Name: Chronotherapy in Inflammatory Bowel Disease

NCT Number: NCT04304950

Chronotherapy in Inflammatory Bowel Disease

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Sponsors: None

Protocol version number: 1

Date: 6/18/2018

Objective: The objective of this study is to determine whether the timing of drug administration to treat inflammatory bowel disease (IBD) has an effect on patient outcomes.
Primary objective: Determine whether there is a difference in outcomes seen when patients are assigned to take their prescribed immunomodulator (IM) - either Azathioprine or 6-Mercaptopurine - at either a morning delivery time or evening delivery time.

Hypothesis: We hypothesize that administration time of immunomodulators (IMs) during the day can affect the clinical outcomes in IBD patients.

Specific Aims:
· Determine whether morning vs. evening dosing of patients' prescribed IMs (either Azathioprine or 6-Mercaptopurine) could affect the subclinical markers of inflammation related to disease.
· Determine whether morning vs. evening dosing of patients' prescribed IMs (either Azathioprine or 6-Mercaptopurine) could affect endoscopic outcomes.
· Determine whether morning vs. evening dosing of IMs affect their biochemical side effects, as is routinely monitored as part of the patients' clinical care.
· Determine if outcomes correlate with patients' chronotype, as determined by standard questionnaires (the Owl and Lark Questionnaire and the Munich Chronotype Questionnaire).

Background

1. Inflammatory Bowel Disease:

Inflammatory Bowel Disease (IBD) affects between 1-1.3 million people in the United States (Center for Disease Control and Prevention, 2014). IBD includes ulcerative colitis and Crohn's disease, both of which are characterized by inflammation of the intestinal mucosa and dysregulation of the mucosal immune system (Ardizzone & Porro, 2005, p. 2255). The pathogenesis of these diseases is still unclear, but current theories emphasize intestinal microbiota, and disruptions in the host immune response due to interactions between genetics and environmental stimuli (Gomez-Gomez et. al, 2015, p. 1283). Normally, the intestinal mucosa is in a state of 'controlled' inflammation involving a balance between pro-inflammatory and anti-inflammatory cytokines (Ardizzone & Porro, 2005, p. 2254). However, in IBD, there is dysregulation of the immune system and chronic inflammation.

The goals of IBD treatment include remission (absence of symptoms) and the prevention of flare-ups by controlling the inflammation in the intestine (Crohn's & Colitis Foundation of America, 2016). IMs such as azathioprine modify the immune system to decrease the inflammatory response in the intestine. IMs are usually used to maintain remission in patients with moderate disease who are steroid dependent or those who do not respond to aminosalicycylates or antibiotics, frequently need steroids, or have reported side effects with corticosteroid treatment (Crohn's & Colitis Foundation of America). IMs in IBD include azathioprine and 6-mercaptopurine, two related molecules.

