Endoscopic Appearance Does Not Predict the Presence of Histologic Eosinophilic Gastritis Among Symptomatic Adults, Indicating That Collection and Evaluation of Biopsies Should Occur Regardless of Endoscopic Appearance: Analysis From a Randomized Trial

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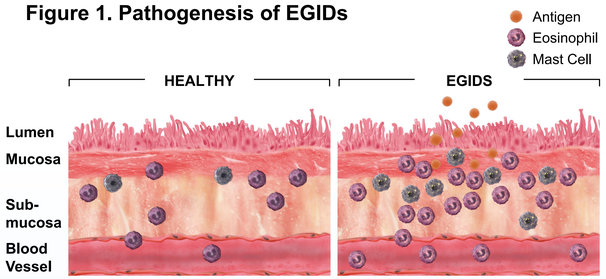
BACKGROUND

- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in multiple chronic inflammatory diseases in 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 debilitating and often nonspecific symptoms such as dysphagia, abdominal pain, abdominal cramping, bloating, early satiety, loss of appetite, nausea, vomiting, & diarrhea

Figure 1. Pathogenesis of EGIDs



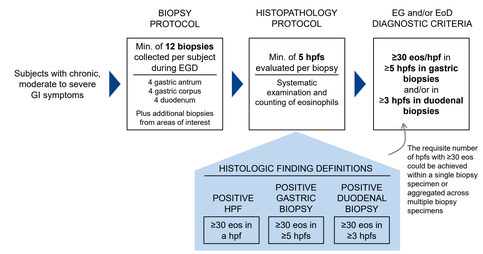
- ENIGMA was a randomized controlled trial conducted in adult EG and/or EoD patients and it established the therapeutic potential of lirentelimab, a monoclonal Siglec-8 antibody that depletes eosinophils and inhibits mast cell activity[3]
- Patients enrolled in the ENIGMA phase 2 study were first screened for moderate-to-severe GI symptoms; if symptom criteria were met, the patient underwent esophagogastroduodenoscopy (EGD) with biopsy and histopathologic evaluation to confirm EG and/or EoD diagnosis (≥30 eosinophils per hpf in ≥5 hpfs in the gastric biopsies and/or in ≥3 hpfs in duodenal biopsies)
- Results from the ENIGMA study revealed that 45% of patients screened had no prior history of EG and/or EoD diagnosis and 29% of whom were found to have EG and/or EoD
- The high discovery rate of de novo EG and/or EoD coupled with studies reporting underdiagnosis of EG and/or EoD prompted further evaluation of the endoscopic findings in patients with confirmed EG and/or EoD
- Utilizing screening EGD data from this prospective, multicenter, phase 2, randomized controlled trial, our primary aim was to better understand the endoscopic presentation of EG and/or EoD patients in order to improve detection of EG and/or EoD

OBJECTIVE

- Characterize the endoscopic findings in subjects with EG and to compare them to those of symptomatic individuals without EG

METHODS

Figure 3. Biopsy and Histopathology Protocol and EG and/or EoD Diagnostic Criteria



- Patients' esophagus, stomach, and duodenum were assessed by EGD
- Features in the stomach were scored by individual investigators according to the Eosinophilic Gastritis Endoscopic Reference System (EG-REFS), which scores 7 parameters in the fundus, corpus, and antrum
- Total EG-REFS scores range from 0 to 46
- A global endoscopic severity score for the stomach was also calculated for each subject (scores range from 0 to 10, with 10 indicating most severe)

Table 1. EG-REFS Scoring Criteria

Granularity	1. none 2. fine 3. course
Erosion/ ulceration	1. none 2. less than 5 erosions 3. 5 or more erosions 4. shallow/superficial ulceration(s) 5. deep/excavated ulceration (ulceration <25% surface area of specified location) 6. deep/excavated ulceration (ulceration 25%–50% surface area of specified location) 7. deep/excavated ulceration (ulceration >50% surface area of specified location)
Raised lesion (nodularity)	1. none 2. mild (raised focal nodules) 3. severe (raised nodules with greater height from width)
Erythema	1. none 2. mild (pink) 3. severe (red/hemorrhagic)
Friability/ bleeding	1. none 2. mild (contact bleeding) 3. severe (spontaneous bleeding)
Folds	1. none 2. thickened folds
Pyloric stenosis (Antrum Only)	1. none 2. present (inability to pass diagnostic 8-10 mm endoscope)

