One-food versus six-food elimination diet therapy for the treatment of eosinophilic oesophagitis: a multicentre, randomised, open-label trial

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Summary

Background Empirical elimination diets are effective for achieving histological remission in eosinophilic oesophagitis, but randomised trials comparing diet therapies are lacking. We aimed to compare a six-food elimination diet (6FED) with a one-food elimination diet (1FED) for the treatment of adults with eosinophilic oesophagitis.

Methods We conducted a multicentre, randomised, open-label trial across ten sites of the Consortium of Eosinophilic Gastrointestinal Disease Researchers in the USA. Adults aged 18–60 years with active, symptomatic eosinophilic oesophagitis were centrally randomly allocated (1:1; block size of four) to 1FED (animal milk) or 6FED (animal milk, wheat, egg, soy, fish and shellfish, and peanut and tree nuts) for 6 weeks. Randomisation was stratified by age, enrolling site, and gender. The primary endpoint was the proportion of patients with histological remission (peak oesophageal count <15 eosinophils per high-power field [eos/hpf]). Key secondary endpoints were the proportions with complete histological remission (peak count ≤1 eos/hpf) and partial remission (peak counts ≤10 and ≤6 eos/hpf) and changes from baseline in peak eosinophil count and scores on the Eosinophilic Esophagitis Histology Scoring System (EoEHSS), Eosinophilic Esophagitis Endoscopic Reference Score (EREFS), Eosinophilic Esophagitis Activity Index (EEsAI), and quality of life (Adult Eosinophilic Esophagitis Quality-of-Life and Patient Reported Outcome Measurement Information System Global Health questionnaires). Individuals without histological response to 1FED could proceed to 6FED, and those without histological response to 6FED could proceed to swallowed topical fluticasone propionate 880 µg twice per day (with unrestricted diet), for 6 weeks. Histological remission after switching therapy was assessed as a secondary endpoint. Efficacy and safety analyses were done in the intention-to-treat (ITT) population. This trial is registered on ClinicalTrials.gov, NCT02778867, and is completed.

Findings Between May 23, 2016, and March 6, 2019, 129 patients (70 [54%] men and 59 [46%] women; mean age 37·0 years [SD 10·3]) were enrolled, randomly assigned to 1FED (n=67) or 6FED (n=62), and included in the ITT population. At 6 weeks, 25 (40%) of 62 patients in the 6FED group had histological remission compared with 23 (34%) of 67 in the 1FED group (difference 6% [95% CI –11 to 23]; p=0·58). We found no significant difference between the groups at stricter thresholds for partial remission (≤10 eos/hpf, difference 7% [–9 to 24], p=0·46; ≤6 eos/hpf, 14% [–0 to 29], p=0·069); the proportion with complete remission was significantly higher in the 6FED group than in the 1FED group (difference 13% [2 to 25]; p=0·031). Peak eosinophil counts decreased in both groups (geometric mean ratio 0·72 [0·43 to 1·20]; p=0·21). For 6FED versus 1FED, mean changes from baseline in EoEHSS (–0·23 *vs* –0·15; difference –0·08 [–0·21 to 0·05]; p=0·23), EREFS (–1·0 *vs* –0·6; difference –0·4 [–1·1 to 0·3]; p=0·28), and EEsAI (–8·2 *vs* –3·0; difference –5·2 [–11·2 to 0·8]; p=0·091) were not significantly different. Changes in quality-of-life scores were small and similar between the groups. No adverse event was observed in more than 5% of patients in either diet group. For patients without histological response to 1FED who proceeded to 6FED, nine (43%) of 21 reached histological remission; for patients without histological response to 6FED who proceeded to fluticasone propionate, nine (82%) of 11 reached histological remission.

Interpretation Histological remission rates and improvements in histological and endoscopic features were similar after 1FED and 6FED in adults with eosinophilic oesophagitis. 6FED had efficacy in just less than half of 1FED non-responders and steroids had efficacy in most 6FED non-responders. Our findings indicate that eliminating animal milk alone is an acceptable initial dietary therapy for eosinophilic oesophagitis.

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Research in context

Evidence before this study

Eosinophilic oesophagitis is a chronic inflammatory and fibrostenotic disorder of the oesophagus that results from the generation of a T-helper type 2 allergic immune response, driven by adaptive and innate immunity triggered by common foods. Although effective pharmacological treatments are available, the most intuitive therapy is to identify and eliminate specific food exposures, thereby preventing initiation of the inflammatory cascade. However, no reliable tests are readily available to identify the triggering foods. As a result, empirical elimination of the six most common food allergens (the six-food elimination diet [6FED]; milk, wheat, soy, eggs, nuts, and seafood) is often used to achieve histological remission. Foods are then added back one by one and the mucosal response is assessed by endoscopy with biopsy. As the 6FED includes common foods that are not easy to eliminate and multiple endoscopies are commonly required to monitor response, it does not have high patient acceptance despite being shown to be highly efficacious (around 70% histological response rate) in non-randomised retrospective and prospective studies. Uncontrolled trials have shown that elimination of a single food (animal milk; 1FED), can lead to remission in 30–60% of paediatric patients with eosinophilic oesophagitis, questioning the need to start with avoidance of the six common foods. We searched PubMed using the terms "eosinophilic esophagitis" and "diet" for articles published from database inception to Sept 1, 2022. No language restriction was applied. The literature search confirmed that no randomised trials have evaluated 1FED or 6FED in adults, despite studies suggesting meaningful efficacy of 1FED in paediatric patients and high response rate to 6FED in adult patients. The effect of diet therapy on a series of validated disease-specific outcomes and biomarkers (in adult or paediatric patients) has also not been reported.

Added value of this study

In this multicentre randomised trial, we compared 1FED and 6FED head-to-head in adults with eosinophilic oesophagitis. This study, with assignment of diet therapy for 6 weeks, found similar efficacy between the diet therapies in achieving histological remission (the primary endpoint; peak oesophageal count <15 eosinophils per high-power field). Improvements were similar in endoscopy and histology scores and no significant difference was found in overall symptom score between the elimination diets, according to validated metrics specific to eosinophilic oesophagitis. Adherence to both diets during the 6 weeks was high. In patients who had a histological response (remission) to the diet therapies, we observed reversibility of diverse molecular pathways in the oesophagus, which is an effect of diet treatment that has not been shown previously. Baseline serum concentrations of milk-specific IgG4 were associated with response to 1FED. Additionally, for non-responders to 1FED who proceeded to 6FED, 43% had a histological response, and for non-responders to 6FED who proceeded to topical swallowed steroid therapy, 82% had a histological response. Few studies have examined a change from dietary therapy to topical steroids, and this study provides data to support this strategy in adults.

Implications of all the available evidence

Our findings show that for patients with eosinophilic oesophagitis who are interested in pursuing empirical diet therapy, an acceptable approach is to start with the easier 1FED strategy (elimination of animal milk only) rather than more restrictive 6FED therapy. Furthermore, the findings indicate that serum IgG4 concentrations to major cow's milk proteins could potentially serve as a marker of milk reactivity in at least some patients. The presented results contrast with the previously reported higher response rates quoted for patients treated with 6FED in non-controlled studies. Taken together, these results highlight diet elimination therapy, particularly with milk elimination alone, as an attractive initial approach for adults with eosinophilic oesophagitis.

Introduction

Eosinophilic oesophagitis is a chronic disease characterised by dense oesophageal mucosal eosinophilia and inflammation leading to structural changes in the oesophagus, including stricture formation.[1] The clinical presentation varies with age, initially reflecting an inflammatory phenotype manifesting with symptoms such as abdominal pain, nausea, and vomiting in childhood, and progressing to a fibrostenotic form signalled mostly by dysphagia in adolescence and adulthood.[2] Disease origins are complex, with contributions from genetic predisposition,[3,4] an impaired epithelial barrier associated with the loss of anti-proteases,[5] a potentially altered microbiome,[6] and key environmental exposures.[7] On a cellular basis, eosinophilic oesophagitis is associated with a T-helper-2 (Th2)-mediated immune pathway and the contribution of key cytokines, such as IL-4, IL-5, and IL-13, and cells in addition to eosinophils, including T and B lymphocytes, epithelial cells, and mast cells.[8]

The mainstays of medical therapy for eosinophilic oesophagitis include swallowed topical corticosteroids and proton pump inhibitors.[9] Biological therapies have also been shown to have efficacy in clinical trials.[10] Biological and non-biological therapies overall have favourable efficacy but are limited by concerns over short-term and long-term side-effects. An effective therapy with minimal side-effects remains a key aim of clinical research. Diet therapy has the potential to fulfil this aim. A large body of data supports food antigen exclusion in the treatment of eosinophilic oesophagitis. For example, the pathogenesis of eosinophilic oesophagitis has many similarities with an allergic response to food allergen exposure,[8] and an elemental

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For the **study protocol** see https://clinicaltrials.gov/ProvidedDocs/67/NCT02778867/Prot_002.pdf

diet, which is devoid of all food antigens, leads to a histological remission rate of more than 90% in adult and paediatric patients with eosinophilic oesophagitis.[11] Similarly, the empirical elimination of common food allergens, including milk, wheat, egg, soy, nuts, and seafood, has been shown to induce histological remission in about 70% of paediatric and adult patients in observational and interventional studies.[11] As a result, a basis of therapy for eosinophilic oesophagitis has been empirical elimination diets based on the most common food allergens.

