Effectiveness of Cycling of Topical Steroid Therapy in Maintaining Clinical and Histologic Remission in Eosinophilic Esophagitis

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Objectives

The purpose of our research study is to assess whether patients with Eosinophilic Esophagitis (EoE) who have achieved clinical remission on topical corticosteroids are able to electively cycle their topical corticosteroid treatment with sustained remission of their EoE. The primary aim is to determine the number of patients who will remain in remission at one year following cycling of topical steroids as compared to those receiving continuous topical corticosteroid treatment. Our hypothesis is that in EoE, cycling topical corticosteroids is effective in sustaining remission and beneficial in decreasing risks of long term use of these medications when compared to continuous therapy.

Our secondary aims are:

i. The percent of patients who develop adverse effects of cycled compared to continuous steroid therapy.
ii. The level of esophageal mucosal biochemical mediators of EoE in patients on cycled compared to continuous steroid therapy.

Background

Eosinophilic Esophagitis is a food antigen driven inflammatory condition characterized by esophageal dysfunction. It was first identified in the 1960s though was only described as its own pathological entity in the 1990s. In the last two decades, knowledge about this disease has grown significantly (14). EoE typically presents in two age peaks, one in childhood and again in adults aged 30- 40 years. Symptoms in children can be broad and include vomiting or regurgitation, dysphagia, heart burn, food impaction, abdominal pain, feeding difficulty, and failure to thrive. Endoscopy (esophagogastroduodenoscopy, EGD) in patients with EoE often reveals esophageal edema, linear furrows, concentric rings, white exudates, esophageal narrowing and strictures. Definitive diagnosis is made histologically with >15 eosinophils per HPF seen on esophageal biopsy obtained via EGD. Treatment options for induction or remission includes high dose PPIs (50-60%effective), topical steroids (50-90% effective) and elimination diets (70% effective) (1). Esophageal dilation is also indicated in those with stricturing disease. Medical treatments are initiated for an 8-12 week course with follow up endoscopy preformed thereafter, for assessment of histologic remission evidenced by <1 Eos per HPF on esophageal biopsies (1).

EoE is now known to be a chronic disease, and if left untreated, can progress from mucosal inflammation to mucosal fibrosis and narrowing, thus causing esophageal strictures. Many studies have shown evidence that despite achieving symptomatic, endoscopic and even histologic remission, all aspects of disease have potential to recur after long term discontinuation of therapy (5,6,7,11). One such study by Liacouros et al. showed that in children with histologic remission after treatment with 4 weeks of either oral or topical steroids, mean eosinophil count had returned to pre-treatment levels on subsequent biopsies 6 months after treatment cessation (11). Due to this, it is suggested that maintenance therapy be initiated. However, to date there is little consensus as to what defines effective maintenance therapy for EoE, which is instead regarded as a “preference sensitive matter” (1). In our institution at Rainbow Babies and Children’s Hospital topical steroids, specifically swallowed viscous budesonide or swallowed fluticasone via metered dose inhaler, are often used successfully in the treatment of EoE. However, when used longer than a three month duration, topical steroids have been shown to increase the risk of candida esophagitis, oral thrush, and adrenal insufficiency (12). Further, compliance and quality of life on long medications continues to be an ongoing concern. Due to this, it can be beneficial to cycle steroid

responsive patients off of medications during times of histologic and symptomatic remission. This study aims to identify whether our current practice of topical corticosteroid treatment in a 3 month on and 3 month off cycle is successful in maintaining symptomatic and histological remission, as well as minimizing adverse effects of long term steroid use.

Inclusion and Exclusion Criteria

Patients will be screened through chart review to see if they meet inclusion criteria as described below.

