# High Discovery Rate of Gastroduodenal Eosinophilia but not Eosinophilic Esophagitis in Patients with Chronic Gastrointestinal Symptoms

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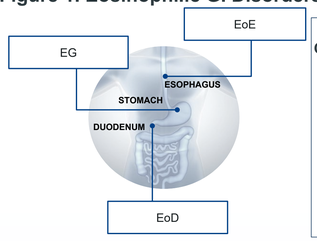
## BACKGROUND

- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in chronic inflammatory diseases of the gastrointestinal (GI) tract, including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis—collectively termed eosinophilic gastrointestinal diseases (EGIDs)[1,2]
- Patients with EGIDs have decreased quality of life due to chronic and often debilitating symptoms such as dysphagia, abdominal pain, bloating, nausea, vomiting, and diarrhea

### Figure 1. Eosinophilic GI Disorders




**EG, EoD, EoE**

**Chronic Eosinophilic Infiltration of the Stomach, Duodenum, or Esophagus**

- Eosinophils and mast cells mediate disease pathogenesis
- Symptoms: abdominal pain, nausea, early satiety, loss of appetite, bloating, abdominal cramping, vomiting, diarrhea, and dysphagia
- No FDA approved treatment for EG, EoD, or EoE
- Currently treated with restrictive diet and/or steroids

- EG and/or EoD are thought to affect 45,000–50,000 persons in the US; this could be an underestimate. There is evidence that these diseases are as common as inflammatory bowel diseases.[3,4] It is thought that EoE is more common than EG and/or EoD and that a large proportion of patients with EG and/or EoD have concomitant EoE[5]
- Current treatment options, such as diet restriction and corticosteroids, have limited efficacy and/or are inappropriate for chronic use

### Figure 2. High Rate of Detection of New Cases of EG and/or EoD in the ENIGMA Study Indicates Underdiagnosis of These Diseases[6]

51 patients without history of EG and/or EoD entered ENIGMA screening

↓

51% (26/51) met symptom criteria for endoscopy and biopsy

↓

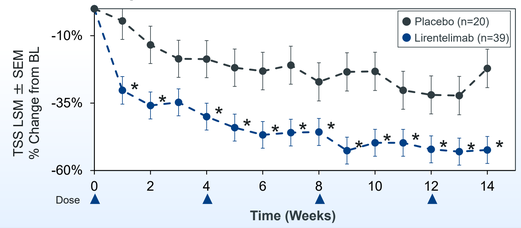
58% (15/26) EG and/or EoD[a]

- 29% (15/51) received a new diagnosis of EG and/or EoD
- Most patients without a previous diagnosis of EG and/or EoD came from general GI practices
- These patients had a history of chronic nonspecific functional GI symptoms or diagnoses

a Patients who met symptom criteria and ≥30 eosinophils per high-power field (eos/hpf) in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs

- Lirentelimab is a humanized monoclonal antibody against Siglec-8, an inhibitory receptor found only on mature eosinophils and mast cells
- Engagement of Siglec-8 by lirentelimab induces:
  - Antibody-dependent cell-mediated cytotoxicity (ADCC, blood) and apoptosis (tissue) of eosinophils
  - Inhibition of mature mast cells in tissue
- EG and/or EoD have been described as rare conditions found in individuals with atopy and increased peripheral eosinophils and/or total IgE. However, this conclusion was based on retrospective studies that included patients already diagnosed with EG and/or EoD
- We conducted a prospective study to evaluate the prevalence of EG and/or EoD among patients with chronic functional GI symptoms and clinical features, to inform diagnostic protocols

### Figure 3. Lirentelimab Significantly Reduced Patient Symptoms in the ENIGMA Study[5]




## METHODS

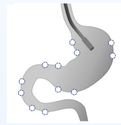
- We performed a prospective, multi-center study to assess the prevalence of EG and/or EoD in patients with chronic functional GI symptoms:
  - a ≥6-month history of GI symptoms without an identified cause
  - no response to pharmacologic or dietary interventions
  - or previous diagnoses of irritable bowel syndrome (IBS) or functional dyspepsia (FD)
- Up to 4 esophageal biopsies (2 distal and 2 mid/proximal) were collected from patients with histories of EoE, esophageal abnormalities during esophagogastroduodenoscopy (EGD), or for other reasons
- We performed a study of healthy volunteers (controls) for comparison
- Primary endpoints included proportion of patients who underwent biopsy and met the histologic criteria for EG and/or EoD (≥30 eos/hpf in 5 gastric or 3 duodenal hpfs)

