Prospective study of an amino acid–based elemental diet in an eosinophilic gastritis and gastroenteritis nutrition trial

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Background: Eosinophilic gastritis/gastroenteritis (EoG/EoGE) are rare disorders with pathologic gastric and/or small intestinal eosinophilia lacking an approved therapy. An allergic mechanism is postulated but underexplored mechanistically and therapeutically.

Objective: We evaluated the effectiveness of a food allergen–free diet (elemental formula) in controlling gastrointestinal eosinophilia in adult EoG/EoGE.

Methods: Adults aged 18 to 65 years with histologically active EoG/EoGE (≥30 eosinophils per high-power field) in the
stomach and/or duodenum and gastrointestinal symptoms within the month preceding enrollment were prospectively enrolled onto a single-arm clinical trial to receive elemental formula for 6 consecutive weeks. The primary end point was percentage of participants with complete histologic remission (<30 eosinophils per high-power field in both stomach and duodenum). Exploratory outcomes were improvement in symptoms, endoscopy results, blood eosinophilia, quality of life, Physician Global Assessment score, and EoG-relevant gastric transcriptome and microbiome.

Results: Fifteen adults (47% male, average age 37.7 years, average symptom duration 8.8 years) completed the trial. Multi–gastrointestinal segment involvement affected 87%. All subjects had complete histologic remission in the stomach (P = .002) and duodenum (P = .001). Scores improved in overall PhGA (P = .002); EGREFS (P = .003); EGDP (P = .002); SODA pain intensity (P = .044), non-pain (P = .039), and satisfaction (P = .0024); and PROMIS depression (P = .0078) and fatigue (P = .04). Food reintroduction reversed these improvements. The intervention was well tolerated in 14 subjects, with 1 serious adverse event reported in 1 subject.

Conclusion: An amino acid–based elemental diet improves histologic, endoscopic, symptomatic, quality-of-life, and molecular parameters of EoG/EoGE; these findings and disease recurrence with food trigger reintroduction support a dominant role for food allergens in disease pathogenesis. ClinicalTrials.gov Identifier: NCT03320369. (J Allergy Clin Immunol 2023;nnn:nnn-nnn.)

Key words: Eosinophilic gastritis, eosinophilic gastroenteritis, elemental diet, food allergy, eosinophilia

Eosinophilic gastrointestinal disorders (EGIDs) are rare, chronic conditions comprising eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic gastroenteritis (EoGE), and eosinophilic colitis. The non–esophageal gastrointestinal disorders—EoG, EoGE, and eosinophilic colitis—are understudied relative to EoE, but recent data suggest that their prevalence is increasing. Although they remain less common than EoE, EoG/EoGE have an estimated prevalence of 22 to 28 per 100,000 persons in the United States.1 In EoG/EoGE, eosinophils infiltrate the gastric and/or intestinal tissue. Multiple bowel layers (mucosal, submucosal, serosal) may be involved. The presenting symptoms often correspond to the bowel layer involved,2,5 with common symptoms including abdominal pain, nausea, vomiting, early satiety, weight loss, and diarrhea. However, EoG/EoGE pathogenesis is poorly understood.

Although elimination and elemental diets are highly effective treatments to reduce mucosal inflammation in EoE, dietary therapy has not been well studied in EoG/EoGE. EoG/EoGE treatment largely relies on systemically active immunosuppressive agents (eg, corticosteroids), although clinical trials are investigating biologic agents.6 Although corticosteroids are effective at reducing eosinophilic inflammation, their long-term adverse effects limit their use as a maintenance therapy. As a result of the significant morbidity of these chronic illnesses and the paucity of data on effective and safe treatment options, improved therapeutic options are needed.3,7,9

Although EoE has been linked to food allergies in adult and pediatric populations (>95% resolution with complete food antigen avoidance), there have been no prospective studies using an amino acid–based elemental diet in adults or children with EoG/EoGE.3,10-12 Because of the paucity of controlled EoG/EoGE studies, EoG/EoGE pathophysiology has not been as well defined as EoE pathophysiology. Prior EoE studies identified a unique esophageal transcriptome and association with atopic conditions, supporting the role of type 2 immunity and food allergen–driven cytokines, such as IL-5 and IL-13.13 Recent EoG/EoGE studies suggest that EoG/EoGE are systemic disorders involving peripheral and gastrointestinal tract eosinophilia, TGFβ2 immunity (similar to EoE), and an altered transcriptome that is both overlapping and distinct from EoE transcriptome.14-16 Given these findings, we hypothesized that the elemental diet, as a food allergen–free diet, would be an effective therapeutic option in EoG/EoGE and would reduce histologic gastrointestinal eosinophilia in individuals with EoG/EoGE.

To test this hypothesis, adults with a confirmed diagnosis of EoG/EoGE were treated with an amino acid–based elemental formula (ELE) and evaluated for a broad range of outcomes, including histologic, endoscopic, molecular, clinical symptomology, and quality of life (QOL) measures. Study results provide insights regarding an alternative to systemic corticosteroid therapy for EoG/EoGE treatment and provide support for a potential underlying role for allergens in non-EoE EGID pathophysiology.

Methods

Objectives

The primary study objective was to evaluate the effectiveness of 6 weeks’ ELE on histologic remission of disease (defined as <30 eosinophils per microscopic high-power field [eos/hpf]; a high-power field was defined as a 0.1256 mm2 circular field at 40×) in adults with EoG/EoGE. Secondary and exploratory

Abbreviations used

CEGIR: Consortium of Eosinophilic Disease Researchers
Ct: Cycle threshold
EGD: Esophagoduodenoscopy
EGDP: Eosinophilic Gastritis Diagnostic Panel
EGHSS: Eosinophilic Gastritis Histology Scoring System
EGID: Eosinophilic gastrointestinal disorder
EGREFS: Eosinophilic Gastritis Reference Score
ELE: Amino acid–based elemental formula
EoE: Eosinophilic esophagitis
EoG: Eosinophilic gastritis
EoGE: Eosinophilic gastroenteritis
eos/hpf: Eosinophils per high-power microscopic field of gastric or duodenal biopsy sample
OU: Operational taxonomic unit
PhGA: Physician Global Assessment
PRO: Patient-reported outcome
PROMIS: Patient-Reported Outcomes Measurement Information System Adult Profile 29
QOL: Quality of life
SOC: Standard of care
SODA: Severity of Dyspepsia Assessment
TARC: Thymus- and activation-regulated chemokine
TSLP: Thymic stromal lymphopoietin
objectives included improvement in endoscopic features, peripheral eosinophilia, molecular signature, symptoms, and QOL scores.

