The Impact of Adjuvant Liquid Alginate on Endoscopic Ablation Therapy of Complicated Barrett's Esophagus: A Pilot Study
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RESEARCH PLAN

PROTOCOL TITLE:

The Impact of Adjuvant Liquid Alginate on Endoscopic Ablation Therapy of Complicated Barrett's Esophagus: A Pilot Study

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Background

Barrett's esophagus (BE) is a pre-cancerous condition in the esophagus that results from constant acid exposure and is a precursor to esophageal adenocarcinoma (EAC). Surprisingly, EAC rates continue to rise despite efforts aimed at addressing BE. Patients with dysplastic BE are at increased risk for developing EAC and in high grade dysplasia (HGD), this risk can be as high as 6% per year. For these reasons, these patients are candidates for ablation therapy, either with cryotherapy, endoscopic mucosal resection (EMR), and/or radiofrequency ablation (RFA). In patients receiving ablative therapy, 3-5 treatments are typically required before there is resolution of all Barrett's epithelium while patients remain on twice daily proton pump therapy[29]. A recent case study by the current authors demonstrated initial failed response of BE with HGD to RFA and subsequently cryotherapy. *Only* after initiation of a liquid alginate solution (Gaviscon Advance - UK formulation) was there a subsequent rapid and complete response to therapy. This case suggests that liquid alginate provided additional esophageal protection allowing mucosal healing and an overall enhanced response to treatment. This finding is mechanistically plausible given existing evidence demonstrating the carcinogenic properties of bile acids and injurious activity of pepsin in non-acid refluxate, and liquid alginate's unique ability to control these components and inhibit acid reflux[1,2,5,6,7,8,10,16,18,21,25,26,34]. We feel further investigation is warranted in studying the role of adjunct liquid alginate solution in patients undergoing treatment for BE.

The ingredient of interest in is alginic acid (alginate), a polysaccharide found in the cell walls of brown algae. Alginates are unique in their ability to form a protective layer above gastric contents upon exposure to gastric acid, thus limiting exposure of esophageal epithelium to gastric acid, bile acid, pepsin, and other parts of the gastric contents. Concurrently, the bicarbonate in alginate-based solutions forms carbon dioxide in the presence of gastric acid, which converts the gel into foam which floats to the surface of the gastric contents. Hence, alginate solutions form "rafts" which provide a physical barrier to acid reflux, as well as a pH-neutral substitute which refluxes preferentially over gastric acid[12,13,17].

It is noteworthy that Gaviscon Advance, which is approved for over-the-counter use in Europe by the European Medicines Agency (EMA) but not FDA approved in the U.S., is qualitatively and quantitatively different from U.S. Gaviscon formulations in terms of alginate composition. Gaviscon Advance, but not American Gaviscon, has demonstrated superiority to placebo, non-inferiority to proton pump inhibitors (PPIs), and efficacy as add-on therapy in patients already on PPI with regard to relieving symptoms of GERD[4,15,22]. Furthermore, only the UK version of dual action antacid (antacid with alginate) has been shown to be superior to antacids alone in reducing post-prandial esophageal acid exposure in GERD patients[19]. Finally, as Dettmar et al. have demonstrated in a comparison of raft characteristics between a range of alginate/antacid formulations, Gaviscon Advance forms alginate rafts more quickly than other

formulations (most notably U.S. Gaviscon formulations), and these rafts are more coherent, have more complete flotation, and are of greater resiliency, weight, strength and volume than regular and extra strength Gaviscon (USA)[30].

Hypotheses & Specific Aims

H1 (primary): Adjuvant treatment with liquid alginate solution in addition to proton pump inhibitor (PPI) therapy will result in complete endoscopic eradication of complicated Barrett's esophagus (BE) more rapidly than endoscopic treatment on PPI therapy alone.

H2 (secondary): Adjuvant treatment with liquid alginate solution in addition to PPI therapy will result in fewer endoscopic treatment sessions necessary to achieve complete eradication of complicated BE compared to treatment with PPI alone.

