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Treatment Trends for Eosinophilic Oesophagitis and the Other Eosinophilic Gastrointestinal Diseases: Systematic Review of Clinical Trials

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ABSTRACT

Background: Eosinophilic gastrointestinal diseases (EGIDs) are chronic inflammatory disorders characterized by persistent gut eosinophilia and symptoms, which include eosinophilic oesophagitis (EoE), gastritis (EoG), duodenitis (EoD), gastroenteritis (EoGE), and colitis (EoC). Currently available treatments have suboptimal efficacy, and several clinical trials are investigating alternative treatments for EGIDs.

Aim: We performed a systematic review of clinical trials to provide a snapshot of where research on EGIDs is heading.

Methods: We searched clinicaltrials.gov up to 5th December 2021 to identify studies investigating EGIDs treatment. We extracted trial number, commencement date, region, therapeutic intervention, method of administration, primary study outcome(s), phase, recruitment and enrolment status, population, and study design.

Results: For EoE, 66 studies were eligible: 26 testing topical corticosteroids (39.4%), 17 (25.8%) monoclonal antibodies, eight (12.1%) dietary measures, five (7.6%) immunomodulators, one (1.5%) oesophageal dilation, and nine (13.6%) other medical treatment strategies. With regard to EoG, EoD, and EoGE, 10 studies were testing monoclonal antibodies (71.5%), one immunomodulators (7.1%), one dietary measures (7.1%), and two other treatments (14.3%). There were no registered trials for EoC. Ongoing studies on corticosteroids are focused on novel delivery systems, including viscous suspensions, orally disintegrating tablets, or capsules. An increase in research on monoclonal antibodies was seen from 2018, with interleukin (IL)-4 receptor-α, IL-5 receptor-α, IL-5, IL-13, IL-15, and Siglec-8 as the targets.

Conclusion: Several clinical trials are investigating possible treatments for EoE, EoG, EoD, and EoGE, predominantly using corticosteroids or monoclonal antibodies. The therapeutic landscape for EGIDs will likely be transformed imminently.

INTRODUCTION

Eosinophils are pleiotropic leukocytes that exert a homeostatic role in the gastrointestinal tract, providing immune protection against parasites and bacteria[1]. Although a certain degree of gut eosinophilia is physiological in gastrointestinal locations below the oesophagus[2], an excessive number of activated eosinophils can cause tissue damage and promote disease pathology[3,4]. In this regard, elevated tissue eosinophilia in combination with persistent gastrointestinal symptoms constitutes a group of chronic inflammatory disorders known as primary eosinophilic gastrointestinal diseases (EGIDs)[4,5]. Primary EGIDs are classified based on the region of the eosinophilic infiltrate, which can occur in any location from the oesophagus to the colon, and include eosinophilic oesophagitis (EoE), gastritis (EoG), duodenitis (EoD), gastroenteritis (EoGE), and colitis (EoC).

EoE is the most frequent and best characterized EGID[6], with available international guidelines[5,7,8]. Incidence rates are currently close to 20 per 100,000 people per year, and prevalence is more than 1 in 1000 people in Western Countries[6,9]. Prevalence estimates of 20 diagnoses every 100,000 oesophago-gastroduodenoscopies (EGDs) have been reported in Asia[10]. The epidemiology of EoE is still evolving, as incidence and prevalence are rising at a rate that outpaces increased recognition[11]. Additionally, EoE is already associated with annual healthcare-related costs that greatly exceed the cost of care of inflammatory bowel diseases and celiac disease [12,13]. EoE characteristically presents with symptoms of oesophageal dysfunction (i.e., dysphagia, chest pain, and food bolus impaction), although vague symptoms are frequent in childhood[6]. Recommended treatment strategies for EoE include proton pump inhibitors (PPIs), topical corticosteroids, dietary measures, or oesophageal dilation, when strictures are present[5,7,8]. However, most therapeutic approaches are recommended based on low quality evidence[5,7,8], have suboptimal efficacy[6], are used off-label or, when approved, are not widely commercially available yet.

