Alignment of parent- and child-reported outcomes and histology in eosinophilic esophagitis across multiple CEGIR sites

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Background: Patient-reported outcome metrics for eosinophilic esophagitis (EoE) have been developed and validated but not used in a multicenter pediatric population or systematically aligned with histology.

Objective: We sought to understand (1) the potential of caregiver report to predict patient self-reported symptoms and (2) the correlation of patient-reported outcome domains with histology.

Methods: Patients with EoE (n = 310) and their parents participating in the Consortium of Gastrointestinal Eosinophilic Disease Researchers (CEGIR) observational clinical trial were queried for baseline patient symptoms and quality of life (QOL) by using the Pediatric Eosinophilic Esophagitis Symptom Score, version 2 (PEESSv2.0), and the Pediatric QOL EoE module (PedsQL-EoE), and biopsy specimens were analyzed by using the EoE Histology Scoring System.

Results: PEESSv2.0 parental and child reports aligned across all domains (r = 0.68-0.73, P < .001). PedsQL-EoE reports correlated between parents and children across ages and multiple domains (r = 0.48-0.79, P < .001). There was a tight correlation between symptoms on PEESSv2.0 and their effects on QOL both on self-report and parental report (P < .001). Self-reported symptoms on PEESSv2.0 (positively) and PedsQL-EoE (inversely) showed a weak correlation with proximal, but not distal, peak eosinophil counts and features and architectural tissue changes on the EoE Histology Scoring System (P < .05).

Conclusions: Parents of children with EoE aged 3 to 18 years accurately reflected their children's disease symptoms and QOL. Self- and parent-reported symptoms correlate with proximal esophageal histology. Our data suggest that parental report in young children can function as an adequate marker for self-reported symptoms and that self-reported symptoms can reflect changes in tissue histology in the proximal esophagus. These findings should be considered during clinical trials for drug development. (J Allergy Clin Immunol 2018;142:130-8.)

Key words: *Eosinophil, eosinophilic esophagitis, eosinophilic oesophagitis, Consortium of Eosinophilic Gastrointestinal Disease Researchers, patient-reported outcomes, pediatric eosinophilic esophagitis symptom score, version 2, pediatric QOL EoE module, symptoms, quality of life*

Eosinophilic esophagitis (EoE), a chronic antigen-mediated disorder of children and adults, is diagnosed and monitored histologically, results in symptoms reflective of esophageal dysfunction, and does not currently have validated surrogate disease markers.[1,2] One barrier to drug development and clinical trials in children is the lack of self-reported patient-reported outcome (PRO) metrics and the assumption that child report is unreliable and that parental report cannot serve as an adequate surrogate for a child's symptoms.[3] Because of these challenges, young children, often the population most in need of novel therapies to halt disease progression and/or alter natural history, are often excluded from clinical therapeutic trials.

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Abbreviations used
CEGIR: Consortium of Eosinophilic Gastrointestinal Disease Researchers
EoE: Eosinophilic esophagitis
EoEHSS: EoE Histology Scoring System
GERD: Gastroesophageal reflux disease
IQR: Interquartile range
OMEGA: Outcomes Measures in Eosinophilic Gastrointestinal Disorders Across the Ages
PedsQL-EoE: Pediatric QOL EoE module
PEESSv2.0: Pediatric Eosinophilic Esophagitis Symptom Score, version 2
PRO: Patient-reported outcome
QOL: Quality of life

There are 2 EoE-specific validated outcome metrics for children and their parents, namely the Pediatric Eosinophilic Esophagitis Symptom Score, version 2.0 (PEESSv2.0), and the age-specific Pediatric QOL EoE module (PedsQL-EoE), version 3.0.[4-11] However, it is currently not clear how well these outcome metrics perform in terms of an accurate reflection of the child's symptoms based on parental report.[5] In addition, it is not clear whether parent-reported or self-reported symptom and/or quality of life (QOL) metrics can perform as surrogate markers of tissue histology in children.[4,12]

The EoE Histology Scoring System (EoEHSS) is a validated module that reports the grade and stage of features of tissue damage and eosinophilia in the esophagus.[13] Eosinophil parameters include features of eosinophilic inflammation, eosinophil abscesses and surface layering, and surface epithelial alteration, as well as the architectural changes of basal zone hyperplasia, dilated intercellular spaces, dyskeratotic epithelial cells, and lamina propria fibrosis. The lack of validated indexes for symptoms/QOL and histology was a prior barrier to completing a systematic assessment of PROs in relation to histology.

Use of multicenter consortia for rare diseases has a number of advantages over single-center studies including data obtained from multiple centers from across the United States and the ability to gather larger amounts of information in a shorter time period. The Consortium for Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is a national collaborative network of 14 academic centers and patient advocacy groups caring for adults and children with eosinophilic gastrointestinal disorders.[14] The CEGIR clinical trial Outcomes Measures in Eosinophilic Gastrointestinal Disorders Across the Ages (OMEGA) is a longitudinal cohort study aimed at understanding the natural history of EoE, eosinophilic gastritis, and eosinophilic colitis during routine clinical care.[15] Using baseline PEESSv2.0 and PedsQL-EoE data generated from CEGIR subjects, we aimed to understand the alignment between parent- and child-reported symptoms and the correlation of symptoms with esophageal histology in a multicenter study.

METHODS

PROs

Three hundred ten children aged 3 to 18 years and their parents completed the PEESSv2.0 child self-report, PEESSv2.0 parental proxy report, age-specific parental report, and/or self-report PedsQL-EoE questionnaires on entry into CEGIR OMEGA in 8 pediatric centers across the continental United States (ClinicalTrials.gov identification number NCT02523118). PedsQL-EoE self-report was used in children aged 5 to 18 years. PEESSv2.0 self-report was obtained from children aged 8 to 18 years. Parents of children aged 3 to 18 years completed the PEESSv2.0 parental report and age-specific PedsQL-EoE. Patients were consented/assented into the central (Cincinnati) and local institutional review board− and National Institutes of Health−approved protocol.

The PEESSv2.0 is a content-validated metric for EoE-specific symptoms in children and assesses items within 4 domains: dysphagia, gastroesophageal reflux disease (GERD), nausea/vomiting, and pain.[4-6] PEESSv2.0 is scored from 0 to 100, with higher scores indicating more severe symptoms.

The PedsQL-EoE, version 3.0, is a content-validated index that measures the effect of various disease domains on QOL. PedsQL-EoE assesses the domains of symptoms I (chest pain, heartburn, stomach aches, vomiting, nausea, and food regurgitation), symptoms II (trouble swallowing, food stuck in the throat/chest, drinking to aid swallowing, and prolonged eating time), problems with treatment (difficulty with medications, doctor visits, endoscopies, and allergy testing), worry (regarding illness, doctor visits, endoscopies, and allergy testing), feelings, communication (parents, adults, friend, practitioners), and food/eating (difficulties with food elimination).[4,8,9] The PedsQL-EoE young child, child, and adolescent are self-reported metrics for children aged 5 to 7, 8 to 12, and 13 to 18 years old, respectively. The PedsQL-EoE for parents is a metric for parents of toddlers (2-4 years old), young children (5-7 years), children (8-12 years), and adolescents

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