SA 1 (primary): Eradication rate at one year will be compared between current recruits (i.e. study patients on adjuvant liquid alginate) and historical controls Patients will be matched by type of therapy, and to the best of our ability, length of Barrett's.

SA2 (secondary): To compare the duration of treatment required to achieve complete endoscopic eradication of BE in patients treated with the combination of PPI and liquid alginate solution vs. those treated with PPI alone.

SA 3 (tertiary): To compare the number of treatment sessions required to achieve endoscopic eradication of BE in patients treated with the combination of PPI and liquid alginate solution vs. those treated with PPI alone.

Study Design

This is a pilot prospective cohort study at a single tertiary care center. Patients with BE and proven dysplasia (high or low grade) or risk of other abnormality presenting to our tertiary care center interested in endoscopic treatment will be asked to participate in the study. Participation will involve taking 10 mL of Gaviscon Advance four times daily along with twice daily PPI during the treatment duration. The control group will be a historical cohort of Barrett's esophagus patients treated in the last 5 years by the same endoscopists using similar approaches—these are patients who were prescribed twice daily PPI therapy alone during treatment.

Eligibility Criteria

Patients who are already scheduled for treatment of their dysplastic Barrett's esophagus or risk of other abnormality who are planning to undergo EMR, or ablation therapy with cryotherapy (spray or balloon) and/or RFA (with or without EMR) will be eligible for enrollment.

Inclusion criteria (all must be present):
(1) Age $\geq$18
(2) Patients already previously scheduled for treatment of complicated Barrett's esophagus
(3) Long Segment Barrett's (>3cm)

Exclusion criteria:
(1) Moderate to severe renal impairment, as defined by eGFR< 60 for 2 consecutive readings
(2) Lack of capacity for decision-making
(3) Allergy to hydroxybenzoates

(4) Patients with uncontrolled hypertension or decompensated heart failure
(5) Pregnancy- patients of child-bearing potential will be tested.
(6) Patients with elevated calcium or potassium on screening laboratory testing (labs completed within the last month)

Enrollment

Eligible patients who provide informed consent will be included in this prospective study and asked to take the alginate solution in addition to their twice daily PPI therapy. If patients are on concurrent H2 blocker therapy, this will be stopped after enrollment in the study. Subjects will be primarily recruited in the office setting, following decision to undergo ablation therapy. Upon the start of ablation therapy, patients will start taking 10ml of Gaviscon Advance 30 minutes after every meal and at bedtime (4 daily doses, after breakfast, lunch, dinner and before bed). This will begin on the day of the first endoscopy, after the ablation treatment. PPI therapy will continue as previously prescribed.

Endoscopic treatment

Standard guidelines will be followed for patients undergoing EMR, RFA or cryotherapy or RFA, up to 8-10 cm can be treated during one session and sessions are scheduled every 10-12 weeks. For cryotherapy, approximately the same area can be treated (8-10cm) during one session, and sessions are scheduled every 8-10 weeks. When initial EMR is performed, follow-up endoscopic ablative therapy will be scheduled approximately 8 weeks later. The decision of which therapy to implement depends largely on anatomy and patient preference and will be determined by the endoscopists involved in the study—Dr. Puja Elias (PI), Dr. Brenda Hoffman, or Dr. B. Joseph Elmunzer. Furthermore, all decisions pertaining to the need for repeat procedures to address inadequate treatment or incomplete tissue sampling, or the decision to refer for the alternate procedure, will be dictated by the above endoscopists. As mentioned previously, number of sessions to achieve complete eradication of Barrett's varies by length, but on average can take anywhere from 3-5 sessions, depending on initial length of BE as well as existence and size of hiatal hernia[31].

