Budesonide for MPA-induced diarrhea in renal transplant recipients

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SPECIFIC AIMS

Renal transplantation is the treatment of choice for patients with advanced renal failure. The current caveats in the transplant medicine are the inadequate treatment options for side effects associated with immunosuppressive drug use.

Mycophenolic acid (MPA) is one of the main immunosuppressive medications prescribed after organ transplant. More than eighty percent renal transplant recipients in the US are on MPA based regimen. Diarrhea is a common side effect of the medication and can be seen in around 12-35% of subjects. Mycophenolic acid-acyl glucuronide (AcMPAG) is a metabolite of MPA, which causes inflammation and cytokine release and has been postulated to play major role in GI side effects. Diarrhea from MPA often leads to reduction and even discontinuation of the drug, thereby increasing risk of transplant organ rejection. Moreover, the subjects could also have weight loss, dyspepsia, nausea, loss of appetite, poor Quality of Life because of gastrointestinal (GI) adverse effects of MPA.

Corticosteroids, due to their anti-inflammatory activity, are the drug of choice for noninfectious inflammatory colitis. Budesonide acts locally in the intestine and is unique in having high first pass hepatic metabolism. It has minimal absorption into the systemic circulation thereby minimizing the systemic effects associated with other oral steroids. Our overall hypothesis is that oral budesonide can improve MPA associated diarrhea. We also plan to study the effect of treatment with Entocort on the gut microbiome in subjects with mycophenolic acid induced diarrhea. The long term goal of this project is to identify an effective treatment for diarrhea associated with MPA, increase MPA tolerability and improve quality of life and graft outcomes. The goal of this pilot study is to evaluate the feasibility of administering budesonide and its clinical efficacy in these subjects. Positive results in this study will be a key to moving forward to a long-term, large scale, randomized controlled study to definitively test whether budesonide improves MPA associated diarrhea and improves patient quality of life and renal graft outcomes. Furthermore, the optimum dose and duration and characteristics associated with response will need to be determined.

We propose prospective trial where renal transplant subjects with MPA associated diarrhea will receive budesonide (Entocort) for 8 weeks and will be followed for additional 8 weeks.

The specific aims of the pilot study are:

Aim 1. To determine the effect of oral budesonide on MPA associated diarrhea in renal transplant recipients. We *hypothesize* that subjects who receive budesonide will have improvement in diarrhea.

Aim 2. To compare the change in GI Quality of life in subjects with diarrhea from MPA with administration of budesonide. We *hypothesize* that subjects who receive budesonide will have improvement in GI quality of life from baseline.

Aim 3. To compare the gut microbiome changes before and after treatment with budesonide. We hypothesize that changes in gut microbiome will corelate with improvement in diarrhea in response to budesonide.

RESEARCH STRATEGY

Significance.

Kidney transplant for end stage renal disease offers increased longevity and better quantity of life. Adverse effects linked to immunosuppressant regimens are a major cause of dose reductions or treatment cessations, which can have a detrimental effect on graft survival [1, 2].

Mycophenolic acid (MPA), also called mycophenolate, is one of the most commonly prescribed immunosuppressant drugs and MPA-based regimens are associated with most successful outcomes in renal

transplant [3, 4]. Furthermore, MPA is also frequently used in the treatment of several auto immune disorders. MPA is a selective inhibitor of inosine monophosphate dehydrogenase (IMPDH), a key enzyme for the *de novo* production of purines in lymphocytes [5]. It is available in two formulations as Cellcept (morpholinoethyl ester of mycophenolic acid) and Myfortic (mycophenolate sodium). The drugs are rapidly hydrolyzed after absorption to mycophenolic acid, its active metabolite. MPA is metabolized to inactive 7-*O*-mycophenolic acid glucuronide (MPAG) and mycophenolic acid acyl glucuronide (AcMPAG) [6]. MPAG is thought to be pharmacologically inactive, but acyl glucuronides are toxic molecules and display pro-inflammatory effects.