	Inclusion Criteria
1.	Pediatric patients between the ages of 4-18 years of age with Eosinophilic Esophagitis followed by the Division of Pediatric Gastroenterology, Hepatology and Nutrition at Rainbow Babies and Children's Hospital at time of recruitment
2.	Patients who are currently on treatment with topical corticosteroids and scheduled for an upcoming endoscopy as part of their routine clinical care (to be used as EGD1) within 3 months of enrollment date
3.	Patients who have achieved documented clinical and endoscopic remission using topical steroids by the time of EGD1 in the study timeline

	Exclusion Criteria
1.	Patients who are not responsive to topical corticosteroid treatment for their EoE as evidenced by failure to obtain clinical or endoscopic remission on any pervious screening EGD
2.	Patients less than 4 years of age and older than 18 years of age at the time of recruitment
3.	Patients with history of or current diagnosis of esophageal strictures

Number of Research Participants

This is a single center prospective study taking place at Rainbow Babies and Children's Hospital consisting of a total of 30 patients. We will enroll 15 subjects to be in the intervention group to electively cycle topical Budesonide or Fluticasone 3 months on and 3 months off for treatment of EoE. 15 Patients will be in the control group for a total of 30 patients in the study.

Recruitment Methods

All subjects who are eligible for either the intervention group or the control group will be identified through our medical records of active EoE patients seen by Rainbow Babies and Children's Hospital Department of Pediatric Gastroenterology, Hepatology and Nutrition who are on topical Fluticasone or Budesonide treatment. Their medical charts will be individually reviewed by the PI to determine if they meet inclusion criteria as noted above.

Once the patients are identified, the primary GI physician for each of the patients will be contacted by the PI to obtain permission to approach his or her patient for recruitment to the study. This will be done via HIPAA protected email or discussed at weekly departmental meeting. Written or verbal permission will be obtained by the PI to approach each individual patient for consent and documented in the research records. Once permission from the primary GI has been obtained, the patients will be recruited to participate in the study.

Patients may be recruited either in person or virtually. For the in person consent process, patients and families will be approached by the PI or other qualified study personnel at a scheduled clinic visit or during inpatient hospitalizations. They will be asked to participate in the study and a copy of the Basic consent form as well as assent form will provided to the patient and family. These forms will be distributed to all participating outpatient sites. The PI will review the research study with the patient and parent and answer any questions they may have. The PI will then inform patient of next steps and obtain agreement for further contact either in person, by phone, or email for duration of the study. A full, written signed informed consent and assent will be obtained from parent(s) and patients who will be enrolled in the intervention and control group of this study.

For virtual recruitment, patients will be initially contacted by email or letter using the interventional recruitment template. After 14 days of initial virtual or in person contact, the patients will be contacted by phone to follow up and review the study. If the parent and patient agree to be a part of the research study, a virtual appointment will be set up via Doxy.me for the consent process as described below.

If the primary GI physician, the patient or the parents do not provide consent to be in the study, the patient will not be approached further by the PI or other study personnel.

Setting

1. All research activity will be conducted at Rainbow Babies and Children's Hospital, satellite campuses, and affiliate hospitals (UH St. John Medical Center). Satellite campuses include the following UH outpatient locations: Landerbrook, Mentor, Medina, Solon, Twinsburg, Parma, Fairlawn, and Firelands.

2. Research team will identify and recruit potential research participants in person at Rainbow Babies and Children's Hospital, UH St. John Medical Center, and UH outpatient clinics. Patients may also be recruited virtually through a video conferencing tool.

3. Lab work will be obtained at Rainbow Babies and Children's Hospital, UH St. John Medical Center, UH outpatient locations

4. Chart review and data collection will be performed within the Division of Gastroenterology, Hepatology & Nutrition at Rainbow Babies and Children's Hospital

Consent Process

Patients who meet inclusion criteria will be identified and recruited for involvement in this study during their outpatient endoscopy or outpatient clinic visits. Patients may also be contacted by email or letter and subsequently by phone for the consent process.

For the in person consent process, patients and families will be approached by the PI or other qualified study personnel to participate in the research study. The PI will review the research study with the patient and parents and answer any questions they may have. They will be given a copy of the Basic consent form, as well as assent form if indicated. If willing to participate, [the patient and parents/legal guardians will sign the informed consent. Then] the patient and family may choose whether they would like to being cycling their steroid therapy or continue on their continuous treatment plan, thereby choosing in which arm of the study they would like to participate. The PI will then inform patient of next steps and obtain agreement for further contact either in person, by phone, or email for duration of the

study. A full, written signed informed consent and assent will be obtained from parent(s) and patients who will be enrolled in the intervention and control group of this study.

