Eosinophilic gastrointestinal disorders: new perspectives and the emerging role of biological therapies

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Abstract
The advent of biological drugs has opened up new therapeutic possibilities in the field of eosinophilic gastro-intestinal diseases (EGIDs). EGIDs are chronic inflammatory diseases of the gastrointestinal tract unrelated to drugs or infections, and eosinophilic esophagitis (EoE) is the most frequent form. EGIDs are complex disorders, which pathogenesis is still partially unknown. The diagnosis of EGIDs relies on the combination of different data, such as clinical manifestations, laboratory tests, endoscopic, and histological data. The gold standard at present is the histological examination obtained from biopsies under endoscopic guidance, but the diagnostic criteria for each disorder are still not fully defined, and few clinical scores are validated, for all these reasons, conducting clinical trials on EGIDs is challenging. The dietary approach remains currently a first-line treatment, despite its efficacy being influenced by patients’ compliance. Exclusion diets, nevertheless, involve potential nutritional deficiencies. Two of the pivotal pharmacological therapies for the treatment of EGIDs are proton pump inhibitors (PPIs), especially for EoE, and systemic or topical steroids. Long-term corticosteroid therapies are, however, associated with even severe side effects, so steroid-sparing therapies are needed to achieve the same results, in the last years monoclonal antibodies have been studied. To date, dupilumab is the only approved biological drug for EoE therapy, but many others are currently being tested in clinical trials also for the other forms of EGIDs. This work presents a complete review of the role of biological drugs in EGIDs to date, systematically structured by pathology.

Keywords
Eosinophilic gastro-intestinal diseases, biological drugs, emerging therapies

Introduction
The advent of biological drugs has opened up new therapeutic possibilities in the field of eosinophilic gastro-intestinal diseases (EGIDs). The main goals of EGIDs therapy are the complete resolution of symptoms and inflammation, both histologically and endoscopically, and the prevention of tissue...
remodelling and possible side effects of long-term therapies [1]. In fact, the drugs most widely used to date for the treatment of EGIDs are oral and topical corticosteroids, such as budesonide or fluticasone [2].

Corticosteroids are effective in reducing tissue and peripheral eosinophilic inflammation and improving symptoms, but their discontinuation leads to a rapid flare-up of the symptoms. Long-term corticosteroid therapies are, however, associated with even more severe side effects, so steroid-sparing therapies are needed to achieve the same results [3].

The study of EGIDs immunopathogenesis is directly related to the identification of target molecules that can serve as therapeutic targets. The pathogenesis of EGIDs is multifactorial and arises from a complex interaction between genetic and environmental factors. In particular, the most current evidence shows a crucial role of type 2 inflammation and related cytokines [4]. EGIDs, and in particular eosinophilic esophagitis (EoE), are closely correlated with forms of atopy such as bronchial asthma, allergic rhinitis, atopic dermatitis, or food allergies. In fact, although everything points to a common mechanism between EGIDs and other forms of atopy, numerous differences in the cell populations involved have been highlighted, e.g., two different types of T helper 2 (Th2) subpopulations involved in immunoglobulin E (IgE)-mediated, and eosinophilic pathologies respectively [5]. The different responses to tested therapeutic approaches, such as exclusion diets, would also suggest pathogenetic differences in the various EGIDs [6].

The aim of this narrative review is to highlight the emerging role of biological therapies in the field of EGIDs, through a division by pathology of the drugs now available or still in ongoing studies.

Methods

From October 2022 to January 2023, clinically relevant studies were selected from PubMed research, using key terms “EGIDs”, “EoE”, “eosinophilic gastritis (EG)”, “eosinophilic gastroenteritis (EGE)”, “eosinophilic colitis (EC)”, “biological therapy” and/or “biologics”. Specifically, the focus was new biological therapies in EGIDs, among original articles, reviews, and case reports, or case series, in English. Information regarding ongoing clinical trials was obtained from clinicaltrials.gov.

