A Randomized, Double-blind, Placebo-controlled Study of the Use of Oral Cromolyn Sodium for the Treatment of Eosinophilic Esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is an increasingly prevalent disease that affects both children and adults. The disease is defined by both its clinical presentation and pathologic findings on biopsy. Pediatric patients typically present with abdominal pain, regurgitation, nausea, and trouble swallowing; with possible ultimate consequences of failure to thrive, food impaction, or esophageal wall rupture. The diagnosis must be confirmed with esophageal biopsy that shows eosinophilic infiltrates specific to the esophagus, after ruling out gastroesophageal reflux disease.

The goal of current therapies for EoE include resolving both tissue eosinophilia and symptoms and to prevent long-term consequences of the disease. The current therapies for EoE are limited to specialized diets and/or pharmacotherapy with swallowed, topical corticosteroids. Unfortunately, while both can be effective, each has its own limitations and risks. Specialized diets can be very difficult to adhere to, can potentially lead to malnutrition, and there is currently no perfect test to identify specific foods that should be removed from the diet. Topical corticosteroids, as an alternative to dietary therapy, can lead to systemic side effects, such as reduction in bone mineral density, poor growth, candidiasis, adrenal suppression, glaucoma, and cataracts. In addition, there is currently no data to suggest if, and when, patients can stop the specialized diets or the swallowed corticosteroids.

There is currently a great need for alternative therapies, especially for children with EoE. The ideal therapy would be effective, safe in children (preferably already studied in children for other conditions), cost-effective, and immune-modulatory. Cromolyn sodium, a medication approved for asthma and systemic mastocytosis, may be an ideal candidate therapy.

Hypothesis:

Oral cromolyn sodium, when made into a viscous preparation, will lead to a decrease in esophageal eosinophilia and in symptoms related to esophageal dysmotility in patients with eosinophilic esophagitis.

Specific Aims:

1. Specific Aim 1: To assess the efficacy of orally ingested viscous cromolyn sodium in reducing the esophageal eosinophilic infiltrate in children with eosinophilic esophagitis.

2. Specific Aim 2: To assess the efficacy of orally ingested viscous cromolyn sodium in reducing the symptoms associated with eosinophilic esophagitis in children.

Background and Significance:

Eosinophilic esophagitis (EoE) is a clinicopathologic disease that is increasing in prevalence in the United States.[1] The disease is defined by the presence of symptoms of esophageal dysmotility with concomitant findings of eosinophlic infiltrates (>15 eosinophils per high powered field on light microscopy) localized to the esophagus, in the absence of other

causes of esophageal eosinophilia (namely gastroesophageal reflux disease).[2] In the pediatric population, the disease typically manifests as abdominal pain, dysphagia, reflux, nausea, and vomiting; a symptom pattern that can lead to failure to thrive.[3] While few natural history studies exist, available data suggest that if left untreated, EoE may lead to food impactions requiring emergent removal food boluses and possible esophageal wall rupture.[4-5]

The exact etiology of EoE has not yet been elucidated, however most data suggest that the disease is immune-mediated and antigen-driven. This has been proven clinically by demonstrating that the majority of patients will have resolution of both symptoms and histologic findings after treatment with an amino-acid based formula that is devoid of protein antigens.[6-7] In addition, most patients with EoE show an immune deviation that differs from healthy controls.[8] A genome wide association study has shown common variants at chromosome 5q22, the location of the thymic stromal lymphopoeitin gene, a gene associated with immune skewing toward a T-helper (Th) type 2 response.[9] In addition, expression of eotaxin-3, interleukin(IL)-4, and IL-5 (Th2 cytokines) have all been shown to be increased in patients with active EoE.[10] These findings suggest that patients with EoE have a genetic predisposition that leads them to an aberrant Th2 type response to non-pathogenic antigens. As would be expected from this hypothesis, the majority of patients with EoE, have some form of atopic/allergic disease.[11]

Currently, Treatment options for patients with EoE include dietary therapy and/or pharmacotherapy.[2] Dietary therapy consists of avoiding antigenic triggers of the disease, and can be in the form of an elemental diet or an elimination diet. An elemental diet can be very difficult to adhere to, even for infants and toddlers, as it allows the patient to only ingest an amino acid-based formula and one other food as their source of nutrition. The elimination diet is more flexible, and can be based on testing or can be done empirically by removing common food triggers (namely milk, egg, soy, wheat, nuts, fish, and shellfish). Unfortunately, there are currently no reliable tests to predict which foods will be the trigger in any given patient, and therefore trial and error of food elimination and re-introduction must constantly be undertaken.