**EG/EoD GI Symptom Questionnaire**

- Developed in accordance with FDA guidance on development of patient-reported outcome (PRO) measurements
- Captures patients' daily GI symptoms
- Measures each of the following symptoms on a scale of 0-10:
  - Abdominal pain
  - Nausea
  - Vomiting
  - Early satiety
  - Loss of appetite
  - Abdominal cramping
  - Bloating
  - Diarrhea
- Patients had daily scores of ≥3 (on a scale from 0 to 10) for any individual symptom and Total Symptom Scores (TSS) ≥10
- Controls had an average daily score ≤1 for all symptoms and no daily score ≥3, on any day, for any symptom

### Figure 4. Systematic Biopsy and Histopathology Assessment

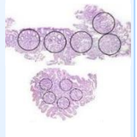
**Biopsy Protocol**



**Stomach**
- **GASTRIC ANTRUM: 4 biopsies** (2-5 cm proximal to the pylorus)
- **GASTRIC CORPUS: 4 biopsies** (2 from the proximal lesser curvature and 2 from the greater curvature)

**Duodenum**
**4 biopsies** from the duodenum, 2 each from the descending and horizontal parts

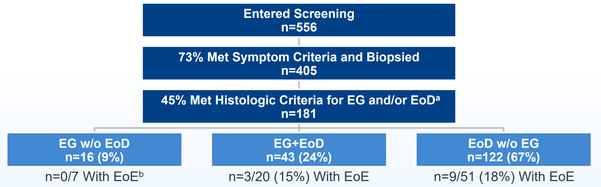
**Assessment Protocol**



- Biopsy samples were collected, sent to the central laboratory for fixing and staining, and then evaluated by central pathologist, blinded to patient demographic, clinical, and endoscopic data
- Eosinophils and mast cells were counted systematically in a minimum of 5 non-overlapping hpfs in at least 12 biopsies to avoid missing areas of infiltration
- Gastric biopsies were graded using the Sydney system for inflammation, metaplasia, atrophy, and reactive gastropathy; duodenal biopsies were graded using the Marsh scale classification system

## RESULTS

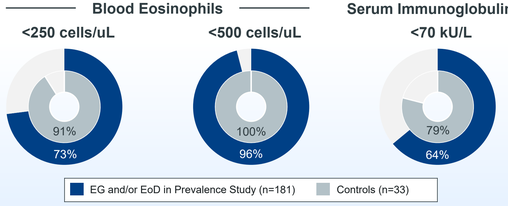
### Figure 5. High Prevalence of EG and/or EoD in Patients with Chronic GI Symptoms




33% (181/556) of patients with chronic functional GI symptoms and 45% (181/405) of patients with moderate–severe symptoms who underwent biopsy met histologic criteria for EG and/or EoD

a Patients who met symptom criteria and ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs
b 12 of 78 (15%) patients with esophageal biopsies met histologic criteria for EoE (≥15 eos in 1 hpf) and EG and/or EoD