Background: epidemiology, clinical manifestations and diagnosis

EGIDs are chronic inflammatory diseases of the gastrointestinal tract unrelated to drugs or infections. EoE is the most frequent form, with an estimated prevalence of 22.7 cases per 100,000 individuals (approximately 43.4 per 100,000 in the adult population, and 29.5 per 100,000 in the pediatric population) [7]. EoE is more frequent in men, unlike the other forms of EGIDs, i.e., EG (prevalence 6.3 per 100,000), EGE (8.4 per 100,000), and EC (3.3 per 100,000), where the female sex is more affected [8]. The symptoms related to EGIDs depend on the involved gastrointestinal tract and wall layer, from mucosa to serosa. The main symptoms of EoE are therefore dysphagia and food impaction, but patients may also report epigastralgia, regurgitation, or chest pain. Abdominal pain, vomiting, difficulty in gaining weight, and diarrhoea, on the other hand, are symptoms that can be correlated with other forms of EGIDs [9]. The non-specificity of symptoms often results in a diagnostic delay (6 years on average), with the consequent risk of disease progression and complications with esophageal fibrostenosis [10].

The diagnosis of EGIDs relies on the combination of different data, such as clinical manifestations, laboratory tests, endoscopic, and histological data. The gold standard at present is the histological examination obtained from biopsies under endoscopic guidance [2].

Unlike in EoE, in which it is common to find abnormalities (rings, whitish plaques, and longitudinal furrows) in EGE the endoscopic findings are non-specific and shared by other pathologies, and cannot be used as diagnostic criteria [11].

Biopsy sampling must be multiple and conducted in multiple areas, as the eosinophilic infiltrate may be patchy. Histological confirmation of EoE requires an eosinophilic infiltrate of at least 15 eosinophils/high-power field (eos/HPF) in at least 5 out of the recommended 6 biopsies as a minimum, in two different localizations, proximal, and distal. Histological confirmation of EGE is more complex, as eosinophils may
also be present in non-pathological conditions, and an eosinophilic infiltrate is present in other diseases [inflammatory bowel disease (IBD), coeliac disease, and parasitic infestation]. The density of the physiological eosinophilic infiltrate also varies depending on the anatomical area (up to 20 eos/HPF in the terminal ileum and cecum). Therefore, an eosinophilic infiltrate higher than the physiological one (> 25–30 eos/HPF) must be found [12].

It is also necessary to exclude secondary causes of eosinophilia, such as infections, drug allergies, hypereosinophilic syndrome (HES), chronic IBD, or other autoimmune diseases [11].

**Therapy and management**

Several therapeutic options have been suggested for EGIDs management: dietary modifications, steroids, proton pump inhibitors (PPIs), leukotriene inhibitors, mast-cell stabilizers, immunomodulators, and biological agents.

Currently, diet is considered a first-line treatment of EoE, while it demonstrated more effectiveness in pediatric population for EGE. The most common dietary approaches are elemental diet and food elimination diet for at least 6 weeks. Elemental diet implies all foods elimination and nutrition exclusively with elemental amino-acid formulas, while food elimination diet consists of the elimination of specific foods: empirically avoiding the six most triggering foods (wheat, soy/legumes, milk, egg, peanuts, and fish/seafood), with a top-down or a step-up approach, or allergy test-directed elimination [13, 14]. The dietary approach showed great efficacy also in the long term, its efficacy is influenced by compliance, and nonetheless, patients should be informed of potential nutritional deficiencies and the necessity to perform frequent endoscopies for histologic remission assessment [13, 15].

Corticosteroids still have an important role in pediatric and adult EGIDs management, but the appropriate therapy duration is still not defined. Prednisone is the first-choice corticosteroid for induction of remission of EGE, 30–40 mg/day for 6–8 weeks and then tapering and maintenance at a low dose or substitution with budesonide. Budesonide acts topically and is effective both in induction and maintenance of remission in EGE and it’s a first-line therapy in EoE, commonly provided through swallowing agents. In the last few years, orodispersible budesonide tablets have been approved for the induction and maintenance of EoE remission [15].