**Design**

In this prospective, single-center study, 21 participants consented to the study during August 2017 to June 2019. During screening, 19 participants were found to have histologically active EoG and/or EoGE via biopsy and were eligible to proceed. The study was conducted as part the Consortium of Eosinophilic Disease Researchers (CEGIR) Pilot Program, part of the Rare Diseases Clinical Research Network, with protocol oversight by the National Institute of Allergy and Infectious Diseases.

**Setting**

In this single-site study, adults (18-65 years of age) were recruited from the Northwestern Medicine outpatient gastroenterology clinic, the Northwestern Memorial Hospital gastroenterology consult service, and gastroenterology, allergy, and multidisciplinary clinics of private and academic hospitals/outpatient medical practices in the United States. After an initial clinical evaluation of EoG/EoGE by 2 gastroenterologists specializing in EGIDs (N.G. and I.H.) and a review of study-protocol inclusion and exclusion criteria, participants were offered study entry.

**Participants**

Adults who were 18 to 65 years of age were eligible for inclusion if they were able to understand and provide informed consent and had a diagnosis of EoG/EoGE with active EGID symptoms within the month before enrollment and histologically confirmed active disease of ≥30 eos/hpf in the stomach and/or duodenum. The eosinophil threshold is based on the most comprehensive study of EoG performed to date, in which over 60 participants (50 adults, 10 children) were histologically studied, and a threshold of ≥30 eos/hpf was advised by the National Institutes of Health study team and the US Food and Drug Administration at the time of protocol development. Actively symptomatic patients included abdominal pain, nausea/vomiting, early satiety, diarrhea, and weight loss. Other causes of mucosal eosinophilia were ruled out as per clinical care. Other exclusion criteria included the presence of known causes of gastrointestinal eosinophilia, pregnancy, immunodeficiency states, prior 6-week ELE treatment with follow-up endoscopy, or participation in any investigative drug study within 6 weeks before study entry. Therapy with swallowed topical steroids, immunosuppression medication, or immunomodulators was permitted if the index endoscopy demonstrated active eosinophilia while receiving these medications, and medications were unchanged throughout the trial. Other information obtained from medical records included complete blood count with differential, serum IgE, comprehensive metabolic panel, and additional nutritional laboratory studies, if indicated and available.

The study was approved by the central institutional review board at Cincinnati Children’s and the local institutional review board at Northwestern Medicine. All participants provided informed consent before enrollment.

**Dietary intervention**

After informed consent was obtained by authorized research personnel, eligibility was confirmed by the gastroenterologist, and participants met with a registered dietician specializing in EGID clinical care. Nutritional goals were identified and adapted for individual participants, and each was offered a palatability trial of a nutritionally complete ELE (investigational agents included Neocate Jr, Neocate Splash, and Elecare Jr) before the start of the study; a complete nutritional profile is provided in this article’s Online Repository available at www.jacionline.org. Although ELE was the sole nutritional source during the 6-week study period, ≥1 formula may have been used to help with palate fatigue. Neocate Splash was only used as a supplement to the powdered formulas (Neocate Jr and Elecare Jr) to provide variety of flavor and ease of travel and to reduce palate fatigue. Dietician assessment also included a baseline dietary questionnaire to measure food allergen intake and evaluate education and counseling on using the ELE. A nutritional assessment was used to estimate calorie and protein needs for each participant. Participants were provided a digital scale to measure baseline and weekly weight changes. Weight and percentage of weight loss, if any, were recorded during weekly wellness checks and were used to determine ELE compliance and adherence (see List E1, Tables E2-E4, and Figs E1-E4 in the Online Repository).

After ≥6 weeks’ ELE, participants completed standard-of-care (SOC) esophagastroduodenoscopy (EGD), with multiple biopsy samples evaluated for eos/hpf. If clinically indicated, complete blood count with differential, complete metabolic panel, and additional nutritional laboratory assessments were obtained at the discretion of the treating physician. Participants may have consented to have additional biopsy samples collected from the esophagus, stomach, and duodenum at the time of endoscopy, stool collection for microbiome analysis, and blood samples for future cytokine and transcriptomic analysis. Participants who underwent SOC food reintroduction consented to post-study data collection on follow-up endoscopy EGID and food trigger identification.

**Endoscopy, biopsy specimens, and histologic analysis**

A SOC EGD was performed using an Olympus GIF-H190 videoscope (Olympus America, Melville, NY) at baseline and at the end of treatment. For the end-treatment EGD and baseline EGDs that were performed at the study center, endoscopic features were recorded before and after treatment using the Eosinophilic Gastritis Reference Score (EGREFS) developed by the CEGIR. This tool focuses on the common endoscopic features in EoG, including erythema, granularity, raised lesions, erosions/ulcers, friability, thickened folds, and pyloric stenosis. Radial jaw-4 standard capacity grasp forceps (Boston Scientific, Natick, Mass) were used to obtain biopsy specimens for tissue analysis during endoscopy. Biopsies were performed according to existing clinical protocol at the study center, with 4 to 6 duodenal samples and 6 to 8 stomach samples taken. If the participant had an EGD as part of clinical care within 3 months before study screening, the EGD results were used to determine study eligibility.

