11/29/17

NCT01458990: Proton Pump Inhibitors and Dysbiosis in Cirrhosis

Protocol Outline for Decompensated cirrhosis portion of the study (the compensated cirrhosis and healthy control portion is published in AJP 2014 and the publication has been uploaded)

RESEARCH PLAN

This will be a prospective 14-day study of outpatients with decompensated cirrhosis (Study overview is presented in the figure). We will recruit subjects from the hepatology clinics at the McGuire VA and VCU Medical Center.

There will be two age-matched patient groups:

Group 1: Patients not on PPI therapy who will be started on omeprazole 40mg/Qday before breakfast

Group 2: Patients on 40mg/day omeprazole or equivalent for an unapproved indication who will be withdrawn from the PPI

Inclusion criteria for both groups:
1. Cirrhosis diagnosed using biopsy, or radiologic/endoscopic evidence of cirrhosis and/or varices in the setting of chronic liver disease.
2. Evidence of decompensation: ascites or hepatic hydrothorax by history, examination due to cirrhosis or controlled using diuretics, history of variceal bleeding or jaundice (bilirubin >5mg/dl) at time of enrollment.
3. Able to give consent

Exclusion criteria for both groups:
1. unclear diagnosis of cirrhosis or of decompensation
2. Alcohol/illicit drug use in the last 3 months
3. Unable to give consent
4. Current hepatic encephalopathy treatment (lactulose, rifaximin), SBP prophylaxis, probiotics
5. Recent (<2 months) infections or treatments with systemic antibiotics or upper GI bleed
6. Allergic to PPI therapy
7. Patients on H2 receptor blockers

Special inclusions/exclusions for Group 2: we will only consider cirrhotic patients on 40mg/day omeprazole equivalent for PPI withdrawal if they are
1. Willing to withdraw this therapy
2. Are on PPI therapy for an indication other than the FDA-approved ones listed below[22]:
(a) Healing and maintenance of erosive esophagitis, (b) Treatment of gastro esophageal reflux disease, (c) Risk reduction for peptic ulcer with non-steroidal anti-inflammatory drugs (d) *Helicobacter pylori* eradication, in combination with antibiotics; (e) Pathological hyper-secretory conditions, including Zollinger-Ellison syndrome; (f) Short-term treatment and maintenance of peptic ulcer therapy.

Justification for study design and inclusion/exclusion criteria: our prior work and previous studies have shown that 14 days can change gut microbiota adequately with therapies. Since a large proportion of patients with decompensated cirrhotics are already on PPI, both a withdrawal and an introduction design will be used to increase the generalizability of the study results. We will exclude patients on recent/current antibiotics, probiotics and hepatic encephalopathy treatment to minimize the confounding factors for microbiota analysis. We chose 40mg/day before

breakfast since this was the dose the majority of our current decompensated cirrhotics are on and also to increase adherence with once-a-day dosing. Additionally this was also the regimen used in our preliminary study[9].

Screening: we will bring potential patients in for re-confirming their eligibility, evaluation of their indication and adherence to PPI use and in those who potentially fall in group 2, to gauge their willingness to stop PPIs for 14 days. Once eligibility is confirmed and informed consent is obtained, a standard diet (35Kcal/kg/day and 1.2-1.5g/kg/day of protein) will be prescribed and a food diary will be issued. Subjects will be given stool collection kits (with RNAlater) and asked to return for visit 2 within 7-14 days after the first visit.

Visit 1: We will reconfirm eligibility and adherence. Blood will be collected for gastrin, calculation of MELD score, and metabolomics; stool will be collected for microbial composition and function; and urine will be collected for metabolomics. After collection of the specimens, patients from group 1 will be started on omeprazole 40mg/day before breakfast for 14 days while those in group 2 will be asked to withdraw their PPI therapy. All subjects will continue on the same diet. Subjects will be given the contact information of the study team in case they experience any change in their medications, urgent clinic visits, antibiotic use or hospitalizations in the interim. Subjects will be paid $50 for completing the first visit activities and will be given a stool collection kit to bring with them for visit 2.

Telephone call one week after visit 1: to reconfirm that study conditions, diet conditions are being met and that there are no changes in the patients' underlying status. In case of initiation of antibiotics, change in PPI dose or re-initiation of PPI (group 2), we will attempt to bring those patients in as soon as possible to analyze microbiota changes.

Visit 2: At the end of 14 days, we will re-evaluate subjects' adherence on the study protocol and will perform all procedures regarding the study samples as in visit 1. At this point, the study participation for subjects will end. At this time, subjects will be paid $125 for their participation.

Detailed analyses of samples: Blood: MELD score laboratories (bilirubin, INR, creatinine)[24] and will be analyzed through the VA hospital clinical laboratory. Stool: Stool: Stool in RNAlater will be used to extract both DNA and RNA at the MBAC at George Mason University, VA using published techniques.

Statistical analysis: in the separate document

Expected outcomes: We expect a significant change in microbiota function and composition with a reduction in dysbiosis and microbial genes activated towards formation of toxic metabolites and altered microbial-mammalian co-metabolites when PPIs are taken out of the patients' systems. We do not expect any additional adverse events, including infections to occur associated with PPI given the relatively short duration of the study but all complications will be noted. To ensure adequate numbers we are accounting for a 15% dropout rate. We will increase enrollment if there are more dropouts than planned.