A controversy in diet-based therapy for eosinophilic oesophagitis is whether to initially exclude a long list of possible food triggers or start with a smaller number of the most common food antigens that trigger oesophageal eosinophilia.[12] Excluding many potential triggers increases the likelihood that histological improvement will be reached at the cost of markedly restricting diet when eliminating six or more commonly consumed food types. Avoiding fewer foods might facilitate improved compliance but presumably lessens the chance of response. Although single and multicentre studies have evaluated more and less restrictive diet exclusion therapy in patients with eosinophilic oesophagitis,[12–15] no randomised trials in adults have compared diet strategies. Although one study used a modelling approach to address this question,[16] patient data comparing diet therapies are scarce. In addition, whether topical steroid therapy is a successful option for patients who do not respond to food elimination is not clear. A further unknown is whether response to diet therapy in adults is associated with molecular improvement in the oesophagus, such as in markers measured with the eosinophilic oesophagitis diagnostic panel (EDP).[3] The value of other biomarkers, such as serum food-specific immunoglobulins, in predicting response to diet therapy also remains uncertain.[17] Therefore, the aims of this study were to compare the efficacy of a one-food elimination diet (1FED; animal milk) with a six-food elimination diet (6FED; animal milk, egg, wheat, soy, fish and shellfish, and peanut and tree nuts) on clinical and histological endpoints in patients with eosinophilic oesophagitis and to assess the association of biomarkers (milk-specific immunoglobulins, T cells, and oesophageal RNA transcripts) with response to diet. We also assessed whether steroid therapy is efficacious in individuals who were non-responsive to 6FED. The primary hypothesis was that 6FED would be superior to 1FED in achieving histological remission.

Methods

Study design and participants

See Online for appendix

We did a multicentre, randomised, open-label trial at ten sites (appendix p 6) of the Consortium of Eosinophilic Gastrointestinal Disease Researchers in the USA. The study protocol was performed in accordance with the principles of the Declaration of Helsinki and is available online. The protocol was approved by the central institutional review board at Cincinnati Children's Hospital Medical Center (Cincinnati, OH, USA) and by institutional review boards at participating sites. All participants provided written informed consent.

Patients eligible for enrolment were aged 18–60 years with a confirmed diagnosis of eosinophilic oesophagitis as per consensus guidelines[18] in place at the time of study initiation, which included non-response to a trial of a proton pump inhibitor. Patients were included if they had histologically active disease within the 12-week screening period (defined as ≥15 eosinophils per high-power field [eos/hpf] in at least one segment among the distal, mid-section, and proximal regions of the oesophagus), and active symptoms of eosinophilic oesophagitis in the month before enrolment. Key exclusion criteria were treatment with topical swallowed steroids within 2 months of enrolment or systemic steroids within 3 months; pathological eosinophilia in the gastrointestinal tract other than the oesophagus; gastrointestinal malabsorption disorders; current avoidance of animal milk due to allergy; current dietary therapy with 1FED or 6FED; and previous non-response to 6FED or 1FED with documentation in the medical record of strict adherence to the diet or non-response to topical steroids (ie, no histological remission at <15 eos/hpf after high-dose topical steroid treatment). Patients were not required to be consuming all other food antigens (ie, egg, wheat, soy, fish or shellfish, and peanut or tree nuts) as some patients might have had concomitant IgE-mediated food allergy to these foods. Medications (proton pump inhibitors, allergy medications, and asthma medications) prescribed before study entry were required to be maintained at the same dose. Full eligibility criteria are listed in the appendix (p 2). Patients were recruited in the clinical practices of each enrolling site and via referral from local health providers.

Randomisation and masking

Patients were centrally randomly assigned (1:1) to 1FED or 6FED according to a restricted randomisation protocol. The allocation sequence was generated by the Data Management and Coordination Center of the Rare Diseases Clinical Research Network at the University of South Florida (Tampa, FL, USA) with a random number generator in SAS software. The Data Management and Coordination Center provided clinical trial data management support and project management support and was not involved in enrolling patients. The treatment allocation sequence was stored at the Data Management and Coordination Center and was not available to enrolling investigators. Randomisation was stratified by age (≤30 years or >30 years), enrolling study site, and gender (male or female) with a block size of four. At randomisation, the Data Management and Coordination Center generated an electronic notification (email) with the treatment assignment, which was sent to the study

coordinator and principal investigator at the enrolling study site. Study site investigators and staff enrolled participants and completed study assessments. As this study followed an open-label design, site investigators, site staff, and participants were aware of treatment assignment after randomisation. Research pathologists assessing biopsies were masked to allocation. Laboratory investigators were masked to histological response to treatment until after samples were analysed but were not masked to treatment assignment. Statisticians were not masked to treatment assignment when conducting analyses.

Procedures

Patients were screened for eligibility during scheduled screening visits and underwent an oesophagogastroduodenoscopy during a 12-week screening period. Historical biopsies were allowed if collected within the screening period. Eligible participants underwent randomisation after the screening period of up to 12 weeks. The study was divided into two treatment phases. After randomisation, in phase 1 of the study, participants followed the 1FED (animal milk elimination) or 6FED (animal milk, egg, wheat, soy, fish and shellfish, and peanut and tree nut elimination) for 6 weeks. The length of the intervention was based on previous diet studies in adults who had histological remission at 6 weeks.[13–15] Patients were counselled to avoid consumption of all foods containing these ingredients. All animal milk was eliminated due to potential cross-reactivity of cow, goat, and sheep milk proteins.[19] Milk was chosen as the single food to avoid on the basis of previous diet studies indicating that milk was one of the most common food triggers in adults with eosinophilic oesophagitis[14,15] and the most frequent single causative food antigen in the majority of children with eosinophilic oesophagitis.[11] Although wheat was identified as the most common trigger in one study in adults,[13] the available evidence at the time of initiating our study also supported milk as the most common single causative food in adults.[15] Patients assigned to 6FED eliminated wheat but were not required to follow a gluten-free diet (ie, the elimination of barley and rye, in addition to wheat, was not required). After diet elimination for 6 weeks, an oesophagogastroduodenoscopy with biopsy was done to assess histological response. Individuals with treatment response (ie, histological remission; peak oesophageal eosinophil count <15 eos/hpf[20]) completed the study at phase 1. Individuals without histological response after study treatment could choose whether to continue into phase 2, in which individuals who did not respond to 1FED advanced to 6FED, and those who did not respond to 6FED proceeded to topical swallowed steroids (fluticasone propionate, 880 µg twice per day).[21] A maximum of 4 weeks was allowed from the completion of phase 1 to the initiation of phase 2. Participants returned to an unrestricted diet before beginning topical swallowed steroid therapy. After 6 weeks of phase 2 therapies, a repeat endoscopy was done and outcomes were re-assessed. The study schematic is provided in the appendix (p 16).

Histological, endoscopic, and patient-reported data were collected at baseline (ie, during the 12-week screening period and the randomisation visit, before starting the treatment) and at the end of phase 1 and phase 2. Biopsies were evaluated in a masked fashion by central pathologists for histological eosinophil count and features with use of the Eosinophilic Esophagitis Histology Scoring System (EoEHSS).[22] Endoscopic evaluations were completed with use of the Eosinophilic Esophagitis Endoscopic Reference Score (EREFS).[23] Patient-reported outcomes, completed solely by patients, were collected with the Eosinophilic Esophagitis Activity Index (EEsAI),[24] the Adult Eosinophilic Esophagitis Quality-of-Life questionnaire (EoE-QOL-A),[25] and the Patient Reported Outcome Measurement Information System Global Health (PROMIS GH)[26] short-form questionnaire. Details of these assessments are in the appendix (p 3). At baseline and the end of phase 1, whole blood was collected for assessment of T cells and serum was collected for assessment of milk-specific immunoglobulins, and biopsies were collected for transcriptome analysis with the EDP[3] (appendix p 4). T cells were analysed for markers of activation ($CD4^+CD154^+$) and cytokine production (IL-4, IL-5, and IL-13) ex vivo. At baseline, participants underwent skin prick testing for eliminated food allergens and those with a negative prick test to cow's milk underwent cow's milk patch testing (appendix p 4). Adverse events were recorded from time of consent until the end of patient study participation. Adverse events were assessed every 1–2 weeks (at study visits) by the site investigator, site staff, or both via observation or interview of the patient. Patients were encouraged to report changes in health in between the study visits. In phase 2, morning cortisol concentrations were measured before and after topical swallowed steroid therapy as a safety laboratory test. Adverse events were reported using National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0).