All biopsy specimens were reviewed by a single gastrointestinal pathologist (G.-Y.Y.) who was unaware of the participant’s treatment status, and the specimen was evaluated for peak

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All biopsy specimens were reviewed by a single gastrointestinal pathologist (G.-Y.Y.) who was unaware of the participant’s treatment status, and the specimen was evaluated for peak
density of eos/hpf (0.1256 mm$^2$ circular field at 40×). At least 5 high-power fields were evaluated for each biopsy sample in the area most densely populated with eosinophils. The biopsy samples were also evaluated for other features with the Eosinophilic Gastritis Histology Scoring System (EGHSS) developed by CEGIR; this tool analyzes and scores on a grade of 0 to 2 for a total composite score for each feature: lamina propria eosinophil sheets, periglandular circumferential collars, eosinophils in surface epithelium, eosinophil glandulitis, eosinophil gland abscess, eosinophils in muscularis mucosa/submucosa, lamina propria fibroplasia, lamina propria smooth muscle hyperplasia, reactive epithelial change, acute inflammatory cells, and surface erosion and ulceration.

Symptom and QOL assessment

Symptoms were assessed using the Severity of Dyspepsia Assessment (SODA) and the Patient-Reported Outcomes Measurement Information System Adult Profile 29 (PROMIS), administered before and after 6 weeks’ ELE. It is important to note that at the time of this study, there were no QOL measures specifically validated for non-EoE EGID, so we used QOL measures approved for use in other CEGIR studies (SODA and PROMIS).

Transcriptome analysis

RNA from gastric biopsy samples that were collected as described above was isolated from participants with EoG/EoGE was reverse transcribed using the iScript cDNA Synthesis Kit (170-8891; Bio-Rad, Hercules, Calif) according to the manufacturer’s protocol. The transcriptomic signature of gastric biopsy samples was obtained using an EoG diagnostic panel (EGDP) comprising a set of 48 gastric transcripts (including 2 housekeeping transcripts) as previously reported. TaqMan reagents for amplification of major EoG signature genes were obtained from Applied Biosystems (Thermo Fisher Scientific, Waltham, Mass), and TaqMan real-time PCR amplification was performed on a Quant Studio 7 device (Life Technologies; Thermo Fisher Scientific). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an expression control for all analyzed genes. Samples with a GAPDH of <30 of the cycle threshold ($C_t$) value were considered acceptable for analysis. The $C_t$ value was subtracted from each EoG gene of interest $C_t$ value to acquire the $\Delta C_t$. The EoG diagnostic panel score was calculated by summing the $\Delta C_t$ values of the most highly dysregulated genes ($\Sigma \Delta C_t$), as described previously.

Measurement of serum cytokine/chemokine levels

Peripheral blood samples were collected before starting dietary therapy. Serum was isolated, and aliquots were frozen and stored at −80°C for batch analysis. The serum levels of cytokines/chemokines—eotaxin-1 (CCL11), eotaxin-2 (CCL24), eotaxin-3 (CCL26), IL-1α, IL-4, IL-5, IL-13, IL-33, thymus- and activation-regulated chemokine/chemokine ligand 17 (TARC/CCL17), and thymic stromal lymphopoietin (TSLP)—were assayed by customized immunoassays and quantified on a Sector Imager 6000 device (Meso Scale Discovery, Gaithersburg, Md) according to the manufacturer’s instructions, as previously reported.

Identification of food triggers after dietary intervention

Enrolled study participants also consented to have food reintroduction data collected after study completion if they chose to undergo the food reintroduction process with their primary clinician. All participants who underwent poststudy food introduction were under the care of a single medical team at Northwestern University (N.G., I.H., B.D.), which developed a specified approach to food reintroduction and clinical follow-up after an elemental diet (Fig E4). Those who attempted reintroduction requested expedited reintroduction of foods in categories A and B (Fig E4). One food was added every 3 to 5 days; if there were no symptomatic recurrence, additional foods were added in this sequential fashion. Endoscopy with biopsy was performed, and follow-up tissue eosinophilia was tracked if participants became symptomatic with a food or if an entire category of foods was added. In participants with baseline peripheral eosinophilia, eosinophilia was followed to determine whether it could serve as a biomarker of disease activity.

Statistical analysis

Before analysis, the quality and distribution of the data were examined. Statistical analyses were performed by R (R Project; www.r-project.org), SAS 9.4 (SAS Institute, Cary, NC), GeneSpring GX 14.9 (Agilent Technologies, Santa Clara, Calif), and GraphPad Prism 9 (GraphPad Software, La Jolla, Calif). Distribution-appropriate statistics on age, sex, race, and clinical characteristics were presented to describe the cohort. Statistical significance was indicated by $P < .05$.

Primary analysis

The complete histologic remission end point was presented as the proportion of participants whose disease activity met the criteria for complete histologic remission (mucosal eosinophilia <30 eos/hpf in participants completing the dietary trial). The exact 95% confidence limits of the proportion were provided.

Exploratory end point analysis

Exploratory outcomes included improvement of SODA, PROMIS, Physician Global Assessment (PhGA), EGREFS, EGHSS, Eosinophilic Gastritis Diagnostic Panel (EGDP), and serum cytokine concentrations after treatment. Serum cytokines analyzed included eotaxin-1, eotaxin-2, eotaxin-3, IL-1α, IL-4, IL-5, IL-13, IL-33, TARC, and TSLP. Outcomes were measured before and after ELE. Because all participants’ disease had complete histologic remission, eosinophil density was not calculated. Depending on the distribution of the outcome measures, either paired t test or Wilcoxon signed rank test was used to test whether there were significant changes in the outcome measures after completing ELE.

We examined correlations between variables and sought to gain a better understanding of how the histologic measures for EoG (eosinophil count, EGHSS, EGREFS, PhGA, EGDP) related to each other and to patient-reported outcomes (PROs: SODA, PROMIS) and serum cytokines by performing pairwise
correlations using pre and post measures. Because of the nonnormal distribution of some measures, Spearman correlations were used. Because we had multiple measures of eosinophil levels (gastric, duodenal) and EGERFS components (erosion, granularity, lesion, erythema, friability, folds), these specific measures were evaluated. For interpretation of correlation coefficients, we considered very strong correlation as 0.8 < r < 1.0, strong correlation as 0.6 ≤ r < 0.8, moderate correlation as 0.4 ≤ r < 0.6, and weak correlation as 0.2 ≤ r < 0.4.