PPIs are now a first-line therapy for EoE in adults, rather than a diagnostic criterion, 20–40 mg in single or double doses for 8–12 weeks, followed by histologic response assessment, which can be seen in up to 50% of patients. PPIs efficacy in pediatric EoE is still not clear, due to the heterogeneity of dose and duration in the studies; comparison studies vs. diet and budesonide are lacking [16].

Leukotriene receptors antagonists such as montelukast, mast-cell stabilizers such as sodium cromoglycate or cromolyn, and antihistamines such as ketotifen are used as an alternative to steroids, but studies to date do not support their use as monotherapy [15].

In the last decade, monoclonal antibodies were proposed as a steroid-sparing therapeutic option. The next section provides an analysis of the role of biological therapies in different forms of EGIDs.

**Biological Therapy**

**EoE**

EoE is the form of EGIDs for which the largest number of clinical trials with biologics is available (Table 1). To date, in the US, food and drug administration (FDA) has cleared the use of a single biologic, dupilumab, for the treatment of EoE in individuals aged 12 years or older and weighing more than 40 kg. Dupilumab is an IgG4 monoclonal antibody directed against the alpha subunit of interleukin 4 (IL4) receptor, which simultaneously blocks the inflammatory cascade of both IL4 and IL13, two major cytokines involved in type 2 inflammation. It has already received approval for atopic dermatitis, moderate-severe asthma, and chronic polyloid rhinosinusitis [17]. A phase 3, multicentre, randomised, double-blind study to evaluate the efficacy, safety, and tolerability of dupilumab in EoE was recently published [18]. These data were preceded
by a phase 2 trial in adults with active EoE, where dupilumab at a dose of 300 mg every other week was shown to improve both symptoms and endoscopic appearance [19]. The phase 3 study included two 24-month treatment periods (part A and part B) that were conducted independently in separate groups of patients, who received a placebo or 300 mg dupilumab every 2 weeks or weekly. The primary efficacy endpoints were the proportion of patients who had a reduction in the level of eosinophils in the esophagus at week 24 [≤ 6 per high-power field (HPF)] and the change in the dysphagia symptom questionnaire (DSQ) score compared to baseline, also at week 24 [18].

Table 1. Randomized clinical trial (RCT) of monoclonal antibodies for the treatment of EoE

<table>
<thead>
<tr>
<th>Monoclonal</th>
<th>Target</th>
<th>Author</th>
<th>Design</th>
<th>Study population</th>
<th>Dose</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>Dellon et al. [18]</td>
<td>Placebo-controlled, phase 3 RCT</td>
<td>n 240 (adolescents and adults)</td>
<td>300 mg s.c. every week or every 2 weeks or placebo</td>
<td>At week 24 histologic remission (≤ 6 eosinophils per HPF) and the change from baseline in the DSQ score</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>Hirano et al. [19]</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>n 47 (adults)</td>
<td>300 mg or placebo weekly</td>
<td>At week 10 change from baseline in SDI, PRO score; histologic features of EoE (peak esophageal intraepithelial eosinophil count and EoE histologic scores)</td>
</tr>
<tr>
<td>Dectrekumab (QAX576)</td>
<td>IL-13</td>
<td>Rothenberg et al. [20]</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>n 23 (adults)</td>
<td>6 mg/kg monthly or placebo</td>
<td>At week 12 responder rate for a greater than 75% decrease in peak eosinophil counts</td>
</tr>
<tr>
<td>Cendakimab (RPC4046)</td>
<td>IL-13</td>
<td>Hirano et al. [21]</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>n 99 (adults)</td>
<td>180 mg, 360 mg, or placebo weekly</td>
<td>At week 16 change in mean esophageal eosinophil count in the 5 HPFs</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Strauman et al. [24]</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>n 11 (adults)</td>
<td>750 mg × 2 or placebo weekly, followed by 2 more infusions of 1,500 mg of drug or placebo in lack of histological response</td>
<td>Reduce peak esophageal eosinophilia to &lt; 5 eos/HPF as assessed by histology in adults with active EoE</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Assa’ad et al. [25]</td>
<td>Phase 2 RCT</td>
<td>n 59 (children)</td>
<td>3 infusions of 0.55, 2.5, or 10 mg/kg monthly</td>
<td>At week 12 proportion of patients with a peak esophageal intraepithelial eosinophil count of &lt; 5 per HPF; safety, tolerability, pharmacokinetics</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Spergel et al. [26]</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>n 227 (children and adolescents)</td>
<td>4 infusions of 1, 2, or 3 mg/kg monthly or placebo</td>
<td>At week 15 changes in peak esophageal eosinophil count and in the physician’s global assessment score</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>Clayton et al. [29]</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>n 30 (adolescents and adults)</td>
<td>0.016 mg/kg per IgE every 2–4 weeks</td>
<td>At week 12 decrease in esophageal eosinophil content</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL5Ra</td>
<td>NCT04543409</td>
<td>Placebo-controlled, phase 3 RCT</td>
<td>EoE</td>
<td>APFS s.c., 1 mL fill volume or placebo</td>
<td>Esophageal eosinophil count ≤ 6 eos/HPF; change from baseline on the DSQ</td>
</tr>
</tbody>
</table>