Follow-up Assessments

All enrolled subjects will be followed until resolution of Barrett's is achieved, as confirmed by biopsy and endoscopic visualization. A measurement system referred to as the Prague classification[32] will be used to document areas of the esophagus with Barrett's and to assess improvement from one endoscopy to another. This system allows the endoscopist to record the area of Barrett's involved by describing the area involved that is circumferential in nature and the area that is patchy. Decrease in surface area involved will help guide the aim for the study. During treatment sessions, pertinent clinical and endoscopic data will be collected (see Appendix A). Immediately prior to each treatment visit, an office visit will take place at the MUSC Gastroenterology endoscopy/outpatient clinic with study personnel including the PI, research coordinator, and/or fellow/resident participating in the study, which will serve to collect data regarding blood pressure, surveillance serum chemistries, treatment experience, adverse events to the drug, or any other issues (see Appendix B). Adherence to the medication regimen will be done by asking patients to bring in all used and unused bottles. IDS will assist in calculating how much drug has been taken and this data will be recorded at each visit.
These data will then be entered into a coded RedCap database. At approximately six week intervals, the study research coordinator will call to verify medication regimen adherence as well as any adverse events associated with the study drug.

From the time of biopsy proven remission, patient medical records will be reviewed for up to 2 years to evaluate recurrences rates.

Outcomes

Eradication rate of intestinal metaplasia (complete remission of intestinal metaplasia – CRIM) at one year will be the primary outcome. The length of time to eradication and the number of endoscopic procedures required for CRIM will be the secondary and tertiary outcomes. CRIM will be defined as visual endoscopic evidence of neo-squamous epithelium occupying previous area of Barrett's epithelium combined with biopsies showing normal squamous esophageal epithelium without intestinal metaplasia.

When endoscopic eradication is observed, tissue biopsies of the GEJ and previously treated epithelium will be taken according to the Seattle protocol which recommends biopsies in a four quadrant fashion every 1 cm for a history of high grade dysplasia and ever 2 cm for a history of low grade dysplasia[33]. For areas of mucosal irregularity, targeted biopsies will also be taken. Patients who have achieved eradication but on subsequent biopsies have recurrence of Barrett's will undergo ablation treatment again until eradication is once again achieved. The presence of dysplasia on any one specimen will prohibit a claim of eradication.

The endoscopic footage from each study procedure will be video recorded. After quality assurance of the footage and removal of all identifiers, videos may be reviewed by a blinded and independent panel to confirm potentially subjective outcomes, such as the presence and extent of residual Barrett's epithelium. De-identified videos may be distributed to reviewers electronically, or may be reviewed during in-person sessions.

Adverse events related to the study drug will be defined according to standard consensus guideline documents published in the gastroenterology literature.

Sample Size Calculation and Statistical Consideration

We will compare the time to complete BE eradication/resolution (CRIM) between the prospective and historical cohorts using Kaplan-Meier time-to-event (time-to-CR) curves. The historical data maintained by the PI have n= 32 patients treated under similar conditions (e.g. facility, physicians) as the study patients who will be prospectively treated. As the purpose of this pilot study is to estimate the time to CRIM with the addition of liquid alginate for approximately 20 enrolled patients, no hypothesis testing will be performed to compare the distributions (hence, no power calculation). Comparisons will be descriptive only. Time-to-CR is assumed to be exponentially distributed and we will use the maximum likelihood estimate to estimate the rate parameter each cohort. Patients who do not reach CR by the end of the study will be censored at that time. The difference in the rate parameter between cohorts will be calculated with a 95% confidence interval. Median time to CR will be estimated based on these parameters. Median time to CR under current treatments is about 22 months [27]. If median time to CR with liquid alginate solution is sufficiently improved (e.g. to < 18 months), we will have high-quality pilot data with which to estimate a sample size for a more definitive randomized trial. Additionally, we will tabulate the number of treatments required to achieve CR and compare descriptively between cohorts as a secondary endpoint. Analyses above will also be stratified according to important covariates, such as disease grade and type of treatment (RFA or Cryotherapy).

Data Collection, Management, and Quality Control Procedures

Data entry will occur through RedCap, which will allow for study data to be directly entered into the database by the site via a secure internet connection. In addition to use of passwords and other security measures, all documents containing identifying information on individuals or physicians are considered confidential materials and will be safeguarded to the greatest possible extent. No information identifying a specific person, hospital, or physician will be released to or discussed with anyone other than study staff members. Appendix C shows the data points that will be collected from both the clinical and endoscopic visits.