Diarrhea is a well-recognized GI side effect associated with MPA use and accounts for increased morbidity and mortality [7, 8]. When severe, it could also result in volume depletion and renal graft dysfunction. Diarrhea associated with MPA often leads to dose reduction or treatment interruption and ultimately to an increased rate of acute rejection [1, 2] and is one of the most frequent adverse events leading to non-compliance. Its pathology is reasonably well studied but the treatment is currently still not available. Histological findings noted on colon biopsy include acute colitis-like findings, inflammatory bowel disease-like characteristics, graft-versus-host disease-like features and sometimes the biopsy may be non-revealing depending on the obtained sample [9].

Intestinal exposure to AcMPAG has been considered to be responsible for GI adverse events. AcMPAG is excreted in the urine and feces [6]. It is also produced in the GI tract from MPA via hepatic and intestinal glucuronidases [10]. AcMPAG is highly reactive and has been shown to cause cytokine release. On exposure to AcMPAG, Interleukin-6 (IL-6) and Tumor necrosis factor alpha (TNF-alpha) release, as well as gene expression of these cytokines was significantly increased in leukocytes [11]**.** The plasma levels of AcMPAG have been found to correlate with IL-6 levels in renal transplant patients[10]. TNF-α produced as a result of exposure of mucosal cells to AcMPAG also plays a role in GI mucosal inflammation. Case reports of use of TNF-α blocker, infliximab leading to improvement of severe diarrhea from mycophenolate in renal transplant subjects further suggests its role in pathogenesis [12, 13]. Furthermore, AcMPAG is also a metabolite of NSAIDS which have a similar GI toxicity profile; this also supports the role of AcMPAG in causing GI toxicity.

The other possible mechanism is inhibition of IMPDH pathway by MPA in GI epithelial cells which can inhibit its replication and repair. However, GI epithelial cells may not be wholly dependent on de novo purine synthesis, as they may be permeable to purines that are released into the intestine during digestion [14],thus bypassing the IMPDH dependent pathway. Therefore, it is now thought that the major cause of GI toxicity is the production of AcMPAG.

MPA associated adverse effects can also extend along the GI tract and subjects may also report dyspepsia, nausea or abdominal discomfort [15]. These side effects can vary in severity and are associated with decrease in Quality of life.

Budesonide, a corticosteroid, decreases levels of inflammatory cytokines such as IL-6, IL-1 and TNF-α through inhibition of protein synthesis and transcription [16].Systemic corticosteroids are associated with numerous cosmetic and serious adverse events including cushingoid features, infection, hypertension, osteoporosis, and diabetes mellitus. Budesonide has extensive first-pass hepatic metabolism by cytochrome P-450 enzymes. Due to limited systemic availability, many of the adverse events associated with systemic corticosteroids are diminished. Most studies report mild adverse events that are transient in nature; more common side effects include headache, nausea, and dizziness[17]. In a study of budesonide for maintenance therapy for patients with Crohn's colitis, 89% of patients rated the tolerability of the drug as "very good" or "good" after 6 weeks of treatment [18]. Budesonide has been effectively used in collagenous colitis, microscopic colitis and graft vs host disease with significant improvement in symptoms and is currently one of the drugs of choice for these conditions. For the treatment of above conditions Entocort, a gastric resistant formulation of budesonide is commonly used. **Entocort capsules contain pellets with slow release properties; this preparation allows the drug to be delivered mainly to the ileum and ascending colon** [19]. The properties of this formulation and extensive first pass liver metabolism of budesonide, offer improved therapy by reducing the risk of steroid associated side effects.

Gut microbiome, there has been emerging evidence that gut dysbiosis is associated with post transplant diarrhea in subjects on mycophenolic acid. In recent study by post transplant subjects on mycophenolate there was significant difference in the gut bacteria between the fecal specimens from the Diarrhea Group and the fecal specimens from the No Diarrhea Group. We want to study if there is change in gut microbiome after

treatment with budesonide and if it correlates with improvement in diarrhea. We will obtain stool specimens at baseline, week 8 when they finish treatment with budesonide, and at 16 weeks

Innovation.
This proposal is innovative in the following ways: To date, a there are no current treatments available except dose reduction or discontinuation of MPA. Using budesonide is an innovative strategy that has biological plausibility and has not been tested.

