Prospective Evaluation of the Clinical Utility of Budesonide for the Prevention of Esophageal Strictures after Endotherapy

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IRB Minimal Risk Protocol Template

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First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
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Modification: To modify this template after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes"..
3. Revise the protocol template to reflect the modification points , save the template to your files
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General Study Information

Principal Investigator: Dr. Michael Wallace

Study Title: Prospective Evaluation of the Clinical Utility of Budesonide for the Prevention of Esophageal Strictures after Endotherapy

Protocol version number and date: 13-009467 Version 1, 12/11/2013

Purpose

Hypothesis:
Oral budesonide prevents esophageal stricture formation in patients who underwent radical EMR or ESD for advanced premalignant esophageal lesions or superficial esophageal cancers.

Aims, purpose, or objectives:

1. The aim of this study is to prospectively record our experience with budesonide for the prevention of esophageal stricture formation after endotherapy (mucosal resection, submucosal dissection) as part of routine medical care.

2. The data will be compared with outcomes with well-annotated historical controls that underwent similar procedure with similar follow up but without budesonide exposure.
3. If sufficient efficacy is seen, these data will be used to plan a prospective controlled clinical trial. All patients in the study group will receive standard medical care and no experimental interventions will be performed.

Background (Include relevant experience, gaps in current knowledge, preliminary data, etc.):
Surgery has been historically the standard of care for advanced pre-malignant lesions and early esophageal cancers (EEC). However, esophagectomy is associated with significant morbidity and mortality [1]. With the technological advances of the current flexible platforms in recent years, there has been a growing interest in multiple minimally invasive endoscopic techniques for these esophageal disorders. Endoscopic mucosal resection (EMR), often in conjunction with mucosal ablative techniques, has been increasingly used for the treatment of dysplastic Barrett's esophagus (BE) and EEC [2], with long-term outcomes similar to traditional surgical intervention [3]. Traditionally highly focal EMR is performed of target lesions (e.g. nodules) followed by ablation, however some patient have large, or even diffuse nodularity that cannot be treated effectively with these methods. Wide spread radical EMR (defined as > 50% circumference resection) and more recently, endoscopic submucosal dissection (ESD), a technique initially developed in Japan, have been adopted as alternative treatments for the management of advanced pre-malignant and EEC [4-6]. ESD has the advantage over mucosal ablative techniques and EMR in that it permits en bloc resection of lesions, irrespective of size; thus, permitting a more precise histological evaluation and possibly a lower risk of recurrence [7,8].

Esophageal stricture (ES) formation is a widely recognized adverse event of radical EMR and ESD. Indeed, ES is the most common complication of radiofrequency ablation (RFA) for BE, with a reported incidence ranging from 5% to 12% [9,10]. A single-center retrospective study reported ES formation in 67% of 73 patients with EMR of at least 50% of their esophageal circumference [11]. Similarly, the incidence of ES development after ESD is between 70-90% when the mucosal defect involves more than three-quarters of the esophageal circumference [5,12]. In aggregate, the extent of the esophageal mucosal defect following endotherapy appears to be the most consistent predictor of ES formation.

Prevention of ES development following endotherapy can significantly improve a patient's quality of life and possibly reduce the potential risks and costs associated with treatment of ES with repeated endoscopic balloon dilations (EBD) [13]. Glucocorticoids have been evaluated as a potential preventive therapy for ES based on their anti-inflammatory properties and inhibitory effects on collagen deposition [14,15]. Several studies from Japan [16, 17] have evaluated the utility of endoscopic triamcinolone injection (ETI) for the prevention of stricture formation after ESD. However, local steroid injection is invasive and can be associated with the potential risk of bleeding and perforation at the newly created mucosal defect.

Oral prednisolone has been shown to be effective as a preventive strategy for ES formation [18]. However, prolonged use of systemic oral steroids can be associated with multiple adverse effects. Budesonide is a synthetic steroid with topical anti-inflammatory properties and high first-pass metabolism; thus, potentially less systemic absorption and side effects. A modified swallowed viscous budesonide/sucralose slurry has been shown to be safe and effective for treatment of esophageal narrowing due to eosinophilic esophagitis [19]. Given these characteristics, oral budesonide has been explored for the prevention of ES [20, 21]. Most recently Mayo Clinic Rochester developed a new budesonide capsule formulation. Alike viscous budesonide the budesonide capsule can be opened and the powder can be mixed with honey or pancake syrup. A similar formulation is currently used in pilot studies for treatment of eosinophilic esophagitis. The advantage of

budesonide capsule is the improve taste in comparison to viscous budesonide originating from budesonide respules which is unpalatable.
Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual:
We plan to include a total of 50 patients into the study group in setting of a pilot study. As part of a multi-center study 25 patients will be recruited at Mayo Clinic Florida into the study group and 25 patients at University of Florida, Gainesville.
The control group will consist of 150 patients (1:3 match) which will be obtained by retrospective chart review from all patients who underwent similar procedures between 1/1/2011 and 12/31/2013. Of 150 patients 75 patients will be provided by Mayo Clinic Florida and 75 patients from University of Florida, Gainesville.

Subject population:
All patients scheduled to undergo EMR or ESD as clinically indicated will be considered for the study. Patients with an esophageal mucosal defect involving more than 50% of the esophageal circumference following EMR/ESD will be offered to participate in this study.