### Figure 6. Proportion of Patients and Controls Meeting Blood Eosinophil or IgE Thresholds

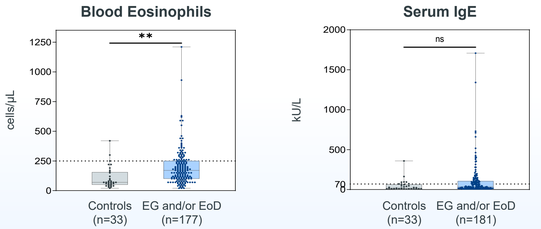



### Table 1. Features of Patients with EG and/or EoD and Controls

| Patient Characteristics | | Met Histologic[a] Criteria for EG and/or EoD n=181 | Controls n=33 |
|---|---|---|---|
| Mean age, years (range) | | 45 (19–78) | 34 (18–51) |
| Female sex, % | | 73% | 39% |
| White, % | | 85% | 100% |
| Weight, median, kg | | 83 | 80 |
| Blood eosinophils | Cells/μL, median (IQR) | 170 (100–250) | 70 (50–150) |
| | Blood eos ≥500 cells/μL, % | 4% | 0 |
| | Blood eos ≥1500 cells/μL, % | 0 | 0 |
| Immunoglobin E | kU/L, median (IQR) | 34 (14–103) | 18 (9–60) |
| TSS [0-80], mean ±SD | | 31.3±11.2 | 0.1±0.2 |
| History of | GI symptoms[b], mean years | 11 | NA |
| | GERD, IBS, FD, and/or EoE, % | 93% | 0 |
| | GERD, % | 65% | 0 |
| | IBS, % | 55% | 0 |
| | FD, % | 15% | 0 |
| | EoE, % | 2% | 0 |
| | Atopy[c], % | 48% | 15% |

a Patients who met symptom criteria and ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs
b Diagnoses of other functional GI disorders, such as chronic abdominal pain or functional diarrhea
c Asthma, allergic rhinitis, atopic dermatitis and/or food allergy
GERD, gastroesophageal reflux disease; IQR, interquartile range; NA, not applicable

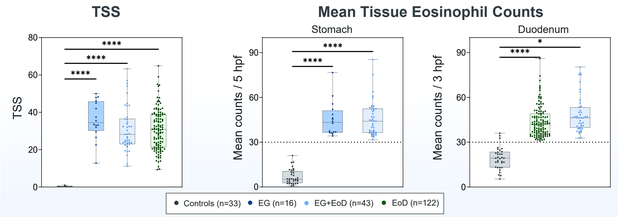
### Figure 7. Blood Eosinophilia and IgE in Patients and Controls




- Of patients who met histologic criteria for EG and/or EoD, 27% and 4% had ≥250 eosinophils/μl and ≥500 eosinophils/μl, respectively
- The median total IgE was 34 kU/L (IQR, 14–103 kU/L); 64% of patients had IgE ≤70 kU/L

* p <0.05; ** p<0.01; *** p<0.0001; **** p<0.0001

### Figure 8. TSS and Mean Eosinophil Counts in Patients vs Controls




45% (181/405) of patients and 6% (2/33) of controls[a] met histologic criteria for EG and/or EoD (odds ratio, 12.52; 95% CI, 3.0–53.0; *P*<0.001)

a Patients and controls used the same PRO questionnaire and underwent identical biopsy protocols. Histologic evaluation for both groups were performed by the same central pathologists

* p <0.05; ** p<0.01; *** p<0.0001; **** p<0.0001

## CONCLUSIONS/DISCUSSION

- Systematic endoscopy and biopsy of patients with moderate–severe chronic functional GI symptoms led to a high discovery rate (45%) of EG and/or EoD
- Most newly identified patients did not have peripheral eosinophilia or elevated IgE, indicating that EG and/or EoD should be considered in symptomatic patients without markers of atopy
- Patients with EG and EoD had significantly higher symptom scores and tissue eosinophil counts than controls
- Most patients with EG and/or EoD did not have concomitant EoE (≥15 eos in 1 esophageal hpf), though this could be partly attributed to methodology, as only 4 esophageal biopsies were collected from select patients (EoE guidelines recommend ≥6) and esophageal biopsies were prompted by history of EoE or endoscopic findings, and were not systematically collected from all patients undergoing EGD
- Further studies of EG and EoD are required to better understand their clinical, endoscopic, and histologic features and identify biomarkers

**Reference:** (1) Caldwell JM, et al. J Allergy Clin Immunol. 2014.; (2) Youngblood BA, et al. Gastroenterology. 2019.; (3) Jensen ET, et al. J Pediatr Gastroenterol Nutr. 2016.; (4) Licari AL, et al. JACI. 2020.; (5) Purssin C. Gastroenterol Clin North Am. 2014 (6) Dellon ES, et al. NEJM. 2020.

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