Systematic Collection of Biopsies and Quantification of Eosinophils in Multiple High-Power Fields is Required for Diagnosis of Eosinophilic Gastritis and/or Duodenitis

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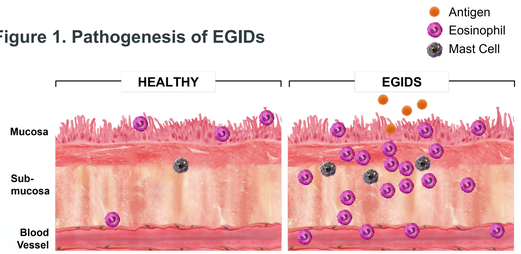
BACKGROUND

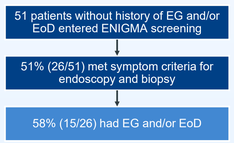
- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in chronic inflammatory diseases in the gastrointestinal (GI) tract, including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis—collectively termed eosinophilic gastrointestinal diseases (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, and diarrhea[3]

Figure 1. Pathogenesis of EGIDs



- ENIGMA was a randomized, controlled, phase 2 trial of adult patients with EG and/or EoD that established the therapeutic potential of lirentelimab, an investigational medicine, which is a monoclonal antibody against Siglec-8 that depletes eosinophils and inhibits mast cell activity[4*]
- Patients enrolled in ENIGMA were first screened for moderate–severe GI symptoms using a daily patient-reported outcome (PRO) questionnaire
- Patients who met the symptom criteria underwent esophagogastroduodenoscopy (EGD) with biopsy and histopathologic evaluation to confirm diagnoses of EG and/or EoD (≥30 eosinophils per high-power field [eos/hpf] in ≥5 hpfs in gastric biopsies and/or in ≥3 hpfs in duodenal biopsies)
- Among patients screened in ENIGMA, 45% had no previous diagnoses of EG and/or EoD; 29% of these patients were found to have EG and/or EoD

Figure 2. New Diagnoses of EG and/or EoD in ENIGMA



- 29% (15/51) of the patients 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 histories of chronic unexplained GI symptoms or diagnoses of functional disorders

- This high discovery rate of EG and/or EoD, along with other studies reporting underdiagnosis of EG and/or EoD, prompted further evaluation of the screening protocol
- We therefore conducted a prospective study of the prevalence of EG and/or EoD in patients with chronic unexplained gastrointestinal symptoms
- We used a systematic histopathology protocol in ENIGMA and this prevalence study to determine the discovery rate of EG and/or EoD

METHODS

Figure 3. Biopsy and Histopathology Protocol and Diagnostic Criteria for EG and/or EoD Used in ENIGMA and Prevalence Studies

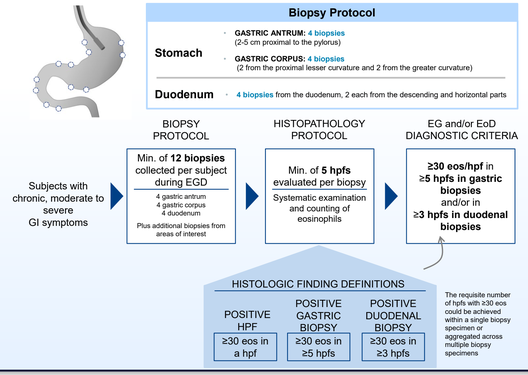
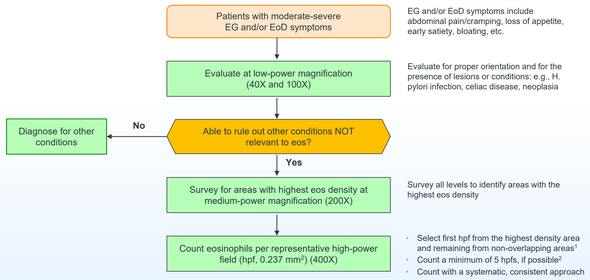


