Mycophenolate mofetil-related diarrhea reports and beta-glucuronidase expression following kidney transplantation.

G. Onyeaghala[1,2], S. Elmer[1], D. Schladt[1], P. Yang[1], M. Wagner[6], L. Teigen[3], M. Al-Kofahi[5], B. Wu[4], W. Guan[4], C. Staley[6], S. Riad[2], A. Matas[6], R. Remmel[5], W. Oetting[5], C. Dorr[1,2], PA. Jacobson[5], A. Israni[1,2,7]

[1]Department of Nephrology, Hennepin Healthcare Research Institute, [2]Department of Medicine (Affiliate), University of Minnesota, [3]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota
[4]Division of Biostatistics, University of Minnesota, [5]Department of Experimental and Clinical Pharmacology (ECP), University of Minnesota
[6]Department of Surgery, University of Minnesota, [7]School of Public Health, University of Minnesota

INTRODUCTION

- Mycophenolate mofetil (MMF) is associated with diarrhea.
- Recipients developing diarrhea are generally managed with lower MMF daily doses or dividing the same daily dose into three times a day dosing.
- Shorter dosing intervals are associated with reduced adherence to immunosuppression and poorer outcomes.

HYPOTHESIS

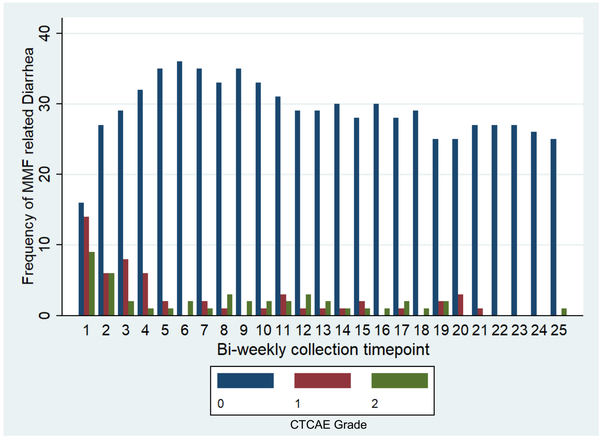
- We hypothesized that bacterial beta-glucuronidase expression in the stool, which is a key enzyme in MMF enterohepatic recirculation, is associated with diarrhea occurrence.

METHODS

- The Microbiome and Immunosuppression in Kidney Transplantation (MISSION) study assessed diarrhea posttx using bi-weekly text-based survey (Mosio Inc, Seattle, WA) in the first 3 months posttx.
- Diarrhea events were defined using the V 5.0 definition of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).
- Diarrhea events of CTCAE grade 2 (increase of 4-6 stools per day compared to the previous week) were the primary outcome.
- Each participant provided a single stool sample at baseline, which underwent metatranscriptomics analysis on NovaSeq. The data were processed using HUMAnN 3.0, and beta-glucuronidase transcripts were determined using level-4 enzyme commission (EC) categories.
- In an exploratory analysis, we used polytomous logistic regression to model the association between diarrhea events and beta-glucuronidase transcripts after controlling for age, gender, race, diabetes and BMI at baseline.

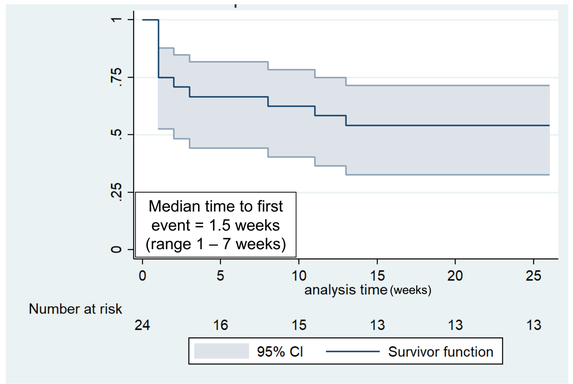
RESULTS

Figure 1: Frequency of MMF-related diarrhea during the first 3 months of follow up



During the first 3 months of follow up, we observed 31 CTCAE grate 1 (5.3% of responses) and 25 CTCAE grade 2 (4.3% of responses) diarrhea events.

Figure 2: Kaplan Meier curve for diarrhea events of CTCAE grade 2+ events during follow up



Data represent the Kaplan Meier estimates for the time to first severe diarrhea event over the first 6 months of follow up. 33% of the study participants reported a CTCAE grade 2 diarrhea event in the first 30 days of follow up.

Table 1: Demographic & clinical characteristics of the study participants

Baseline Demographics	Did not develop CTCAE grade 2 Diarrhea (N=13)	Developed CTCAE grade 2 diarrhea* (N=11)
Age (Mean (STD))	45.6 (15.3)	50.3 (12.1)
BMI (Mean (STD))	28.8 (3.3)	28.9 (5.9)
White (%)	6 (46.1%)	9 (81.8%)
Male (%)	8 (61.5%)	9 (81.8%)
Diabetes at baseline (%)	4 (30.1%)	2 (18.2%)

*CTCAE grade 1 indicates loose stool, but no increase in frequency. CTCAE grade 2 was the main outcome of this analysis

Table 2: Association between beta-glucuronidase transcripts and MMF related diarrhea events using multinomial regression

Diarrhea CTCAE Grade	Number of diarrhea events	Beta_Glucuronidase Mean copies per million (standard deviation)	Relative Risk	p-value
CTCAE grade 0	526	107.4 (200.8)	Reference	
CTCAE grade 1	31	60.5 (98.8)	0.997 (0.995 - 1.000)	0.13
CTCAE grade 2	25	71.2 (118.9)	0.999 (0.995 - 1.001)	0.38

The multinomial logistic regression model was adjusted for age at transplant, sex, race, diarrhea reported timepoint, bmi and diabetes status at baseline.

CONCLUSIONS

- 33% (8 out of 24 participants) reported a CTCAE grade 2 diarrhea event within the first 30 days of follow up.
- Although beta-glucuronidase expression in the stool was lower among participants who developed CTCAE grade 2 diarrhea (mean of 71.2 cpm, vs 107.4 cpm in CTCAE grade 0 participants) we did not observe an association between beta-glucuronidase transcripts and diarrhea (RR: 0.999, p-value: 0.38) (Table 2).
- A larger sample size is needed to simultaneously collect longitudinal microbiome data and MMF adverse events to understand the interplay between the gut microbiome and MMF adverse events in kidney transplantation.

Acknowledgements: This study was supported in part by NIH/NIAID grant **5R01AI140303** and HHRI's Post-doctoral Support Career Development Award