Microbiome analysis

To assess impact of ELE on the microbiome, we assessed stool samples before and after treatment in the 5 participants for whom samples were available. Stool DNA was isolated and subjected to 16S sequencing (pair end; V3–V4; 250 bp). Quantification of the operational taxonomic unit (OTU) abundance and taxonomy assignment were performed using the CLC ProSuite Microbial Genomics Module (Qiagen). Briefly, after quality assessment of raw reads, low-quality bases were trimmed, and all the sample reads were rectified by 170,000 reads per sample. Demultiplexed reads were clustered into OTUs using the open reference OTU picking protocol at 97% sequence identity against the Greengenes database (08/2013 release), followed by chimeric sequence removal and taxonomy assignment. Statistical parameters were chosen as indicated.

RESULTS

Participant characteristics and clinical features

Table I. Demographic and clinical features of 15 randomized participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>47% (7)</td>
</tr>
<tr>
<td>White race*</td>
<td>100% (14)</td>
</tr>
<tr>
<td>Age (years), mean (SD) [range]</td>
<td>37.7 (13.3) [21.3-59.2]</td>
</tr>
<tr>
<td>Duration of symptoms (years), mean [range]</td>
<td>8.8 [1-20]</td>
</tr>
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Presenting symptoms

- Abdominal pain: 73% (11)
- Dysphagia: 73% (11)
- Diarrhea: 47% (7)
- Nausea: 33% (5)
- Vomiting: 27% (4)

Organs involved

- Esophagus: 66% (10)
- Stomach: 80% (12)
- Duodenum: 53% (8)
- Atopy: 93% (14)
- Asthma: 33% (5)
- Eczema: 20% (3)
- Food allergy: 73% (11)
- Peripheral eosinophilia (abs >600K/µL): 33% (5)
- Range (K/µL): 700-4700
- Mean: AEC2560

SOC therapy before elemental diet†

- PPI: 64% (9)
- Histologic response: 0
- Topical steroids: 36% (5)
- Histologic response: 20% (1)
- Systemic steroids: 7% (1)
- Histologic response: 0
- Dietary therapy (SFED): 7% (1)
- Histologic response: 0

Immunosuppressive agents (Imuran)

- Combination: PPI, cromolyn, topical steroids: 14% (2)
- Histologic response: 100% (2)
- Systemic steroids: 14% (2)
- Histologic response: 50% (1)

Endoscopic findings

- Granularity: 80% (12)
- Erosions/ulcers: 60% (9)
- Raised lesions: 27% (4)
- Erythema: 93% (14)
- Friability: 20% (3)
- Thickened folds: 20% (3)

Histologic remission

The primary end point of histologic remission was met in all 15 participants who completed the trial (exact 95% confidence level, 78-100%). On average, eosinophil levels decreased significantly from 50 to 11 eos/hpf in the stomach (P < .001, paired t test) and 49 to 16 eos/hpf in the duodenum (P = .001, paired t test) after 6 weeks’ ELE (Fig 1).

Endoscopic and clinical remission

The median (IQR) values of the overall PhGA scores were 5 (4-5) and 2 (1-2) before and after treatment, respectively. After treatment, PhGA decreased significantly (median [IQR] 3 [2-3], P = .002, signed rank test), suggesting overall improvement in
disease activity. In addition to clinical improvement, endoscopic improvement was observed. The median improvement in EGREFS scores was 4.9 (IQR 1-10; \( P = .010 \), signed rank test). All 6 EGREFS features improved, although statistical significance was not detected for all features, likely as a result of our small sample size (Fig 2). Representative images of endoscopic improvement are presented in Fig 3, A. The medians (IQR) of the peripheral eosinophilia were 400 (200-1330) \( \mu L \) and 250 (150-400) \( \mu L \) before and after treatment, respectively. A significant decrease was detected after treatment (median [IQR]: 250 (0-1515) \( \mu L \), \( P = .009 \), signed rank test) (Fig 3, B). Two participants had abnormal baseline albumin levels, consistent with EoG/EoGE-associated protein-losing enteropathy observed in non-EoE EGID (<3.5 mg/dL); after treatment, the mean albumin level had improved (post 3.95 mg/dL vs baseline 3.05 mg/dL).

Dietary compliance

Dietary questionnaires, dietary compliance checklists, and weight measures were used weekly and reviewed by the study dietician. Dietary questionnaires showed 100% compliance throughout all but the initial week. In the first week, 77% of participants were compliant with the recommended ELE volume. A participant’s perception of the amount of effort needed to adhere to the diet ranged from 0 to 100% during the study period but tended to decrease as the study progressed. The average perceived effort was 55% over the study course, starting at 81% on week 1 and decreasing to 37% by week 5.

The dietary compliance checklist showed that compliance with weekly checks with staff was 100%. Weekly sessions with the team assessed adherence and percentage weight loss, allowing for adjustments in prescribed volume to prevent weight loss. Percentage weight loss was 5.9% and depended on the participant’s ability to maintain caloric intake, as ELE was intended to be eucaloric to maintain body weight. Some participants did experience weight loss related to their inability to meet the recommended formula volume; however, the average percentage of adherence to the prescribed ELE volume was 92.7% (range, 60-100%).

Patient-related outcomes and QOL

PRO scores improved in pain intensity (\( P = .004 \)), non-pain scores (\( P = .036 \)), and satisfaction scores (\( P < .001 \)) using the SODA instrument. PROMIS scores improved in depression (\( P = .008 \)); fatigue exhibited a trend of improvement (\( P = .07 \)) (Table II).

