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Protocol #: 21-4826

Project Title: Evaluating Adrenal Insufficiency in Adults with Eosinophilic Esophagitis on Chronic Swallowed Topical Steroids

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I. **Hypotheses and Specific Aims**: Eosinophilic esophagitis (EoE), a chronic inflammatory disease of the esophagus, is a clinical and financial burden to patients if left untreated. Often the natural history of the disease includes development of fibrosis and stricturing of the esophagus, acute food impactions, unplanned emergency room visits, and invasive procedures such as endoscopy. Currently there are no Food and Drug Administration (FDA) approved medications for the treatment of EoE. As such, pharmacologic options approved for use in asthma are used for treatment of EoE and include proton pump inhibitors and swallowed topical steroids. These medications are prescribed chronically as EoE is considered a lifelong disease. Chronic administration of exogenous steroids, when given in inhaled or systemic preparations, can lead to adrenal insufficiency (AI). AI is seen in 7.8% of patients receiving chronic inhaled steroids and 48.7% of patients receiving chronic systemic steroids (10). The administration of steroids in EoE is unique, as patients typically swallow topical preparations of the drug. The risk of secondary AI from taking swallowed topical steroids is currently unknown, as there has been no study in an adult population assessing this risk as a primary endpoint. Pediatric studies of patients with EoE have shown the risk of AI from swallowed topical steroids to be 5-10% (1, 4, 5). Based on the risk of AI with inhaled steroids (7.8% prevalence) and the prevalence of AI from swallowed topical steroids in pediatric populations (5-10%), we hypothesize that the risk with swallowed topical steroids is >5%. This could warrant consideration of screening given the potentially serious consequences of undiagnosed AI. To address this hypothesis, this project aims to define the prevalence of developing AI in adults with EoE taking swallowed topical steroids and compare that prevalence to a similar control population of adults with EoE who are taking proton pump inhibitors.

Aim 1: To measure the prevalence of adrenal insufficiency in adult patients with eosinophilic esophagitis taking chronic swallowed topical steroids.

Approach in Aim 1: We will collect questionnaire data and perform diagnostic testing in patients followed in the University of Colorado - Anschutz Digestive Diseases clinic for the diagnosis of eosinophilic esophagitis.

Aim 2: Determine if any clinical parameters are associated with an increased risk of developing AI.

Approach in Aim 2: We will collect clinical and lab data, then analyze any relationships to development of AI using multivariate statistics.

II. **Background and Significance**: Adrenal insufficiency (AI) occurs when the exogenous administration of corticosteroids causes the human body to stop producing steroids on its own, manifesting as vital sign abnormalities, electrolyte changes, and severe symptoms such as vomiting, fatigue, and light-headedness. If left untreated or undiagnosed adrenal crisis can occur, often necessitating the need for hospitalization. Exogenous steroids have been extensively shown to cause AI in systemic and inhaled delivery preparations, however the risk with swallowed topical steroids is less certain. Swallowed topical steroids have high "first-pass metabolism" with less systemic absorption, thus they are given chronically with little care or monitoring for the development of AI. There is a paucity of literature investigating the risk of AI with swallowed topical steroids in adult patients, leaving many prescribers without objective data in which to counsel patients.

Current literature surrounding this topic exists primarily in pediatric populations, where three large studies showed the incidence of AI from swallowed topical steroids for EoE to be 5-10% (1, 4, 5). Hsu et al (5) additionally identified that patients concurrently taking inhaled or systemic preparations of steroids for asthma, which is commonly encountered as patients with EoE often suffer from other atopic conditions, is a risk factor for the development of AI.

In adults with EoE, two randomized controlled trials indirectly tried to measure the effect of swallowed topical steroids and development of AI (3, 6). Both studies found no statistically significant increased risk for development of AI from swallowed topical steroids, though there were limitations to these studies that may question wide applicability. Both studies excluded patients on concurrent steroid formulations and the length of treatment was only 12 weeks or less. Dellon et al (3) revealed that AI occurred in 5.9% of patients receiving swallowed topical steroids compared to 4.8% in the placebo arm. Similarly, Miehlke et al (6) demonstrated AI in 1.8% of patients on swallowed topical steroids, compared to 0% receiving placebo. While the randomized controlled trials failed to detect statistically significant changes in the incidence of adrenal function, they were likely underpowered for these secondary outcomes.

Given the ongoing need for chronic steroid administration in EoE, the morbidity associated with adrenal crisis should AI occur, and the lack of dedicated research in this area, we feel there exists a need to define the prevalence of AI in adults taking long term swallowed topical steroids.

III. **Preliminary Studies/Progress Report:** No preliminary studies have been performed as of yet, however an analysis using Epic's SlicerDicer found that there were a total of 497 patients with a diagnosis of eosinophilic esophagitis who were seen in the University of Colorado - Anschutz Digestive Disease clinic over the last 12 months.

IV. Research Methods

Aim 1: To measure the prevalence of adrenal insufficiency in patients with eosinophilic esophagitis taking chronic swallowed topical steroids.