Standardised instructions for following the elimination diets were created by registered dietitians with expertise in food elimination therapies and were used across all sites (appendix pp 24–43). Patients were instructed on reading food labels to identify allergens, dining out while on the diet, and avoiding cross contact with allergens. Substitution guides (allowed foods) for eliminated allergens were also provided. A dietary questionnaire (administered to patients at week 5) to help detect whether food antigens were successfully eliminated, 3-day food diaries completed by patients during week 5 of the intervention, and dietitian input from evaluations of patients' diets or information received during phone visits were used to determine compliance with the

elimination diets. Participants who excluded all foods containing the allergens according to their assigned diet and those who had only rare (less than once a week) exposure to excluded allergens were considered compliant with the assigned diet. The rare exposures could include one or more allergens. The standardised instructions provided to patients for administering topical swallowed fluticasone propionate during phase 2 of the study are provided in the appendix (p 3).

Outcomes

The primary endpoint was the proportion of participants with histological remission (peak oesophageal count <15 eos/hpf)[20] at the end of therapy at 6 weeks (phase 1). Key secondary endpoints in phase 1 included the proportions of patients with complete remission (peak count ≤1 eos/hpf) and partial remission (peak counts ≤10 eos/hpf and ≤6 eos/hpf) and change from baseline in peak eosinophil count and in EoEHSS, EREFS, EEsAI, EoE-QOL-A, and PROMIS GH scores. Other secondary endpoints included EDP total score; the association of baseline characteristics, baseline skin prick and patch test results, and EDP with histological response to the diets; the correlation of patch test results with T cells; and the association of T cells and markers and serum concentrations of milk-specific immunoglobulins with histological response to 1FED. The association of T cells and markers with histological response in all participants and the association of consuming barley and rye with histological response to 6FED were added as post-hoc endpoints. The secondary endpoint in phase 2 was the rate of histological remission (peak count <15 eos/hpf) in non-responders to 6FED who proceeded to fluticasone propionate and in non-responders to 1FED who proceeded to 6FED, measured after 6 weeks of the secondary therapies. Post-hoc endpoints in phase 2 included additional rates of remission (peak counts ≤10 eos/hpf, ≤6 eos/hpf, and ≤1 eos/hpf) and change from the start of phase 2 in peak eosinophil count, EoEHSS, and EREFS. All histology outcomes, including peak eosinophil count for the primary outcome, were assessed by the central review pathology committee of the Consortium of Eosinophilic Gastrointestinal Disease Researchers.

Statistical analysis

The sample size was based on the primary endpoint. We estimated that histological remission rate at the end of phase 1 would be 45% for the 1FED group and 70% for the 6FED group.[11,13–15] A sample size of 60 patients per group (120 total patients) would provide at least 80% power to detect a difference in rates between groups of 25% with a two-sided α value of 0·05. Sample size calculations were done in PASS software (version 12). To ensure sufficient power even after dropout, the targeted sample size was increased to 136 total participants to allow 15% dropout. In May, 2019, the dropout rate was evaluated and found to be 3·9%, and thus recruitment was stopped at 129 participants, with five patients not completing the study.

The analysis population for the primary and key secondary endpoints in phase 1 was the intention-to-treat (ITT) population, which included all patients who completed the enrolment visit after the screening period and were randomly assigned into the study. Enrolled patients who withdrew from the study were imputed as non-responders (ie, did not reach histological remission). Data missing at the end of treatment for continuous outcomes were imputed with the last measure carried forward. A prespecified complete case analysis for primary and key secondary endpoints was conducted as a sensitivity analysis to compare with the ITT population. Complete cases included patients who completed phase 1 with observed data at baseline and week 6 for the outcome of interest. The analysis population for secondary and post-hoc endpoints in phase 2 was the ITT population, which included all patients who opted to proceed into phase 2. Patients who withdrew from phase 2 were imputed as non-responders, and data missing at the end of treatment for continuous outcomes were imputed with the last measure carried forward. The association of baseline characteristics and skin prick and patch test results with histological response to the diets was also conducted in the ITT population. Molecular biomarker analysis (EDP, T cells, and serum immunoglobulins; appendix p 4) was completed on the subset of patients with intact samples. Safety analysis was conducted on data collected from the ITT populations (all patients who were randomly assigned into phase 1 and all patients opting into phase 2).

Baseline characteristics were summarised for the two treatment groups as mean (SD) or median (IQR) for continuous variables and frequency (%) for categorical variables. Comparisons between groups were made with the two-sample *t* test (normally distributed data) for continuous variables and the Fisher's exact test for categorical variables. Comparisons within groups were assessed with paired *t* tests. Distributions were assessed using the Kolmogorov-Smirnov test with the univariate procedure in SAS (version 9.4). Log transformation was used in the analysis of data that followed a log normal distribution. Log data were back-transformed to geometric means for presentation. Differences in log data (change from baseline and differences between groups) were back-transformed to geometric mean ratios. To assess associations of allergy testing, EDP score, T-cell results, milk-specific immunoglobulins, and consuming barley and rye with histological response to treatment, comparisons between histological responders and non-responders were made with two-sample *t* tests for continuous variables and Fisher's exact tests for categorical variables. Logistic regression was used to test the association of baseline characteristics (age, gender, race, oesophageal peak eosinophil count, diet treatments, and atopy) with week 6 remission in the overall population. Association was tested using Fisher's exact

test stratified by diet if significant interaction was found. Statistical significance was indicated at a nominal two-sided α of 0·05. For continuous variables, 95% CIs for arithmetic means and mean differences were calculated with use of Student's *t* distribution; 95% CIs for geometric means and mean ratios were calculated using proc ttest in SAS (version 9.4); and for proportions and proportion differences, 95% Wald confidence limits were used. Statistical analyses were done with SAS software (version 9.4). A data and safety monitoring board, independent of trial investigators, reviewed all safety data and the conduct of the trial once a year. This study was registered with ClinicalTrials.gov, NCT02778867.

Role of the funding source

The funder of the study had a role in study design via a medical monitor and research nurse appointed by the US National Institutes of Health. The funder did not have a role in data collection, data analysis, data interpretation, or writing of the report.

Results

Patients were enrolled between May 23, 2016, and March 6, 2019. Of 143 patients screened for the trial, 129 were eligible, completed enrolment, and were randomly assigned to diet therapy. 67 patients were allocated to 1FED and 62 to 6FED, comprising the ITT population. Recruitment was stopped once 129 patients were enrolled (with 124 completing phase 1 of the study) as the estimated sample size to meet the target power was achieved. Study allocation, discontinuations, and analysis populations are summarised in figure 1. The mean age of participants was 37·0 years (SD 10·3). Gender was distributed almost evenly (70 [54%] men and 59 [46%] women) and 124 (96%) patients were White. Patient demographics and baseline characteristics were mostly similar between the two treatment groups (table 1), except for peak oesophageal eosinophil count, which was higher in the 1FED group than in the 6FED group.

In the ITT population, the proportion of patients who had the primary endpoint of histological remission (peak oesophageal eosinophil count <15 eos/hpf) after 6 weeks of diet therapy was 25 (40%) of 62 in the 6FED group, compared with 23 (34%) of 67 in the 1FED group, representing a non-significant difference of 6% (95% CI –11 to 23; p=0·58). We also found no significant difference between the groups at stricter thresholds for partial remission (≤10 eos/hpf difference 7% [–9 to 24], p=0·46; ≤6 eos/hpf, 14% [–0 to 29], p=0·069). By contrast, the proportion with complete remission (peak count ≤1 eos/hpf) was 12 (19%) of 62 in the 6FED group, compared with four (6%) of 67 in the 1FED group, representing a significant difference of 13% (2 to 25; p=0·031; table 2). Both 1FED and 6FED were associated with decreases compared with baseline in maximum oesophageal eosinophil count, and the magnitude of the reductions was similar between the 1FED and 6FED groups (table 3; appendix p 17).

EoEHSS total score was improved from baseline in both groups with a mean change of –0·23 points (95% CI –0·32 to –0·14) in the 6FED group compared with –0·15 points (–0·25 to –0·06) in the 1FED group (mean change difference –0·08 [95% CI –0·21 to 0·05]; p=0·23; table 3). Improvement in EoEHSS inflammatory feature subscore in the 6FED group was similar to improvement in the 1FED group (–0·24 [95% CI –0·35 to –0·13] *vs* –0·20 [–0·31 to –0·08]) with a small difference between the groups (–0·05 [95% CI –0·20 to 0·11]; p=0·56). Mean change in EoEHSS histological architectural feature subscore in the 6FED group was more than twice that in the 1FED group (–0·23 [95% CI –0·32 to –0·13] *vs* –0·10 [–0·21 to 0·0042]) but the difference between groups was not significant (–0·13 [95% CI –0·27 to 0·01]; p=0·077; appendix p 18).