Molecular efficacy of elemental diet

Ten participants with paired gastric biopsies performed before and after successful ELE had EGDP gene expression analysis.\(^{22}\) To determine the gastric efficacy of ELE at the molecular level, we assessed the EGDP\(_{18} \) score, reflecting molecular severity, before and after treatment. ELE improved the EGDP\(_{18} \) score (\( P = .002 \)) (Fig 4, A) collectively (Fig 4, B) and on an individual-participant basis (Fig 4, C). There was marked improvement in the expression patterns of individual genes; ELE associated with marked changes in gene expression of eosinophil markers (eg, CLC), eosinophilic chemotactants (CCL24, CCL26), type 2 immunity (AREG), tissue remodeling (MUC4, COL2A), and neuroimmune responses (NP4) (Fig 4, D).

Cytokine/chemokine assessment

To assess the potential systemic effects of ELE, we analyzed 10 serum cytokines/chemokines relevant to EoG in paired samples from the same individual before and after treatment (\( n = 10 \)); no serum cytokines/chemokines were significantly changed, possibly as a result of the small sample size. Although 7 participants did overlap with those who underwent the RNA analysis, they were not the exact same cohort because participants could opt out of additional specimen collection at any time.

EGHSS assessment

The EGHSS scoring tool was used to assess other features in the histologic specimens before and after therapy. EGHSS scores improved significantly by 0.23 (\( P < .001 \), paired \( t \) test, Fig 5, A).

Outcome measure relationships

When evaluating the correlations for histologic measures (see Fig E3 in the Online Repository available at www.jacionline.org), we found that most measures correlated with each other, with the exception of some EGREFS subcomponents. Notably, correlations were of higher magnitude for gastric eosinophilia than duodenal eosinophilia except for some EGREFS subcomponents. EGDP negatively correlated with all histologic measures, as expected. When comparing histology and PROs (Fig E3), the strongest correlations were moderate, but most correlations were weak to negligible. The moderate correlations were between duodenal eosinophilia and SODA satisfaction (\( r = -0.58 \)), duodenal eosinophilia and PROMIS depression (\( r = 0.46 \)), erosion and SODA satisfaction (\( r = -0.47 \)), and granularity and non-pain (\( r = -0.46 \)). When relating histology and cytokines/chemokines (Fig E3), \(~20\%\) of the correlations were strong to moderate, but most correlations were weak to negligible. Moderate-to-strong correlations were found between serum eotaxin-3 and EGREFS (total, erythema, granularity, lesion \( r \geq 0.45 \)), PhGA (\( r = 0.42 \)), and duodenal eosinophilia (\( r = 0.44 \)); IL-4 and erosion (\( r = 0.53 \)); IL-5 and EGREFS (total, granularity, lesion, erythema \( r \geq 0.41 \)); IL-13 and EGREFS (thickened folds, lesion \( r \geq 0.46 \)); TARC and EGREFS (total, granularity, lesion, erythema \( r \geq 0.40 \)); TSLP and erosion (\( r = 0.50 \)); and IL-1\( \alpha \) and EGREFS (total, granularity \( r \leq -0.40 \)).

Food reintroduction

Thirteen of 15 participants chose to undergo food reintroduction after the initial study. Food reintroduction followed a predetermined standardized food reintroduction protocol previously established by the treating medical team (N.G., I.H., B.D.) (Fig E4). This portion of the study was pursued as clinical care and was individualized to the patient. Eleven (85%) of these 13 participants underwent follow-up endoscopy indicating histologic recurrence (\( \geq 30 \) eos/hpf) in the stomach (8/11, 73%) and/or duodenum (7/11, 64%) after reintroduction of specific food triggers (Fig 5, B). Two of these 13 participants completed multiple food reintroductions with follow-up endoscopy without histologic recurrence; however, on reintroducing the presumed trigger food, they had symptom
recurrence and chose to remove the food rather than confirm by repeat endoscopy. Overall, 5 (38%) of 13 participants had symptom recurrence to ≥1 group A food, 5 (38%) of 13 participants reacted to ≥1 group B food, and 11 (85%) of 13 participants experienced a reaction to ≥1 group C food. All participants had symptoms with ≥1 group D food and continued to restrict ≥1 group D food. Nine (69%) of 13 participants had recurrence of peripheral eosinophilia with food reintroduction with identified trigger foods. The most common food triggers are listed in Table E1 in the Online Repository available at www.jacionline.org.

**Microbiome assessment**

A preliminary analysis of stool microbiome was performed before and after 6 weeks’ ELE in 5 subjects. Abundance analysis showed increased Firmicutes, Porphyromonadaceae, and Veillonellaceae; and decreased Bacteroidetes, Ruminococcaceae, and Bacteroidaceae. The differential abundance confirmed a significant posttreatment decrease in Ruminococcaceae (~10-fold; \( P < 3.2E-06 \)) and Lachnospiraceae (~11-fold; \( P < 3.3E-05 \)) (see Table E5 and Fig E2 in the Online Repository available at www.jacionline.org).

**Safety and tolerability**

The study intervention was well tolerated (see Table E6 for adverse events); only 1 of the 10 events was related to the study intervention. This single event, hyponatremia, was a serious adverse event. This participant had renal insufficiency, was receiving multiple diuretic medications, and reported taking the recommended amount of formula; however, the investigators determined that this participant was taking significantly less formula than self-reported and consumed more free water than advised. The resulting hyponatremia required study withdrawal. No participant had weight loss during the study that necessitated study withdrawal or met any other study-stopping criteria.

**DISCUSSION**

This is the first prospective dietary trial in EoG/EoGE and provides insight into the pathophysiology of these disorders. We show that a food allergy–free diet effectively improves histologic, symptomatic, endoscopic, and molecular disease activity and that food reintroduction induced disease relapse, suggesting a dominant role for food antigens in EoG/EoGE pathogenesis. Before this study, EoG/EoGE treatment paradigms centered on medical treatment with oral steroids, which can have deleterious effects with long-term use. This study not only supports using dietary therapy in non-EoE EGIDs but also provides insights into disease mechanisms.