s.c.: subcutaneous; SDI: straumann dysphagia instrument; PRO: patient-reported outcome; APFS: single accessorized prefilled syringe

The DSQ is a questionnaire that measures swallowing difficulty associated with EoE with a total score ranging from 0 to 84; the higher the score, the worse the symptom control. In Part A, histological remission at week 24 was achieved in 25 out of 42 patients (60%) who received dupilumab every week and in 2 out of 39 patients (5%) on placebo with an average improvement of 22 points in the DSQ, compared to 10 points in placebo patients. In Part B, histological remission was achieved in 47 of 80 patients (59%) on dupilumab...
every week, in 49 of 81 patients (60%) on dupilumab every 2 weeks, and in 5 of 79 patients (6%) on placebo. The improvement in the DSQ score was only shown in the group receiving dupilumab every week (−24 points compared to −14 points on placebo), not in the group of patients on dupilumab every 2 weeks. The most frequent adverse effect during the trial was infusion site reactions, which had a similar incidence in all groups. One of the main limitations of the study is the short duration of the placebo-control period; in fact, a third part of the study extension to 52 weeks has been planned [18].

It has been shown that another effector cytokine in EoE pathogenesis is IL13, acting on mucosal barrier function and tissue remodelling, as well as promoting eosinophil recruiting [4].

Dectrekumab (QAX576) is an anti-IL13 monoclonal antibody. A double-blind, placebo-controlled study on 23 adults demonstrated a 60% reduction in mean eosinophil count at week 12, but no patient achieved histological remission. However, a trend, albeit not significant, of symptom improvement and a stabilizing effect at the gene level was reported, with reduced expression of some EoE-related genes, such as eotaxin-3 and peristatin. The development of this drug is currently blocked [20].

Another anti-IL13 monoclonal antibody is cendakimab (PRC4046), which blocks IL13 by preventing its binding to the α1 (IL13Ra1) and 2 (IL13Ra2) subunits. The safety and efficacy of cendakimab vs. placebo were demonstrated in a 16-week phase 2 randomised controlled trial: 50% of patients in both groups (360 mg subcutaneously per week vs. 180 mg subcutaneously per week) achieved a statistically significant reduction in mean eosinophil count (< 15 eos/HPF) compared to placebo. However, the same result was not achieved on symptoms, where only the 360 mg dosage showed a non-significant clinical improvement [21]. Data from the open-label extension of the trial, at 52 weeks, were recently published, which confirmed the efficacy of the drug from an endoscopic point of view by means of the EoE endoscopic reference score (EREFS), histological with the EoE histologic scoring system score (EoEHSS) and clinical with the EoE symptom activity index (EEsAI) score. These data indicate a long-term effect of the drug, although further data are needed to assess the drug's ability to induce long-term remission in patients with EoE [22].