RESULTS

Figure 4. EG and/or EoD Diagnosis Rate

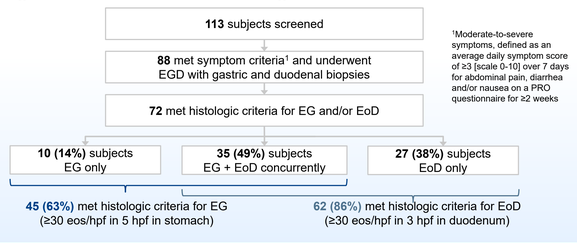


Table 2. Patient Demographics

	Met EG and/or EoD Criteria N=72	EG±EoD N=45	EoD w/o EG N=27
Mean age, years (range)	42 (18-74)	41 (18-68)	43 (19-74)
Female sex, n (%)	43 (60%)	25 (56%)	18 (67%)
White, n (%)	66 (92%)	41 (91%)	25 (93%)
Weight, mean (range), kg	82 (47-171)	82 (47-171)	82 (48-119)
Total Symptom Score at baseline, mean ± SD	31 ± 14	33 ± 14	29 ± 13
History of asthma, allergic rhinitis, atopic dermatitis, and/or food allergy	48 (67%)	33 (73%)	15 (56%)
Absolute eosinophil count			
Mean ± SD	654 ± 951	766 ± 1030	467 ± 784
Subjects with ≥250/µl, n (%)	45 (63%)	32 (71%)	13 (48%)
Subjects with ≥500/µl, n (%)	26 (36%)	21 (47%)	5 (19%)
Prior history, n (%)			
Eosinophilic gastritis and/or duodenitis (EG and/or EoD)	57 (79%)	38 (84%)	19 (70%)
Functional gastrointestinal disorder (irritable bowel syndrome, functional abdominal pain, functional diarrhea, or functional constipation)	24 (33%)	13 (29%)	11 (41%)
Gastroesophageal reflux disease (GERD), acid reflux, or heartburn	24 (33%)	16 (36%)	8 (30%)
Peptic ulcer	9 (13%)	8 (18%)	1 (4%)
Chronic gastritis/duodenitis	4 (6%)	1 (2%)	3 (11%)
Physician-guided treatment, n (%)			
Proton pump inhibitor	35 (49%)	22 (49%)	13 (48%)
Diet modification	11 (15%)	6 (13%)	5 (19%)
Low-dose systemic corticosteroid[a]	7 (10%)	5 (11%)	2 (7%)
Topical steroid (budesonide) capsule	7 (10%)	6 (13%)	1 (4%)

[a]Prednisone ≤10mg daily or equivalent as a pre-existing regimen and taken throughout the study