Prior EoG/EoGE dietary therapy studies were limited to small retrospective reviews and often combined therapy with concomitant medications, making the overall effectiveness of pure dietary intervention challenging to extrapolate. In our study, the only intervention used was ELE. Although concomitant topical corticosteroids and immunosuppression were allowed, only 1 participant was receiving topical corticosteroid therapy for esophageal involvement during the study period; the general lack of these concomitant therapies in study participants further strengthens...
the evidence of the improvement’s being related to food elimination alone.

The participant cohort was reflective of prior descriptions of non-EoE EGID populations, with the most common presenting symptom being abdominal pain. Notably, 93% of our participants had concomitant atopic disease, which is similar to what has been described for EoE and non-EoE EGIDs. Individuals with EoGE often have symptoms for many years before diagnosis and then experiencing remission; our participants experienced symptoms for an average of 8.8 years before study entry. During this time, many treatments (eg, oral corticosteroids) had been previously tried, with suboptimal remission (Table I).

All study participants met the primary end point of histologic normalization of tissue eosinophil levels in the stomach and duodenum. Because gastric and duodenal mucosa have resident eosinophils under healthy homeostatic conditions, the threshold for response was defined not as zero but rather as below the diagnostic threshold of <30 eos/hpf. This was based on the diagnostic threshold used by CEGIR at the time of study development in 2016. In addition to the overall decrease in eosinophil density, other inflammatory features measured in the EGHSS scoring tool also improved, further supporting mucosal healing after ELE intervention. Compared to steroids and eosinophil depleting antibodies, ELE still maintained baseline normal levels of gastrointestinal eosinophils, which may be advantageous, based on the potential homeostatic role of gastrointestinal eosinophils. This study also demonstrated that individuals with duodenal involvement have a similar clinical presentation and treatment response to individuals with isolated gastric and combined gastric/duodenal involvement. Despite the small number of study participants with isolated duodenal disease—the result of the rarity of these disorders—this study provides unique insights suggesting that food allergens are a trigger in both duodenum and stomach. This treatment response in isolated duodenal disease—the result of the rarity of these disorders—this study provides unique insights suggesting that food allergens are a trigger in both duodenum and stomach. This treatment response in isolated duodenal disease—the result of the rarity of these disorders—this study provides unique insights suggesting that food allergens are a trigger in both duodenum and stomach. This treatment response in isolated duodenal disease—the result of the rarity of these disorders—this study provides unique insights suggesting that food allergens are a trigger in both duodenum and stomach. This treatment response in isolated duodenal disease—the result of the rarity of these disorders—this study provides unique insights suggesting that food allergens are a trigger in both duodenum and stomach. This treatment response in isolated duodenal disease—the result of the rarity of these disorders—this study provides unique insights suggesting that food allergens are a trigger in both duodenum and stomach. This treatment response in isolated duodenal disease—the result of the rarity of these disorders—this study provides unique insights suggesting that food allergens are a trigger in both duodenum and stomach.

FIG 2. Endoscopic features by EGREFS before and after 6 weeks’ elemental diet. Individual data are shown as dots; data pairs from same subjects are connected. Red bars show medians before and after treatment. Medians and interquartile ranges (IQRs) of paired change are shown as red triangles and vertical bars, respectively. Paired change was tested against 0 by Wilcoxon signed rank test.
6 weeks. In addition, in individuals with EoG/EoGE-associated protein-losing enteropathy, treatment helped restore nutritional status and resolved enteropathy. Notably, the 2 participants who terminated study participation at 4 days and at 2 weeks of formula both had complete resolution of peripheral eosinophilia, suggesting that ELE may induce histologic remission in less than 6 weeks. However, we used an intervention period of 6 weeks to be comparable with prior dietary trials for EGIDs. 10,29,30

Informatively, peripheral eosinophilia resolved after ELE, further supporting peripheral eosinophilia as an inflammation biomarker in a subset of individuals with EGIDs. The resolution of peripheral eosinophilia in patients who had comorbid atopic conditions suggests that the reduction was solely the result of the ELE and improvement in gastrointestinal tissue eosinophilia because no adjustments to therapy for allergic comorbidities were pursued during the study period.

Although histologic improvement was the primary end point, nearly all other disease parameters improved. Using the EGREFS score as a marker of endoscopic improvement, we saw a significant reduction in the overall endoscopic score. The most common areas of improvement were in erosions, raised lesions, friability, and thickened folds. As we are learning more about

**FIG 3.** Representative endoscopies and peripheral eosinophilia. A, Representative endoscopies. In subject 1, gastric improvement in friability and erythema is noted after treatment. In subject 2, gastric improvement in granularity, friability, thickened folds, and raised lesions are noted after treatment. In subject 3, duodenal improvement in denuded patches are noted after treatment. B, Peripheral eosinophilia. Individual data are shown as dots; data pairs from same subjects are connected. Red bars show medians before and after treatment. Individual and median paired changes (interquartile ranges [IQRs]) are shown as red triangles and vertical bars, respectively. Paired change of peripheral eosinophilia was tested against 0 by Wilcoxon signed rank test. Eos, Eosinophils.