Study design: This will be a prospective observational study. A cohort of patients with eosinophilic esophagitis will be enrolled and placed into two groups, those taking swallowed topical steroids (budesonide, fluticasone) and those taking proton pump inhibitors. The patients will be recruited during visits in the University of Colorado - Anschutz Digestive Diseases clinic, where they will already be following up for treatment of their eosinophilic esophagitis. All study participants will participate in a written questionnaire as well as undergo one diagnostic test (morning serum cortisol level), with remaining diagnostic testing performed depending on the findings of the initial test. A power analysis to determine sample size estimated 304 patients were needed for our primary endpoint (prevalence of adrenal insufficiency) to be adequately powered. The power analysis was performed with Stata using a two-sample proportion Pearson's chi-squared test with variable as follows: power 0.8, significance level 0.05, risk of AI in budesonide group of 5%, and risk of AI in PPI group (1 in 1 million). If the prevalence of AI is closer to 10%, which was seen in pediatric populations, then even less patients would be needed for the primary endpoint to be sufficiently powered.

Description of Population to be Enrolled:

a) **Inclusion Criteria:** 300 adult male or female patients between 18 and 85 years of age with a diagnosis of EoE who have been on swallowed topical steroids or proton pump inhibitor therapy (any dosing) for at least 3 months.
b) **Exclusion criteria:** We will exclude control patients on proton pump inhibitor therapy if they have used any form of exogenous steroids within the past one year.

Protocol: All subjects will be enrolled during clinic visits, where they will complete a written questionnaire about any baseline symptoms they may be experiencing. From there they will present to the outpatient laboratory for collection of a fasting morning serum cortisol level. The labs will be drawn between 7-9am with the patient holding their morning steroidal dose. If the level is normal, defined as greater than 5μg/dL, they are done with the study protocol. If the level is abnormal, defined as less than 5μg/dL, another blood specimen will be collected at a follow up visit to confirm the abnormal result. If the 2nd sample is again abnormal the subject will undergo an adrenocorticotrophic stimulation test, which is a 3rd blood collection. This testing is performed by administering cosyntropin, a synthetic version of adrenocorticotrophic hormone, then collecting serum cortisol levels prior to injection, 30 minutes after injection, and 60 minutes after the injection. If that result is abnormal, defined as failure to achieve a cortisol level above 20μg/dL, they will be diagnosed with adrenal insufficiency and referred to our collaborating endocrinologist for further management. Additionally, for all subjects enrolled in the study we will perform a chart review and document clinical parameters as follows: basic demographic information (age, sex, BMI, ethnicity), medical history, medication history (dose of steroid, duration of use, any additional steroids they are taking for unrelated condition), basic labs (complete blood count, metabolic panel, liver function tests), and recent endoscopic findings (endoscopic reference score, presence of esophageal strictures).

Data analysis plan: First we will generate descriptive data of cohort demographics, medical history, steroid dose/duration, basic labs, symptoms, and diagnostic testing results. Patient information will be collected using REDCap, where it will stored securely in a HIPAA-compliant manner. The only people with access to the database will be study collaborators with individual, password-protected access logins. We will then perform descriptive statistics, including chi square, Fisher's exact test, t-tests, and Mann-Whitney U testing when appropriate comparing attributes in subjects taking chronic swallowed topical steroids with those taking chronic proton pump inhibitors. Specifically, we will use a paired t-test to compare the mean prevalence of AI between the two groups. We will also use Mann-Whitney U testing to compare differences between cortisol levels in both groups. We will then use multivariable logistic regression in order to identify factors associated with AI from the gathered clinical parameter data. Using forward selection, we will then conduct exploratory multivariable analyses between significant univariable predictors and AI.

Risks to subjects: For the blood collection patients will be at risk for typical venipuncture risks including a small chance of extravasation, bruising, and infection. Administration of cosyntropin can cause transient flushing, anxiety, nausea, and sweating (9). Because cosyntropin is administered as an intravenous "push," patients are additionally at risk for phlebitis, extravasation, venous spasm, and medication error. Lastly, patients will be at risk of loss of confidentiality during the protocol process.

Aim 2: Determine if any clinical parameters are associated with an increased risk of developing AI.

Protocol: As outlined in Aim 1, for all subjects enrolled in the study we will perform a chart review and document clinical parameters as follows: basic demographic information (age, sex, BMI, ethnicity), medical history, medication history (dose of steroid, duration of use, any additional steroids they are taking for unrelated condition), basic labs (complete blood count, metabolic panel, liver function tests), and recent endoscopic findings (endoscopic reference score, presence of esophageal strictures). Additionally, symptoms will be noted and organized using a symptom questionnaire recorded during their clinic visit.

Data analysis plan: Descriptive data of cohort demographics, medical history, steroid dose/duration, basic labs, symptoms, and diagnostic testing results will be generated. Patient information will be collected using REDCap, where it will stored securely in a HIPAA-compliant manner. The only people with access to the database will be study collaborators with individual, password-protected access logins. We will then perform descriptive statistics, including chi square, Fisher's exact test, t-tests, and Mann-Whitney U testing when appropriate comparing attributes in subjects taking chronic swallowed topical steroids with those taking chronic proton pump inhibitors. Specifically, we will use a paired t-test to compare the mean prevalence of AI between the two groups. We will also use Mann-Whitney U testing to compare differences between cortisol levels in both groups. We will then use multivariable logistic regression in order to identify factors associated with AI from the gathered clinical parameter data. Using forward selection, we will then conduct exploratory

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V. Summarize Knowledge to be Gained: Upon completion of this study we will be able to define the prevalence of adrenal insufficiency from taking chronic swallowed topical steroids for eosinophilic esophagitis in an adult population. We hope information from this study will help inform providers in the future regarding monitoring for adrenal insufficiency and be used to create guidelines surrounding prescribing practices.

VI. References:

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