Figure 4. Histopathologic Evaluation Process: Steps for EG and/or EoD



1 Non-overlapping hpfs could be, but are not required to be, adjacent to the first hpf, depending on the distribution of eosinophils in the specimen
2 If the size of a specimen is insufficient to evaluate 5 independent fields, eos are to be counted in as many non-overlapping fields as available
Note: a separate endoscopy study of healthy volunteers (controls) was conducted for comparison

Figure 5. Ideal Biopsy Specimen and Countable Eosinophils

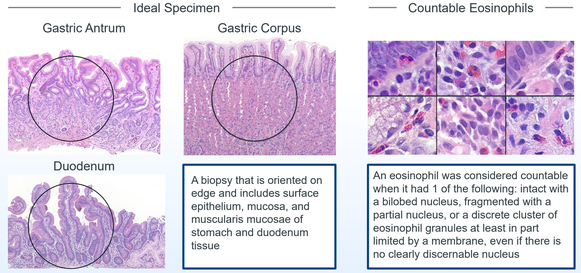
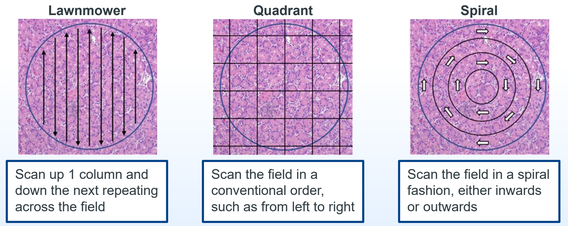
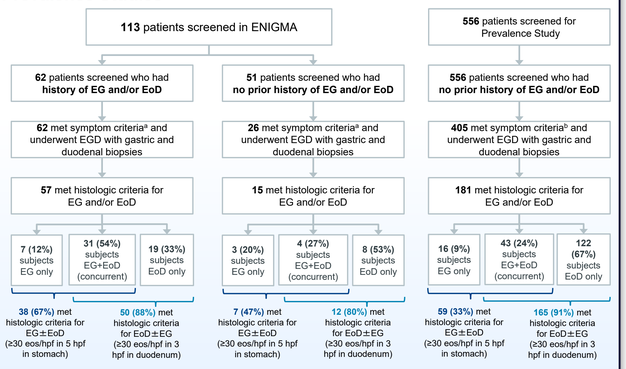


Figure 6. Three Systematic Approaches to Counting Eosinophils



RESULTS

Figure 7. Detection Rate of EG and/or EoD Across ENIGMA and Prevalence Studies



[a]Moderate–severe symptoms, defined as an average daily symptom score of ≥3 (scale 0-10) over 7 days for abdominal pain, diarrhea, and/or nausea on a PRO questionnaire for ≥2 weeks
[b]Moderate–severe symptoms, defined as an average daily symptom score of ≥3 (scale 0-10) for at least 2 of 3 weeks for abdominal pain, abdominal cramping, nausea, vomiting, diarrhea, bloating, or early satiety on a PRO questionnaire and average Total Symptom Score (TSS) ≥3 [scale 0-80]

Table 1. Patient Demographics

Patient Characteristics	ENIGMA+Prevalence			Healthy Controls N=33
	EG w/o EoD N=26	EG+EoD N=78	EoD w/o EG N=149	
Mean age, years (range)	42 (18-72)	46 (18-76)	44 (19-78)	34 (18-51)
Female sex, n (%)	21 (81%)	48 (62%)	106 (71%)	39%
White, n (%)	24 (92%)	66 (85%)	130 (87%)	100%
Weight, mean (range), kg	80 (47-136)	88 (50-180)	83 (45-138)	79 (46-113)
Total Symptom Score (TSS) at baseline, mean ±SD	38 ±11	31 ±13	30 ±11	0.1 ±0.2
Atopy[a]	17 (65%)	47 (60%)	79 (53%)	5 (15%)
Prior history, n (%)				
Eosinophilic gastritis and/or duodenitis (EG/EoD)	7 (27%)	31 (40%)	19 (13%)	0
Functional gastrointestinal disorder[b]	19 (73%)	49 (63%)	132 (89%)	0
GERD, acid reflux, or heartburn	12 (46%)	43 (55%)	102 (68%)	0
Peptic ulcer	4 (15%)	6 (8%)	9 (6%)	0
Chronic gastritis/duodenitis	2 (8%)	4 (5%)	18 (12%)	0
Physician-guided treatment, n (%)				
Proton-pump inhibitor	8 (31%)	35 (45%)	54 (36%)	0
Diet modification	3 (12%)	4 (5%)	12 (8%)	0

