Six Food vs One Food Eosinophilic Esophagitis Elimination Diet (SOFEED) Followed by Swallowed Glucocorticoid Trial

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Statistical Analysis Plan
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Six Food vs One Food Eosinophilic Esophagitis Elimination Diet followed by Swallowed Glucocorticoid Trial

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Purpose of Study

The primary objective of this proposal is to conduct a prospective, non-blinded randomized trial comparing rates of remission of empiric elimination dietary therapies in eosinophilic esophagitis (EoE) in order to assess the therapeutic viability of empiric elimination diets. Moreover, we aim to assess response to topical swallowed steroids in non-responders to empiric six food dietary therapy regimens and the response to 6FED in 1FED non-responders. Participants aged 18 to 60 years with active EoE will be enrolled and the primary efficacy outcome will be the rate of histologic remission assessed using esophageal biopsies obtained following a six week randomized trial of one of two empiric diets. During the screening process, active EoE will be confirmed by local pathology review (histologic evaluation) of esophageal biopsies obtained during by esophagogastroduodenoscopy (EGD) in subjects with a history consistent with EoE.

Study design

We will be recruiting a total of 136 participants, between the ages of 18-60. Participants will be enrolled in this study based on the presence of active eosinophilic esophagitis and adherence to the inclusion and exclusion criteria. We intend to conduct a prospective non-blinded randomized trial that compares a 1-food elimination diet (1FED) versus a 6-food elimination diet (6FED) for six weeks (Phase 1). Subsequently, non-responders to 1FED dietary elimination therapy will be treated with 6FED and non-responders to 6FED will be treated with SGC (swallowed fluticasone at a dose of 880 mcg twice a day) for six weeks (Phase 2) while on an unrestricted diet, if the participant chooses to continue in to Phase 2. The empiric dietary therapy interventions are as follows: 1-food elimination diet (1FED)—avoidance of milk vs. 6-food elimination diet (6FED)—avoidance of milk, egg, wheat, soy, fish/shellfish, and peanut/tree nuts, for six weeks. Milk elimination for both 1FED and 6FED includes all mammal milk (i.e. goat, sheep, and cow's milk must all be eliminated). The study design is shown schematically in Figure 1 Study Design Flowchart.

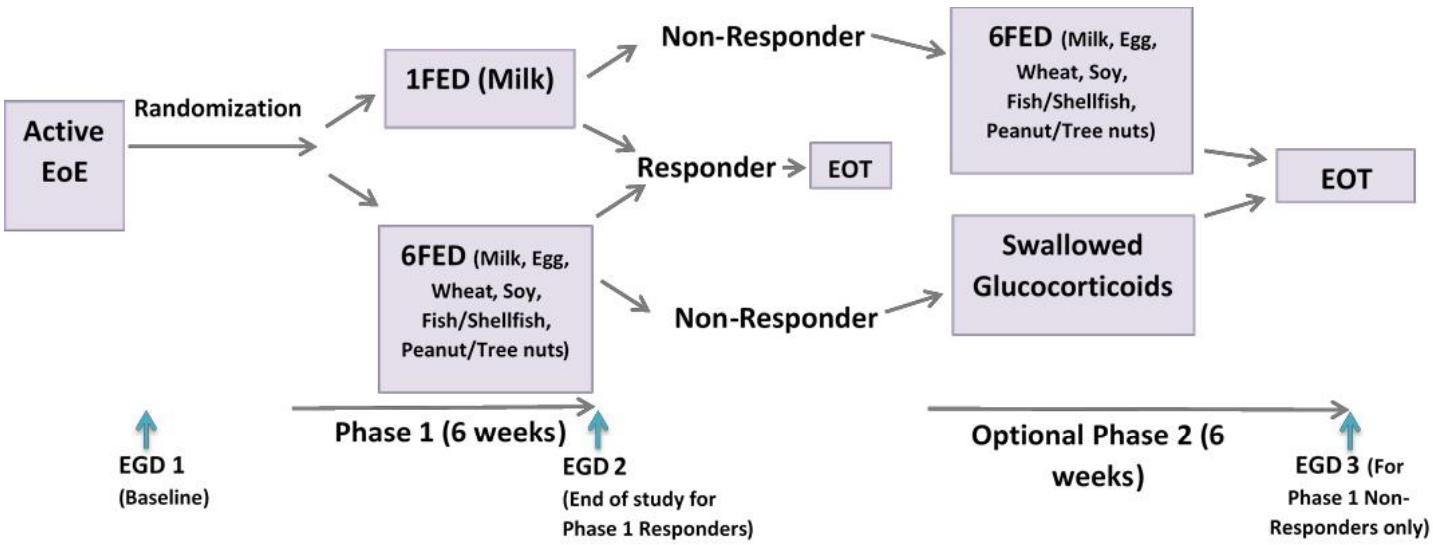
In Phase 1, participants will be randomized 1:1 to either 1 food elimination (milk elimination alone, 1FED) or 6 food elimination (milk, egg, wheat, soy, fish/shellfish, peanut/tree nuts elimination, 6FED) therapeutic diet. At the end of this phase, an EGD will be performed to assess remission. Attainment of remission (esophageal eosinophil counts <15 eosinophils/high powered field) after Phase 1 will result in study discontinuation and maintenance of the "successful" dietary therapy. Treatment non-responders may choose whether or not to continue into Phase 2. Dietary therapy non-responders who were on 6FED in Phase 1 and continue on to Phase 2 will receive topical swallowed steroids for six weeks (Phase 2) followed by EGD with esophageal biopsies. These participants will return to an unrestricted diet (i.e. stop 6FED) prior to beginning topical swallowed steroid therapy. Dietary non-responders in Phase 1 who were on 1FED and continue on to Phase 2 will continue to a 6FED