EGIDs affecting the gastrointestinal tract below the oesophagus are far less well characterized. Although histological diagnostic thresholds for each condition have been proposed (**Supplementary Table 1**), standardized clinical guidelines on these diseases are still lacking.

A recent meta-analysis found that the prevalence of non-EoE EGIDs could be as high as 2.4% among patients experiencing gastrointestinal symptoms[14]. Epidemiology studies conducted using electronic health records of individuals from the United States (US) found that the overall prevalence of EoGE and EoC were 5.1 per 100,000 and 2.1 per 100,000 individuals, respectively. The prevalence of non-EoE EGIDs was higher in Caucasians than Asians or African-Americans, while EoGE was more prevalent in childhood, and EoC in adulthood[15]. In another study of more than 75 million individuals, the standardized estimated prevalence of EoG, EoGE, and EoC were 6.3 per 100,000, 8.4 per 100,000, and 3.3 per 100.000 individuals, respectively[16]. Lastly, data from the ENIGMA trial, showed that more than 50% of subjects with moderate-to-severe gastrointestinal symptoms could have EoG or EoD, when an extended histological sampling protocol was applied[17]. Clinically, EGIDs other than EoE are often characterized by persistent and non-specific gastrointestinal symptoms, including abdominal pain, nausea, vomiting, failure to thrive, diarrhea, and weight loss[6,15]. In some instances, EGIDs may commence with more severe presentations including ascites, volvulus, intussusception, perforation, or obstruction[4]. Accepted treatment strategies for EGIDs other than EoE include dietary measures and systemic corticosteroids, although most evidence is weak and comes from small uncontrolled studies[4].

The lack of approved effective therapeutic strategies represents a substantial unmet clinical need in EGIDs. However, although accepted management options are limited, several clinical trials are currently focusing on the investigation of novel treatments, including monoclonal antibodies, immunomodulators, topically delivered corticosteroids, dietary measures, and others. On this basis, it is predictable that novel treatments for EGIDs will be available in the coming years. Therefore, we

performed a systematic review of clinical trials registered on clinicaltrials.gov to provide a snapshot of where research on EGIDs is heading, as well as to anticipate future treatments that will be available.

METHODS

Search Strategy

We searched clinicaltrials.gov (https://clinicaltrials.gov), from inception to 5th December 2021 to identify interventional studies investigating treatments for EGIDs, including EoE, EoG, EoD, EoGE, and EoC. We conducted a literature search using relevant terms (a detailed search strategy is reported in the **Supplementary Materials**). There were no language restrictions, as all studies registered on clinicaltrials.gov are published in English. For each retrieved study, the title, study description, and brief summary were screened for potential suitability. All studies that appeared relevant to the aim of this systematic review were analysed in more detail subsequently.

Study Selection

The eligibility assessment was performed independently by two investigators (PV, MG) using pre-designed eligibility forms. We included interventional studies investigating both medical and non-medical treatments for the management of EGIDs. We excluded studies focusing exclusively on epidemiology, pathogenesis, or treatment monitoring or follow-up strategies, observational studies, and studies that were withdrawn or whose status was unknown. Disagreements were resolved by consensus opinion among reviewers, and the degree of agreement was measured with a kappa statistic. Ethical approval was not required for this evidence synthesis exercise.

Data Extraction and Analysis

Data were extracted independently by two authors (PV, MG) onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA). The following data were extracted for each study: number of clinical trial (NCT) and start date; geographical region; intervention(s); method of administration; primary study outcome(s); phase of the study; state of recruitment (ongoing/completed/not yet recruiting/terminated); patient population (age range and

sex); design of the study (single-/multi-centre), enrolment (target/actual). Microsoft Excel spreadsheets were used for the statistical analysis of the dataset and data plotting.

