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Tacrolimus concentration to dose ratio in solid organ transplant patients treated with fecal microbiota transplantation for recurrent *Clostridium difficile* infection

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Abstract

Fecal microbiota transplantation (FMT) is increasingly being performed for *Clostridium difficile* infection in solid organ transplant patients; however, little is known about the potential pharmacokinetic or pharmacomicrobial effects this may have on tacrolimus levels. We reviewed the medical records of 10 solid organ transplant patients from September 2012 – December 2016 who were taking tacrolimus at time of FMT for recurrent *Clostridium difficile* infection. We compared the differences in tacrolimus concentration / dose ratio (C/D ratio) three months prior to FMT vs three months after FMT. The mean of the differences in C/D ratio calculated as ng/mL / mg/kg/day was -17.65 (95% CI -1.25 – 0.58) ng/mL / mg/kg/day, p-value 0.43 by Wilcoxon signed-rank test. The mean of the differences in C/D ratio calculated as ng/mL / mg/day was -0.33 (95% CI -1.25 – 0.58) ng/mL / mg/day, p-value 0.28 by Wilcoxon signed-rank test. Of these patients, 2/10 underwent allograft biopsy for allograft dysfunction in the year after FMT, with no evidence of allograft rejection on pathology. These preliminary data suggest that FMT may not predictably alter tacrolimus levels and support its safety for solid organ transplant patients however further study in randomized trials is needed.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by *Transplant Infectious Disease*.

INTRODUCTION

Fecal microbiota transplantation (FMT) is a highly effective treatment for recurrent *Clostridium difficile infection* (RCDI), but its pharmacologic effects are poorly understood. (1–3)

Solid organ transplant (SOT) recipients are typically prescribed a cocktail of immunomodulatory medications to prevent allograft rejection. Many of these medications have a narrow therapeutic index, with potential toxicity at excessive drug levels and increased risk of allograft rejection at sub-therapeutic drug levels. Important drug-drug and drug-food interactions that can affect immunomodulatory drug levels have been described, which aid in anticipating dose changes to remain in the therapeutic range.(4) In a recent prospective microbiome analysis of patients undergoing renal transplantation, Lee et al noted that *Faecalibacterium prausnitzii* fecal microbiota sequence reads were seen in greater abundance among patients who required increases in tacrolimus dosing compared to patients who did not require dose increases.(5) This suggested an association between *F. prausnitzii* and increased tacrolimus dose requirements. FMT is increasingly being performed for RCDI in immunocompromised patients without report of any adverse effects that have been directly attributed to the fecal material. However, outcomes should be carefully studied in the event FMT should be considered an indication for closer tacrolimus monitoring or dose adjustment.(6–8)

We conducted a retrospective review of 10 SOT patients who were prescribed tacrolimus for immunosuppression who underwent FMT for RCDI at our center to evaluate if they required changes in tacrolimus dosing in the three months following FMT. Based on the prior report that gut microbiota influence tacrolimus dose requirements, we aimed to evaluate if there was a difference in tacrolimus concentration / daily dose ratio (C/D ratio) three months after FMT.

MATERIALS AND METHODS

Study center and design

This was a single-center retrospective review of all SOT recipients who underwent FMT at Emory University from July 1, 2012 to December 31, 2016. Emory University Hospital is a tertiary care center located in Atlanta, Georgia, and is licensed for 605 beds. Since 2012, 257 patients have undergone FMT for RCDI at Emory University Hospital and the Emory Clinic and been registered in a secure dataset. All patients included in this dataset with history of SOT were identified by chart review. Patient demographics and key study characteristics were manually extracted by chart review and entered into a secure Excel spreadsheet (Microsoft, Redmond, WA). Data extraction was confirmed by validation sample of (5/10, 50%) reviewed charts of SOT patients undergoing FMT. Observations were censored at date of last tacrolimus laboratory value, last clinic visit, or death. IRB approval was obtained (study IRB #71277) for this study.

Fecal donor characteristics

All fecal donors were screened with an initial questionnaire followed by blood and stool testing to exclude potential pathogens as previously described.(7) During the study period, only one patient received fecal material from a known relative, the remaining nine patients studied received fecal material from anonymous, screened universal fecal donors.