therapeutic diet (Phase 2) for six weeks followed by EGD with esophageal biopsies to assess remission.

The instructions for the 1FED and 6FED therapeutic diets will be standardized across sites by providing consensus documents produced by registered dietitians who are experts in dietary elimination in EoE. There are currently no validated dietary questionnaires for measuring food allergen intake in adults in the US. Dietary intake and *consumption* of the allergens will be measured at the start of the trial and adherence to the dietary elimination (i.e. *avoidance* of the allergens) during the trial will be measured using modified versions of the NCI's usual dietary intake/diet history questionnaires and 3-day food diaries (http://cancercontrol.cancer.gov). Stool samples may be collected from subjects who consent to stool collection to evaluate the effect of diet on the microbiome.

Similarly, standardized instructions for using SGC will be provided, based on our prior studies. We have chosen to use fluticasone propionate (FP) rather than budesonide in this study, given our prior work in this area, and our recent finding that high-dose fluticasone is well tolerated and highly effective, and our preliminary findings concerning esophageal transcripts that predict responsiveness to FP therapy. The study design is shown schematically in Figure 1 Study Design Flowchart.

Figure 1 Study Design Flowchart



Analysis Populations

The analysis population for the primary and secondary endpoints will be the intent-to-treat population with the goal of including patients who have been randomized in the analyses. However, we will exclude patients who were inappropriately randomized and never completed the enrollment visit. Patients for which the primary endpoint of histological remission cannot be determined will be imputed as treatment failures. To maximize comparability with other studies, we will also perform per protocol analyses, including only individuals who complete the study phase of interest for all proposed studies.

Variables of Interest

Primary outcome:

1) Remission rate (<15 peak eosinophils/hpf)

Secondary outcomes:

1) Change in eosinophils/hpf from baseline to post treatment
2) Remission status: Patients will be classified into 3 remission categories: complete histological remission (≤ 1 peak eosinophils/hpf); partial remission (2-14 peak eosinophils/hpf); no remission (≥15 peak eosinophils/hpf)
3) Histology Scoring System (HSS): Will include the overall score, grade score, stage score, and the inflammatory and structural sub-scores. Scores will be reported as distal, proximal, and maximum
4) HSS score by remission status (complete, partial, and no remission).
5) Endoscopy Scoring System (EREFS): Will include the overall score and the inflammatory and fibrostenotic sub-scores. Scores will reported as distal, proximal, and maximal score.
6) EoE Diagnostic Panel (EDP): The summary EoE score (EDP total score) will be a secondary outcome.

Derived Variables.