One of the key cytokines for the maturation and activation of eosinophils is IL5, which has been used as a therapeutic target in bronchial asthma. Its role in EoE has also been demonstrated in biopsies of patients with active disease, in which IL5 was up-regulated; it has also been shown that IL5 concentration correlates with the severity of esophageal tissue eosinophilia [1].

Mepolizumab is an anti-IL5 monoclonal antibody already approved for the treatment of eosinophilic bronchial asthma, eosinophilic granulomatosis with polyangiitis, and HES [23]. Mepolizumab in EoE was studied in both adult and pediatric populations. The adult trial was a phase 2, randomised controlled trial, involving a limited number of patients (11), in which none of the patients achieved both histological remission and clinical and endoscopic improvement [24]. In the pediatric trial, on the other hand, 59 children were randomised: only 8.8% achieved histological remission (< 5 eos/HPF), and no change in symptoms was recorded during therapy [25]. A multicentre, randomised, double-blind, placebo-controlled trial in adults and adolescents with mepolizumab 300 mg or 100 mg per month with a primary endpoint of change in dysphagia assessed by the EEsAI (NCT03656380) is currently ongoing (Table 2).

Table 2. Ongoing trials with biological drugs for EGIDs

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>Target</th>
<th>Clinicaltrials.gov ID</th>
<th>Design</th>
<th>Indication</th>
<th>Dose</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>NCT03656380</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>EoE</td>
<td>300 mg s.c. monthly for 6 months or placebo</td>
<td>Mean change in dysphagia from baseline to 3 months post-treatment assessed by EEsAI</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL5Rα</td>
<td>NCT03473977</td>
<td>Placebo-controlled, phase 2/3 RCT</td>
<td>EGE</td>
<td>30 mg s.c. every 4 weeks or placebo</td>
<td>At week 12 % of patients in histological remission (&lt; 30 eos/HPF)</td>
</tr>
</tbody>
</table>

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<td>At week 12 % of patients in histological remission (&lt; 30 eos/HPF)</td>
</tr>
</tbody>
</table>
## Table 2. Ongoing trials with biological drugs for EGIDs (continued)

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>Target</th>
<th>Clinicaltrials.gov ID</th>
<th>Design</th>
<th>Indication</th>
<th>Dose</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>NCT03678545</td>
<td>Placebo-controlled, phase 2 RCT</td>
<td>EGE</td>
<td>600 mg s.c. initial dose and 300 mg s.c. subsequent doses every two weeks for 6 injections</td>
<td>At week 12 relative change from baseline of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body</td>
</tr>
<tr>
<td>Lirentelimab (AK002)</td>
<td>Siglec-8</td>
<td>NCT04322708</td>
<td>Placebo-controlled, phase 2/3 RCT</td>
<td>EoE</td>
<td>1 mg/kg, 3 mg/kg or placebo monthly for 6 doses</td>
<td>At week 24 proportion of patients achieving esophageal intraepithelial eosinophil count of ≤ 6 eos/HPF and mean absolute change DSQ score from baseline to week 23–24</td>
</tr>
<tr>
<td>Lirentelimab (AK002)</td>
<td>Siglec-8</td>
<td>NCT04322604</td>
<td>Placebo-controlled, phase 3 RCT</td>
<td>EGE</td>
<td>1 mg/kg followed by 5 monthly doses of 3 mg/kg or placebo</td>
<td>At week 24 proportion of patients achieving eosinophil count ≤ 4 cells per HPF in 5 gastric HPF and/or eosinophil count ≤ 15 cells per HPF in 3 duodenal HPF; mean absolute change in 6 symptoms total symptom as measured by the PRO questionnaire</td>
</tr>
</tbody>
</table>

Siglec-8: sialic acid-binding immunoglobulin-like lectin 8

Reslizumab is another anti-IL5 monoclonal antibody, which is exclusively administered intravenously. This molecule was studied in a population of 227 children in phase 2, a randomised, controlled trial in which only a reduction of the eosinophilic infiltrate was achieved, but not disease remission [26]. A report was subsequently published on the follow-up data of 12 children who continued therapy for 9 years for compassionate use. Despite the limitations of these data (open-label study and a small number of patients), a reduction in eosinophil count to < 5 eos/HPF and clinical improvement occurred in 92% of the children, and the safety of the drug was confirmed [27].