Maximum EREFS total scores decreased from baseline in both groups, with a mean change of –1·0 points (95% CI –1·5 to –0·4) in the 6FED group compared with –0·6 points (–1·0 to –0·2) in the 1FED group (mean change difference –0·4 [95% CI –1·1 to 0·3]; p=0·28; table 3). The mean change in

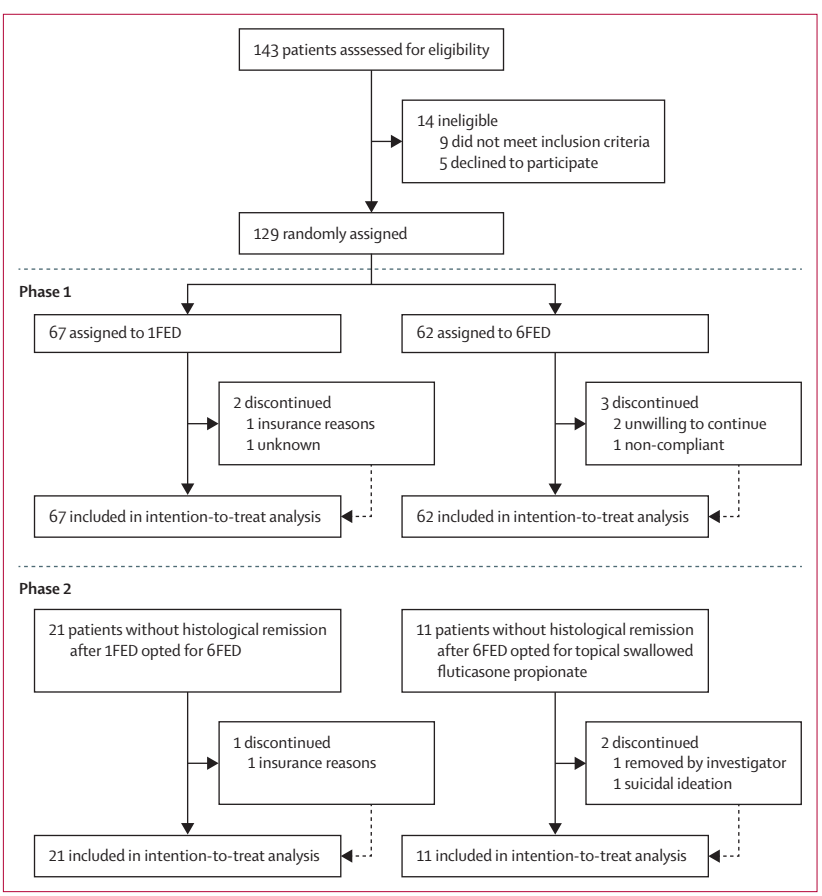


Figure 1: **Trial profile**
1FED=one-food elimination diet. 6FED=six-food elimination diet.

	1FED (n=67)	6FED (n=62)
Age, years	36·4 (10·2)	37·8 (10·4)
≤30 years	18 (27%)	15 (24%)
Gender		
Male	37 (55%)	33 (53%)
Female	30 (45%)	29 (47%)
Race		
White	63 (94%)	61 (98%)
Asian	2 (3%)	0
White and Asian	1 (1%)	0
Black	0	1 (2%)
Refused	1 (1%)	0
Eosinophilic oesophagitis history		
Years since diagnosis	0·3 (0·1–2·1)	0·2 (0·1–1·8)
Previous dilation	29 (43%)	26 (42%)
Concomitant proton pump inhibitor treatment	41 (61%)	43 (69%)
Symptoms		
Food impaction	32 (48%)	30 (48%)
Dysphagia	57 (85%)	55 (89%)
Chest pain	31 (46%)	17 (27%)
Heartburn	40 (60%)	34 (55%)
Abdominal pain	21 (31%)	14 (23%)
Symptom and quality-of-life scores		
EEsAI total	29·3 (19·3)	30·1 (18·2)
EoE-QoL-A total	68·9 (15·5)	64·2 (17·0)
PROMIS GH physical health T-score	49·4 (5·9)	50·6 (6·9)
PROMIS GH mental health T-score	50·0 (6·3)	51·7 (7·3)
Atopic conditions		
Asthma	11 (16%)	17 (27%)
Food allergies	16 (24%)	8 (13%)
Eczema	2 (3%)	3 (5%)
Allergic rhinitis or sinusitis	22 (33%)	28 (45%)
Urticaria	0	1 (2%)
Oral allergy syndrome	2 (3%)	0
Endoscopic findings		
Oedema	43/58 (74%)	39/49 (80%)
Rings	41/58 (71%)	42/49 (86%)
Exudates	33/58 (57%)	33/49 (67%)
Furrows	46/58 (79%)	40/49 (82%)
Stricture	20/58 (34%)	15/49 (31%)
Stricture diameter, mm	15·0 (2·4)	14·7 (3·0)
EREFS*		
Total score	3·7 (1·8)	4·2 (1·8)
Inflammatory score	2·4 (1·2)	2·5 (1·2)
Fibrostenotic score	1·3 (1·0)	1·7 (1·0)
(Table 1 continues in next column)		
(Continued from previous column)		
Histological features		
Peak eosinophil count†, eos/hpf	58 (25–79)	38 (25–61)
EoEHSS‡		
Total score	0·83 (0·26)	0·81 (0·25)
Grade	0·43 (0·16)	0·42 (0·14)
Stage	0·39 (0·13)	0·39 (0·13)
Inflammatory score	0·62 (0·34)	0·59 (0·34)
Architectural score	1·09 (0·26)	1·10 (0·23)

Data are n (%); n/N (%), where N is patients with available data; mean (SD); or median (IQR). 1FED=one-food elimination diet. 6FED=six-food elimination diet. EEsAI=Eosinophilic Esophagitis Activity Index. EoE-QOL-A=Adult Eosinophilic Esophagitis Quality of Life. EREFS=Eosinophilic Esophagitis Endoscopic Reference Score. eos/hpf=eosinophils per high-power field. EoEHSS=Eosinophilic Esophagitis Histology Scoring System. PROMIS GH=Patient Reported Outcome Measurement Information System Global Health. *Maximum score between distal and proximal oesophagus in patients with available data in the 1FED group (n=58) and 6FED group (n=49). †Peak eosinophil count is the highest eosinophil count among the distal, mid-section, and proximal oesophagus. ‡Maximum score among distal, mid-section, and proximal oesophagus.

Table 1: **Baseline characteristics (intention-to-treat population)**

	1FED (n=67)	6FED (n=62)	Percentage point difference*	p value
<15 eos/hpf†	23 (34%; 23 to 46)	25 (40%; 28 to 53)	6% (–11 to 23)	0·58
≤10 eos/hpf	20 (30%; 19 to 41)	23 (37%; 25 to 49)	7% (–9 to 24)	0·46
≤6 eos/hpf	12 (18%; 9 to 27)	20 (32%; 21 to 44)	14% (–0 to 29)	0·069
≤1 eos/hpf	4 (6%; 0 to 12)	12 (19%; 10 to 29)	13% (2 to 25)	0·031

Data are n (%; 95% CI) or % (95% CI). p values were calculated with Fisher's exact test. 1FED=one-food elimination diet. 6FED=six-food elimination diet. eos/hpf=eosinophils per high-power field. *6FED versus 1FED. †Primary endpoint.

Table 2: **Proportion of patients in histological remission (intention-to-treat population)**

EREFS fibrostenotic feature subscore was –0·09 (95% CI –0·28 to 0·11) in the 1FED group and –0·35 (–0·55 to –0·14) in the 6FED group, representing a difference of –0·26 (95% CI –0·54 to 0·02; p=0·068). Changes in EREFS inflammatory abnormalities were similar between the 6FED and 1FED groups (–0·63 [95% CI –1·09 to –0·17] *vs* –0·52 [–0·86 to –0·17]) with a difference of –0·12 (95% CI –0·67 to 0·44; p=0·68; appendix p 18). Changes in individual endoscopic feature scores are summarised in the appendix (p 7).

Mean changes in EEsAI total score were –8·2 points (95% CI –12·6 to –3·8) in the 6FED group compared with –3·0 points (–7·2 to 1·2) in the 1FED group (mean change difference –5·2 [95% CI –11·2 to 0·8]; p=0·091; table 3). Subscores measuring pain associated with swallowing decreased by a significantly greater extent in the 6FED group than in the 1FED group (appendix p 8).