1) HSS scores. Sum of the feature scores divided by the maximum possible score for the biopsy for grade and stage. The total score is the sum of the grade and stage scores. Inflammatory sub- scores include the following features: eosinophils, abscesses, surface layering, and surface necrosis. Structural sub-scores include basal layer hyperplasia, dilated intercellular spaces, apoptotic epithelia, and lamina propria fibrosis.
2) HSS remission. HSS remission is defined as a having both a grade and stage total score less than or equal to 3 and an eosinophil grade score no greater than 1. This is calculated separately for distal and proximal biopsies. When both distal and proximal biopsies are in remission, this is considered complete remission, when only one of the two biopsies meet these criteria, it is partial remission. When neither meet these criteria, it is no remission. Analyses will include full remission vs other and full+partial remission vs no remission.
3) EREFS. Total EREFS score will be calculated by summing the grades for all five of the features. The inflammatory score contained the sum of the exudate, edema, and furrows scores (this could range from 0 to 5), and the fibrostenotic score contained the sum of the rings and stricture scores (this could range from 0 to 4).
4) Adherence. Adherence will be dichotomized into mostly adherent vs not-mostly adherent. The judgement of adherence will be based on questionnaires about food intake and dietitian input. If inconsistent, food diaries will be reviewed. The final adherence call will be provided to the statistician.
5) Atopy. Atopy is a multi-faceted disease. Individuals will be defined as atopic if they report a history of asthma, eczema, allergic rhinitis, allergic conjunctivitis, IgE mediating food allergy

and/or atopic dermatitis.

6) Time since diagnosis will be calculated as the study date at baseline minus the date at diagnosis.

Prior to any hypothesis testing, all variables will be reviewed for plausibility. Any values which are considered suspect will be reviewed by the clinical team to ensure accuracy. Continuous data will be evaluated for distributional assumptions of normality. Natural log-transformation will be considered for right skewed non-normally distributed data (the most typical skew seen in physiologic data).

Demographics/Patients Characteristics

Demographic, patient characteristics, medication use and study completion status will be summarized for the two treatment groups using median [interquartile range] for continuous variables and frequency and percentages for categorical variables. Treatment comparisons will be performed for demographics and patient characteristics using the Wilcoxon Rank sum test for continuous variables and the Fisher's Exact test for categorical variables. All tests will be conducted at $\alpha=0.05$.

Demographics and patient characteristics will be summarized within each Phase1 treatment group between patients who choose to continue into Phase 2 and those who opt out. Any apparent difference will be noted.

Analysis of Primary Outcome

Primary Objective:

1. Determine the rate of remission following 1FED vs. 6FED and evaluate the relative efficacy of these dietary therapies.

Statistical hypothesis for the primary outcome:

H0: p1FED = p6FED
H1: p1FED ≠ p6FED

where p1FED=percentage of patients in histologic remission (<15 peak eosinophils/hpf) on the 1FED diet at end of Phase 1
p6FED=percentage of patients in histologic remission (<15 peak eosinophils/hpf) on the 6FED diet at end of Phase 1

This hypothesis will be tested using the generalized linear mixed effects model with the logit link (for binary outcome) that accounts for the clustering within sites. Covariates to be considered in this model are sex, current age, baseline esophageal eosinophil count, adherence, presence of atopy, and time since diagnosis. All tests will be conducted at $\alpha=0.05$.

Analyses of Secondary Endpoint(s)/Outcome(s)

Following are the secondary objectives of the study:

1) To extend Phase 1 of this study with a prospective non-blinded trial that determines the rate of remission following SGC in the 6FED non-responders and the rate of remission following 6FED in the 1FED non- responders (Phase 2).
2) To evaluate the effect of each therapy on histological remission defined by a variety of changes in eosinophils, including (a) pre- minus post-therapy peak eosinophil counts; (b) partial

remission (2-14 peak eosinophils/hpf); and (c) complete histological remission (≤ 1 peak eosinophils/hpf).

3) To evaluate the effect of each therapy by utilizing the histology scoring system (HSS) created to express the severity and extent of other abnormalities in the gastrointestinal (GI) tract that often accompany eosinophilic inflammation.
4) To evaluate endoscopic outcomes as assessed by the endoscopy scoring system (EREFS).
5) To determine the impact of each therapeutic intervention on biomarkers using the EoE Diagnostic Panel (EDP).