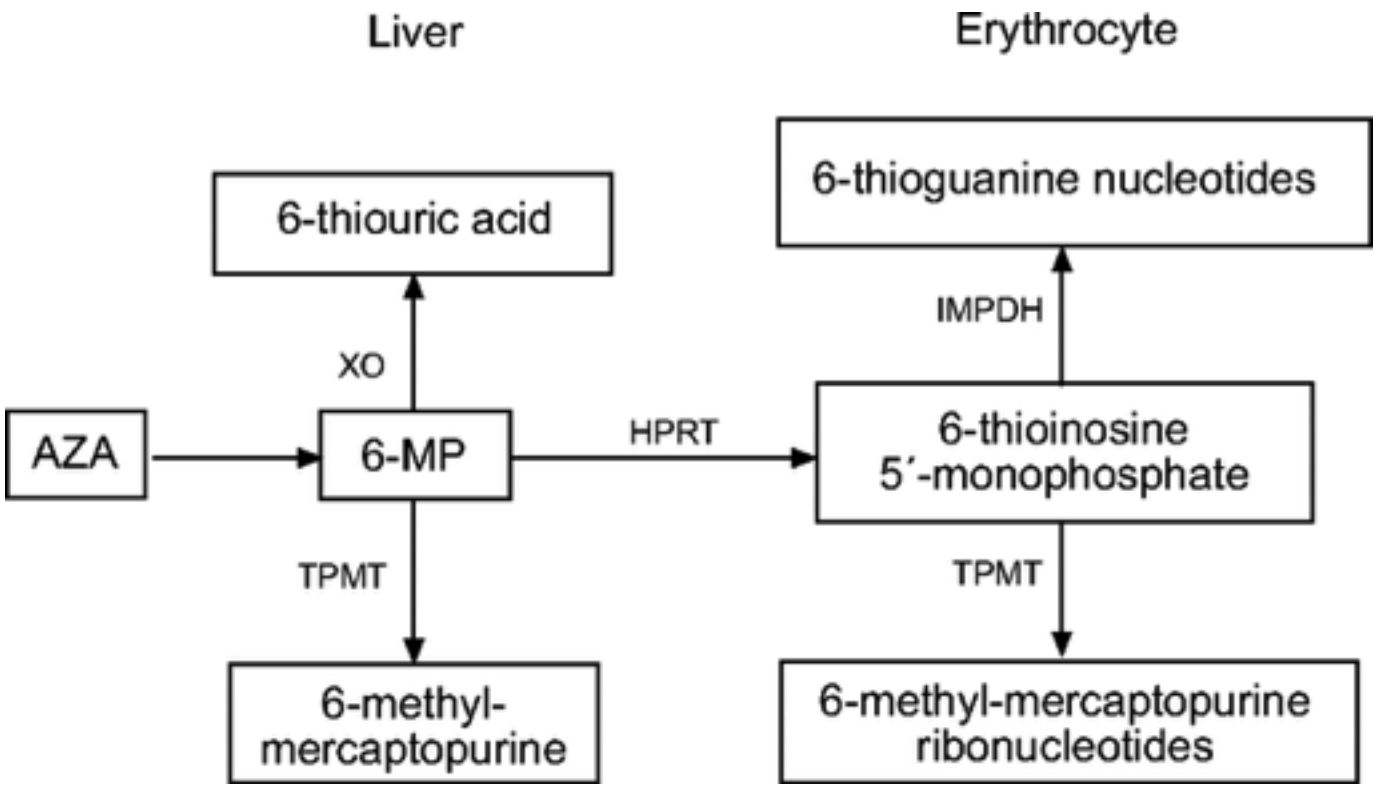
Data supports that IMs are effective for promoting remission in IBD. A meta-analysis of placebo-controlled studies of patients with Crohn's disease found that 57% of patients responded to azathioprine for treatment of active disease and remission maintenance indications, and 67% of patients responded similarly to 6-mercaptopurine (Belaiche et. al, 2001, p. 71). However, there are significant clinical side effects of IM therapy, and around 30-50% of patients discontinue IM use due to their side effects or because of a lack of efficacy of the medication (Bradford & Shih, 2011). Allergic reactions to the medications include rash, joint pain, fever, and pancreatitis (Grevenitis et. al, 2015, p. 1163). More serious complications include myelosuppresion and hepatotoxicity. A close biochemical monitoring of these medications (white blood count and liver function tests) is needed for dose adjustment or cessation of the medications.

2. Potential Role of Chronotherapy in IBD

An intrinsic circadian rhythm, set by the suprachiasmatic nuclei (SCN), regulates the temporal aspect of cellular and physiological function, and ensures that our behavior and physiological processes are timed in such a way that is optimal for interaction with the environment (Buttgerfeit et. al, 2015, p. 1). The SCN acts as the master clock that coordinates peripheral clocks (internal synchronization) and is also synchronized by external conditions, specifically, light-dark cycles. This leads to time-dependent responses such as the release of certain hormones, including melatonin, which regulates pro-inflammatory cytokine expression and leukocyte functions, as well as oscillation in activities of enzymes that are involved in generation of active or toxic forms of medications (p. 2). Chronotherapy is defined as the "timing of medical interventions according to biological rhythm determinants as a means to optimize treatment outcomes and minimize or avoid adverse effects" (Haus et. al, 2012, p. 8).