**TABLE II.** Elemental diet impact on QOL according to SODA and PROMIS score

<table>
<thead>
<tr>
<th>Tool</th>
<th>Domain</th>
<th>Screening</th>
<th>End of treatment</th>
<th>Paired change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODA Pain</td>
<td></td>
<td>21.8 (16.1, 27.5)</td>
<td>14.9 (9.4, 20.3)</td>
<td>−6.9 (−11.3, −2.6)</td>
<td>.004</td>
</tr>
<tr>
<td>Non-pain score</td>
<td></td>
<td>15.7 (13.8, 17.7)</td>
<td>14.1 (12.3, 16.0)</td>
<td>−1.6 (−3.1, −0.1)</td>
<td>.036</td>
</tr>
<tr>
<td>Satisfaction</td>
<td></td>
<td>9.2 (6.1, 12.3)</td>
<td>15.3 (13.0, 17.7)</td>
<td>6.1 (3.7, 8.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PROMIS Physical functioning</td>
<td></td>
<td>56.9 (45.3, 56.9)</td>
<td>56.9 (45.3, 56.9)</td>
<td>0.0 (−7.8, 0)</td>
<td>.50</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td>53.7 (40.3, 59.5)</td>
<td>51.2 (40.3, 55.8)</td>
<td>−4.6 (−7.7, 0)</td>
<td>.29</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>51.8 (41.0, 57.3)</td>
<td>41.0 (41.0, 51.8)</td>
<td>−1.6 (−8.0, 0)</td>
<td>.008</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>55.1 (46.0, 64.6)</td>
<td>48.6 (46.0, 60.7)</td>
<td>−6.5 (−9.1, 1.9)</td>
<td>.07</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td></td>
<td>52.4 (43.8, 57.9)</td>
<td>48.4 (43.8, 59.8)</td>
<td>−3.9 (−8.1, 4.6)</td>
<td>.39</td>
</tr>
<tr>
<td>Social roles and activities</td>
<td></td>
<td>51.6 (46.4, 64.1)</td>
<td>51.6 (44.8, 64.1)</td>
<td>0.0 (−4.4, 7.1)</td>
<td>.78</td>
</tr>
<tr>
<td>Pain interference</td>
<td></td>
<td>53.9 (41.6, 61.2)</td>
<td>52.0 (41.6, 55.6)</td>
<td>0.0 (−8.1, 0.0)</td>
<td>.73</td>
</tr>
<tr>
<td>HUI-3</td>
<td></td>
<td>0.88 (0.80, 1.00)</td>
<td>0.91 (0.68, 1.00)</td>
<td>0.02 (−0.12, 0.12)</td>
<td>.85</td>
</tr>
<tr>
<td>Overall pain rating</td>
<td></td>
<td>3.5 (2.0, 5.1)</td>
<td>1.9 (0.9, 3.0)</td>
<td>−1.6 (−3.2, −0.0)</td>
<td>.046</td>
</tr>
</tbody>
</table>

Subdomains of SODA and overall pain rating are shown as mean (95% confidence level) and were tested by paired t test; subdomains of PROMIS and HUI-3 are shown as median (IQR) and tested by signed rank test. HUI-3, a component of the PROMIS score, is a multiattribute health status classification system. CZ, Confidence level; IQR, interquartile range; HUI, Health Utility Index.
EGIDs and their similarities with other inflammatory conditions (e.g., inflammatory bowel disease), a multipronged approach to disease remission is critical. Attempts to achieve mucosal healing in addition to histologic and symptomatic outcomes may be warranted. This is a similar approach to that used in inflammatory bowel disease, for which mucosal healing serves as an important clinical end point and has been incorporated into clinical guidelines.31 Given the complications that can occur with EGIDs (e.g., perforating ulcers, bowel obstructions, malnutrition), endoscopic healing is also an important end point to meet.32 These results are promising, and using EGREFS in future studies may strengthen these findings.

Although there are no agreed-on validated symptom scoring tools for EoG/EoGE, we used the SODA symptom questionnaire, which has been used in other longitudinal CEGIR studies and was the only symptom metric available at the time of study design. This metric showed significant reduction in pain intensity and non-pain scores as well as improvement in overall satisfaction after 6 weeks’ ELE. Given that the most common presenting symptom of EoG/EoGE is abdominal pain, these findings are relevant. This study was designed in 2016, before the start of other clinical trials in EoG, and therefore, at the time, no other symptom assessment tools were available for use. Use of newer targeted symptom assessment tools may have shown greater response if used in this study. A limitation to note was that this study did not have a placebo arm with a sham elemental diet that had allergenic proteins. While this could more accurately address any placebo response or the effect of spontaneous remission, the difficulty with pursuing formula diet in any patient and the severity of patient’s illness and concern for worsening disease with a sham elemental formula was deemed too great a patient burden by the study investigators and was not pursued. Although the dietary intervention of exclusively ELE can be severely restricting, we were impressed to find that QOL metrics improved after intervention according to PROMIS assessment; participants had improved depression and fatigue after 6 weeks’ ELE. These findings suggest that despite the restrictions that ELE can place on an individual, the effect of the treatment leading to improved symptoms may lead to improved satisfaction and QOL. Notably, the participants’ perceived effort in adhering to ELE decreased as the study continued. Further investigation of these posttreatment scores with a larger sample size may validate this finding.

Other exploratory end points, such as improvement in gastric transcriptome analysis, were noted. Participants had dysregulated

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**FIG 4.** Molecular efficacy of 6 weeks’ elemental diet in EoG. **A,** Paired comparison of EGDP_{18} score is plotted by group for before and after treatment. Markers represent individual subjects. EGDP_{18} score is inversely correlated with disease severity, with increase representing improvement. ****P < .01 by Wilcoxon matched-pairs signed rank test. **B** and **C,** Heat diagram of diagnostic subset of genes from EoG transcriptome (EGP18). Each column indicates collective gastric biopsy specimens taken from subjects before (left) and after treatment (right) in this prospective trial (ELEMENT study). **C,** Consecutive columns indicate gastric biopsy specimens taken from subjects of historic cohort (left, positive control) and before and after treatment in this prospective trial (ELEMENT study) (right). **D,** Differences in gene expression before and after treatment. Y-axis represents negative log_{10} P value determined by differential expression; red indicates genes significantly improved after versus before treatment. X-axis is organized by genes within functional groupings. NL, Healthy control.
EGDP scores that improved after 6 weeks’ ELE. Transcriptomic changes included improvements in pathways involved in type 2 inflammation, fibrosis, and neurosensation, collectively indicating a broad-spectrum benefit of the therapy. Although there was molecular improvement after treatment collectively, molecular responses were variable in each participant, potentially suggesting heterogeneity in EoG similar to the heterogeneity in EoE previously identified as endotypes. The improvements in genetic dysregulation and tissue eosinophilia are further findings indicative of tissue healing. Larger scale studies may validate these interesting findings.