For the virtual consent process, patients and families will be initially contacted by email or letter. After 14 days, the patients will be contacted by phone to follow up on the email or letter and review the study. If the parent and patient agree to be a part of the research study, another virtual appointment will be set up via Doxy.me for the consent process. The consent form will be sent to the patient prior to the appointment via email. During the virtual appointment, the parents will verify identity by showing an identification card. The patient's identity will be verified by the parent. If the bandwidth or connection does not permit a virtual visit with audiovisual capabilities, the potential participant can take a picture of their face and a picture of their photo ID and email both of these photographs to the study team's University Hospitals email address to verify identity. If the adult is a legal guardian and not the parent, a photo of the legal documentation will also be requested and emailed to the PI. The child will sign the assent form if age 7- 13 and on the consent form if age 14 and older. Once identity has been verified, the full informed consent process will take place during the virtual visit. If the participant decides to enroll, an electronic signature can be obtained from the REDCap e-consent link during the virtual visit. If the potential participant is unable to utilize the electronic format signature, he/she can print off a paper copy, sign the paper during the virtual visit, and take a picture of the signature page. The picture can be sent to the study team's UH email address at the end of the virtual visit.

Sharing of Results with Research Participants

Results of the study will be shared with the study participant as well as the subject's primary GI physician and will be given via phone call or letter. The information to be shared with the primary GI physician and patient includes routine biopsy results from all endoscopies preformed for the study, biopsies stained for eotaxin or IL-13, and morning cortisol levels preformed throughout the study.

Study Design

This will be a single center prospective study, consisting of one intervention group and one control group. The intervention group will consist of a total of 15 patients who are recruited to the study as outlined below to electively cycle topical steroid treatment in a 3 month on 3 month off fashion. The control group with also consist of 15 patients to be recruited as discussed below. Data will be collected prospectively at each designated study visit. Demographic data will be collected retrospectively.

Study Procedures

Recruitment: Please refer to "Recruitment Methods" section above.

0-3 month period: For this period of the study, study procedures are the same between the two groups. Newly diagnosed EoE patients who consent to study participation will initiate therapy with either Fluticasone or Budesonide per primary GI and patient preference. Patients who are already on topical steroid therapy will continue on their prescribed therapy. The screening EGD (listed as EGD 1 in the study timeline) will occur after 3 months of steroid treatment in the newly diagnosed patients. For those patients who were already on continuous topical steroid therapy, the screening EGD will occur at the time of their next clinically indicated EGD, which was scheduled per their primary GI physician. That is to say, as per the inclusion criteria, those children who are known EoE patients and already on topical steroids at the time of recruitment are only eligible for this study if their next clinically indicated EGD is

within 3 months of recruitment. For example, if a patient is on topical steroid therapy and has their yearly EGD scheduled in 2 months, they will be eligible for the study where this scheduled EGD will relate to the study EGD1. We will also allow patients to be enrolled in a retrospective manner, if their surveillance EGD was within one month of recruitment. For these patient's EGD1 will not include extra biopsies or scope day cortisol levels. For both new and known EoE patients who have enrolled in the study, this screening EGD (EGD 1) must show documented endoscopic remission in order to proceed further in the study. If the patient is not in endoscopic remission at EGD1 they will be considered a "treatment failure" and removed from the study.

Control group medications and endoscopies- months 3-12: Patients who consent to participate in the study and chose to remain on continuous steroid therapy will be in the control arm of the study. Patients in the control group will remain on topical Fluticasone or Budesonide and be followed clinically for a total of 12 months. They will be contacted in person at their scheduled surveillance endoscopy or via telephone at 3 months, 6 months, 9 months and 1 year time point. At these time points, clinical symptom assessments and quality of life surveys will be obtained.). If during any of the clinical symptoms assessments it is noted that symptoms return, or during the surveillance endoscopy a patient is noted to have an endoscopic flare of their EoE, they will be taken off topical corticosteroid, exited from the study and regarded as "treatment failure" in the study, and work with their primary GI doctor for an alternative treatment plan.

Patients in the control group will have routine biopsies obtained at their 3 month and 12 month EGDs and any other EGDs required per primary GI discretion as part of the management of their EoE. During the 3 month and 12 month EGDs, we will also obtain 2 extra biopsies to stain for IL-13 and eotaxin, biomarkers which are thought to be involved in recruitment of eosinophils from the blood stream into tissue. They will also have blood work drawn for morning cortisol levels to be obtained at 3 month and 12 month EGDs for screening of adrenal insufficiency. Blood volume will be limited to 0.8mL per blood draw.