Approach
The overall goals of this pilot study are to demonstrate the efficacy and tolerability of budesonide in MPA associated diarrhea and improvement in GI quality of life with its use in renal transplant subjects. The subjects will receive oral budesonide 6mg (the dose commonly used for inflammatory colitis) for 8 weeks and will be further followed for additional 8 weeks.
Aim 1. To determine the effect of oral budesonide on MPA associated diarrhea in renal transplant recipients. We *hypothesize* that subjects who receive budesonide will have improvement in diarrhea.

Aim 2. To compare the change in GI Quality of life in subjects with diarrhea from MPA with administration of budesonide. We *hypothesize* that subjects who receive budesonide will have improvement in GI quality of life from baseline..

Aim 3. To compare the gut microbiome changes before and after treatment with budesonide. We hypothesize that changes in gut microbiome will corelate with improvement in diarrhea in response to budesonide.

Overall study design: Twenty subjects will be enrolled in the study. This is in addition to 9 subjects who were enrolled in the previous version of the protocol. The subjects will be recruited from the kidney transplant clinic at KUMC. The transplant center at KU performs around 130 kidney transplants each year and the subjects are closely followed and we anticipate no problems in recruiting enough subjects for this study in timely fashion. Subjects will be enrolled only if they meet all inclusion and none of the exclusion criteria.

Inclusion criteria:

1. Male or female >18 years of age
2. Kidney only transplant recipients > 1 month post-transplant
3. No h/o chronic diarrhea pre transplant
4. ≥3 watery/soft stools on at least 4 days in the week w/o anti-diarrheal for at least 2 weeks or using anti diarrheals for at least 4 days in the week > 2 weeks

5. Subjects on at least 180mg twice a day of mycophenolate-sodium or 250 mg twice a day of cellcept 6. Recent colonoscopy to rule out other causes of diarrhea.

Exclusion criteria:

1. Any known colonic diseases (i.e. Crohn's disease, ulcerative colitis, ischemic colitis, Celiac disease), partial colonic resection, small bowel resection, diarrhea caused by cholecystectomy, Irritable Bowel Syndrome, fecal incontinence, Bacterial overgrowth, infectious diarrhea (c difficle, cryptospora, giardia, isospora, Human Immunodeficiency Virus), Cytomegalovirus colitis.
2. Subjects with recent acute rejection treated with high dose steroids will be excluded.
3. Subjects taking *Boswellia serrata* extract, OTC herbs, cholestyramine, nonsteroidal salicylates (other than daily ASA).
4. Subjects with active malignancy, liver cirrhosis, active peptic ulcer disease, known intolerance or resistance to budesonide, mental retardation and inability to consent will be excluded.

5. Pregnant or nursing females, where pregnancy is confirmed by a positive hCG laboratory test.

Study procedures will occur according to this table.

	Screening	Baseline	Week 4	Week 8	Week 12	Week 16
Medical History, demographics, medications	X					
Vital signs (BP, HR) and weight		X		X		X
GIQLI		X		X		X
One week symptom diary		X		X		X
Phone interview			X		X	
Adverse event assessment	a	X	X	X	X	X
Dosing		Begins after completion of baseline 1week symptom diary	X	X (ends at week 8)		
Stool collection for gut microbiome analysis		X		X		X

GI symptoms assessment questionnaire

Diarrhea, defined as the occurrence of liquid stools for at least 2 weeks, with ≥3 stools/ day and ≥1 watery stool per day in the week. Complete remission (CR) is defined as a mean of <3 stools/day and a mean of <1 watery stool per day without use of anti-diarrheal drugs. Patient will be asked to keep a one week symptom diary.