Inclusion Criteria:
1. Age 18 years or older
2. Diagnosis of esophageal lesion treated with ESD or EMR which involves ≥ 50% of the esophageal circumference.

Exclusion Criteria:
3. Locally advanced disease
4. Prior esophageal surgery
5. Participation in another research protocol that could interfere or influence the outcome measures of the present study.
6. The subject or legal representative is unable/unwilling to give informed consent. (study group)
7. Medications or conditions for which there is a contraindication to use of budesonide (see pharmacology section below)
8. Concomitant use of systemic steroids or other immune suppressive medication for a different condition
9. Pregnant women

Will a Certificate of Confidentiality be obtained? No

Study Design

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

1. Informed Consent: The investigators will explain the nature of the study to each patient scheduled to receive budesonide following endotherapy and invite the subject to participate and provide a copy of the informed consent form. Each patient will be told prior to their participation that they are free to withdraw from the study at any time and that participation in this study will not alter their scheduled

medical care. They will read and sign the consent form prior to their participation of the study and they will be asked if they have any questions or need clarification after they have read the consent form and prior to their signing of the form.

2. Study Group: Participants will be instructed to swallow budesonide 3mg twice daily for eight consecutive weeks following endotherapy with EMR or ESD. Budesonide will be provided in a capsule containing 3mg budesonide only by Mayo Clinic Pharmacy with full 8 weeks supply. The patient will require opening the capsule and mixing the budesonide powder in 10ml (2 teaspoons) honey, or pancake syrup.
3. Patients will be instructed not to ingest any solid or liquids for 30 minutes before and after taking the budesonide. . For purposes of this study, budesonide is used off-label but according to the same dose and efficacy as has been demonstrated in other esophageal inflammatory conditions. [19] Patients will receive a handout with exact instructions how and when to take Budesonide gel. (attached)

3. Historical Control Group: Consists of patients who have undergone EMR or ESD for similar indications as the study group between 1/1/2011 and 12/31/2013 at Mayo Clinic Florida. The inclusion and exclusion criteria for the historical control group are the same as the study group. All data will be abstracted by retrospective chart review. Patients will not be contracted by study team. Consent will be not obtained from this group.

4. Follow-Up and Endpoints: Esophagogastroduodenoscopy (EGD) and endoscopic balloon or boogie dilation (EBD) will be performed on demand for dysphagia score ≥ 1 (scale 0-4) if symptoms cannot be attributed to a cause other than esophageal stricture (ES). Dilation will be continued until dysphagia score of 0 is reached. Additional ablation will be performed as clinically indicated, typically after stricture dilation has achieved luminal diameter of at least 10mm. For patients with dysphagia, the stricture diameter will be measured according to the largest balloon size at which no friction is seen with standard endoscopic passage. For patients without dysphagia, the diameter will be estimated base on luminal inspection using an open biopsy forceps for reference. An ES will be defined as inability to pass standard endoscope during EGD. Clinical symptoms of dysphagia will be evaluated with validated symptom scores (Eckardt and validated dysphagia scores) [22] with phone call at 1, clinic visit at 2 months and at the time of EGD at 3 months. All patients will undergo a follow-up EGD and barium esophagography to evaluate for asymptomatic ES at 12 weeks after endotherapy with EMR/ESD. Patient who have severe dysphagia (score 3 or 4 corresponding to ability to swallow liquids only or worse) will be offered earlier evaluation as clinically indicated.

5. Additional Data: Patients' perceptions, compliance and tolerability of Budesonide as treatment for prevention of ES will be recorded at 1 and 2 month follow up. Presence of esophageal candidiasis at time of EGD. Number of dilations sessions to achieve dysphagia score of 0.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

Dr Wallace will be the principal investigator (PI) supervising the study. Dr Wolfesen will be the co-PI. Dr Bartel will perform the chart review and will abstract the data into spreadsheets. Drs Wallace, Wolfsen and

Bartel will perform the patient requirement and obtain the consent form during the clinic visits prior the endotherapy.
Clinic visits as well as endoprocedures will take place in regular gastroenterological clinic setting.

Check all that apply. If none apply, leave blank:

x This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

☐ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement*.

☐ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

☐ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☐ The study involves audiotaping or videotaping

Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

☐ **From healthy, non pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

☐ **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)_____

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Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. (*Example: 01/01/2000 to 12/31/2012*)

Date range: From _1__/_1__/_2011____ to _12__/_31__/_2014____

Check all that apply:

☐ This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

☐ This study involves only data and/or specimens that will be collected after submission to the IRB.

x The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

☐ Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained and check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol*.

IRB Number(s):

□Subjects have provided consent for use of their data and/or specimens, as described in this protocol.

☐ Other data sources will be utilized in this study. When checked, provide all data sources:

Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject's relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.
External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS **Check all that apply**	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name	x	
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number	x	
Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data	x	x
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	x	x
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	☐ None	☐ None

Statistical Information

Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Statistical Considerations

Power Statement: pilot study

Data Analysis Plan:
Incidence of esophageal stricture and frequency of required endoscopic balloon dilation will be compared between historical control and study groups. Statistical significance of comparisons between the groups will be determined by using the Fisher exact test, chi-square test, Student t test, and Mann-Whitney test, as appropriate. P values <0.05 will be considered significant.

Endpoints

Primary:
Measure the incidence of dysphagia following ESD or EMR in both historic control group and study intervention group.
Need for repeat balloon dilation for esophageal stricture after 3 months following ESD or EMR in both historic control group and study intervention group.

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