Mean EoE-QoL-A total scores did not change within either group compared with baseline (table 3). Subscore related to eating and diet impact worsened in both groups, although the changes were small and not significantly different between the groups (appendix p 9). We identified small improvements in the PROMIS GH mental health T-scores and physical health T-scores after treatment

	1FED (n=67)			6FED (n=62)			6FED *vs* 1FED	
	Baseline	Week 6	Change from baseline to week 6	Baseline	Week 6	Change from baseline to week 6	Change difference (95% CI)	p value
Peak eosinophil count, eos/hpf	50·3 (42·2 to 60·0)	20·8 (15·0 to 28·9)	0·41 (0·29 to 0·57)	38·4 (32·8 to 44·9)	10·9 (7·3 to 16·5)	0·29 (0·20 to 0·43)	0·72 (0·43 to 1·20)	0·21
EoEHSS total	0·83 (0·77 to 0·90)	0·68 (0·60 to 0·76)	–0·15 (–0·25 to –0·06)	0·81 (0·74 to 0·88)	0·58 (0·50 to 0·65)	–0·23 (–0·32 to –0·14)	–0·08 (–0·21 to 0·05)	0·23
EoEHSS grade	0·43 (0·39 to 0·47)	0·34 (0·30 to 0·38)	–0·09 (–0·14 to –0·04)	0·42 (0·39 to 0·46)	0·30 (0·26 to 0·33)	–0·13 (–0·17 to –0·08)	–0·04 (–0·11 to 0·03)	0·26
EoEHSS stage	0·39 (0·36 to 0·42)	0·33 (0·29 to 0·37)	–0·06 (–0·11 to –0·01)	0·39 (0·35 to 0·42)	0·28 (0·24 to 0·32)	–0·11 (–0·15 to –0·06)	–0·04 (–0·11 to 0·02)	0·21
EREFS total	3·7 (3·3 to 4·2)	3·0 (2·5 to 3·4)	–0·6 (–1·0 to –0·2)	4·2 (3·7 to 4·7)	2·8 (2·3 to 3·3)	–1·0 (–1·5 to –0·4)	–0·4 (–1·1 to 0·3)	0·28
EEsAI total	29·3 (24·5 to 34·2)	26·1 (21·3 to 30·9)	–3·0 (–7·2 to 1·2)	30·1 (25·4 to 34·7)	21·7 (17·5 to 25·9)	–8·2 (–12·6 to –3·8)	–5·2 (–11·2 to 0·8)	0·091
EoE-QoL-A total	68·9 (65·0 to 72·7)	67·1 (62·7 to 71·5)	–0·9 (–3·5 to 1·6)	64·2 (59·9 to 68·6)	63·9 (59·7 to 68·1)	–0·3 (–3·3 to 2·7)	0·6 (–3·3 to 4·5)	0·76
PROMIS GH physical health T-score	49·4 (48·0 to 50·9)	50·8 (49·3 to 52·2)	1·3 (0·4 to 2·2)	50·6 (48·8 to 52·4)	52·2 (50·7 to 53·8)	1·6 (0·5 to 2·8)	0·4 (–1·0 to 1·7)	0·61
PROMIS GH mental health T-score	50·0 (48·4 to 51·5)	51·6 (50·0 to 53·2)	1·5 (0·4 to 2·7)	51·7 (49·8 to 53·5)	52·5 (50·6 to 54·4)	1·1 (–0·3 to 2·5)	–0·4 (–2·2 to 1·3)	0·62

EoEHSS and EREFS score are the maximum score among evaluated oesophageal sections (distal, mid-section, and proximal). Peak eosinophil count is the highest eosinophil count among the distal, mid-section, and proximal oesophagus and is shown as geometric mean (95% CI) with change from baseline and change difference as geometric mean ratio (95% CI). Other variables are shown as mean (95% CI). p values were calculated with the two-sample *t* test. 1FED=one-food elimination diet. 6FED=six-food elimination diet. eos/hpf=eosinophils per high-power field. EoEHSS=Eosinophilic Esophagitis Histology Scoring System. EREFS=Eosinophilic Esophagitis Endoscopic Reference Score. EEsAI=Eosinophilic Esophagitis Activity Index. EoE-QOL-A=Adult Eosinophilic Esophagitis Quality of Life. PROMIS GH=Patient-Reported Outcome Measurement Information System Global Health.

Table 3: **Histological, endoscopic, symptom, and quality-of-life scores in phase 1 (intention-to-treat population)**

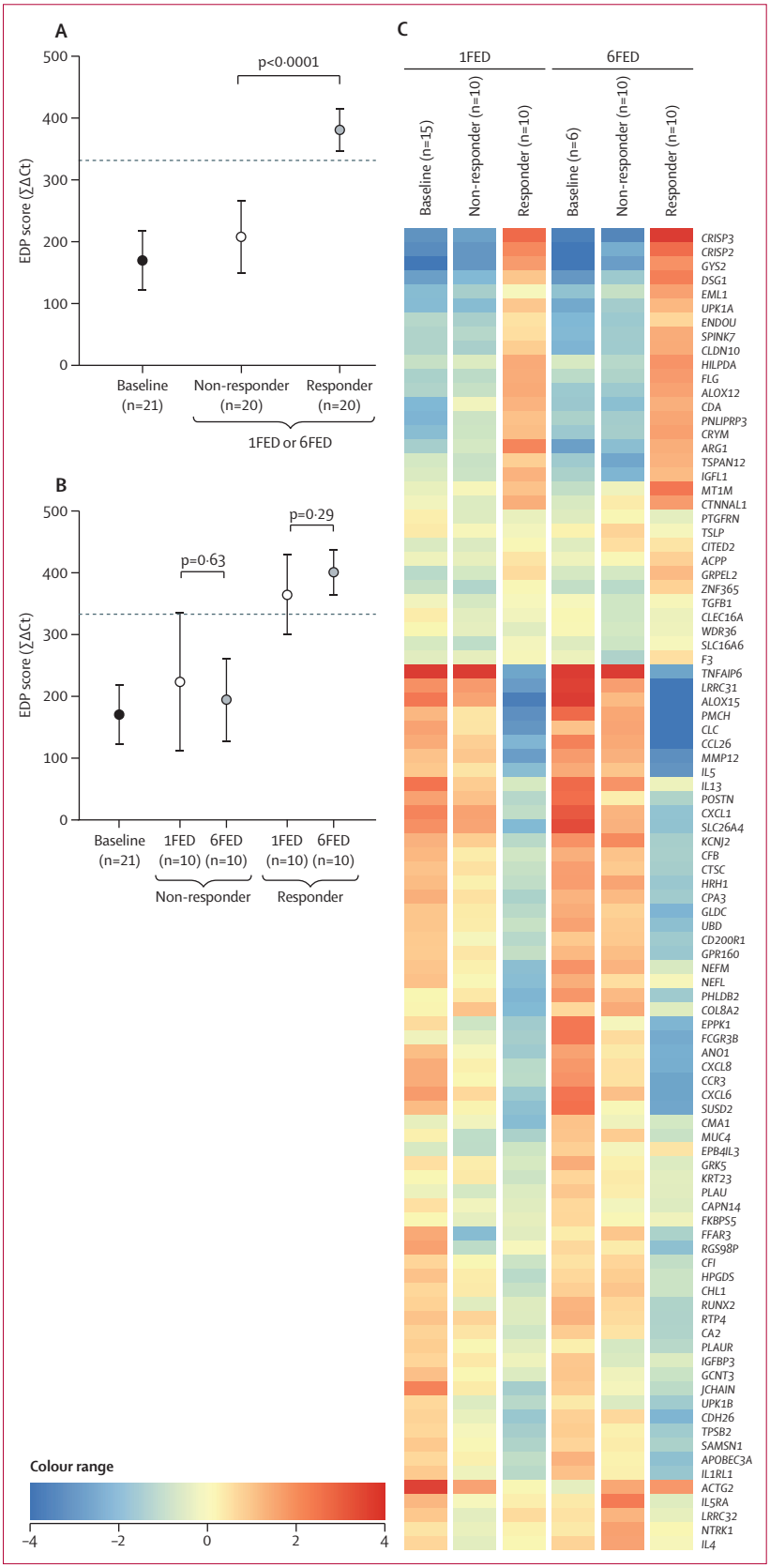
(table 3). Among patients with evaluable diet records completing the study, 63 (98%) of 64 adhered to 1FED and 57 (97%) of 59 to 6FED. Whether one patient adhered to 1FED was indeterminable.

In the overall study population, patients with a histological response (peak count <15 eos/hpf) to diet therapy showed normalisation of gene expression and a significantly higher mean EDP score than patients without a histological response (figure 2A). EDP scores did not vary by diet (figure 2B) and post-treatment transcriptomes were qualitatively similar in the 1FED and 6FED groups (figure 2C). When comparing responders and non-responders to either diet, we detected a marked bidirectional change in the expression of 75 genes in treatment responders, indicating normalisation of gene expression, compared with a change in four genes in treatment non-responders (appendix p 19). An evaluation of the value of baseline EDP results in predicting response to diet was not undertaken due to the small number of intact baseline biopsies.

A complete cases analysis (patients completing the study without missing data) was conducted as a sensitivity analysis for phase 1 of the study. Among these patients, 25 (42%) of 59 in the 6FED group compared with 23 (35%) of 65 in the 1FED group were in histological remission (difference 7% [95% CI –10 to 24]; p=0·46). Sensitivity analyses of the key secondary outcomes also showed no important differences compared with the main ITT analysis (appendix pp 10–11).