Symptom burden will be assessed with a **1-week symptom diary** registering presence of diarrhea, number of stools per day, number of watery stools per day, urgency (0 = no urgency, 1 = need to defecate within 30 minutes, 2 = immediate need to empty the bowel, 3 = fecal incontinence), abdominal pain (0 = no pain, 1 = mild, 2 = moderate, 3 = severe pain), name and dose of anti-diarrheal used per day. Mean number of stools and watery stools per day will be calculated by adding up the number of stools registered during 1 week divided by 7.

The **Gastrointestinal Quality of Life Index** (GIQLI) is a 36-item questionnaire to assess the impact of GI disease on daily life. The GIQLI has 5 subscales (GI symptoms, emotional status, physical functions, social functions, and stress of medical treatment), producing a total score of the 36 items. Lower scores represent more dysfunction. It has been validated in renal graft recipients [20, 21].

We will obtain stool specimens at baseline, week 8 when they finish treatment with budesonide and at 16 weeks. DNA will be isolated from the fecal specimens and the high-quality DNA suitable for 16S rRNA Microbiome profiling will be used to identify the microbiome. Subjects will be provided with kits to take home to collect the sample.

Statistical Methods:

Aim 1. To determine the effect of oral budesonide on diarrhea due to MPA in renal transplant recipients. Our **Primary outcome** for this study is clinical remission (CR) by week 8. We will calculate the proportion of patients who are in CR at week 8.. Time to remission, relapse during treatment-free follow-up, number of watery and solid stools per week (measured at baseline, weeks 8, and 16 weeks),

Aim 2. To compare the change in GI Quality of life in subjects with diarrhea from MPA with administration of budesonide. Secondary efficacy outcome for the study is improvement in GIQLI score after administration of budesonide. GIQLI will be measured at baseline, weeks 8, and 16 weeks. To utilize all available data, we will use repeated measures mixed model analyses with time (measured in weeks) as the within subject factor. Our main mixed model analysis will include GI QLI score as the dependent variable and time. We will also conduct exploratory analysis using the other variables (as listed below) to identify any predictors of response.

Aim 3. To compare the gut microbiome changes before and after treatment with budesonide. We obtain stool sample at baseline, weeks 8 and weeks 16. We will compare if the changes in gut microbiome corelate with improvement in diarrhea in response to budesonide.

Other variables. We plan to gather the following additional information from time of consent until the week 16 visit: Patient demographics; medical history; use and amount of immunosuppressive medications; weight; n; other GI symptoms as noted by GSRS questionnaire; adverse events as outlined in safety evaluation; episode of cellular or antibody mediated graft rejection; graft function as measured using serum creatinine. General laboratory tests including complete blood count and basic metabolic panel, s that are routinely done for renal transplant recipients will be recorded.
Proportions will be compared by the χ^2 or Fisher's exact tests. Quantitative variables will be compared with the non-parametric Mann–Whitney test or Student's t-test. A P-value below 0.05 will be considered to be statistically significant.

Sample size justification: Our sample size was selected based on logical/feasibility constraints-not just of the funding mechanism, but also of the early phase of discovery. The goal at this phase is to study feasibility and efficacy of budesonide in MPA associated diarrhea. Since no preliminary information is available for our study, no formal sample size calculations are provided. Regardless, valuable information gained from this study—including feasibility of administering this medication over such a period of time—will provide critical information in consideration for subsequent research. Within the limitations of a pilot study, we have selected to not do randomization as subjects who have diarrhea from the medication would want to be treated.

Data management: Study data will be collected and managed using the Research Electronic Data Capture (REDCap), a web-based, electronic data capture tools hosted on a secure, HIPPA compliant server at KUMC[22]. Data will be entered by the research coordinators and validated with real-time entry validation and offline validation by the investigators. The database will be maintained in a secure institutional server that will have regular back-up, with only the PI, co-PI and coordinator having access.

Timeline: We anticipate 16 weeks follow up for each patient. We will recruit 20 patients around 18 months. We anticipate about 2 months for statistical analysis. We anticipate 3-4 months for manuscript writing and future grant applications.