Pharmacotherapy for EoE entails swallowing topical corticosteroids, with the goal of prolonged exposure of the corticosteroid to the esophagus, thus limiting systemic absorption. In fact, double-blind, randomized, placebo-controlled trials have shown efficacy of both swallowed fluticasone and swallowed budesonide.[12-13] Unfortunately, there is no consensus on the duration of therapy, and studies to date have shown recurrence of eosinophilia and symptoms within months of stopping therapy, even with addition of steroid-sparing agents, such as montelukast.[14-15]

Given that none of the current treatment options are ideal, there is clearly a need for novel and effective therapies for EoE. One candidate therapy that is yet to be studied is oral cromolyn sodium. Oral cromolyn is an attractive alternative to swallowed steroids for EoE for a number of reasons.

First, oral cromolyn has minimal to any systemic absorption. In fact, in studies of adults and children, less than 1% of orally administered cromolyn gets absorbed.[16] Due to this, cromolyn is a first line agent in the treatment of the gastrointestinal manifestation of systemic mastocytosis, but not for the systemic manifestations of the disease. Second, due to its poor absorption, the side effect profile of cromolyn sodium is almost non-existent, and it is FDA-approved for use down 2 years of age.[17] Third, data exist to show increased numbers of mast cells in the esophageal tissue of patients with EoE, and that these mast cells are associated with smooth muscle contraction, and thus are perhaps the cause of the symptomatology of EoE.[18] Therefore, by targeting and stabilizing mast cells (the major action of cromolyn), in addition to

eosinophils, one may be able to effectively treat EoE with non-steroid medications. Finally, cromolyn, when inhaled and used in asthmatics, causes a reduction in sputum eosinophils; and the clinical benefit in asthma has been directly linked to a reduction in eosinophils in bronchial alveolar lavage specimens.[19] This suggests that in addition to its known mast cell stabilizing properties, cromolyn exerts some effect on eosinophils as well. In fact, after 16 weeks of treatment with inhaled cromolyn, researchers have shown a significant decrease in activated eosniophils in bronchial submucosa; an effect that was similar to treatment with fluticasone propionate, but not seen with placebo or salmeterol (a long acting β2-agonist).[20]

Given these properties of cromolyn sodium, we propose that it would be an ideal candidate to investigate as a treatment option for patients with EoE.

Protocol Design and Experimental Methods:

The proposed research protocol design is a randomized, double blind, placebo-controlled trial to determine if oral administration of viscous cromolyn sodium will be effective in the treatment of eosinophilic esophagitis.

Primary Outcome Measure:
The primary outcome measure will be the change in esophageal eosinophilia after 8 weeks of treatment with cromolyn as compared to placebo.

Secondary Outcome Measures:

1. The change in symptoms scores from baseline and at weeks 0, 4, and 8.
2. The incidence of adverse events throughout the study

Inclusion Criteria:

- Established diagnosis eosinophilic esophagitis.
- >2 years of age, < 18 years of age

Exclusion Criteria:

- Concomitant treatment with swallowed corticosteroids. Any prior use of swallowed corticosteroids will require a 4 week washout period.
- Pregnancy
- Evidence of pathologic eosinophilia in other locations in the GI tract.
- Participation in another research protocol
- Renal or Hepatic Insufficiency

Study Medication
The study medication is oral cromolyn sodium, made into a viscous preparation by the addition of powdered sugar.
The medication is supplied as a 100 mg/5 mL suspension and should be made into a thickened slurry prior to ingestion with 1 tablespoon of powdered sugar. This should also make the medication more palatable for children.
Dosing will be 100 mg 4 times daily for children ages 2 – 12 years of age and 200 mg 4 times daily for children ages 12 – 18 years of age. The medication should be taken 30 minutes before meals and before bedtime.