RESULTS

Literature Search

The systematic literature review retrieved 832 study records. After duplicate removal, 177 were retrieved for evaluation. Of these, 81 studies were excluded, and 96 were included for full assessment. A total of 17 studies did not meet predefined eligibility criteria and were excluded. Thus, 79 studies were included in the qualitative synthesis. For EoE, 66 studies were eligible for inclusion, 26 on topical corticosteroids (39.4%), 17 (25.8%) on monoclonal antibodies, eight (12.1%) on dietary measures, five (7.6%) on immunomodulators, one (1.5%) on oesophageal dilation, and nine (13.6%) on other medical treatment strategies. With regard to EGIDs, 14 studies were eligible for inclusion (with one of them including treatment of both EoE and EoGE), 10 on monoclonal antibodies (71.5%), one on immunomodulators (7.1%), one on dietary measures (7.1%), and two on other treatments (14.3%). There were no registered trials on EoC. Agreement between investigators for assessment of study eligibility was excellent (kappa statistic = 0.87). **Figure 1** shows the literature research process.

Study Characteristics and Population

Table 1 and **Table 2** report the characteristics of all included studies. **Figure 2** shows the geographical distribution of registered clinical trials on EGIDs.

With regard to EoE, 34 studies (51.5%) had a monocentric design, 30 (45.5%) were multicentre, and in two cases (3.0%) the design was not available. Most of the studies (53/66, 80.3%) were located in a single geographical region, while five were located in three (7.6%) or two (7.6%) geographical regions, one study (1.5%) was located in four geographical regions. The location was not available for two studies (3.0%). All studies included both sexes, 12 studies (18.2%) included a population of children, adults, and older adults, 17 (25.8%) included children and adults, 26 (39.4%) adults and older adults, seven (10.6%) children only, and four (6.0%) adults only.

With regard to non-EoE EGIDs, eight studies (57.1%) had a monocentric design and six (42.9%) were multicentre. All studies were located in America and included both sexes. Two studies

included a population of children, adults, and older adults, one included children and adults, nine adults and older adults, and two children only.

Recruitment status and study phases

For EoE, at the time of the literature research, most of the studies had completed recruitment (39/66, 59.1%), a considerable number were actively recruiting (15/66, 22.7%), five (7.6%) had terminated recruitment because of recruitment problems, insufficient funds, or because the principal investigator had left, and seven were in other recruitment phases **(Table 1)**. Of the included studies, the majority were in phase 2 (27/66, 40.9%) and a substantial proportion were in phase 3 (14/66, 21.2%). Twenty-five studies were in other study phases **(Table 1)**.

As for EGIDS, half of clinical trials had completed recruitment (7/14, 50%), two were actively recruiting (14.3%), and five were in other recruitment phases **(Table 2)**. The majority of trials on non-EoE EGIDS were in phase 2 (5/14, 35.7%) or phase 3 (3/14, 21.4%) **(Table 2).**

Interventions, comparators, and method of administration

Figure 3 reports the number of clinical trials for each therapeutic intervention for EoE. **Table 1** and **Table 2** report the details of interventions, comparators, and method of administration used in each trial.

Of the 17 studies on monoclonal antibodies for the treatment of EoE, five studies investigated an anti-interleukin (IL)-5 (mepolizumab or reslizumab), four an anti-IL-13 (dectrekumab or cendakimab), three an anti-IL-4 receptor-α (dupilumab), and one an anti-IL5 receptor-α (benralizumab), anti-IL15 (CALY-002), anti-IgE (omalizumab), anti-Siglec-8 (lirentelimab), or anti-TNF-α (infliximab). Among these, the majority compared monoclonal antibodies with placebo (13/17, 76.5%) **(Table 1).** Among monoclonal antibodies, nine were administered via intravenous infusion, and eight via subcutaneous injection.

There were five trials on immunomodulators, investigating etrasimod, sirolimus, BT-11, IRL201104, or OC000459. In four trials the comparator was placebo, and there was no comparator in one study. Four treatments were administered orally, and one intravenously.