Benralizumab is an anti-IL5Rα monoclonal antibody approved for severe eosinophilic asthma. Its mechanism of action differs from that of other anti-IL5 drugs, partly because it is able to activate the low-affinity immunoglobulin gamma Fc region receptor III-A (FcγRIIIa) receptor on natural killer cells resulting in the rapid depletion of eosinophils. A multicentric phase 3 study on benralizumab (NCT04543409) in adolescents and adults has recently been interrupted as the drug didn’t reach the end-point of clinical improvement, defined as a change from baseline on the DSQ (Table 1).

Although EoE often correlates with forms of atopy, the pathogenetic mechanism is not yet fully elucidated. In both EoE and food allergy, Th2 response drives the inflammation, through cytokines like IL-4, IL-13, and IL-5 [28]. The role of IgE is less clear. Actually, the monoclonal anti-IgE antibody, omalizumab, failed to induce a clinical and histological response in patients with EoE. In the same trial, an IgG4-type response, both tissue and peripheral, to common food allergens were also demonstrated, but not IgE involvement [29].

**EG and EGE**

Unlike EoE, the other forms of eosinophilic disorders of the gastro-intestinal tract are rare and more difficult to diagnose. Firstly because the symptoms are non-specific (abdominal pain, vomiting, and/or diarrhoea), then because eosinophils are resident cells of the distal gastrointestinal tract. It is often a diagnosis of exclusion. Furthermore, there are no standardized clinical and/or endoscopic scores [9].

These aspects are the main difficulties in evaluating the efficacy of monoclonal and non-monoclonal therapies through clinical trials; most of the available data is derived from case reports or single centers experiences (Table 3). As with EoE, the association with other forms of atopy is strong for EGE. This is another reason for the suspicion that the pathogenesis of EGE is also associated with Th2-type mechanisms. This is why the target molecules are often the same as those already studied in EoE [30].
Concerning the IL4/IL13 axis, a phase 2 clinical trial (NCT03678545), randomised, double-blind, placebo vs. controls, in adolescents and adults, in which dupilumab 300 mg is administered every other week after the 600 mg loading dose for 12 weeks, followed by an open-label phase for a total of 24 weeks, is still ongoing (Table 2). The primary end-point was the remission of eosinophilic inflammation in the gastrointestinal tract.

An up-regulation of IL5 was also seen in EG/EGE patients. The first data on a potential role of anti-IL5 drugs came from a study on the use of benralizumab in patients with platelet-derived growth factor receptor A (PDGFRA)-negative HES. Seven patients fulfilled the diagnostic criteria for EGID. The clinical, endoscopic, and histological responses were seen after 3 and 6 months of benralizumab therapy [31]. The study then continued with an open-label phase for a further 24 weeks. The clinical benefit of the drug was maintained, although heterogeneously among patients. A possible explanation could be a latency between eosinophil depletion and normalisation of the mucosa. In fact, in this study, the persistence of symptoms and mucosal remodeling (e.g., basal zone hyperplasia or spongiosis), despite eosinophil depletion, was shown for the first time [32]. A randomised, double-blind, placebo-controlled study on benralizumab (NCT03473977) was recently concluded (Table 2). Although the results have not yet been officially published, available data indicate histological remission in 77% of patients vs. 8% of placebo patients, with no severe side effects. Currently, The HUDSON GI Study (NCT05251909), a 24-week, double-blind, placebo-controlled phase 3 trial, exclusively targeting patients over 12 years with EGE or duodenitis, is ongoing (Table 2).

No clinical studies are available for the other anti-IL5 drugs (mepolizumab and reslizumab), only case reports or case series [33, 34].