[a]History of asthma, allergic rhinitis, atopic dermatitis, and/or food allergy
[b]Irritable bowel syndrome, GERD, chronic gastritis/duodenitis, or functional dyspepsia

Figure 8. Sydney and Marsh Scores in Subjects with EG and/or EoD vs Controls

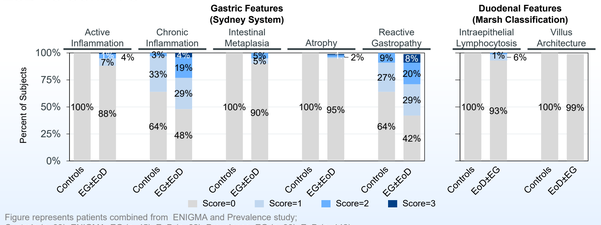
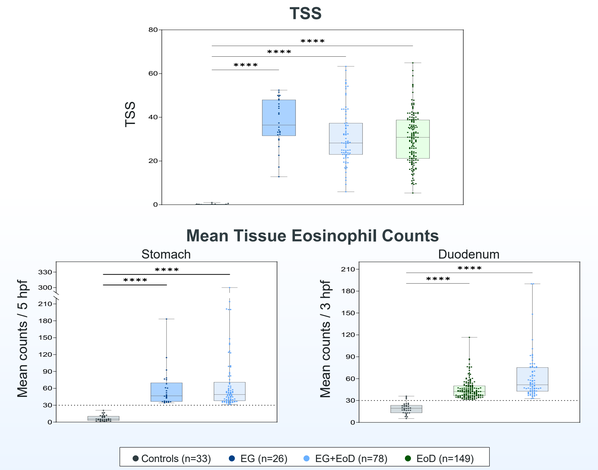


Figure represents patients combined from ENIGMA and Prevalence study; Controls (n=33); ENIGMA, EG (n=45), EoD (n=62); Prevalence, EG (n=38), EoD (n=142)

Figure 9. TSS and Mean Eosinophil Counts in Patients vs Controls



51% (253/493) of patients and 6% (2/33) of controls[a] met histologic criteria for EG and/or EoD (odds ratio, 16.34; 95% CI, 3.9–69.0; *P*=0.0001)

Figure represents patients combined from ENIGMA and Prevalence study
[a]Patients and controls used the same patient-reported-outcome questionnaire and underwent identical biopsy protocols. Histologic evaluation for both groups were performed by the same central pathologists

CONCLUSIONS/DISCUSSION

- A systematic histopathology protocol with evaluation of gastric and duodenal eosinophilia in patients with chronic, moderate–severe GI symptoms, in 2 prospective studies, revealed that about a third of patients without previous diagnoses of EG and/or EoD met histologic criteria for these disorders
- Results of Sydney and Marsh scoring suggest that low power evaluation of GI biopsies is not sufficient to detect EG and/or EoD
- Given the high diagnostic yield, a standardized biopsy and histopathology protocol should be used to evaluate patients for EG and/or EoD, so that they can receive an accurate diagnosis

Reference: (1) Caldwell JM, et al. J Allergy Clin Immunol. 2014.; (2) Youngblood BA, et al. Gastroenterology. 2019.; (3) Chehade M, et al. JACI in Practice 2020.; (4) Dellon ES, et al. NEJM. 2020.
*Lirentelimab is an investigational medicine, its efficacy and safety profile have not been established, and it has not been approved by the FDA

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