Twenty-six clinical trials investigated EoE treatment with topical corticosteroids (one of these investigated two different corticosteroids). The majority used fluticasone (11/26, 42.3%) or budesonide (11/26, 42.3%), and compared active treatment with placebo (20/26, 76.9%) **(Table 1)**. In all 26 trials the treatment was administered orally, and in three studies there were two drug chemical formulations. Topical corticosteroids were administered via either orally disintegrating a tablet (n=6), a viscous suspension (n=10), a capsule (n=1), a tablet (n=1), inhaled or swallowed (n=9). In two cases the method of administration was reported as oral, without further details.

Eight trials investigated dietary measures for the treatment of EoE. Most trials were on elimination diets and one on oral food desensitization. Comparators used in dietary measures trials were variegated and are reported in **Table 1**.

Of the nine studies investigating other medical treatments for EoE, two used montelukast, two losartan potassium, one omeprazole, one famotidine plus loratadine, one sucralfate, one bethanechol (a muscarinic agonist), and one cromolyn sodium. Of these, four studies compared active treatment with placebo, while five did not use a comparator arm.

Finally, one study investigated the use of a combination of oesophageal dilation, dexlansoprazole, and fluticasone compared with oral medical treatment alone **(Table 1)**.

Figure 4 reports the number of clinical trials for each therapeutic intervention for non-EoE EGIDs. Five were on anti-Siglec-8 (lirentelimab; EoG n=4, EoD n=4, EoGE n=3), two studies were on anti-IL5 for EoGE (mepolizumab, SCH55700), and one was on either anti-IL-5 receptor-α, anti-IL4 receptor-α, or anti-IgE (benralizumab for EoG or EoGE, dupilumab for EoG or EoGE, omalizumab for EoGE). Among these trials, in five cases the comparator was placebo, while there was no comparator in five studies. Seven monoclonal antibodies were administered intravenously, and three via subcutaneous injection.

One trial investigated an immunomodulator (sirolimus) administered orally in the context of EoGE without a comparator treatment. One trial investigated oral montelukast for EoGE with no comparator, and one study investigated biofeedback-assisted relaxation training in combination with standard medical treatment compared with standard medical treatment alone for the treatment of EoD. Finally, one study investigated an elemental diet for EoGE with no comparator arm.

Primary study outcomes

As regard primary outcomes, 44 clinical trials on EoE (66.7%) investigated histologic response, 19 (28.8%) clinical response, and 11 (16.7%) evaluated the incidence of adverse events, safety, and tolerability. Other single studies investigated changes in high-resolution impedance manometry, the sensitivity of atopy patch-test for guiding elemental diet, the rate of treatment failure or relapse during treatment, changes in physician's global assessment, the presence of anti-drug antibodies, or the volume of distribution of the investigational drug.

In trials conducted in non-EoE EGIDs, the primary outcome was histologic response in nine studies (64.3%), clinical response in six studies (42.8%), safety, tolerability, or toxicity in six studies (42.8%), reduction of peripheral eosinophilia in two studies (14.3%), and feasibility of biofeedback-assisted relaxation training, eosinophil activation, mast cell density, serum eosinophils, and eosinophil cationic protein in one study (7.1%).

Temporal trends

Figure 5 shows the temporal trend of interventional studies on the treatment of EoE. The first registered clinical trial on EoE commenced in 2002 and investigated the use of topical corticosteroids. Twenty-five more studies focusing on corticosteroid treatment for EoE were commenced in the following years, with a relevant increase after 2019, making topical corticosteroids the most investigated drugs in clinical trials for EoE to date. Monoclonal antibodies currently represent the second most studied treatment in clinical trials for EoE. The first trials investigating a monoclonal

antibody for the treatment of EoE started in 2005, and a gradual increase was seen afterwards. However, a sharp increase in studies on monoclonal antibodies for EoE was recorded subsequently, with six studies commencing in the past 2 years. With regard to immunomodulators for EoE, although only two studies had started in the period 2010-2020, two more studies were commenced in 2021 and one is due to start in 2022. The first registered clinical trial for the dietary treatment of EoE was commenced in 2012. Although an initial increase was observed subsequently, with five more studies started in the following four years, the two most recent studies on dietary regimens for EoE date back to 2018. From 2007 to 2020, 10 clinical trials investigating other treatments for EoE were commenced.