EG and EGE share many pathogenetic aspects with EoE. Precisely by hypothesizing the role of IgE in disease activity, the effect of anti-IgE omalizumab was studied in an open-label clinical trial on 9 patients with EG. The results of this study were encouraging in the sense of improvement of peripheral eosinophilia and gastrointestinal symptoms, and a trend, albeit not significant, towards a reduction of tissue eosinophils in the gastric antrum and duodenum. However, results were heterogeneous among patients, suggesting the need for careful selection of patients who might benefit from anti-IgE therapy [35]. As mentioned in the previous section, studies on omalizumab in EoE did not yield the expected results [29].

A therapeutic target recently featured in trials in allergic diseases is Siglec-8, an inhibitory receptor present on the membrane of mature eosinophils and mast cells, which is also involved in their apoptosis [36].

AK002, or lirentelimab, is an anti-Siglec8 monoclonal antibody capable of inducing eosinophil depletion via a cytotoxic mechanism mediated by natural killer cells; it is also capable of inhibiting mast cell activation, degranulation, and secretion of inflammatory mediators. Currently, lirentelimab is being studied...
in chronic urticaria (NCT03436797), severe allergic keratoconjunctivitis (NCT03379311), and nasal polyposis (NCT02734849). The first data on the potential efficacy of this therapeutic target come from mouse models. The ENIGMA trial (NCT04322604) is a multicentre, randomised, placebo-controlled phase 2 study to test the efficacy and safety of lirentelimab in adults with EGE and/or duodenitis. The primary endpoint was the percentage change in the mean peak eosinophilic count in the gastric or duodenal mucosa from the start to the end of treatment, 2 weeks after the last dose of the drug. Secondary endpoints were the clinical response to therapy as a > 30% reduction in the symptom score, calculated from a questionnaire completed by the patients, and a > 75% reduction in the gastrointestinal eosinophilic count. A low (0.3 and 1 mg/kg) and a high (0.3, 1, and 3 mg/kg) dosage were tested. The results showed that the drug, in both dosages, was effective in reducing gastric and duodenal tissue eosinophilia counts and symptoms after one week. An improvement in dysphagia was also seen in patients with concomitant EoE. Lirentelimab also proved to be safe, with the most frequent side effect being mild-to-moderate reactions at the infusion site, especially after the first administration of the drug. Reactions became less frequent with continued therapy, as demonstrated in the open-label extension study, which also confirmed symptomatic improvement and histological eosinophil depletion [37]. A phase 3 trial (ENIGMA 2–NCT04322604) in patients with EGE and duodenitis, and a multicentre phase 2/3 trial (KRYPTOS–NCT04322708) in adults and adolescents with EoE, are currently ongoing (Table 2).

As previously cited, eosinophils are present in varying proportions in other sites of the gastrointestinal canal, except for the esophagus, and may also increase in other pathologies than EGIDs, as occurs for example in IBD. One of the mechanisms of the eosinophils homing is related to the expression of α4β7 integrin, also present on T lymphocytes and natural killer cells, which binds to its receptor mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), an endothelial adhesion molecule specific to the gastrointestinal tract. In particular, the β7 subunit is specifically present in eosinophils [1]. Integrins are already a therapeutic target in some inflammatory diseases, such as IBD. Vedolizumab, a monoclonal antibody that specifically blocks α4β7 integrins has an important selective anti-inflammatory action on the gastrointestinal tract. No clinical trial is currently ongoing, but other reports are available. In particular, a retrospective study of 5 patients in whom vedolizumab was used off-label after the failure of all available therapies, including infliximab and omalizumab. Two out of 5 showed a clinical and histological response, resulting in a reduction of the systemic steroid. Another patient also showed clinical improvement but refused a second endoscopic evaluation [38]. A second case series of refractory and steroid-dependent patients showed a response to vedolizumab in 3 out of 4 subjects. Obviously, these experiences have the limitations of the small number of patients and the retrospective nature of the analysis, indicating the need for dedicated clinical trials of this drug [39].