Data extraction and definitions

RCDI was a clinical diagnosis made by treating physicians and a requirement for referral for FMT and subsequent inclusion in this institutional dataset. RCDI is commonly defined as 3 or more episodes of mild to moderate CDI or 2 episodes resulting in hospitalization.(9) All included patients in this study had two or more periods of frequent, watery diarrhea with positive laboratory testing for *C. difficile* on a PCR platform. Transplant patients at Emory are not routinely screened for *C. difficile* and all patients who go on to receive FMT must first demonstrate improvement on standard of care regimens for *C. difficile* with recurrence occurring after the discontinuation of antibiotics, consistent with clinical infection and recurrence.

The primary outcome for this study was difference in tacrolimus C/D ratio. Patients with diarrhea often have coincident renal injury from volume loss, potential for decreased drug absorption from enterocolitis-associated reduced transit times and P-glycoprotein disruption from active enteritis. As these factors could confound estimates of changes in tacrolimus dose requirements, C/D ratio was abstracted from the medical record at three months prior to first FMT and compared to three months after first FMT.

Other factors that are known to influence tacrolimus C/D ratios including drug-drug interactions, hemoglobin concentration, albumin concentration, alanine aminotransferase (ALT), body mass index (BMI) and hepatitis C virus (HCV) seropositivity were abstracted from the medical record from the laboratory value or medical note on the date of first FMT or first value prior.

Tacrolimus levels were manually extracted from the medical record. Tacrolimus dose was defined as the most recent charted tacrolimus dose prescribed prior to date of tacrolimus level. Dates of abstracted values were selected in reference to date of first FMT. There were no changes in tacrolimus assay platform used at Emory during the study period. The first tacrolimus level and prescribed dose three months before and after (or next closest available date) first FMT were used for test of difference. Three months was chosen based on prior reports and tacrolimus dose prescribed and C/D ratio closest to time of FMT and at one month after FMT were also compared (although fewer patients had tacrolimus levels during these time points, [n=5]). Durable differences in tacrolimus concentration/dose ratios discriminating fast and slow metabolizers have been described as early as one month after transplantation in liver transplant patients. Differences in tacrolimus dose requirements were statistically significant by diversity analysis with 16S ribosomal gene sequencing at 28 days after transplantation in renal transplant patients. (5,10) This time point was also thought to limit potential confounding by other factors that influence tacrolimus concentration/dose ratios as further outlined in the discussion section. For plot of trend in C/D ratio, the first

nine dates with available data from date of first FMT, each separated by at least two days, were selected. There is variation in how C/D ratio is reported in the literature, which is occasionally reported as level in (ng/mL) / (mg/kg/day) and in other cases as level in (ng/mL) / (mg/day). Both methods were used in C/D ratio calculations and in plot of C/D ratio trend. A non-parametric smooth plot was made to illustrate potential non-linear changes.

Adverse effects were abstracted from the medical record and defined as one or more of the following signs or symptoms: abdominal pain, bloating or non-painful abdominal discomfort, nausea, vomiting, worsening of diarrhea, persistence of diarrhea, bacteremia, other infection within 48 hours, allograft biopsy within 1 year, allograft rejection within 1 year, CDI-related mortality within 30 days, all-cause mortality within 30 days.

Statistical methods

Difference in C/D ratio was tested for statistical significance by paired Wilcoxon signed-rank test at three months before and after FMT and at time of FMT compared to one month after FMT. Given the limited sample size and inconsistent frequency of tacrolimus level assessment, C/D ratio by date since first FMT was plotted for illustration of trend and linearity. Data were analyzed with SAS version 9.4 (SAS institute, Cary, NC) and R (version 3.4.2) using the RStudio interface version 1.1.383 (RStudio Team, Boston, MA). Modeling approaches to adjust for potential confounders were precluded by the small sample size and inconsistent timing of tacrolimus level measurement. However, potential pharmacologic confounders were manually extracted from the medical record and described among the study population. To more clearly demonstrate changes in the post FMT period, plots were also produced excluding observations >180 days from date of first FMT and included as supplemental figures.

RESULTS

Among 257 patients undergoing FMT from 2012–2016, 17 unique patients were identified by chart review who had received a SOT. Seven of the 17 patients who had received a solid organ transplant were excluded from this study. Of these seven excluded patients, five were excluded because they were not prescribed tacrolimus as part of their immunosuppressive regimen at the time of FMT and two were excluded because they underwent FMT prior to the time of SOT. Ten patients were ultimately included in this analysis. Demographic data and key patient characteristics of the study population are presented in Table 1. The median number of days since last SOT was 492, (IQR 298 – 1181). One patient was missing data for tacrolimus level at 3 months after date of first FMT and was excluded from the Wilcoxon signed-rank test of difference in C/D ratio and total daily dose but included in the plot for illustration of trend. Potential pharmacologic confounders were extracted from the medical record and presented in Table 2.