While circadian based medicine is novel and not yet included in mainstream medical practice, chronotherapy has already shown to be beneficial for treating Rheumatoid Arthritis (RA), another chronic inflammatory disease. In RA, there is temporal variation in cytokine secretion, regulated by the circadian clock, and research has shown that administering drugs at a specific time of day has led to a reduction in symptoms felt by the patient (Buttgerfeit et. al, 2015, p. 4). As explained by Haus et. al, morning stiffness, joint pain, and functional disability in RA is due to differences in the concentration of anti-inflammatory hormone cortisol compared to the concentrations of the pro-inflammatory cytokines that circulate at different times during a 24 hour period (2012, p. 6). Thus, prednisone, a common treatment for RA, if prescribed based on the circadian rhythm levels of IL-6, can control symptoms more effectively (p. 9). Similar to RA and other autoimmune diseases, IBD is characterized by a pro-inflammatory cytokine upregulation with treatments targeting this autoimmune response. Indeed, there is a significant overlap between IBD and RA treatments. Therefore it is possible that time of medication use in IBD may potentially impact the disease outcome. In this regard, we chose to focus on timing of IM delivery because 1) the drug metabolism of IMs is well-characterized (as is explained in detail below) 2) the effective and detrimental metabolites are well known; 3) the levels of these metabolites are clinically monitored in patients on IM therapy; and 4) unlike steroids, where their use should be limited, patients are maintained on IMs for extended time periods.

3. Metabolism of Azathioprine/6-Mercaptopurine



Azathioprine is first converted to 6-mercaptopurine in the liver. In red blood cells, hypoxanthine guanine phosphoribosyltransferase (HPRT) converts 6-mercaptopurine to 6-thioniosine-5'monophosphate, which is then converted to either 6-thiogunaine nucleotides (6-TG) or 6-methyl-mercaptopruine ribonucleotides (6-MMP). 6-TG is the metabolite that is associated with immunosuppression, and thus may help decrease disease activity and lead to or maintain remission in IBD (Belaiche et. al, 2001, p. 72). It has a long half-life in red blood cells and other tissues. Thus, prolonged treatment is needed for it to accumulate to steady-state levels (p. 72). 6-TG is also cytotoxic and associated with suppression of bone marrow at levels greater than 400 pmol/$8x10^8$ RBC (MacDermott, 2016). However, levels between 230 and 400 pmol/$8x10^8$ RBC seem to be optimal for treating IBD and achieving remission. The other end metabolite of azathioprine/6-mercaptopurine, 6-MMP, is associated with hepatotoxicity at levels greater than 5700 pmol/$8x10^8$ RBC (MacDermott, 2016). If thiopurine methyltransferase (TPMT) is deficient, bone marrow toxicity can occur due to elevated levels of 6-TG nucleotides. Thus, it is important to monitor the metabolism of azathioprine and 6-mercaptopurine through the levels of 6-TG and 6-MMP.

Methods

Research design: The study will be a prospective study in a cross over design, with each patient acting as a control for him/herself. Subjects will be patients contacted from a Rush University Medical Center database that are currently prescribed azathioprine and/or 6-mercaptopurine. They will be asked to take their medication at a determined time each day (morning or evening), complete questionnaires, and come in to get labs drawn. Data obtained will be analyzed according to statistical methods listed below in order to determine significance of association.

Power and Sample Size: There have been no prior studies testing the role of chronotherapy and IBD, therefore no knowledge exists on the anticipated effect. We aim for a prospective study to offer enrollment to all subjects who meet the study qualifications. For a mean difference of 5% and standard deviation of 20, we calculated that we will need to enroll 128 subjects to provide a power of 80% for a significance level of a=0.05.

Inclusion Criteria: Patients with IBD who have taken, or are currently taking, azathioprine or 6-mercaptopurine.

Exclusion Criteria: 1) Subjects who cannot give informed consent, 2) vulnerable populations including subjects < 18 years old, pregnant women, prisoners, non English-speaking and cognitively impaired individuals, 3) breastfeeding subjects, 4) patients treated with dual corticosteroid and immunomodulator therapy 5) patients who have had a history of complications related to immunomodulator therapy