Safety Evaluation. Patient will have face to face interview and vitals (BP, HR, weight) at enrollment (baseline), week 8 and 16. Phone interview will be done at 4and 12 weeks to monitor compliance, changes in medication and occurrence for adverse events
Potential adverse effects of steroids including insomnia, rash, palpitations, headache, hyperglycemia and dizziness will also be noted. Any symptoms noted at enrollment will be considered medical history. Any worsenin in severity of symptoms after enrollment will be considered adverse events.
Withdrawn
. If subjects withdraw consent and discontinue treatment, they will be requested to complete the week 8 and 16 visit procedures.

Adverse events will be collected from the time of signing the informed consent until the week 16 visit.
After study completion/withdrawal, patients could continue therapy with commercially available budesonide at the discretion of the clinician/ /patient.

Potential limitations. Due to budget limitations, we will not be able to do a large placebo controlled trial. However, if results are encouraging, we will use preliminary data from the proposed study for the procurement of future funding to support such investigations. The extent of symptoms reporting by patients will depend on patient's subjective assessment. Also, there is no standardized approach to define and describe the severity of diarrhea in these patients [23, 24]. The lack of a validated, reproducible and uniform approach to the clinical evaluation of GI symptoms makes it difficult to compare GI effects. Despite these limitations, questionnaires may be a useful way of various regimens to assess fluctuating (especially symptom diary) and variable symptoms in individual patients. They can also give a good indication of an individual patient's subjective perception of the severity of their symptoms and the relative impact of the symptoms on their overall quality of life. We will not be performing colonoscopy as part of the protocol. Subjects > 50 are screened with colonoscopy as part of transplant care. If clinical symptoms warrant colonoscopy it will be done as a part of clinical care.

Anticipated Impact and future funding

Achieving the aims of the application will result in the advancement of scientific knowledge regarding the treatment options available for MPA associated diarrhea in renal transplant recipients. Such knowledge will facilitate adequate evaluation and appropriate treatment of diarrhea rather than MPA dose reduction. It may have the potential of improving quality of life and lowering the healthcare costs by improving patient morbidity and graft survival. MPA is also used in other conditions including other organ transplants and multiple autoimmune disorders. Clearly, in view of the significant use of MPA and prevalence of GI adverse effects, the impact of the proposed project will not be limited to the renal transplant population, but can be generalized to the other conditions where its use is limited by diarrhea.

The PI is a junior investigator who has a strong interest in clinical and translational research in the field of nephrology especially Transplant. The results of this study will provide the applicant with preliminary data to facilitate a proposal for a NIH research grant as well as Career Development Grant from the American Society of Nephrology and American Society of Transplantation. The PI plans to use the preliminary results generated from this study for prospective large randomized control trial with long term follow up. This will help to identify the subjects who will benefit, the optimal duration of treatment as well as how it can translate to better patient and long term graft outcomes.

Environment

The Center for Transplantation at The University of Kansas Hospital is the largest and most successful transplant program in the state. Patients from across the country turn to our nationally recognized program because of our reputation, expertise, reduced wait times and exceptionally high standards for comprehensive care. Our patient survival rates are higher than regional and national averages, and our organ waiting list times are significantly shorter. At the Center for Transplantation, specialists offer the most advanced treatment options. This includes highly specialized procedures, such as desensitization and individualized immunosuppressive therapies, in addition to the resources of the region's premier academic medical center. We also provide ABO-incompatible transplantation and the only paired kidney exchange program in the Kansas City area. The transplant physicians and surgeons have the experience and expertise to provide patients with the most advanced transplant care possible. Patients from across the country turn to our nationally recognized Center for Transplantation, which provides advanced, comprehensive care in one location.
This research project will also be supported by the Kidney Institute at the University of Kansas Medical Center. The Kidney Institute is a world-class, internationally recognized research center comprised of 44 doctoral level faculty investigators and provides clinician-scientists and basic-scientists opportunities to closely interact on joint research projects and clinical trials.
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