Symptoms after first FMT were documented in clinical notes for 9/10 patients. Of these patients, 4 (44%) had no documented adverse effects. Of the patients who experienced adverse effects, these were minor and presented in Table 3. Two patients underwent allograft biopsy in the year following FMT for allograft dysfunction but these showed no histopathologic evidence of allograft rejection.

Of included patients, 4/10 underwent a second FMT procedure (patients 1, 2, 5 and 8 as shown in Figures 1, 2, 3, and 4) and 1/10 underwent a third FMT procedure (patient 1) before diarrhea resolved. Of the patients who underwent more than one FMT, this was generally in attempt to treat either persistent diarrhea after FMT (patients 1 & 2, 2/4, 50%) or recurrent symptoms with positive *C. difficile* testing >2 weeks after FMT with interim negative *C. difficile* PCR testing (patients 5 & 8, 2/4, 50%). In these patients requiring more than one FMT, they were generally well-tolerated and uncomplicated, however one patient had prolonged recovery from anesthesia after colonoscopy and found the next morning to have had a stroke with indeterminate timing relative to FMT. The patients in this series undergoing multiple FMTs had generally complicated solid-organ transplant courses. Patient 1 was status post three deceased-donor renal transplants (DDRT) for recurrent focal-segmental glomerulosclerosis with the last transplant complicated by low grade BK viremia and had episodes of CDI, each within about three weeks after antibiotics for recurrent urinary tract infection. Patient 2 received a DDRT for hypertensive nephrosclerosis, which was complicated shortly after transplant by pyelonephritis and bacteremia and had eight episodes of CDI prior to improvement with second FMT. Patient 3 received a living donor renal transplant (LDRT), followed by DDRT with three episodes of CDI prior to first FMT. Patient 4 underwent bilateral lung transplantation for alpha-1 antitrypsin deficiency, with course complicated by bronchiolitis obliterans syndrome and five episodes of positive CDI testing (though symptoms improved prior to treatment in two of these episodes) prior to FMT.

Median tacrolimus C/D ratios and prescribed total daily tacrolimus doses, IQR, mean of differences, 95% confidence interval and p-values for test of significance by paired Wilcoxon signed-rank test are presented in Table 4. The mean of the differences in C/D ratio calculated as ng/mL / mg/kg/day was -17.65 (95% CI -1.25 – 0.58) ng/mL / mg/day, (p-value 0.43). The mean of the differences in C/D ratio calculated as ng/mL / mg/day was -0.33 (95% CI -1.25 – 0.58) ng/mL / mg/day, (p-value 0.28).

DISCUSSION

These data from 10 SOT patients prescribed tacrolimus as part of an immunosuppressive regimen at the time of undergoing FMT for RCDI did not show a significant difference in tacrolimus total daily dose or C/D ratio at three months after FMT compared to three months prior to FMT.

In our retrospective study, stool samples were not available for microbiome analyses, thus we were unable to ascertain impact of specific bacteria, such *F. prausnitzii*, on tacrolimus levels. However, these data report important clinical outcomes of 10 SOT patients undergoing FMT for RCDI. Four of these described 10 patients underwent multiple FMT procedures prior to resolution of symptoms, indicating that there may be some heterogeneity either at the patient gut microbiome level or perhaps in the material that was transplanted, however there was no control group in this small series, limiting our evidence to comment on potential causal differences in response. Allograft biopsy was only clinically indicated in two patients and pathology did not show evidence of allograft rejection that might be attributable to pharmacomicrobial or direct immunomodulatory effects of the transplanted

fecal material itself. Further, the lack of difference in tacrolimus C/D ratio suggests that FMT may be safe without impacting this important outcome in SOT patients. However, this hypothesis requires further study in prospective clinical trials.

Prior work in mouse models and human studies have suggested immunomodulatory and pharmacomicrobial (pharmacodynamic-modulating) effects of gut microbiota that could have important impact in SOT patients. *Bifidobacterium spp* have been associated with improved cell-mediated tumor killing (tumor T-cell infiltration) in a mouse model. (11) In another mouse model, Vétizou et al reported that the activity of anti-CTLA-4 antibodies as a therapy for cancer depend on *Bacteroides spp*.(12) Recent studies of hematopoietic cell transplant recipients have shown improvement in gastrointestinal graft vs host disease after FMT.(6,13,14) In a pilot study of changes in microbiota after renal allograft transplantation, significant differences were noted in diversity in patients who had acute rejection compared to those who did not (*Lactobacillales* were higher in acute rejection cohort and *Clostridiales* and *Bacteroidales* were lower). (15) On the other hand, in a pilot study profiling microbiome changes of 23 renal transplant patients, there was no clustering by PCoA by sampling time point, serum creatinine or rejection events and overall comparisons were not similar between patients.(16) The authors of the report from this pilot study noted that sampling time points did not correlate well with rejection events so it was challenging to estimate the association of changes in microbiota reads and acute rejection.(16) Further study of these potential immunomodulatory and pharmacomicrobial effects in SOT is needed.