Intervention group medication cycling and Endoscopies- 3-12 month period: After documented endoscopic remission on topical steroids at EGD1, patients will begin their first off cycle of their topical corticosteroid treatment. Patients will continue to be cycled off of the topical steroid medication for a 3 month duration (months 3-6 of this study). If at any point symptoms return during the off cycle time period, the patient will be restarted on the topical corticosteroid, exited from the study and regarded as "treatment failure" in the study. If patients remain in clinical remission after three months of medication free cycle, they will undergo surveillance EGD (defined as EGD 2 under Study Timeline). If during the surveillance endoscopy a patient is noted to have an endoscopic flare of their EoE they will be restarted on the topical corticosteroid, exited from the study and regarded as "treatment failure" in the study. If patients are noted to still be in endoscopic remission at EGD2, they are considered responsive to medication cycling. Patients will subsequently be restarted on topical corticosteroid for months 6-9 of this study followed by another medication free cycle from months 9-12.

Clinical symptoms and QOL assessments will be completed between each three month cycle either in person at scheduled EGDs or via telephone or virtual visit. After completing two rounds of on/off medication cycling, patients will undergo a final surveillance Endoscopy at month 12 (EGD3 on study timeline). In a one year period, each patient in the intervention group will undergo 3 endoscopies; 3 months after treatment initiation, 3 months after treatment cessation or "off cycling", and 12 months

after treatment initiation. During all EGDs, we will also obtain 2 extra biopsies to stain for IL-13 and eotaxin, biomarkers which are thought to be involved in recruitment of eosinophils from the blood stream into tissue

All the endoscopies to be performed during the study are standard of care in our division. In our group, it is protocol to perform an EGD to re-evaluate remission 3 months after any new change in treatment. Specifically, with every new treatment, EoE patients must undergo a surveillance endoscopy 3 months after initiation of this new treatment. For example, 3 months after initiating treatments such as topical steroids, PPI, or food elimination patients will undergo EGD to evaluate appropriate response to this treatment. Should the patient be found responsive, no further EGD is necessary until 1 year unless symptoms arise. Should the patient be found unresponsive to treatment, a change in treatment will be instated and the patient will once again undergo EGD in 3 months to evaluate for appropriate response. Thus, when applied to patients who cycle steroids, they are first started on topical steroids followed by a surveillance EGD at 3 months. Should they be in remission they are then allowed to cycle off of their topical steroids for 3 months. They undergo another surveillance EGD 3 months after cycling off steroids in order to evaluate for sustained remission. Should EGD reveal sustained remission of their EoE they are deemed responsive to cycling in a 3 month on 3 month off fashion, and are allowed to continue this method without further surveillance EGDs until 1 year from treatment initiation unless symptoms arise.

Outpatient visits and symptom monitoring: All patients will continue to have outpatient clinic visits with their primary GI physician in the year during which the study is ongoing. The number of medical visits will be at the discretion of the patients' primary gastroenterologist. They will also have routine EGDs as stated above. QOL and clinical assessment evaluations will be given at 3 month intervals during the study, either in person at surveillance endoscopies or via virtual visit.

Endoscopic biopsies and blood work: During the surveillance endoscopies, biopsies will be obtained. 6 standard biopsies will be obtained, four in the distal esophagus and two in the mid esophagus as indicated by the AGA for diagnosis of EoE. We will also obtain 2 extra biopsies to stain for IL-13 and eotaxin, biomarkers which are thought to be involved in recruitment of eosinophils from the blood stream into tissue. Blood work for early morning cortisol levels will also be obtained at each surveillance endoscopy for evaluation of medication side effects such as adrenal insufficiency. Blood volume will be limited to 0.8mL per blood draw, which will occur 3 times in the intervention group and 2 times in the control group during the year-long study. Blood draws will occur with IV placement during scheduled endoscopies to limit the need for multiple needle sticks and minimize patient discomfort. Should cortisol levels result <10mcg/dL they will be referred to a pediatric Endocrinologist for further evaluation of adrenal insufficiency.