Among the patients without a histological response, 21 opted to follow 6FED after non-response to 1FED, and 11 patients opted to receive swallowed fluticasone propionate after non-response to 6FED in phase 2. One patient who proceeded to 6FED and two patients who proceeded to swallowed fluticasone dropped out before completing phase 2 (figure 1). After 6 weeks in phase 2, nine (43%) of 21 patients who proceeded to 6FED and nine (82%) of 11 who proceeded to swallowed fluticasone were in histological remission (peak count <15 eos/hpf) in the ITT population. Six (29%) on 6FED and six (55%) on fluticasone had complete remission (peak count ≤1 eos/hpf). All levels of remission are shown in the appendix (p 12). In post-hoc analyses, mean EoEHSS and EREFS total scores, as well as peak eosinophil count, significantly decreased from the start of phase 2 to the end of treatment in patients who proceeded to 6FED and in those who proceeded to swallowed fluticasone (table 4).

Gender, age, race, diet treatment, and baseline peak eosinophil count were not associated with remission after the diet therapies (data not shown). When 1FED and 6FED were combined, no significant effect of atopy on remission was observed (data not shown). When stratified by treatment, 16 (62%) of 26 patients without atopy compared with nine (25%) of 36 with atopy were in remission after 6FED (p=0·0080 with Fisher's exact test). This association was not seen in patients after 1FED, where eight (28%) of 29 patients without atopy compared with 15 (39%) of 38 with atopy were in remission (p=0·44).



For baseline allergy skin prick testing for eliminated foods, neither positive nor negative skin prick tests to milk were associated with histological response in the 1FED group (appendix p 13). Among patients in the 6FED group, seven (70%) of ten patients with a positive skin prick test to egg were in remission compared with six (27%) of 22 patients with a negative test to egg (p=0·049). All skin prick test results are shown in the appendix (p 13). Of the 67 patients who underwent milk patch testing, only one patient had a borderline positive result, and thus we did no additional analyses for this outcome.

At baseline, serum concentrations of cow's milk-specific IgG4 to the proteins Bos d 4 (also known as α-lactalbumin) and Bos d 5 (β-lactoglobulin) were significantly higher in patients with a histological response than in patients without a response in the 1FED group (appendix p 20). After 1FED, concentrations of IgG4 to Bos d 4, Bos d 5, and Bos d 8 (casein) significantly decreased from baseline in histological responders and non-responders (appendix pp 20–21). Reductions in IgG4 were greater in histological responders than in non-responders, but the differences were not significant (appendix p 21). Baseline IgE concentrations to cow's milk proteins were similarly low in responders and non-responders (appendix p 20) and concentrations were not significantly changed from baseline after 1FED (appendix p 21). Ratios of IgG4 to IgE for milk components were high, ranging from around 9000:1 to around 37 000:1, and were not different between histological responders and non-responders at baseline or after 1FED therapy (appendix p 14).

The baseline proportion of $CD4^+CD154^+$ T cells ex vivo, and Th2 cytokine expression (IL-4, IL-5, and IL-13) in $CD4^+CD154^+$ T cells, were similar in histological responders and non-responders to either diet therapy in our post-hoc analysis (appendix p 22). After 6 weeks of diet therapy, IL-4 expression in $CD4^+CD154^+$ T cells was significantly lower in histological responders than in non-responders to diet therapy. In a subset of patients (n=12) with both pre-diet and post-diet measures, for whom we did a paired samples analysis, the proportion of $CD4^+CD154^+$ T cells and Th2 cytokine expression in $CD4^+CD154^+$ T cells were significantly decreased from baseline only in histological responders (appendix p 23). Given the absence of positive patch test results, patch testing was not correlated with circulating T cells. Due to

***Figure 2*: Analysis of gene expression in oesophageal biopsies before and after diet therapy**

(A) EDP score in histological responders (peak oesophageal count <15 eosinophils per high-power field) and non-responders to either study diet. (B) EDP score in histological responders and non-responders by diet therapy. Baseline data were combined due to low sample size. Scores higher than 333 (dotted line) represent normalisation of the transcriptome.[3] Data are presented as means with 95% CI. p values were calculated with the two-sample *t* test. (C) Comparison of oesophageal transcriptomes by response to 1FED and 6FED. The colour key numbers represent normalised expression values. EDP=eosinophilic oesophagitis diagnostic panel. 1FED=one-food elimination diet. 6FED=six-food elimination diet. ΣΔCt=sum of change in normalised cycle threshold values.

small sample size, the planned secondary analysis of T-cell association with histological response to 1FED alone was not undertaken because of power concerns.

As a post-hoc analysis, the effect of consuming barley and rye on histological remission to 6FED was assessed in patients with available data (n=59). No patients reported consuming rye. Five (29%) of 17 patients who reported consuming barley and 20 (48%) of 42 who avoided barley were in remission (p=0·25). A primary source of barley intake was barley-based beer.

No adverse events were reported at a frequency greater than 5% in patients in either diet group in phase 1 (appendix p 15). However, mean weight loss in the 6FED group was significantly higher than in the 1FED group (–2·2 kg [SD 2·5] *vs* –1·1 kg [2·6]; p=0·027). During phase 2, among the 11 participants who proceeded from 6FED to swallowed propionate, one who had normal serum cortisol (14 µg/dL) before initiation of phase 2 had low serum cortisol (<1 µg/dL) after 6 weeks of swallowed fluticasone but did not have clinical symptoms of adrenal insufficiency. A repeat measurement 10 days after the patient stopped fluticasone was normal (16 µg/dL). Another patient treated with fluticasone reported a serious adverse event (suicidal ideation), which was assessed as unrelated to therapy (appendix p 15). The serious adverse event was assessed as grade 4 (life-threatening consequences). All other adverse events were grade 1 (mild) or grade 2 (moderate).

	Week 6	End of treatment*	Change from week 6 to end of treatment	p value
6FED (n=21)				
Peak eosinophil count, eos/hpf	47·7 (34·5 to 66·1)	10·7 (4·6 to 25·2)	0·23 (0·12 to 0·43)	0·0001
EoEHSS total	0·81 (0·69 to 0·94)	0·60 (0·43 to 0·77)	–0·22 (–0·35 to –0·08)	0·0028
EREFS total	3·0 (2·1 to 3·8)	2·2 (1·5 to 2·8)	–0·8 (–1·5 to –0·1)	0·035
Topical swallowed fluticasone propionate (n=11)				
Peak eosinophil count, eos/hpf	40·4 (28·0 to 58·3)	3·0 (1·0 to 9·6)	0·08 (0·03 to 0·20)	0·0002
EoEHSS total	0·82 (0·70 to 0·94)	0·40 (0·18 to 0·61)	–0·42 (–0·61 to –0·23)	0·0007
EREFS total	2·8 (1·7 to 3·9)	1·7 (0·7 to 2·8)	–1·1 (–2·2 to 0·0)	0·045

Peak eosinophil count is the highest eosinophil count among distal, mid-section, and proximal oesophagus and is shown as geometric mean (95% CI) with change as the geometric mean ratio (95% CI). Other variables are shown as mean (95% CI). p values were calculated with the paired *t* test. 6FED=six-food elimination diet. eos/hpf=eosinophils per high-power field. EoEHSS=Eosinophilic Esophagitis Histology Scoring System. EREFS=Eosinophilic Esophagitis Endoscopic Reference Score. *Patients who switched therapy at week 6 (end of phase 1) were on the new therapy for 6 weeks in phase 2.

Table 4: **Histological and endoscopic response in phase 2 (intention-to-treat population)**

Discussion

In this study, the standard 6FED was not superior to dietary elimination of animal milk alone in the treatment of adults with eosinophilic oesophagitis. Both diets had similar efficacy across multiple metrics. Notably, our findings are derived from the first multicentre randomised trial of dietary elimination therapy in adults with eosinophilic oesophagitis, and similar results were found in both ITT and complete cases analyses for a series of primary and secondary outcomes, which consistently showed efficacy of 1FED. Among individuals following the diets, we found similar improvements in endoscopic appearance (EREFS), histological features (EoEHSS), and peak eosinophil counts. Histological response to either diet reversed the EDP score associated with active eosinophilic oesophagitis. Symptoms significantly improved from baseline in the 6FED group, but the difference in the change in overall symptom score (EEsAI) was not significant compared with the 1FED group and did not lead to improvements in quality of life. Encouragingly, 43% of patients who did not respond to 1FED attained histological remission after therapy with the more restrictive 6FED. Furthermore, 82% of individuals who did not respond to 6FED had histological remission with swallowed fluticasone therapy. Taken together, the results of this study show that 1FED is a reasonable first-line diet therapy option in adults with eosinophilic oesophagitis and that steroid therapy is an option for those who do not respond to limited and restrictive diet therapy.