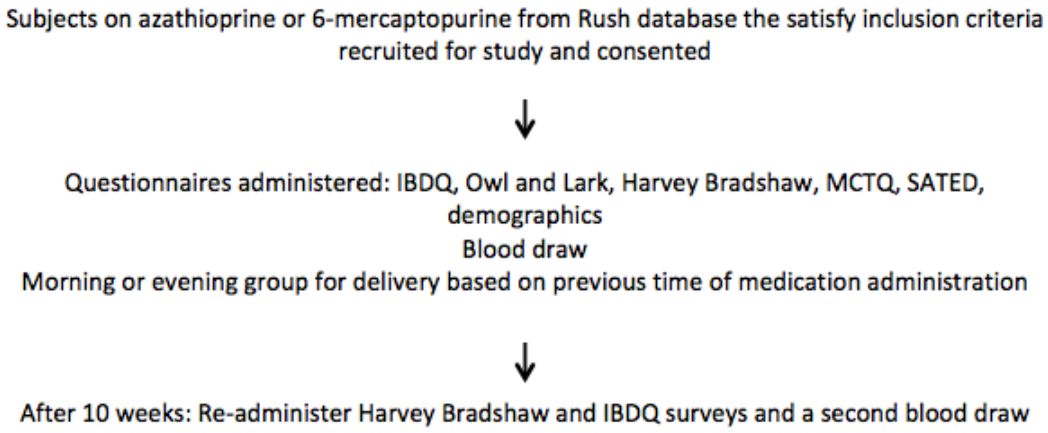
Subject Consenting and Recruitment: Potential subjects will be identified through a Rush University Medical Center Database, and contacted via telephone. Subjects will also be recruited during their scheduled clinic appointments with Rush University Gastroenterologists. A newsletter will also be posted on rush.edu/clinical-trials for patients to identify whether they would be interested in the study. A study staff member will explain the study to them. If the subject meets study qualifications and they are interested, they can choose to have the consent

form physically mailed or emailed to them (if they were recruited by telephone). If they were recruited during a scheduled clinic appointment, they can sign the consent form or take it home and return it by mail. The PI, co-investigators, and other key study personnel will obtain the consent from the subjects using an IRB-approved consent form for participation in the study. They will also answer any questions that the subjects may have regarding the study. Subject participation is voluntary. Consent will be obtained by having the subjects sign either a paper copy or an online copy of the approved consent form in a private setting. Subjects are allowed to take the consent form home to review it on their own time.

Early Withdrawal: Subjects can withdraw from the study at anytime upon their request.

Description of Procedures: After signing the informed consent form, subjects will be asked to answer the Inflammatory Bowel Disease Questionnaire (IBDQ), the Munich Chronotype Questionnaire (MCTQ), the Owl and Lark Questionnaire, the Harvey Bradshaw questionnaire, the RU SATED questionnaire, and a demographics survey. All six of these questionnaires are included with this IRB. Next, patients will be assigned a time (morning or evening) to self-administer their prescribed medication for 10 weeks. Patients who currently take their medication in the morning will be asked to switch to an evening delivery and patients who currently take their medication at night will be asked to switch to a morning delivery. The group assigned to morning delivery time will be told to take their medication between 6am and 11am. The group assigned to evening delivery time will be told to take their medication between 6pm and 11pm. Lastly, patients will be asked to give a blood sample to test for complete blood count (CBC), comprehensive metabolic panel (CMP), C-reactive protein (CRP), methylmercaptopurine (6-MMP), and thioguanine nucleotides (6-TG). Plasma and serum isolated from the blood sample will be temporarily stored to measure inflammatory cytokines after every 20 subjects complete the study.
Within a 6-10 week window, as part of their clinical care, subjects will come in to assess their clinical status while undergoing biochemical monitoring every 2-4 weeks. Data from their endoscopic examination, if done, will also be collected.
After 10 weeks, the subjects will be asked to complete the IBDQ and Harvey Bradshaw questionnaire. In addition, a blood sample will be obtained to measure the same metabolite levels and other biochemical indications of disease as stated above. Again, plasma and serum will be isolated from the blood sample and stored.

Study Design Flow:



Data Collection: Collected data will be logged in a secure database. The subject's name and birthdate will be obtained when the subject agrees to take part in the study and signs the written informed consent. The consent form is physically different from the actual questionnaire forms and therefore cannot be linked with reasonable ease to the subjects' responses to the questionnaires. No personal identifiers will be included in the spreadsheet. Each participant will be assigned a code for data collection. Only the key personnel listed in the IRB review application will be able to enter data into and access the database. All access into the database will be electronically monitored, complete with time and date of access, to ensure security and fidelity of the database material. The database will be stored electronically on a secure server in the PI's office in the Rush Professional Office Building Suite 206 and will be password protected. The database will be saved and maintained for approximately 5 years.

