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IRB Proposal
CRC Design and Statistics

“Clinical effectiveness of oral Montelukast compared to placebo on prevention of dysphagia in patients with Eosinophilic Esophagitis.”

A: Background:

Eosinophilic esophagitis (EoE) has emerged as an important cause of dysphagia in young adults. Previously considered a rare condition, an increasing number of cases of EoE have been attributable to a rising incidence and a growing awareness of the condition. Eosinophilic esophagitis is an allergic inflammatory condition of the esophagus. As defined by consensus guidelines, people with eosinophilic esophagitis have the following:

- 1.) clinical symptoms such as difficulty swallowing, food impaction, regurgitation, chest pain
- 2.) elevated intraepithelial eosinophil count (>20 in one high power field (HPF) or >15 in >1 hpf on biopsy at endoscopy)
- 3.) consistent endoscopic findings which include concentric mucosal rings, linear furrowing, white exudates, and a narrow caliber esophagus.
- 4.) Refractory to acid-reducing medications

The condition is not well understood and there is no clear cause of EoE. Theories of the pathogenesis relate to an immunoglobulin E (IgE) mediated mechanism, by which dietary, environmental and immunological factors may contribute¹. Clinical presentation of EoE typically involves a pediatric population and younger adults ages 20-40 years old with a Caucasian male predominance.² There is often a personal or family history of allergic conditions including asthma, atopic dermatitis, eczema, seasonal allergies and food allergies. The three main treatment modalities that have been used with varying degrees of success are dietary modification (elimination diet), endoscopic intervention (dilation), and pharmacotherapy (oral or topical (swallowed) corticosteroids, mast cell inhibitors, leukotriene receptor antagonists and immune modulators). There is, however, no universal approach to treatment. The majority of treatment data comes from studies of pediatric populations, with results extrapolated to the adult population. Optimal treatment for eosinophilic esophagitis has not been defined and has been based mostly on clinical experience, case series, and small controlled trials.

B. Study Purpose

The research study will be designed to evaluate the clinical effectiveness of oral Montelukast compared to placebo as maintenance therapy and prevention of dysphagia in patients with Eosinophilic Esophagitis.

C. Rationale:

Eosinophilic Esophagitis remains a disease lacking a defined treatment approach. Previous studies have documented therapies for EoE of variable efficacy.

Dietary modifications with food elimination diets based on the results of skin prick (IgE-mediated) and/or skin patch testing (non-IgE-mediated) show improvement in clinical symptoms and esophageal histology in 98% of children compliant with a restricted diet after allergen identification.³ However, most adult patients have great difficulty adhering to these highly restrictive diets, and is seldom used outside the pediatric population.⁴⁻⁵

Endoscopic therapy mainly consists of dilation procedures aimed at relieving the dysphagia caused by strictures or fixed rings.⁶ While patients may experience initial symptomatic relief, dilation does not address the underlying inflammatory changes and reoccurrence rates are high.⁷

The first-line medical therapy is the use of topical corticosteroids, commonly administered as swallowed aerosolized fluticasone propionate. Second-line options include systemic corticosteroids, cromolyn sodium and leukotriene receptor antagonists, and anti-IL-5 antibody mepolizumab. In an RCT of fluticasone for pediatric EoE, 50% of FP-treated patients achieved histologic remission compared with 9% of patients receiving placebo (P= .047) with resolution of vomiting occurring more frequently in FP than placebo

group (67% vs. 27%; P=0.04).⁸ A 10 year retrospective study, all 17 pediatric patients treated with swallowed aerosolized fluticasone had a significant histologic improvement within four weeks. Thirteen of 17 patients experienced partial or complete resolution of their symptoms of reflux and dysphagia. However, recurrence of eosinophilic infiltration to near pre-treatment levels and recurrence of symptoms (45%) occurred six months after medication withdrawal.^{3,10} Despite the lack of a significant longitudinal study in adults, many adult patients in case series and uncontrolled trials have dramatic improvements in both symptoms and histology with the use of swallowed fluticasone. Symptoms, however, soon relapse after stopping therapy and the need for re-treatment is not uncommon. Chronic use of topical steroids is not recommended because of potential side effects, including oral candidiasis. Montelukast, a leukotriene receptor antagonists interferes with the eosinophilic infiltration and degranulation cascade. Montlukast may be a viable steroid sparing option.⁹

The research study will be designed to evaluate the clinical effectiveness of oral Montelukast compared to placebo as maintenance therapy and prevention of dysphagia in patients with Eosinophilic Esophagitis. Montelukast is commonly used for the maintenance treatment of asthma and to relieve symptoms of allergic rhinitis. A previous case study demonstrated symptomatic improvement in 8 of 12 adults with isolated eosinophilic esophagitis.⁹ However, controlled clinical trials involving the use of montelukast, in the management of adult eosinophilic esophagitis have not yet been conducted.