EC

EC is considered the rarest form of EGIDs. Although due to the difficulty in best defining the disease, the actual frequency in the general population may be underestimated. In fact, several pathological conditions can be associated with the presence of eosinophils in the colon, such as IBD, where the correlation between IBD and eosinophilic infiltration is not equally clear. Moreover, the differential diagnosis is complicated by the physiological presence of eosinophils in the colon, where they perform the homeostatic activity and respond to different stimuli as well as injury, allergens, or pathogens. Primitive EC remains an exclusion diagnosis: various infectious diseases or drugs correlate to colonic eosinophilia [40]. EC diagnosis is challenging and no formal guidelines exist to date. In particular, a reference cut-off of eosinophils in the colonic mucosa is still lacking. Collins proposed an extreme numerical increase (> 100 per HPF) of eosinophil as a diagnostic of EC. Moreover, differentiating the reference eosinophilic value for different colon sites may help to increase the diagnostic accuracy [41].

The pathogenesis of EC itself is not entirely clear. A recent study evaluated the gene expression (transcriptome) of patients with EC by genetic analysis (RNA sequencing) on colic mucosa, comparing the results with Crohn’s disease patients and healthy controls. Data were compared to those obtained with previous genetic evaluations in patients with EoE and EG. It was shown how the EG transcriptome is
associated with the level of eosinophils and disease activity; it is also different from other EGIDs transcriptome, suggesting that EC might differ from a pathogenetic point of view, being the role of Th2 inflammation less predominant [42].

However, data from Jensen et al showed that 41.8% of patients affected by EC suffered atopic comorbidities. This condition was more common in pediatric population than in adults (52% vs. 35.9%) [43].

There are currently no approved therapies for EC. Available data are based on case series and case reports. The first therapeutic approach is exclusion diets, which are more effective in childhood than in adulthood. In the event of failure or impracticability of the dietary approach, systemic oral corticosteroids are used.

However, no clinical trials are available and there are no ongoing studies on biological drugs in EC. The only available data concern an antibody directed against C-C chemokine receptor type 3 (CCR3), expressed on eosinophils, in mouse models, with reduction of eosinophilic inflammation and diarrhoea [44]. Despite the need for an alternative, steroid-sparing therapies in EC are still not available.

**Conclusions**

In recent years, eosinophils and related pathologies have been a subject of increasing interest, which has led to a greater knowledge of these particular cells, involved in both homeostatic processes and pathogenic mechanisms in many organs.

EGIDs represent a challenge in terms of both diagnostic and therapeutic possibilities.

The field of EGIDs counts many unmet needs, starting with not having diagnostic criteria defined, and reliable disease scores to base clinical trials on, to assess the efficacy of new drugs.

Currently, the only approved biological drug for EoE is dupilumab, as it reached both clinical and histological endpoints in clinical trials. For non-EoE EGIDs, no biologics have been approved yet. Further studies are needed to assess the ability of other biological drugs to achieve clinical response and disease control.

Lastly, having an alternative to the elimination diet and corticosteroids available has opened up other discussion points. First of all, the timing of biological therapy and the issue of costs. Therefore, a multidisciplinary approach to the patient is necessary to select the best therapy available, according to the patient’s immunophenotypic characteristics and comorbidities.

**Abbreviations**

DSQ: dysphagia symptom questionnaire
EC: eosinophilic colitis
EEsAI: eosinophilic esophagitis symptom activity index
EG: eosinophilic gastritis
EGE: eosinophilic gastroenteritis
EGIDs: eosinophilic gastro-intestinal diseases
EoE: eosinophilic esophagitis
eos/HPF: eosinophils/high-power field
HES: hypereosinophilic syndrome
HPF: high-power field
IBD: inflammatory bowel disease
Ig: immunoglobulin
IL: interleukin
PPIs: proton pump inhibitors
PRO: patient-reported outcome
RCT: randomized clinical trial
Siglec-8: sialic acid-binding immunoglobulin-like lectin 8
Th2: T helper 2

Declarations

Author contributions
FL: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. AC: Writing—review & editing, Writing—original draft, Supervision. All authors read and approved the submitted version, and have reviewed, discussed, and agreed to their individual contributions ahead of this time.

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