This dosing regimen is based on current dosing strategies for systemic mastocytosis.

Randomization /Placebo Administration

Cromolyn/Placebo will be administered in a blinded fashion. The pharmacist will perform the randomization and will allocate 8 weeks of cromolyn/placebo to the patient. The patient and physicians caring for the patient will be blinded as to which medication the patient is receiving.

Symptom Scores

Symptoms will be assessed at baseline, week 4, and week 8 by the patients and caregiver. This will done using an established symptom scoring diary known as the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS).[21] Figure 2.

FIGURE 2. The Pediatric Eosinophilic Esophagitis Symptom Score

Symptom Score

FREQUENCY	Never	1-3/month	Once/week	2-6/week	Daily	> 1/Day
Nausea	0	1	2	3	4	5
Vomiting	0	1	2	3	4	5
Abdominal Pain	0	1	2	3	4	5
Chest Pain	0	1	2	3	4	5
Heartburn	0	1	2	3	4	5
Regurgitation	0	1	2	3	4	5
Dysphagia	0	1	2	3	4	5
Food impaction	0	1	2	3	4	5
Poor appetite	0	1	2	3	4	5
Early Satiety	0	1	2	3	4	5

Frequency Score (add all circled entries): _____

SEVERITY	None	Mild	Moderate	Severe
Nausea	0	1	2	3
Abdominal Pain	0	1	2	3
Chest Pain	0	1	2	3
Heartburn	0	1	2	3
Dysphagia	0	1	2	3
Poor appetite	0	1	2	3
Early Satiety	0	1	2	3
Inadequate weight gain	0	1	2	3

Severity Score (add all circled entries and **multiply x2**): _____

Total score:_____

In past studies using this diary, parents/caregivers helped with the survey for younger children <10 years of age, and children older than 10 years of age were typically able to complete it on their own.

Monitoring During Study

Patients will have a baseline physical exam performed at the initial study visit by the prinicipal investigator. They will be supplied with 8 weeks of study medication to be administered at home. They will have a study visit (Visit 2) done at week 4 for recording of vital signs, review of adverse events, and symptom assessment. Finally they will have a physician visit at the 8 weeks for physical exam and endoscopy with biopsies.

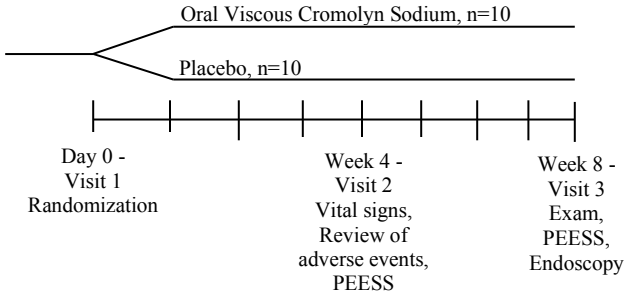
Adverse events will be recorded on a blank calendar for each month that the patient is enrolled in the study.

Endoscopy with biopsy:
All qualifying subjects will have had an upper gastrointestinal endoscopy with biopsies performed prior to the baseline visit to establish a diagnosis of EoE.
As part of routine clinical care, all subjects will again have post-therapy endoscopy with biopsies performed at week 8.

Allergy Skin Prick Testing:
As part of routing clinical care, all patients will have allergy skin prick testing performed to evaluate for environmental and food allergies. The allergens tested will be tree pollens, grass pollens, weed pollens, molds, dust mite, cockroach, cat, dog, milk, egg white, soy, wheat, peanut, walnut, shrimp, and catfish.

Study Protocol and Timeline:
The proposed study timeline is shown in Figure 3.

Figure 3. Study Timeline



The a priori power of the primary end-point analysis was estimated using Fisher's exact test with .05, two-tailed significance level. Assuming a histologic response rate of 80% in the oral viscous cromolyn group and 10% in the placebo group, there was 85% power to detect a significant between-group difference with sample sizes of 10 subjects in each group.

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