Other work has shown, somewhat inconsistently, that administration of immunosuppressive medications may cause changes in gut microbiota composition. A mouse model evaluating the changes to the intestinal microbiota after administration of various immunomodulating agents demonstrated that the combination of tacrolimus, MMF, and prednisolone led to increased growth of *Escherichia coli*, including uropathogenic strains.(17) In a separate mouse model evaluating effects of immunosuppressive therapies, prednisolone was associated with decreased *Bacteroidetes* and increased *Firmicutes* though the changes were not consistent in study replications and were not seen reliably in combination treatments with MMF and tacrolimus, which is how they are more typically administered in clinical settings.(17) Better understanding of how immunomodulatory medications may affect the gut microbiota will inform further development of microbial therapeutics for this patient population.

Our study had several important limitations. Given the early state of the practice of FMT in SOT patients, available data are few, which limits statistical power and increases risk of type II error. Tacrolimus C/D ratio is affected by multiple factors, including renal function, gut transit time, concurrently administered medications and genetic factors, which may potentially confound analyses of these data. Tacrolimus is a substrate of CYP3A4 and CYP3A5 enzymes as well as P-glycoprotein. CYP profiling was not available for these patients and it is unclear to what degree intestinal inflammation from CDI could have disrupted normal P-glycoprotein function, which is normally found in the intestinal lumen. While prior reports have suggested association of *F. prausnitzii* and increased tacrolimus dose requirements, it is not clear how antibiotic treatment (either prescribed for other infections prior to CDI or for CDI) may impact colonization with this taxon or taxa that may

have pharmacomicrobial effects. With multiple potential competing effects and confounders on tacrolimus C/D ratio, it is challenging to assess causality of changes in tacrolimus dose requirements. Further study with microbiome and pharmacodynamics/pharmacomicrobial analyses in SOT patients undergoing FMT will improve understanding of its safety in this patient population. Further study of potential direct immunomodulatory effects of FMT are also needed.

Future directions

Multiple clinical trials are underway investigating the therapeutic potential of FMT for indications beyond RCDI. As FMT utilization increases, further study of its pharmacologic effects on immunomodulatory therapies and its impact on alloimmunity will be important to limit deviations from the narrow therapeutic range of these medications and limit potential risk of allograft rejection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ALT	alanine aminotransferase
BMI	body mass index
CDI	<i>Clostridium difficile</i> infection
C/D ratio	concentration / dose ratio
CI	confidence interval
FMT	Fecal microbiota transplant
HCV	hepatitis C virus
IQR	interquartile range
MDRO	Multi-drug resistant organism(s)
PCR	polymerase chain reaction
RCDI	Recurrent <i>Clostridium difficile</i> infection
SOT	Solid organ transplant
SSRI	selective serotonin reuptake inhibitor

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Table 1

Characteristics of SOT patients prescribed tacrolimus at time of first FMT for RCDI from 2012–2016.

Characteristic	Value
Total number of patients	10
Age, median (IQR)	53, (45 – 64)
Female sex, n(%)	6, (60%)
Race	
Caucasian	6, (60%)
African-American	4, (40%)
Ethnicity	
Non-Hispanic	10, (100%)
SOT type	
Renal	4, (40%)
Liver	2, (20%)
Heart	1, (10%)
Lung	2, (20%)
Simultaneous liver & kidney	1, (10%)
Total n of SOT, median (range)	1, (1 – 3)
Days since last SOT, median (IQR)	492, (298 – 1181)
Maintenance Immunosuppressive regimen	
Belatacept	1, (10%)
Mycophenolate	5, (50%)
Prednisone	9, (90%)
Tacrolimus	10, (100%)
eGFR at time of FMT, mL/min/1.73m ² , median (IQR)	70, (44.0 – 70.0) *

SOT – solid organ transplant, FMT – fecal microbiota transplant, RCDI – recurrent *Clostridium difficile* infection, IQR – interquartile range, eGFR – estimated glomerular filtration rate,

* eGFR >70 reported as 70

Table 2

Factors known to influence tacrolimus blood concentration among SOT patients on tacrolimus at time of undergoing first FMT for RCDI, n = 10 unless otherwise noted.