Montelukast has minimal risk of adverse reactions compared with steroid therapy and may offer longer period of clinical relief in adults with eosinophilic esophagitis. If patient's have clinical relief of symptoms over a longer period of time, physicians can prescribe Montelukast as an effective maintenance treatment and an alternative to long term corticosteroid therapy.

D. Hypothesis:

Fluticasone plus Montelukast maintenance therapy will decrease dysphagia symptoms by 20% compared to Fluticasone alone in patients with eosinophilic esophagitis over a period of 12 months

E. Materials and Methods

Selection of Patients:

The patients will be recruited from gastroenterology clinics in New York City, NY (CUMC, Mt. Sinai Hospital, Bellevue) over a period of 2 years. Eligible patients are adult men and women ages 18 or older, with a diagnosis of eosinophilic esophagitis confirmed histologically and clinically by dysphagia questionnaire.

Inclusion criteria:

- Histologic evidence of EoE with a peak eosinophil count of >15 eosinophils /HPF, on biopsies of mid-esophagus, before treatment
- Treatment with PPIs for two weeks prior to EGD and topical corticosteroids treatment (in order to attribute eosinophil count secondary to EoE vs. GERD)
- History of clinical symptoms of esophageal dysfunction intermittently or continuously- evidenced by a dysphagia questionnaire (yes/no, severity, frequency) prior to topical steroid treatment
- Normal dysphagia questionnaire 1-4 weeks after topical steroid treatment (Ie: answering no to difficulty swallowing)
- Willingness and ability to continue the medical regimens and EGD/biopsies.
- Written informed consent

Exclusion Criteria:

- Evidence of active infection with *Helicobacter pylori*
- Current use of immunomodulatory therapy
- Current disease of the gastrointestinal tract aside from the current EoE diagnosis
- Evidence of concurrent eosinophilic gastritis, enteritis, colitis, or proctitis
- Evidence of unstable asthma or on asthma or allergic rhinitis therapy
- Current evidence of oropharyngeal or esophageal candidiasis
- Pregnant women

F. Study Design:

The study will be a randomized, double-masked, placebo-controlled, intention to treat, prospective study to evaluate the efficacy of montelukast compared with placebo as maintenance therapy.

1. All eligible patients with history of EoE by inclusion criteria will undergo treatment with 6 weeks of topical corticosteroid therapy, fluticasone MDI 440mcg 2 swallowed puffs BID. Those that are in remission and report a score of (0) no difficulty swallowing on dysphagia questionnaire 2 weeks after completion of steroidal treatment
2. Study Arms: Patient's will then be randomly assigned to receive either:
 - a. oral montelukast 40 mg daily
 - b. placebo once daily for 1 year.
3. Randomization: A clinical research coordinator will dispense the active medications or placebo to each patient in a computer-generated randomization. All participants and study personnel will be blinded to treatment assignment.
4. Stratification: Caucasian men are more likely to have symptoms of eosinophilic esophagitis, and therefore, patients will be stratified by gender and race.
5. Clinical symptom information, including side effect questions, will be performed at months 3, 6, 9, 12. Patient's will be given a calendar at start of trial and be instructed to record the time of each medication dose and write each day of dysphagia. Examination of calendars collected at follow-up appointments will record compliance to medication regimen.

G. Outcome and Statistical Analysis

Definition of Relapse:

- a. dysphagia score >2 on questionnaire at 12 months
- b. eosinophils >15 eosinophils/HPF on EGD biopsy

Primary Outcome Measures:

1. effectiveness of oral montelukast in treatment of EoE by evaluating relapse rate at 12 month

Secondary Outcomes

2. median of relapse at 3, 6, 9 months in treatment of Montelukast and Placebo.