Diet exclusion therapy has been a foundational treatment for eosinophilic oesophagitis since attenuation of oesophageal eosinophilia with an elemental diet was first shown.[27] After the discovery that food antigens were associated with oesophageal injury, researchers directed their attention towards identifying common food triggers, and evaluated the efficacy of excluding six common food allergens (milk, egg, wheat, soy, fish, and nuts) on oesophageal eosinophilia in children and adults.[11] Due to the high histological response rate (around 70%) found in these studies, 6FED became a frequently used dietary approach to manage eosinophilic oesophagitis. In more recent years, less restrictive diets that remove one to four of the most common food antigens have been evaluated in non-randomised studies and have been shown to improve oesophageal eosinophilia in clinically meaningful numbers of adults and children.[12,15,28,29] Our study extends two decades of research by comparing a minimally restrictive elimination diet (animal milk) with the highly restrictive 6FED in a multicentre randomised trial of adults with eosinophilic oesophagitis, with use of newly developed, validated instruments to comprehensively establish the relative efficacy of these diets, the mechanisms involved, and the value of skin testing and circulating biomarkers in predicting outcome.

In this largest randomised trial to date of dietary therapy in adults with eosinophilic oesophagitis, our findings were unexpected. Although studies of elimination diets for children with eosinophilic oesophagitis suggest that 30–60% might achieve remission with 1FED,[11,12,28,30] a 2018 study in European (Spanish and Italian) adults with eosinophilic oesophagitis found that milk was the only eosinophilic oesophagitis trigger in fewer than 20% of participants.[12] Differences in immune response by

geographical region might explain why 1FED remission rates are different.[31] Non-randomised prospective studies in adults with eosinophilic oesophagitis suggest that around 70% might reach histological remission with 6FED,[12–14] a rate higher than that found in the present study. Two of the previous studies in adults also eliminated legumes[12,14] and gluten (wheat, barley, and rye),[12] which could account for the higher response rate. In our study, the remission rate was lower in patients who consumed barley (29%) than in those who did not (48%), although the difference was not significant. Adherence to 6FED was high (97%); however, rare exposure to antigens (known or unknown) might have contributed to the lower response rate. In one study, patients with known antigen exposure during the food elimination period underwent a food wash-out period before the post-intervention endoscopy, which resulted in higher histological response rates than in our study.[13] Additionally, the previous study, which was the only prospective US study evaluating 6FED in adults, was conducted at a single centre.[13] Because our study included ten sites across the USA, it probably included a broader (perhaps more representative) range of the adult population with eosinophilic oesophagitis. Furthermore, recruits who suspected that egg, wheat, soy, fish, or nuts were potential eosinophilic oesophagitis triggers were randomly assigned to 1FED or 6FED in our study, which reduced selection bias that might have contributed to the higher response rates in the non-randomised studies. Although the length of intervention in this study matched other 6FED studies,[13,14] a 2018 study found that 6 weeks of diet therapy might not be sufficient to obtain histological remission for a subset of patients with eosinophilic oesophagitis.[32] Patients without histological response but with improvement in symptoms, endoscopic appearance, and eosinophil counts after 6 weeks of therapy reached histological remission when diet therapy was extended in the previous study.[32] However, in our study, improvement in these three features occurred in approximately 10% of non-responders to 6FED (n=4), suggesting a longer intervention might have only marginally improved overall remission rate under this hypothesis. Our study results should temper the previous response rates quoted to patients for 6FED from non-controlled studies.

Using validated tools (EREFS and EoEHSS) developed to assess endoscopic and histological abnormalities in eosinophilic oesophagitis, we found that both diets improved abnormal endoscopic features and the extent and severity of histological findings. Other studies of 1FED and 6FED have relied on subjective endoscopic review[13] or evaluation of the presence of endoscopic abnormalities.[14,28] Additionally, our diet elimination study is the first to use EoEHSS in adults. The granular review of endoscopic and histological features in our study revealed mostly similar improvements, particularly in inflammatory features, with 1FED and 6FED. However, improvement in scores for histological and endoscopic features associated with remodelling were larger in the 6FED group than in the 1FED group, although the differences were not significant. The elimination of multiple foods in 6FED might have increased the chance that at least one trigger was eliminated, potentially yielding some benefit even in the absence of histological remission.

6FED had efficacy in 43% of patients who did not respond to 1FED in our study. Additionally, topical swallowed steroid had efficacy for 82% of patients who did not respond to 6FED. Molina-Infante and colleagues were the first to find step-up diet therapies had efficacy in achieving remission.[12] Our study builds on this finding to show that for patients who do not initially respond to a milk elimination diet, escalating to 6FED not only reduces oesophageal eosinophil counts but also significantly improves histological and endoscopic abnormalities. Given the presumably long-term sustainability of less restrictive diets and the need for fewer endoscopies than with more restrictive diets (for which endoscopy is repeated when eliminated foods are reinstated),[12] starting with a low number of eliminated foods and escalating as necessary might be a worthwhile strategy for many patients. Such a strategy might also reduce cases of suboptimal nutritional intake observed with more restrictive diets, although even patients following a milk-only elimination diet should be monitored for optimal intake of calcium and vitamin D. Few studies have examined a change from dietary therapy to topical steroids, and having data to support this strategy in adults is reassuring, although our sample size was too small to be certain about the findings.

We evaluated clinical and laboratory characteristics of patients for their association with response to therapy. Among patients on 6FED, those without atopy were more likely to achieve histological remission than those with atopy. This finding contradicts previous food elimination studies in adults,[12–14] in which atopic background did not predict response to diet, and further replication of this assessment is needed. IgG4 proteins to Bos d 4 (α-lactalbumin) and Bos d 5 (β-lactoglobulin) were detected in significantly higher amounts at baseline in responders to 1FED than in non-responders, suggesting that milk components could potentially serve as a predictive marker of milk reactivity in eosinophilic oesophagitis. By contrast, IgE antibodies to milk proteins were low at baseline and unchanged after 1FED. These findings are consistent with previous data supporting a strong role of IgG4, but not IgE, in eosinophilic oesophagitis.[17] For example, studies have found increased amounts of tissue and serum IgG4 to milk proteins in patients with eosinophilic oesophagitis.[17,33] By contrast, non-response to omalizumab, an anti-IgE drug,[33] and little predictive value of skin prick testing to identify eosinophilic oesophagitis antigens[34] indicate that eosinophilic oesophagitis is largely independent of IgE. Indeed, in our study, skin prick and patch tests were also not useful in predicting response to diet. Although our

study does not support assessments of skin tests in patients with eosinophilic oesophagitis, immunological or allergy testing should still be considered for the management of other atopic conditions that are sometimes associated, such as asthma, rhinitis or dermatitis, whereby treatment of these conditions can be aided by such testing. The small dataset in our study, suggesting that activated T cells and Th2 cytokine expression in activated T cells are low or markedly decreased in patients with a histological response to the diet therapies, should be further investigated as a potential blood biomarker of response to treatment in eosinophilic oesophagitis.

This study is the first in adults to evaluate the transcriptome response to elimination diets. In patients with histological response to diet therapy, we observed a pronounced reversal (normalisation) of the expression of 75 genes associated with eosinophilic oesophagitis. These findings indicate that diet therapy has a profound effect on reversing the pathobiology of eosinophilic oesophagitis, substantiating the importance of antigen hypersensitivity as the primary disease mechanism.

Our study had limitations. First, excluding patients who responded to proton pump inhibitors might have excluded a subset of the patient population with eosinophilic oesophagitis. However, a recent study suggests that patients with eosinophilic oesophagitis responsive to proton pump inhibitors respond to diet therapy,[35] similar to patients in this study. We also cannot completely exclude a synergistic effect of continued proton pump inhibitors with diet in affecting outcomes.[36] Second, as in any clinical study, whether patients completely adhered to dietary exclusions is not certain despite our efforts to detect non-compliance. Additionally, we cannot be certain that rare antigen exposure (in our definition of compliance) did not influence efficacy results. Third, symptom response might have been biased in this unmasked study. Fourth, in the event that dropouts were related to poor treatment outcome, results might be biased. Fifth, although we found no significant differences between 1FED versus 6FED in most secondary endpoints, the study was not powered for secondary endpoints so we cannot be certain that differences do not exist. Notably, rates of complete remission (≤1 eos/hpf) were higher with 6FED than with 1FED. Finally, median peak eosinophil count at baseline was higher in the 1FED group than in the 6FED group. If a factor, this variance would have potentially made the response to 1FED less robust; this fact further supports the efficacy of this diet when compared with 6FED. The major strength of this study was the multicentre randomised design with adults recruited from ten sites throughout the USA, and the rigorous methodology, including regulatory oversight by the US National Institutes of Health, used for the study. Consequently, selection bias that was a factor in other studies might have been minimised, and the present findings might be more generalisable to the adult population with eosinophilic oesophagitis. Our study also included disease-specific validated instruments for measuring symptom, histological, and endoscopic responses in eosinophilic oesophagitis. Furthermore, dietary education and skin prick and patch testing were standardised across all sites.