Study Timeline

For all patients enrolled at diagnosis, study enrollment will last 12 months from the time of initiation of topical steroid treatment. For known EoE patients enrolled after already having been initiated on topical steroid treatment at the time of recruitment, study enrollment will last 9-12 months depending on the time from enrollment to their scheduled EGD1.

	Pre-Screening (consent for control or intervention group)	Clinically indicated EGD used as screening EGD 1 (3 months for control and intervention group)	surveillance EGD 2 (6 months intervention group)	Virtual visit 1 (9 months both groups)	surveillance EGD 3 (1 year control and intervention group)
Estimated time requirement of visit	15 minutes				
Clinical symptoms and QOL assessment		15 minutes	15 minutes	15 minutes	15 minutes
Surveillance Endoscopy		60 minutes	60 minutes		60 minutes
Morning cortisol level		5 minutes	5 minutes		5 minutes

Data to be Collected for your study

(AFTER consent and HIPAA Authorization have been obtained)

Data will be collected prospectively, with the exception of demographic data which will be collected retrospectively. Data to be collected includes standard biopsies taken during EGDs as well as one additional biopsy set to be processed for eotaxin and IL-13. Morning serum cortisol levels will also be drawn two or three times during the line placements during EGDs.

Data Analysis Plan

The Division of Pediatric Gastroenterology, Hepatology & Nutrition cares for over 350 patients with EoE. Though this is a pilot study, we did perform a sample size calculation for a non-inferiority (equivalence) study using values based upon our clinical experience and published literature (75% remission in control; 70% remission in test; 65% non-inferiority limit). If there is a difference of the continuous therapy of 5% (70% vs 65%), a sample size of 10 per group will be required to be 90% sure that the upper limit of a

onesided 95% confidence interval will exclude a difference in favor of the control of more than 65%. Our goal for recruitment is 15 patients per group to account for patient dropout.

Demographic characteristics will be summarized using standard descriptive summaries such as means and standard deviations for continuous variables and percentages for categorical variables. The primary endpoint summarized using percentages. The secondary endpoint will be summarized using percentages and means and standard deviations and compared using parametric and non-parametric tests.

Confidentiality

Multiple measures will be undertaken to adhere to patient confidentiality. Data collection will be limited to the amount necessary to achieve the aims of this research. All communication regarding research activities including obtaining consent and reviewing study procedures will be conducted in a private room or location. Data will be coded to remove direct identifiers and stored electronically in a password protected server and password protected documents.

Risks to Research Participants

Risks pertaining to the intervention group includes recurrence of EoE symptoms during cycling topical corticosteroids. Should this occur patients will be re-started on topical corticosteroids at the time of symptom recurrence and be considered failure of treatment in investigational arm of the study. There is also increased risk to the intervention group as compared to the control group associated with an increase in the number of endoscopic evaluations they will undergo. Patients in both arms of the study will undergo a surveillance endoscopy 3 months after initiation of steroids and one year after initiation of treatment. However, patients in the intervention group will also undergo an additional surveillance endoscopy at about 6 months from treatment initiation correlating with the end of their first “off medication” cycle. The additional EGD is standard of care for all of our patients who are cycling steroids and is preformed regardless of research study participation.

The risks secondary to EGD will be monitored closely and treated as part of standard of care at our center. In addition, I will have a Data Safety Monitoring Committee (DSMC) to serve as an Independent Safety Monitor (ISM) and monitor any adverse events. Adverse events will be reported to the IRB as well as to the ISM and the patient’s primary GI physician. The ISM will receive notification of an adverse event through a written report that will be sent via HIPAA protected email from the primary investigator.

Risks that pertain to both the intervention group and the control group includes the risk of the two extra biopsies taken during surveillance endoscopies. This includes increased risk of bleeding and perforation. The extra biopsies should not add more than 30 seconds of time to the procedure and thus risk from increased time under anesthesia is minimal. Both groups also have the potential risk of emotional discomfort due to answering questionnaires throughout the year, occurring at 3 months, 6 months, 9 months and 1 year.

