatment of non-EoE EGIDs.

**Mast-cell stabilizers**

Oral sodium cromoglycate (SCG) prevents the release of histamine and leukotrienes among other mediators by blocking mast-cell degranulation. This ensures the inhibition of eosinophil chemotaxis (17,41). The dose varies among different reports but ranges from 100-300mg 3-4x/d and is usually given over a long period of time (41). A few older case reports show a significant efficacy with SCG monotherapy (78,79). Histologic remission was shown in one report after 4-5 months of therapy but others have reported minimal to no response (6,65,80). The last study dates from 2009 when Sheikh et al. reported 3 cases with only a partial response to SCG. In each of the cases, CS had to be associated (33).

**Antihistamines**

Ketotifen belongs to the second generation H1-antihistamines and is also known to stabilize mast cells (59). It is usually dosed at 1-2mg 2x/d (59). A case series by Melamed et al. reported successful treatment with Ketotifen monotherapy in 6 patients with EGE. All patients reported symptomatic improvement and histologic remission was demonstrated in all 4 patients in whom repeat endoscopy was performed (81). Bolukbas et al. reported a single case treated with monotherapy ketotifen with similar results (82). In contrast to this, another case has been reported where endoscopic and histologic abnormalities appeared to progress under ketotifen monotherapy (83). More studies are needed to determine the potential role.

**Immunomodulators**

Azathioprine (AZA) is a prodrug which converts to 6-Mercaptopurine (6MP). AZA and 6MP are myelosuppressive drugs that act by inhibiting purine synthesis (DNA/RNA synthesis) and proliferation of B and T lymphocytes (84). They have been shown to induce clinical and histological remission in EoE in a 3 patient case series (84). To our knowledge, there are no studies using 6MP in non-EoE EGID patients. Azathioprine has been shown to maintain remission after treatment with CS in a patient with EGE (77,85).

**Biological agents**

**Lirentelimab**

Lirentelimab (AK002) is an antibody directed against siglec-8. Siglecs contribute to the binding to the endothelial wall and are expressed by eosinophils, basophils and mast cells. AK002 depletes eosinophils but also inhibits mast-cell activation and thereby reduces the recruitment of other immune cells (29,86). Clinical activity has been reported in chronic urticaria and allergic conjunctivitis among other allergic diseases (86). A phase 2 trial with 65 EG and EoD patients has shown a treatment response (defined as a >30% reduction in symptom score and a >75% reduction in GI tissue eosinophil count) of 63%, significantly more than the placebo group (86). A follow-up phase 3 trial in EGE patients is enrolling at the moment as well as a phase 2 trial in EoE patients (87,88).

**Vedolizumab**

Vedolizumab is an antibody directed against α4β7 integrin located on lymphocytes, thereby inhibiting the binding of lymphocytes to endothelial cells. RCTs with vedolizumab in EGID patients are still lacking to date. In a case series of 5 patients with non-EoE EGIDs, only 2 of 5 patients had clinical and histological improvement and could wean off corticosteroids (89). In a retrospective cohort of 22 patients with EGE, 4 out of these 22 patients were steroid-refractory and treated with vedolizumab. Clinical and histological improvement was observed in 3 of these patients (90).

**Dupilumab**

Dupilumab is an antibody directed against the IL-4 receptor and thereby inhibits both the IL-4 and IL-13 pathway which are important in the pathogenesis of EGIDs (25, 29). A phase 2 randomized trial in EoE patients showed a significant effect of dupilumab on symptoms and histology (91). A phase 2 randomized controlled trial in EG and EGE patients is currently enrolling with an estimated completion date of 2024 (92).

**Omalizumab**

Omalizumab is an anti-IgE antibody. As EGIDs are hypothesized to be partly IgE driven, omalizumab was
expected to be an effective antibody in the treatment of EGIDs (29). In the first trial with 9 EGE patients, treatment with omalizumab resulted in a decrease in symptoms and peripheral eosinophil count but no histologic remission was seen (93). There have been 2 subsequent RCTs in EoE patients which have not shown convincing evidence on the effectiveness of omalizumab either (94,95).

Anti IL-5 antibodies

Mepolizumab, reslizumab and benralizumab are antibodies that target IL-5. All 3 antibodies have been approved for treatment of eosinophilic asthma (29). Mepolizumab and reslizumab have only been studied in EoE patients with mixed results (29). Mepolizumab was found to give a reduction in esophageal eosinophils but few patients reached full histological remission (<5 eosinophils/HPF) or a significant change in symptoms (96-98). Benralizumab has been studied in a randomized trial with 24 patients with hypereosinophilic syndrome. Seven of these patients had GI tissue eosinophilia which was completely depleted after benralizumab treatment and all patients reported improvement in GI symptoms (99). One RCT with benralizumab in EGE patients is finished but no results have been published yet (100).

Conclusion

Non-EoE EGIDs including eosinophilic gastritis, eosinophilic enteritis and eosinophilic colitis are rare conditions but may be underdiagnosed as studies found a high percentage of patients with chronic functional GI symptoms meeting the histologic criteria of non-EoE EGID and the frequency of diagnosis is increasing over time. The pathophysiology of non-EoE EGIDs is less elucidated but they is hypothesized to be a combination of IgE-mediated and T helper type 2 driven diseases. The diagnostic approach most widely used to date is meeting the 3 criteria proposed by Talley, i.e. symptoms, compatible histology and exclusion of alternative causes of eosinophilia. In the future, the recently created blood-based diagnostic platform may help to raise the index of suspicion. However, current diagnosis is still based on histological findings in biopsies. The recently developed tissue based diagnostic platform, using differentially expressed genes in the GI tissue might be implemented in the future for patients with eosinophilia around the cut-off value. Guidelines are lacking for the treatment of non-EoE EGIDs. Watchful waiting is known to be a valid treatment option as 40% patients go into spontaneous remission. Corticosteroids have been the cornerstone of the treatment of non-EoE EGIDs because of the high clinical response rate reported in most case series. Topical corticosteroids like budesonide are preferred over systemic steroids because of the systemic exposure being substantially lower while maintaining a similar efficacy. Other main treatments like dietary therapy, PPIs, LRAs, mast-cell stabilizers, antihistamines and immunomodulators have some successful case reports but conclusive evidence is lacking. Comparative trials and RCTs are needed to determine the potential role of these therapeutics in the management of non-EoE EGIDs. Lastly, novel biological agents with great potential have become available. Lirentelimab in particular has promising phase 2 data and a phase 3 trial is currently enrolling.

Conflict of interest

TV has served on the speaker bureau and has served as a consultant for Dr. Falk Pharma.

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References

15. PESEK RD, REED CC, COLLINS MH, MUIR AB, FULKERSON PC, MENARD-KATCHER C, et al. Association Between Endoscopic and


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