Despite the data reported herein, important gaps in the knowledge related to diet therapy in eosinophilic oesophagitis remain. The optimal duration of diet therapy to maximise the chance of reaching histological remission, for example, is uncertain. Additionally, despite decades of diet therapy research, few data have described the nutritional and psychological effects of elimination diets, especially with long-term use. Furthermore, although food triggers might vary by geographical location, the extent of these differences is uncertain, and the current findings might be limited to the USA. Future diet studies, whether interventional or observational, should aim to answer these questions and extend to broader geographical areas.

In summary, the findings reported herein show that 1FED and 6FED had similar efficacy in achieving histological remission and improving multiple metrics of response in this first comparison randomised trial of dietary elimination in adults with eosinophilic oesophagitis. The data also show that 6FED had efficacy for 43% of 1FED non-responders and steroids had efficacy for most 6FED non-responders. The study shows the benefit of diet therapy as assessed by histological and endoscopic metrics, and that diet therapy reverses the underlying disease pathogenesis, by correcting the molecular transcriptome associated with eosinophilic oesophagitis. Furthermore, our findings direct attention away from the value of skin prick and patch testing and call attention to the association of food-specific IgG4, but not IgE, with histological remission. Thus, our study indicates that the elimination of food and beverages containing animal milk might be an acceptable initial dietary treatment choice, especially if a step-up dietary strategy is being used, and further informs clinicians about effective therapies in cases of non-response to diet treatment.

Contributors

MER and VAM conceptualised the overall study. KLK, NG, ESD, MC, MHC, SKG, IH, VAM, JMS, GTF, and MER participated in designing the study methodology. KLK, NG, ESD, DAK, JPA, SSA, JAB, PAB, JMC, AC, MC, GWF, IH, JL, PM-K, VAM, KAP, TS, and MER conducted the research and investigations. NCA, KEC, MHC, and G-YY performed the research pathology assessments. AKRS had a role in project administration. JPK collaborated in study planning for database development. KLK, NG, ESD, DAK, TS, and MER had supporting roles in data analysis. LJM and XZ conducted the formal data analysis. KLK, NG, ESD, DAK, and MER wrote the original draft. KLK and TS were responsible for preparation of the tables and figures. MER acquired the funding and provided oversight of the research. MER, KLK, XZ, and LJM accessed and verified the data. All authors participated in data interpretation and manuscript review and editing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

NG receives royalties from UpToDate; is a consultant for Allakos, Regeneron-Sanofi, AstraZeneca, AbbVie, Takeda, Knopp, Bristol Meyers

Squibb, and Nutricia; and has received payment or honoraria for speaker's bureaus for Takeda and Regeneron-Sanofi. ESD has received research support from Ellodi (formerly Adare), Allakos, Arena, AstraZeneca, GlaxoSmithKline, Meritage, Miraca, Nutricia, Celgene (formerly Receptos and a subsidiary of Bristol Myers Squibb), Regeneron, Revolo, and Shire (a subsidiary of Takeda); is a consultant for Abbott, AbbVie, Ellodi, Aimmune, Akesobio, Allakos, Amgen, Arena, Aslan, AstraZeneca, Avir, Biorasi, Calypso, Celgene, Celldex, Eli Lilly, EsoCap, GlaxoSmithKline, Gossamer Bio, Invea, Landos, Lucid Diagnostics, Morphic, Nutricia, Calyx (formerly Parexel), Phathom, Regeneron, Revolo, Alimentiv (formerly Robarts), Salix, Sanofi, Shire, and Target RWE; and has education grants with Allakos, Banner, and Holoclara. DAK has received consulting fees and payments for presentations from Celgene; has served on a data and safety monitoring board at the University of North Carolina; and serves on the governing board of the American Gastroenterological Association. JPA has received research support from Cures Within Reach and Celgene; has received payment or honoraria for lectures from Takeda; and has served on a data and safety monitoring board for Octapharma USA. SSA has received research support from Implicit Biosciences and the Campaign Urging Research for Eosinophilic Disease (CURED) Foundation; has received consulting fees from Bristol Meyers Squibb, Regeneron-Sanofi, and AstraZeneca; has received payment for presentations or events from Regeneron-Sanofi; and receives patent royalties and is co-inventor of oral viscous budesonide, patented by University of California San Diego and licensed by Shire. KEC is employed by and has an equity interest in Alnylam. MC has received consulting fees from Regeneron, Allakos, Ellodi, Shire, AstraZeneca, Sanofi, Bristol Myers Squibb, Phathom; has received research support from Regeneron, Allakos, Shire, AstraZeneca, Ellodi, and Danone; and holds leadership roles in the American Partnership for Eosinophilic Disorders (APFED) and the American Academy of Allergy, Asthma and Immunology (AAAAI). AC has received research support from Aimmune and DBV Technologies; has served on a data and safety monitoring board for Regeneron, Sanofi, AstraZeneca, and DBV Technologies; and holds leadership roles in the AAAAI, European Academy of Allergy and Clinical Immunology, and American College of Allergy, Asthma and Immunology. MHC is a consultant for Allakos, AstraZeneca, Bristol Myers Squibb, Esocap, GlaxoSmithKline, Shire, Regeneron, Celgene, Sanofi, and Ellodi; has received research funding from Shire, Regeneron, Celgene, and AstraZeneca; holds leadership roles in the APFED, CURED Foundation, and The International Gastrointestinal Eosinophil Researchers; and has received travel support from Regeneron and Celgene. GWF is a consultant for Ellodi, Allakos, Celgene, Lucid, Nexstone, Phathom, Regeneron, Bristol Myers Squibb, Upstream Bio, and Shire; has served on a data and safety monitoring board for Revolo; has a leadership role in the International Society for Diseases of the Esophagus; and has equity in Bristol Myers Squibb. SKG has received research support from Allakos, Ellodi, and AstraZeneca; receives royalties from UpToDate; is a consultant for Ellodi, Bristol Myers Squibb, QOL Medical, Takeda, and Viaskin; has received payment from Medscape and PeerView Institute for Medical Education; has served on a data and safety monitoring board for Bristol Myers Squibb; and has a leadership role in the Association of Pediatric Gastroenterology and Nutrition Nurses, American Gastroenterological Association, and Journal of Pediatric Gastroenterology and Nutrition. JL has received research funding AstraZeneca, Allakos, Takeda, Provention Bio, Ellodi, Arena Pharmaceuticals, GI Health Foundation, Ellodi, ALK Abelló, Revolo Biotherapeutics, Bristol Myers Squibb, Regeneron, Phathom Pharmaceuticals; has received consulting fees from Guidepoint, Takeda, Third Bridge, Boston Consulting Group, AbbVie, Sanofi, Huron Consulting Services, Ribon Therapeutics, Tegus, Slingshot, Cowen, and AstraZeneca; has received speaker payments from Regeneron, Sanofi, AGA Carney, AGA Tufts, and Maine Medical Center; has received payment for expert testimony for Devine, Millimet and Branch Professional Education; and has a leadership role with Kwong Kow Chinese School. IH has received consulting fees from Ellodi, AstraZeneca, Arena, Allakos, Calyx (formerly Parexel), Celgene, Celldex, Regeneron, Esocap, Gossamer Bio, Lilly, Phathom, Sanofi, and Shire; has received research funding Meritage, Ellodi, Celgene, Regeneron-Sanofi, and Shire; and participated in a speaker bureau for Regeneron and Sanofi. LJM has received honoraria from Akron's Children's Hospital and is co-inventor on a patent for Cysteamine. VAM has received consulting fees from Shire, Allakos, Regeneron, and Sanofi; and has received research funding and support from Meritage and Shire. 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MER is a consultant for AstraZeneca, Bristol Myers Squibb, Regeneron-Sanofi, Revolo Biotherapeutics, Celldex, Nexstone One, and Guidepoint; has received research support from AstraZeneca, Regeneron-Sanofi, GlaxoSmithKline, the CURED Foundation, Food Allergy Fund, and a US–Israel Binational Grant (number 2019016); has equity interest in PulmOne Therapeutics, Spoon Guru, ClostraBio, Serpin Pharm, Celldex, Nextstone One, and Allakos; receives royalties from Ception Therapeutics (for reslizumab), Mapi Research Trust (for the Pediatric Eosinophilic Esophagitis Symptom Score version 2) and UpToDate; has received equipment from Phadia; has a leadership role in the International Eosinophil Society; has received payment for expert testimony from Tucker Ellis; and is an inventor on a patent (US patent 9,345,763) owned by Cincinnati Children's Hospital Medical Center. All other authors declare no competing interests.

Data sharing

Data will be shared via the US National Institutes of Health policy and processes established by the Rare Disease Clinical Research Network. Genomic data will also be shared via EGIDExpress (https://egidexpress.research.cchmc.org). Researchers can request participant-level, deidentified clinical data pertaining to this study. Emails can be sent to the corresponding author (rothenberg@cchmc.org) for details regarding data availability and instructions for requesting information. The study protocol, statistical analysis plan, informed consent form, and summary data are available on the ClinicalTrial.gov website (https://clinicaltrials.gov/ct2/show/NCT02778867).

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