Provisions to Protect the Privacy Interests of Research Participants

To minimize the risk of breach of confidentiality, we will not use the subject’s name or medical record number to identify them on any study records. Instead, a unique study number will be assigned to each subject. Only this number will be used on study documents that relate to the subject. The list containing subject names, medical record number and corresponding unique study number will be kept

electronically on a password protected server and password protected document. In addition, patients will be taken to a private area when obtaining consent and discussing study procedures.

Potential Benefit to Research Participants

Subjects who consent to the intervention arm of the study may have direct benefit of decreasing the amount of days a year in which they must take daily medications and thus decrease potential for side effects from these medications, however these benefits may vary and are not guaranteed. There will not be a direct benefit to subjects who will be in the control group. The results of this study may potentially benefit other patients with EoE as it would provide more flexibility for treatment duration and lower risks of long term steroid use.

Withdrawal of Research Participants

Subjects may withdraw from the investigational arm of the study at any time without affecting their care. They may also be discontinued from the study at the discretion of the primary investigator due to failure to comply to cycling times, loss to follow-up, failure to respond clinically to topical steroids, recurrence of symptoms during an off steroid cycle, or if they experience an adverse drug effect. It will be documented whether or not each subject completes the investigational arm of the study and if/why steroid cycling is discontinued. Subjects will be notified in writing if they are withdrawn from the investigational arm of the study.

Alternatives to Participation

The alternative is to not participate in the investigational arm of this study or in the control group. If patients do not want to participate in the study, they will continue with their current treatment plan with topical Budesonide or Fluticasone. If patients do not want to participate in the study but have an interest in cycling their topical steroid treatment, this can be discussed with their primary GI physician. Currently there is no evidence based guidelines for elective cycling of steroids in standard practice, but this can be done on an individual basis by physicians based on their previous experiences.

Costs to Research Participants

There will not be any additional costs to research participants. Their outpatient medical visits and basic laboratory work will be within the standard of care for treatment of EoE at our center. The additional EGD in the intervention group will be covered by the patient's insurance as this "extra" EGD is standard of care for any patient wishing to cycle off of topical steroid medication. The costs of extra biopsies and morning cortisol levels will be covered by FRAP grant awards, and will be processed at research laboratories at Case Western University for cost minimization.

Research Participant Compensation

Subjects in the intervention or control group of the research study will be given a $25 gift card for each QOL/clinical assessment questionnaire that is completed with maximum of $100. The gift cards will be paid within 4 weeks of completion of the study by mail to their home address that is provided in the electronic medical record. If the patient withdraws from the study, they will be paid for the portions that they completed. Participants will not be reimbursed for transportation expenses, or parking to get EGD or bloodwork done.

Provisions to Monitor the Data to Ensure the Safety of Research Participants

Data will be monitored for completeness, accuracy and adherence to protocol on a bimonthly basis by the primary investigator and/or research team. In addition, patients' clinical symptoms will be assessed every 90 days by the PI either by phone or in-person to ensure there are no serious adverse side effects of topical corticosteroids as well as no increase rate in disease recurrence in the intervention arm. The clinical symptoms will be assessed by administration of the dysphagia symptom questionnaire (DSQ) assessment. The QOL questionnaires will also evaluate for problems related to mental health. Should these questionnaires reveal that patients are sad or upset, the PI (who is pediatric board certified and with clinical experience and expertise assessing for depression and suicide risk) will subsequently preform a PHQ-9 assessment. If the assessment is positive the PI will then evaluate for active suicidal ideation with a plan or intent as needed. If assessment is negative, the PI will refer either to the participant's own mental health provider if he/she has one, or to community resources as listed in the supplemental material. If the assessment is positive for suicide risk, Frontline Cuyahoga County 216-623-6888 or 911 will be contacted on behalf of the participant. Should these patients be found to have depressive symptoms related directly to participation in the study, patients will be withdrawn from further participation. All questionnaires will be reviewed in real time during the in person or virtual visits with the PI every 3 months. There will be a designated DSMC who will review the adverse effects with the PI every 3 months. Additionally, research data will be reviewed at the 6 month mark and if greater than 50% of patients have discontinued topical corticosteroid cycling, the study will be discontinued.

Drugs or Devices

Swallowed Fluticasone propionate using a metered dose inhaler without a space and swallowed oral viscous Budesonide are topical steroid medications that are FDA approved for treatment of Eosinophilic Esophagitis. Will attach the drug insert to this application for further information.

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