Figure 6 shows the temporal trend of interventional studies on the treatment of EoG, EoD, and EoGE. Monoclonal antibodies are by far the most investigated treatments for non-EoE EGIDs. The first registered trials on monoclonal antibodies for EGIDs started in 2001. Although only one study on monoclonal antibodies was commenced over the following 17 years, seven studies were commenced over the past 3 years. From 2004 to 2017, single studies on other treatments, including biofeedback, montelukast, immunomodulators, and elemental diet were commenced.

DISCUSSION

This systematic review provided a snapshot of ongoing research on the treatment of EGIDs to assess the state of current research and possibly forecast future developments in the field. EGIDs are chronic gastrointestinal diseases whose epidemiology is rapidly changing as a consequence of a combination of increased recognition and incidence rates[11]. Concerning EoE, currently recommended management strategies include corticosteroids, dietary measures, PPIs, and possible dilation of stenoses, while oral corticosteroids and dietary interventions are suggested for non-EoE EGIDs[4,5,7,8]. However, most treatments are currently not approved by the United States Food and Drug Administration and European Medicines Agency, have very low to moderate levels of evidence, and possible novel strategies, such as monoclonal antibodies, currently lack any recommendations because of knowledge gaps[4,5,8]. However, there is a considerable number of active clinical trials aiming to fill these unmet needs, and it is predicted that novel treatments for EGIDs will be available imminently. We screened 832 clinical trials, of which 79 were eligible for inclusion. Sixty-five investigated treatments for EoE, one for EoE and EoGE, and 13 investigated treatments for EoG, EoD and/or EoGE. There were no trials on EoC.

As regard EoE, off-label inhaled/swallowed topical corticosteroids have demonstrated effectiveness on histology and symptoms in patients with EoE in previous meta-analyses[18,19]. Accordingly, in the past 20 years, 26 clinical trials on the use of topical corticosteroids for EoE were commenced. Analysis of temporal trends of studies on corticosteroids showed a gradual increase until 2020, when a sharp rise occurred. It appears that research on corticosteroids is heading towards the development of ad-hoc topical corticosteroids for the treatment of EoE. Although some studies are aimed at assessing the efficacy of inhaled or swallowed topical corticosteroids, the latest studies focused consistently on novel delivery systems that could improve the administration of the drug, including viscous suspensions, orally disintegrating tablets, or capsules. In contrast, although patients with lower EGIDs are commonly and effectively treated with systemic corticosteroids[4], there were no registered trials investigating corticosteroid drugs in EoG, EoD, or EoGE. Although systemic

corticosteroids are well known anti-inflammatory drugs, their effectiveness and safety in the context of non-EoE EGIDs still needs to be assessed in registered clinical trials.

Current guidelines, which have been published in 2017 and 2020[5,8], are generally against, or provide no recommendation on, the use of monoclonal antibodies for the treatment of EoE. Meta-analyses on a very limited number of studies on monoclonal antibodies for EoE were published only recently[20,21]. However, an increase in research on monoclonal antibodies was seen after 2018, in parallel with the discovery of new potential targets (i.e., IL-4, Il-5, IL-13, IL-15, and Siglec-8), and several studies will be completed in the coming years. Consistently, we found that most studies on monoclonal antibodies were in advanced phases or had already completed recruitment at the time of this systematic review. Additionally, from 2018 onwards, there has been a shift towards a subcutaneous, rather than intravenous, route of administration of monoclonal antibodies, and this may result in self, rather than in-hospital, administration of novel molecules. Similarly, trials on monoclonal antibodies for other EGIDs have gradually increased since 2001, have had considerable growth from 2018, and now represent the most investigated drug for EoG, EoD, and EoGE. Based on the status of current research on monoclonal antibodies for EGIDs, it is predictable that several monoclonal antibodies will be available and possibly be recommended by clinical guidelines soon. However, we observed a lack of interest in evaluating these novel drugs in EoC, which will likely remain without labelled therapeutic options in the longer term.

