Gastroenterology 2016;■:1–11

Symptoms Have Modest Accuracy in Detecting Endoscopic and Histologic Remission in Adults With Eosinophilic Esophagitis

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BACKGROUND & AIMS: It is not clear whether symptoms alone can be used to estimate the biologic activity of eosinophilic esophagitis (EoE). We aimed to evaluate whether symptoms can be used to identify patients with endoscopic and histologic features of remission. **METHODS:** Between April 2011 and June 2014, we performed a prospective, observational study and recruited 269 consecutive adults with EoE (67% male; median age, 39 years old) in Switzerland and the United States. Patients first completed the validated symptom-based EoE activity index patient-reported outcome instrument and then underwent esophagogastroduodenoscopy with esophageal biopsy collection. Endoscopic and histologic findings were evaluated with a validated grading system and standardized instrument, respectively. Clinical remission was defined as symptom score <20 (range, $0-100$); histologic remission was defined as a peak count of <20 eosinophils/mm^2 in a high-power field (corresponds to approximately <5 eosinophils/median high-power field); and endoscopic remission as absence of white exudates, moderate or severe rings, strictures, or combination of furrows and edema. We used receiver operating characteristic analysis to determine the best symptom score cutoff values for detection of remission. **RESULTS:** Of the study subjects, 111 were in clinical remission (41.3%), 79 were in endoscopic remission (29.7%), and 75 were in histologic remission (27.9%). When the symptom score was used as a continuous variable, patients in endoscopic, histologic, and combined (endoscopic and histologic remission) remission were detected with area under the curve values of 0.67, 0.60, and 0.67, respectively. A symptom score of 20 identified patients in endoscopic remission with 65.1% accuracy and histologic remission with 62.1% accuracy; a symptom score of 15 identified patients with both types of remission with 67.7% accuracy. **CONCLUSIONS:** In patients with EoE, endoscopic or histologic remission can be identified with only modest accuracy based on symptoms alone. At any given time, physicians cannot rely on lack of symptoms to make assumptions about lack of biologic disease activity in adults with EoE. ClinicalTrials.gov, Number: NCT00939263.

Keywords: EEsAI; Remission; Endoscopic Grading; Disease Monitoring.

Eosinophilic esophagitis (EoE) has been defined recently by an expert group as "a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."[1,2] Dysphagia is the leading EoE symptom in adult patients, but swallowing-associated pain and heartburn not responding to acid-suppressive medication can also occur.[1,2] In Europe and the United States, a steady increase in EoE incidence and/or prevalence has been observed during the past 2 decades with a current prevalence of about 1/2,000 inhabitants.[3–10]

Despite the urgent need for EoE-specific therapies, to date, no such therapy has been approved by regulatory agencies, including the US Food and Drug Administration and the European Medicines Agency. There are 2 major hurdles in the way of seeking regulatory approval for EoE-specific therapies: first, standardized and validated instruments for reliable assessment of disease activity have been lacking for a long time and, second, there is an ongoing debate among different stakeholders regarding the choice of clinically relevant end points for use in clinical trials and natural history studies.[11,12]

Recently, considerable progress has been made toward developing and validating instruments for standardized disease activity assessment. Among others, the EoE endoscopic reference score, developed by Hirano et al, for grading the severity of distinct EoE-associated endoscopic features (edema, rings, exudates, furrows, and strictures) and the eosinophilic esophagitis activity index (EEsAI) patient-reported outcome (PRO) instrument for assessing clinical activity in adult patients, are now available for use in various studies.[13,14]

A dissociation between EoE symptom severity and histologic activity was documented in some, but not other studies.[15–18] This leaves clinicians with uncertainty as to the elements upon which their therapeutic decisions should be based. Specifically, it is currently unknown whether physicians can rely solely on EoE-related symptoms when estimating the severity of endoscopic and histologic activity in a given patient.

The purpose of this study was to examine the relationship between clinical activity and biologic activity (endoscopy, histology) of EoE. Specifically, we aimed to examine the ability of the EEsAI PRO score to detect endoscopic and histologic remission in adult EoE patients. We also aimed to examine whether the previous EoE-specific treatment impacts the relationship between clinical and biologic EoE activity, and, in so doing, alters the ability of the EEsAI PRO score to detect biologic remission. This study may help to elucidate whether treatment decisions can be based solely on symptoms, or whether the biologic findings obtained during more invasive procedures, such as esophagogastroduodenoscopy (EGD) with biopsy sampling, should also be taken into consideration.

Methods

Study Population

The study was registered on ClinicalTrials.gov (NCT00939263) and approved by local institutional review boards and ethics committees. All authors had access to the study data and reviewed and approved the final manuscript.

Adult EoE patients (≥17 years of age) were consecutively recruited in 1 ambulatory care clinic and 5 hospitals in Switzerland and the United States between April 2011 and June 2014. All patients were treated by 6 gastroenterologists (AMS, JA, ED, NG, IH, and AS) specializing in EoE (each gastroenterologist has treated >50 EoE patients and performed >1000 EGDs). Patients provided written informed consent for participation in the study. All patients in need of an EGD for initial diagnosis, for confirming a suspected diagnosis, or for monitoring previously diagnosed EoE were invited to participate in the study. Patients were diagnosed by investigators according to standardized criteria.[1,2] EoE patients with concomitant gastroesophageal reflux disease were also included, provided that they fulfilled the following criteria: they were on continued proton-pump inhibitor therapy at the time of EGD; they had no symptoms of gastroesophageal reflux disease; and they had no evidence of acute reflux-related lesions. Before undergoing EGD, patients completed the EEsAI PRO instrument (in paper form).[14]

Assessment of Symptoms and Behavioral Adaptations to Living With Dysphagia

Development and validation of the EEsAI PRO instrument has been described recently.[14] The EEsAI PRO instrument was developed in accordance with the US Food and Drug Administration guidelines.[19,20] The instrument queries the following symptoms and behavioral adaptations to living with dysphagia recalled during a 7-day period: frequency of trouble swallowing, duration of trouble swallowing, thoracic pain when swallowing, trouble swallowing caused by foods of different consistencies, and behavioral adaptations to living with dysphagia, including avoidance; modification; and slow eating.[14] The EEsAI PRO score ranges from 0 to 100 points.

Assessment of Eosinophilic Esophagitis–Associated Endoscopic and Histologic Findings

During EGD, at least 4 biopsies from the proximal and 4 biopsies from the distal esophagus were obtained. For this study, we defined "distal" esophagus as the section of the esophagus 5 cm above the gastroesophageal junction and "proximal" esophagus as the section spanning the top half of the esophagus. Assessment of severity of EoE-associated endoscopic findings, such as edema, rings, exudates, furrows, and stricture(s) in the proximal and distal esophagus, was

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Abbreviations used in this paper: AUC, area under the curve; CDAI, Crohn's Disease Activity Index; EEsAI, Eosinophilic Esophagitis Activity Index; EoE, eosinophilic esophagitis; EGD, esophagogastroduodenoscopy; hpf, high-power field; PRO, patient-reported outcome; ROC, receiver operating characteristic.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.11.004