Factor	Value
Patients with coincident prescription of medications with known drug-drug interactions, n, (%)	
Amiodarone/Dronedarone	0, (0%)
Aprepitant/Fosaprepitant	0, (0%)
Azole antifungal	0, (0%)
Boceprevir	0, (0%)
Calcium channel blocker	2, (20%)
Caspofungin	0, (0%)
Cinacalcet	0, (0%)
Clarithromycin or Erythromycin	0, (0%)
Crizotinib	0, (0%)
Danazol	0, (0%)
Dasatanib	0, (0%)
Deferasirox	0, (0%)
Efavirenz	0, (0%)
Ertapenem	0, (0%)
Fosphenytoin	0, (0%)
Grazoprevir	0, (0%)
Laxative	0, (0%)
Narcotics	1, (10%)
SSRI (other than trazodone)	6, (60%)
Rifampin	0, (0%)
Corticosteroid co-administration, n, (%)	
5mg prednisone daily	7/9, (77.8%)
7.5mg prednisone daily	1/9, (11.1%)
20mg prednisone daily	1/9, (11.1%)
Hemoglobin concentration, median, (IQR)	10.7, (9.7 – 12.5)
Albumin concentration, median, (IQR)	3.5, (2.8 – 3.8)
Baseline ALT, median, (IQR)	19.5, (15.0 – 25.0)
BMI in kg/m ² , median, (IQR)	27.6, (20.9 – 31.1)
HCV positivity, n, (%)	2/9, (22.2%)

SOT – solid organ transplant recipient, FMT – fecal microbiota transplant, RCDI – recurrent *Clostridium difficile* infection, SSRI – selective serotonin reuptake inhibitor, ALT – alanine aminotransferase, BMI – body mass index, HCV- hepatitis C virus, IQR – interquartile range

Table 3

Adverse effects documented within two weeks of first FMT procedure among SOT patients on tacrolimus after undergoing FMT for RCDI from 2012–2016.

Adverse Event	Value n, (%)
Abdominal pain	3/9, (33%)
Bloating or Abdominal discomfort	1/9, (11%)
Nausea	0, (0%)
Vomiting	0, (0%)
Persistent diarrhea	3/9, (33%)
Fever	0, (0%)
Bacteremia	0, (0%)
Patients with allograft biopsy within 1 year after FMT	2/10, (20%)
Allograft rejection events within 1 year after FMT	0, (0%)
30-day mortality	0, (0%)

FMT – fecal microbiota transplant, SOT – solid organ transplant, RCDI – recurrent *Clostridium difficile* infection.

Table 4

Comparison of tacrolimus dose and C/D ratio at 3 months prior to FMT compared to 3 months after FMT among SOT patients undergoing FMT for RCDI from 2012–2016.

Tacrolimus exposure and units	3 months prior to first FMT ^a (n=9)		3 months after first FMT ^a (n=9)		Time of first FMT ^b (n=5)		1 month after first FMT ^b (n=5)		p	Mean of differences, (95% CI)	p	Mean of differences, (95% CI)
	median, (IQR)		median, (IQR)		median, (IQR)		median, (IQR)					
Total daily prescribed tacrolimus mg / day	4 (2.25 to 5.50)		3 (2.00 to 4.00)		4 (3 to 4)		4 (3 to 4)		0.09	0.89 (-1.16 to 1.94)		0.20 (-0.36 to 0.76)
C/D ratio ng/mL / mg/day	1.63 (0.79 to 2.96)		1.86 (1.32 to 2.73)		4 (2 to 4)		3 (2 to 4)		0.28	-0.33 (-1.25 to 0.58)		-0.08 (-1.23 to 1.08)
C/D ratio ng/mL / mg/kg/day	116.80 (47.57 to 240.60)		127.80 (76.81 to 250.30)		163.8 (153.7 to 172.1)		179.0 (15.3 to 320.0)		0.43	-17.65 (-82.3 to 47.0)		-4.28 (-86.7 to 78.1)

C/D ratio – concentration / dose ratio, FMT – fecal microbiota transplant, SOT – solid organ transplant, RCDI – recurrent *Clostridium difficile* infection, IQR – interquartile range, CI – confidence interval.

^a – or next closest value,

^b – or next closest within 30 days (fewer cases had tacrolimus data at these time points),

^c unable to compute Wilcoxon signed rank test due to ties.