PPIs are currently considered as one of the possible first line treatments for EoE[5,7,8] because they are effective in controlling oesophageal inflammation and symptoms[22,23]. However, since 2008, only five trials registered on clinicaltrials.gov investigated treatment with PPIs, either as monotherapy or in combination with other treatments. Although two of these studies commenced in the past 3 years and are currently recruiting, it is likely that PPIs will continue to be used off-label for the foreseeable future. Studies on immunomodulators for EGIDs are in their early phases or are not yet recruiting. Therefore, it is likely that the availability of these drugs will take longer, compared with other medical treatments. Elimination diets are a recognized treatment for EGIDs[5,7,8], and represent a long-term,

drug-free, and effective treatment for EoE, comparable to topical corticosteroids and PPIs[24]. Until 2016, most clinical trials on elimination diets for EoE focused on allergy test-based or multiple food elimination regimens. Since 2018, there has been a tendency to move towards simpler and more tolerable one-food elimination strategies. A possible explanation for this shift is that almost 50% of patients can achieve remission with a two-food elimination diet, and that up to 70% of responders to this diet have only one food trigger[25]. Additionally, less restrictive dietary regimens are more tolerable for patients and may be more easily applicable to clinical practice outside clinical trials[24]. As for EoGE, a unique trial on therapeutic dietary restrictions (elemental diet) was retrieved. Overall, elimination diets are still being investigated in the EoE setting, while they seem rather under-investigated in other EGIDs.

Primary study endpoints of included trials were mostly histology-centred (66.7% of studies on EoE and 64.3% of studies on EGIDs). Although oesophageal inflammation seems to be the main determinant of disease progression[11], EoE is a complex disease with histological, clinical, and endoscopic markers of disease activity whose response to treatment may be inconsistent[24]. Accordingly, to fill major gaps in knowledge related to measuring treatment response, it would be desirable to include standardized definitions of symptoms and endoscopy findings among primary treatment outcomes. In this regard, in 2018, a systematic review individuated significant heterogeneity in outcome measurement and outcome definitions used for histology, endoscopy, and patient-reported endpoints in clinical trials on EoE[26], which makes the management of patients more challenging. In addition, as hypervigilance, anxiety, and esophageal motor disorders have been demonstrated to be involved in refractoriness of symptoms[27,28], the standardized and concomitant assessment of these factors in the setting of clinical trials may help to further elucidate the efficacy of treatments.

This study has some limitations. First, clinicaltrials.gov was the only database searched for eligible studies and unregistered trials have not been included. However, clinicaltrials.gov currently covers around 400,000 research studies in 220 countries and represents the largest clinical trial

registry worldwide. Second, the results of clinical trials were not included in this study. In this regard, meta-analytic studies investigating efficacy estimates of treatments for EoE[18-21,23,29,30] already showed that a considerable proportion of patients do not achieve disease remission while con currently available treatments. Accordingly, treatment efficacy outcomes were beyond the scope of this systematic review, which aimed at providing an overview of treatment trials in EGIDs registered in clinicaltrials.gov to provide a summary of current research trends. Reasons why research on EGIDS is heading towards the development of therapeutic alternatives include the suboptimal efficacy of current treatments, the recognition of novel key inflammatory molecular targets, and the development of new pharmacologic techniques.

In conclusion, numerous clinical trials are investigating possible treatments for EoE, EoG, EoD, and EoGE, with corticosteroids and monoclonal antibodies making up the majority of these and overall research showing increasing trends. It seems likely that the therapeutic landscape of EGIDs will widen imminently.

GUARANTOR OF THE ARTICLE

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AUTHOR CONTRIBUTIONS

PV, MG, NdB, EVS conceived and drafted the study. PV and MG collected and interpreted all data. PV, MG, BB, DM, EG, VS, CJB, ACF, NdB, EVS drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

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DATA SHARING STATEMENT

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