Data collected on subjects will include:

1. age and gender
2. prescribed medication (Azathioprine or 6-mercaptopurine)
3. subset of IBD (Crohn's or Ulcerative Colitis)
4. Data collected from questionnaires
5. laboratory values that correlate with clinical disease activity
6. endoscopic findings
7. imaging

The surveys are scored as followed:

1. Short IBD Questionnaire (SIBDQ): higher values represent better quality of life

2. Munich Chronotype Questionnaire (MCTQ): MSFSC < 2.17: extreme early type; 2.17 < MSFSC < 7.25: normal type; MSFSC > 7.25: extreme late type
3. Owl and Lark: extreme morning type: 70-86; moderately morning type: 59-69; neutral type: 42-58; moderately evening type: 31-41; extreme evening type: 16-30
4. Harvey Bradshaw Questionnaire: >16 severe disease, 8-16 moderate disease, 5-7 mild disease, <5 remission
5. RU SATED Questionnaire: higher values represent better sleep health

Study and Data Analysis:

All power estimates were computed using R package pwr, and we assume a Type I error rate of 0.05 and a 2-sided test for all analyses. Power estimates were derived from the data from prior unpublished studies. The primary endpoint of this study will be metabolites of 6-mercaptopurine. For Aim 1, previous studies have found that circadian enzymes can alter metabolites about 12% by different circadian controlled genes. With 128 UC subjects and effect size of 0.1 this will give us a 98% power to detect a difference in serum metabolites with a paired Wilcox Signed Rank test at alpha=0.05 level, and 84% power if gender is used as an independent variable. These conservative estimates provide a good estimate of the power to detect differences in metabolites chronotherapy in IBD patients. We anticipate we will have nonparametric data and will use the Wilcoxon match-pair test for analysis for inflammatory cytokines. This will be a nonrandomized trial that will not control for order effects, but other factors that are recorded such as cigarette smoking will be used as a covariate in multivariate analysis with analysis of variance (ANOVA) and linear regression as indicated. For Aim 2, a validated chronotype questionnaire (Munich Chronotype Questionnaire) will be compared optimal 6-mercaptopurine. Corrected midpoint of sleep will then be compared to 6-MP metabolites to see if chronotype impacts metabolite profiles. Data will be presented as median ± range for variables that can be considered nonparametric. All analyses will use R (v.3.2.5) and SPSS (SPSS Inc., Chicago, IL).

Our study is based on the potential circadian oscillation of the enzymes responsible for metabolizing IMs (as above), as well as that of the pro- and anti-inflammatory cytokines also described above. The oscillatory nature of these enzymes and cytokines may differ amongst individuals based on their circadian makeup, which we hope to assess via the chronotype surveys (Owl and Lark, MCTQ, RU SATED). We will assess the potential benefit of taking IMs in the morning vs evening by assessing changes in clinical outcomes, laboratory data, endoscopic findings/imaging (if subjects undergo a colonoscopy or imaging as part of their standard care while a part of this study), and quality of life surveys (Harvey Bradshaw, IBDQ). The study is a prospective cross-over study in which each patient is assigned to the morning or evening group based on when they currently take their medication. Therefore, each subject serves as his/her own control.

Study Outcomes: The goal of this study is to determine whether time of delivery of medication affects the efficacy or side effects of this medication. The study outcomes include 1) IBD clinical status as either a) remission defined per no need for step-up therapy (steroid, initiation of anti TNF, change of TNF, or surgery), or b) complications (fistula or abscess)
2) changes in the IBDQ and Harvey Bradshaw questionnaires.

Expected Outcomes: The expected outcome of this study is that there will be a difference seen in disease outcomes for IBD between the different groups based on what time they are taking their medication. Based on the known enzymatic pathways of IM metabolism and their potential circadian rhythm, we expect to see variation in the efficacy as well as toxicity of IMs when administered at different times of the day. Understanding these variations and determining the predicting factors (e.g., chronotypes) can lead to circadian-based administration of IMs to increase the efficacy of the drug while minimizing its side effects. We expect to see differences in the IBD quality of life questionnaire and the Harvey Bradshaw questionnaire from before the intervention to after the intervention, as well as differences in clinical disease activity as determined by levels of metabolites, endoscopic findings, and imaging, between the two groups.

Safety and Adverse Events: We do not predict any adverse events from modifying the timing of the medication delivery since there is no specific time of day currently prescribed to patients by their physician to take their medication. Additionally, we are not changing the dose or frequency of delivery of the medication. However, we will do continuous safety monitoring of our patients.

Data Management and Acquisition: Each study participant is assigned a code, and his/her data will be entered anonymously into a chart. We will then link the questionnaire and endoscopic results to this data via participant codes. Permission controls and passwords will assure that only authorized personnel will have the ability to enter data into the study database.

Confidentiality: Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

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