For secondary objectives 1, the remission rate at the 6-week time point for non-responders in Phase 1 who proceeded to Phase 2 will be summarized separately depending on the treatment patients received during Phase 1. The 95% two-sided confidence interval for the rate will be provided. If the remission rate is missing for patients that entered Phase 2, it will be imputed as a treatment failure.

To test hypotheses for each of the secondary objectives 2-5, treatment group comparisons at the end of Phase 1 will be performed using the generalized linear mixed effects model using the link that is appropriate for the endpoint (i.e. logit for binary, cumulative logit for ordered multinomial categories, identity for continuous). These models will account for the clustering within sites and will consider sex, baseline esophageal eosinophil count, adherence, presence of atopy, and time since diagnosis as covariates. For continuous data, appropriate transformations will be considered (e.g. log, square root, rank) to satisfy the assumptions of the analyses. If the remission status for the categorical outcomes is missing, we will evaluate how to treat the observation. If the study subject prematurely quit the clinical trial, then we will consider the observation a treatment failure. However, if the data was not captured (as in the case of a biopsy which did not capture both distal and proximal findings then we will consider imputation. Missing data for continuous outcomes may be imputed using multiple imputation techniques. Covariates for imputation will include investigative site, sex, presence of atopy and duration of disease. Secondary outcomes 2-5 will be tested at the two-sided $\alpha=0.01$ to account for multiple testing.

Analyses of Exploratory Endpoint(s)/Outcome(s)

Exploratory Variables:

1) Change in Patient Reported Outcome (PRO) metrics (pre- minus post- treatment)
    a. EoE Adult Symptom Score Activity Index (EESAI)
        i. VDQ, AMS, Overall PRO
    b. Adult EoE Quality of Life Score
        i. Social impact, emotional impact, disease anxiety, eating/diet impact, choking anxiety
    c. PROMIS General Health Questionnaire
2) Clinical parameters
    a. Baseline disease activity measures (peak eosinophil count, EREFS, HSS)
    b. Body mass index (BMI)
    c. Presence of atopy and specific atopic diseases (e.g., is asthma associated with tx response/non-response)
    d. Demographics (sex, age, race)
3) Biomarkers
    a. Serum food specific IgE

b. CRD – food specific components for IgE and IgG4
c. Serum food specific IgG4
d. EDP score

4) Skin testing results
    a. Skin prick tests to milk, egg, wheat, soy, peanut, shellfish, fish, and 5 tree nuts.
    b. Positive is defined as >= 3mm.
5) Milk driven T-cells
    a. T-cell count
    b. Cytokine levels

Exploratory objectives are detailed below:

1) To evaluate the clinical and psychosocial effect of each therapy utilizing patient reported outcomes (PROs) to assess EoE symptoms and problems/feelings related to eating.
2) To evaluate factors predicting treatment response including
    a) Clinical parameters
    b) Serum food specific IgE, CRD, and IgG4
    c) Skin testing results, in the form of prick and patch testing
    d) Milk-driven T cells in blood

To test hypotheses for exploratory objective one, we will compare the treatment arms using general linear mixed models as described for the secondary outcome measures. To test hypotheses for exploratory objective 2, we will compare responders to non-responders using the generalized linear mixed effects model using the link that is appropriate for the endpoint (i.e. logit for binary, cumulative logit for ordered multinomial categories, identity for continuous). Covariates will be considered as appropriate. For continuous data, appropriate transformations will be considered (e.g. log, square root, rank) to satisfy the assumptions of the analyses.

Adverse Events

Adverse events (AE) that occur during Phase 1 and Phase 2 will be summarized within each treatment group using frequency and percent of patients with at least 1 occurrence and total number of occurrences (nAEs). These summaries will be done by SOC/AE level using the CTCAE 4.0 system. The percentage of patients experiencing at least one occurrence of an AE at the SOC/AE level will be compared using Fisher's Exact Test.

Software Used (with References) and Specialized Macros (with References)

SAS version 9.4

This SAP has been reviewed and approved by:

Investigator Date