As part of the exploratory outcomes, we evaluated correlation between histologic, biological, and clinical parameters to gain mechanistic insight into the disease. Measures of histology exhibited moderate-to-strong correlation with each other, consistent with prior studies. Notably, we found that most histologic measures exhibited weak-to-modest correlation with PROs captured by PROMIS and SODA. Importantly, PROMIS is a general questionnaire and may fail to capture disease-specific aspects of EoG/EoGE. Furthermore, SODA was designed to capture dyspepsia-related health and thus may not be the optimal measure to capture EoG/EoGE-related symptoms. Measures of histology (especially EGREFS, either total or components) were positively associated with serum eotaxin-3, IL-4, IL-5, IL-13, TARC, and TSLP but were negatively associated with IL-1α.

ELE was associated with apparent changes in commensal microbiota. There were significant decreases in Ruminococcaceae and Lachnospiraceae after treatment. Notably, Lachnospiraceae and Ruminococcaceae are associated with food allergies, and dietary interventions have been shown to affect the microbiome in prior studies, suggesting that these observed changes may be meaningful. Further investigations into EoG/EoGE populations before and after dietary interventions are warranted to understand whether these associations persist and their potential significance, given our small sample size.

To further evaluate whether food allergens drive inflammation in EoG/EoGE, we completed a systematic food reintroduction on participants whose disease had responded to therapy. Nearly all participants had recurrent disease, as demonstrated by recurrent histologic eosinophilia, after specific food triggers were reintroduced. Recurrence did not occur immediately after introducing table foods but rather when specific food triggers for each patient were encountered. These findings substantiate that withdrawal of food triggers, rather than bowel rest, is mechanistically responsible for the therapeutic benefit of ELE. The data presented have limitations. Some participants who had symptomatic recurrence
to foods stopped these foods before undergoing an endoscopy to minimize the number of endoscopic interventions performed, thereby potentially limiting identification of all potential food triggers. Development of minimally invasive tools or biomarkers to replace endoscopy for disease activity assessment could provide additional clarity in future studies. These data do, however, substantiate that individuals with EoG/EoGE have a multitude of food triggers driving their disease process, unlike individuals with EoE alone, who commonly have only single food triggers.37

This study demonstrates the effectiveness of ELE in treating EGIDs; however, there are considerations when using this approach. Importantly, ELE should be pursued by a trained team with proper dietary support. In this trial, all of the participants solely drank formula; no one utilized nonoral feeding. Participants had free access to their care providers throughout the trial and were closely monitored by a registered dietitian and gastroenterologists trained in treating EGID. Close clinical support affected a participant’s perception of effort on the diet; participants’ perceived effort decreased as the study progressed, highlighting that the initial transition to ELE is key, although ELE is not meant for long-term restriction. We suspect that the high adherence to ELE in this study compared to others using elemental formula in adult EoE was due to the patients’ disease severity, and therefore adherence may not be as stringent in milder forms of EoG/EoGE. Those pursuing this approach should take caution in patients with chronic kidney disease who are receiving multiple diuretics, given the concern for hypotension in this patient population if they are not following the recommended guidance on formula and free fluid intake. Cost of implementation of the formula diet is also of concern, as formula coverage is not universal in all states. These factors should be considered carefully before embarking on elemental formula therapy.

In conclusion, an amino acid–based elemental diet effectively improves histologic, symptomatic, endoscopic, and molecular disease activity. These data, along with disease relapse after food reintroduction, suggest a dominant role for food allergens in EoG/EoGE pathogenesis. These data provide evidence for the effectiveness of dietary therapy in individuals with non-EoE EGIDs, providing a much-needed alternative to corticosteroids and demonstrating improvement in PROs. Further investigation into the optimal length and type of dietary therapy in non-EoE EGIDs can facilitate personalizing this effective approach.

DISCLOSURE STATEMENT

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Disclosure of potential conflict of interest: N. Gonsalves serves as consultant (Allakos, Sanofi-Regeneron, AstraZeneca, Abbvie, Nutricia, Knopp Pharma, BMS) and on speakers bureau (Takeda, Sanofi-Regeneron) and receives royalties (UpToDate). B. Doerfler serves as consultant (Trellus) and on speakers bureau (Nutricia). T. Shoda is coinventor of patents for the EG Diagnostic Panel owned by Cincinnati Children’s Hospital Medical Center. S. Acieves serves as consultant (AstraZeneca, Regeneron), speaker (MedScape, Sanofi-Genzyme [Regeneron]), and coinventor of oral viscous budesonide (patented by the University of California, San Diego, and licensed by Takeda). G. Furuta is a founder of EnteroTrack and serves as consultant (Shire/Takeda), M. E. Rothenberg is consultant (Pulm One, Spoon Guru, ClostraBio, Serpin Pharm, Allakos, Celldex, Bristol Myers Squibb, AstraZeneca, Ellodi Pharma, GlaxoSmithKline, Regeneron/Sanofi, Revolo Biotherapeutics, Guidepoint) and has equity interest in the first 6 listed and royalties from restizumab (Teva Pharmaceuticals), PEESSv2 (Mapi Research Trust), and UpToDate; and is an inventor of patents owned by Cincinnati Children’s Hospital. I. Hirano receives research funding (Adare/Ellodi, Allakos, Arena, AstraZeneca, Meritage, Celgene/Receptors/BMS, Regeneron, Shire/Takeda) and is a consultant (Adare/Ellodi, Allakos, Amgen, Arena, AstraZeneca, Celgene/Receptors/BMS, Eli Lilly, EsoCap, Gossamer Bio, Parexel/Calyx, Phathom, Regeneron/Sanofi, Shire/Takeda). The rest of the authors declare that they have no relevant conflicts of interest.

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Clinical implications: An elemental diet is effective in controlling gastrointestinal eosinophilia in EoG/EoGE, with demonstrated improvement in histologic, endoscopic, symptomatic, QOL, and molecular parameters after treatment.

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