Figure 5. Baseline Individual EG-REFS Scores in Subjects with EG

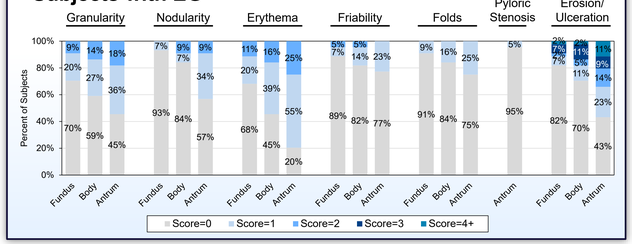


Figure 6. Percent of Subjects with Abnormality in Any Area of the Stomach

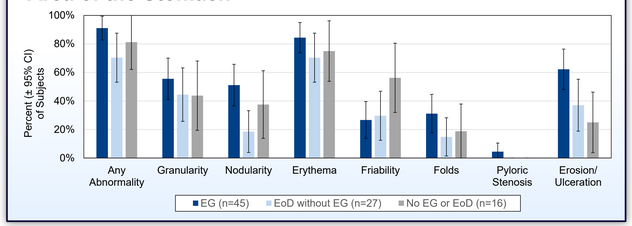
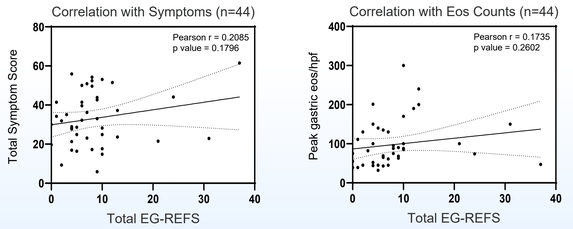
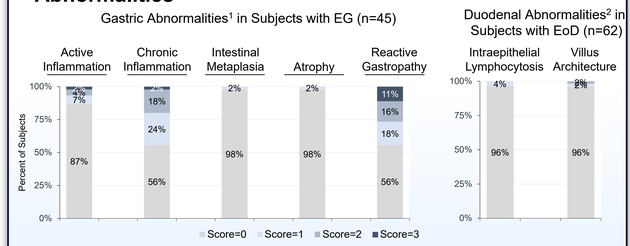


Figure 7. EG-REFS Does Not Correlate with TSS or Eos



- Total symptom score and peak eos/hpf in the stomach of subjects with EG did not correlate with the total EG-REFS

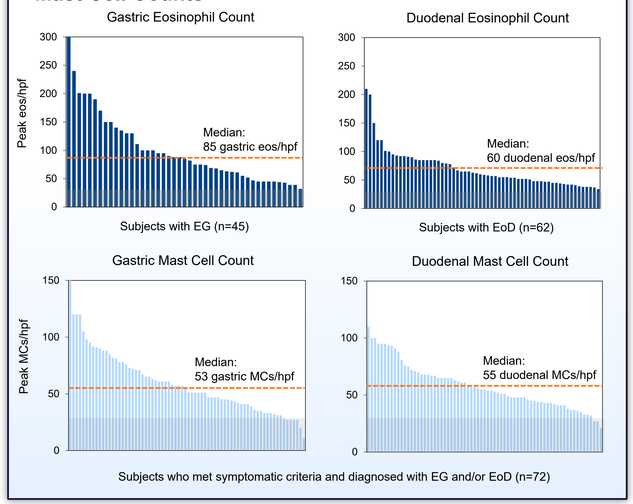
Figure 8. Gastric and Duodenal Histopathologic Abnormalities



[1]Active inflammation, intestinal metaplasia, atrophy score >0 and/or chronic inflammation, reactive gastropathy score >1 per Sydney System
[2]Score >0 per Marsh Classification

- In most cases, tissue eosinophils did not form sheets that were readily visible under low-power magnification (i.e. 100X or below)

Figure 9. Peak Gastric and Duodenal Eosinophil and Mast Cell Counts



CONCLUSIONS/DISCUSSION

- Endoscopic and macro histopathologic findings were normal or mild in many subjects with EG and/or EoD in this study
- Furthermore, endoscopic abnormalities may not be specific to EG and endoscopic severity did not predict the presence of histologic EG
- Mast cells also appear to be elevated in number, supporting their pathogenic role in EG and EoD
- Limitations to this analysis include the lack of central endoscopic scoring and a healthy subject comparator
- Use of preexisting medications or diet therapy in some subjects may have reduced detection of abnormalities
- These findings emphasize the importance of systematically collecting biopsies and counting tissue eosinophils in symptomatic patients, regardless of endoscopic findings

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Reference: (1) Caldwell JM, et al. J Allergy Clin Immunol. 2014.; (2) Youngblood BA, et al. Gastroenterology. 2019.; (3) Dellon ES, et al. NEJM. 2020.