H. Statistical Analysis

The study will use the Chi squared test to analyze the data and compare the proportion of remission in the two groups: Montelukast vs. Placebo. The primary outcome will be analyzed using the chi square test.

I. Sample Size and Power Analysis:

In order to achieve 80% power with a P value of 0.05, a sample size of approximately 103 in each arm was calculated using the Chi squared test, assuming a treatment effect of 50% (relapse rate) versus a placebo response of 30% (relapse rate). Assuming 80% eligibility, a sample size of 258 will need to be screened.

J. Study Medications:

1. Fluticasone propionate MDI 440mcg 2 puffs every 12 hours for 6 weeks
 - a. Mechanism of Action: synthetic trifluorinated corticosteroid with potent anti-inflammatory activity which has been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, neutrophils) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines)
 - b. Although there are no controlled dose-ranging trials to determine the optimal dose for fluticasone propionate MDI in the treatment of EoE, most controlled trials have demonstrated efficacy after using FP 440mcg dose, and therefore, it will be used.

Fluticasone propionate is an FDA approved drug for the treatment of asthma and allergic rhinitis.

c. Adverse Effects: >10%

Headache (2-14%), URTI (14-21%), throat irritation (3-22%), Fever (1-7%), Nausea/vomiting (1-8%), abdominal pain (1-5%), myalgias (2-5%), oral candidiasis (10%), infection (1-3%) bone mineral density loss, acne, adrenal suppression, cataracts and depression (case reports)

2. Montelukast 20mg orally daily

a. Mechanism of Action: Leukotriene Receptor antagonist

b. FDA approved drug for the prevention and long-term treatment of asthma, exercise-induced asthma, and to control symptoms of allergic rhinitis

c. Adverse Effects: Dizziness (2%), fatigue (2%), weakness (2%) fever (2%), headache (>1%), rash (2%), dyspepsia (2%), gastroenteritis (2%), transaminitis (1%), cough (1%), URTI (1%), sinusitis (1%)

K. Study Devices:

An EGD, which is commercially available, will be utilized to observe esophageal tissue changes as well as perform biopsies at months prior to study and at 0 months. If patient develops dysphagia, EGD will be performed.

L. Study Questionnaire:

Patients will fill out a validated dysphagia and side effect questionnaire before, during, and at the end of therapy that will involve yes or no questions regarding symptoms, frequency (episodes/week).

Ie: DIFFICULTY SWALLOWING QUESTIONNAIRE

Severity

___ 0 = NO SYMPTOMS

___ 1 = MILD SYMPTOMS

intermittent and no interference with normal activity or sleep

___ 2 = MODERATE SYMPTOMS

slow relief and mild interference with normal activity or sleep

___ 3 = SEVERE SYMPTOMS

– no relief and marked interference with normal activity or sleep

Frequency

___ 0 = ABSENT

___ 1 = OCCASIONAL symptoms < 2 day a week

___ 2 = FREQUENT– symptoms 2 – 4 days a week

___ 3 = VERY FREQUENT symptoms > 4 days/ week

M. Recruitment of Patients:

Potential subjects will be informed of studies by gastroenterologists and physicians at medical centers in New York City. Physicians and gastroenterologists that are informed of study, will determine whether the patient is suitable for the study. The physician will ascertain from the patient that he or she is willing to discuss the study within the research team before any approach may be attempted by the investigators.

N. Confidentiality of Study Data

All data and personal identifiers, including hospital unit numbers, social security numbers, subject initials, phone numbers, and addresses will carry unique code number for all study subjects. Data will be stored in a secure location, accessible only to investigators.

O. Potential Conflict of Interest

There are no potential conflicts of interest to disclose.

P. Location of Study

This study will be conducted at Columbia University Medical Center and Weil-Cornell

Q. Potential Risks

The potential risks include that the treatment has no effect and possible side effects of the study medication as outlined above.

R. Potential Benefits

The potential benefits include reduction in dysphagia

S. Alternative Therapies

N/A

T. Compensation to Subjects

The study drug will be provided free of cost during the study. All medical visits and endoscopic examination will also be provided free of charge. No other compensation will be provided.

U. Costs to Subjects

Subjects will not incur any additional costs as a result of participating in the study.

V. Minors as Research Subjects

Minors will be excluded from the study

W. Radiation or Radioactive Substances

N/A

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