Study Sites and Timeline

This is a single center study which will be conducted solely at MUSC Patients will be monitored with a telephone call every six weeks as mentioned above and they will be provided with information to get in touch with the study team if they have problems between their visits.. Enrollment will be ongoing until an adequate number of subjects have been recruited. Thus, we anticipate that the study can be completed within 2 years.

Monitoring

All study data will be monitored routinely for completeness, timeliness, and consistency by the project manager. Data accuracy will be verified on a quarterly basis by the project manager and principal investigator. Due to a relatively small "n", all subjects' data will be reviewed. Discovered discrepancies between recorded study data and information found in medical records will be addressed through discussions between the PI and research coordinator. Subjects may be withdrawn from the study if they are lost to follow up, or if they endorse lack of compliance with liquid alginate solution and/or PPI therapy.

Safety

Gaviscon Advance is considered a very safe medication with a very mild side effect profile. It is widely available in the UK but not available in the US. An FDA IND application has been filed for its use for this study. Gaviscon Advance will be purchased directly from the pharmaceutical company, Reckitt Benckiser. Each 10 mL oral suspension contains 1g sodium alginate and 200 mg potassium hydrogen carbonate (active ingredients). The formulation also contains calcium carbonate, carbomer, sodium saccharin, sodium hydroxide, and so any patients who have been advised to restrict their diet from any of these substances should consult a doctor before taking Gaviscon Advance. Patients who suffer for have suffered from significant kidney or heart disease should speak with a physician before taking Gaviscon. Finally, the formulation includes methyl and propyl para-hydroxybenzoates which may cause allergic reactions (less than 1 in 10,000 patients), including skin rash, itching, difficulty breathing, dizziness, or swelling. Overdosing of the medication may cause bloating. Please see summary of product characteristics – Appendix D).

Any adverse event, either related to Gaviscon Advance or not, will be recorded in pre-treatment clinic and/or treatment visits, and will be evaluated by a safety review committee (see below).

Safety Review Committee

A safety review committee will be assembled for this clinical study. This committee will be composed of 3 persons who are not study investigators. The overall goals of the committee will include the following: 1) identify unacceptably slow rates of accrual, 2) identify high rates of ineligibility, 3) identify protocol violations that suggest clarification of changes to protocol are needed, 4) identify unexpectedly high dropout rates that threaten the trial's ability to produce credible results, 5) ensure the credibility of the study, 6) ensure the validity of study results, and most importantly, 7) protect the safety of trial participants. The safety review committee will meet quarterly. If irregularities are identified in any of the goal areas listed above, the committee will propose changes to the protocol or study infrastructure in order to remedy the problem. In the event of a severe problem, the committee may advise termination of the study.

Potential Problems and Pitfalls

There are several potential pitfalls that may affect this study. However, if these are anticipated and managed appropriately, we believe they will not significantly impact the validity of the findings.

We have been conservative with the estimate of the anticipated number of subjects during the funding period. There are typically only several patients at MUSC's GI clinic per month that present with dysplastic Barrett's (or Barrett's with IMC) who are naïve to treatment. Therefore, we are proposing a pilot study with a conservative initial enrollment goal of 20 patients. This number can be increased to compensate for subjects who are potentially withdrawn or LTFU. If this pilot study proves to be informative, a multicenter initiative would be the next step.

Another challenge will be ensuring subject compliance with both PPI and liquid alginate therapy. This is particularly salient in patients who experience improvement in symptoms, and feel that they don't need to take medicine anymore, especially since the recommended dose of the study drug will be four times a day. We will contact the patients in between each 2-3 month visit, via telephone call and routinely reiterate the importance of medication compliance. We will also accurately record adherence, as mentioned above, by asking patients to bring in all bottles (used and unused) that were dispensed to them. Moreover, in the cases that prompted this line of research, we observed benefit associated with only twice daily dosing of alginate, making it feasible that our hypotheses could be met even if half the recommended dose is taken

Lastly, the small sample size will limit the validity and generalizability of our observations. The numbers may be further be limited as patients undergoing RFA and cryotherapy will be analyzed separately. As mentioned above, this is intended to be a hypothesis-generating study that may inform the design of a larger multi-center initiative.

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