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Blood Profiles of Gut Bacterial Tacrolimus Metabolite in Kidney Transplant Recipients

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Tacrolimus is the mainstay immunosuppressant drug used in solid organ transplant recipients. It has significant inpatient trough variability, which has been associated with adverse outcomes, such as allograft loss.¹ Minimizing tacrolimus trough variability is an important goal in improving transplant outcomes.

There is increasing evidence supporting a role of the gut microbiota in direct metabolism of tacrolimus. Our group reported that fecal abundance of *Faecalibacterium prausnitzii* was associated with future tacrolimus dosing requirements in kidney transplant recipients.² In a follow-up study, we found that multiple gut bacterial species including *F. prausnitzii* directly metabolize tacrolimus to M1, a C9 keto-reduction product.³ M1 is a novel metabolite of tacrolimus uniquely formed by gut bacteria,³ as hepatic microsomes do not produce M1.³ However, the extent to which gut bacteria metabolize tacrolimus and influence inpatient tacrolimus trough variability is unknown.

In this study, we investigated whether M1 can be detected in vivo as a surrogate biomarker for gut bacterial metabolism of tacrolimus. We recruited 10 kidney transplant recipients at the time of transplantation and evaluated the pharmacokinetics of M1 after oral administration of tacrolimus. M1 and parent tacrolimus concentrations were determined by LC-MS/MS. The Weill Cornell IRB approved this study. The kidney transplant recipients had a median age of 50 and were male in 8 cases, were African American in 3 cases, and had deceased donor transplantations in 2 cases. Detection of M1 was observed in all patients within the first 4 h after oral administration (Figure 1). M1 levels were highly variable with some patients having at least 5% of parent tacrolimus concentration after oral administration (patient 1, 5, and 6).

Our data reveal that the bacterial M1 product is present in the blood, supporting the concept of active metabolism of tacrolimus by gut bacteria. Our prior work shows that M1 is 15-fold less immunosuppressive than parent tacrolimus,³ and it is unlikely that M1 contributes significantly to immunosuppressive effects on the host. However, gut bacteria may eliminate a significant fraction of orally administered tacrolimus and account for the previously unexplained elimination route of orally administered tacrolimus.^{4,5} This suggests that changes in the gut microbiota via antibiotics or diet could impact tacrolimus trough variability. In a retrospective cohort study of 260 kidney transplant recipients, our group recently identified that antibiotic administration is associated with tacrolimus trough variability, thus indirectly supporting a potential role of the gut microbiota on tacrolimus trough variability.⁶

The blood M1 concentration is lower than parent tacrolimus by at least 5-fold and a limitation of our study was that we were unable to determine whether changes in the gut microbiota could lead to changes in M1 concentration and tacrolimus trough variability. However, it is worth noting that first-pass metabolism of M1 is unknown and that none of the transplant recipients were at steady state and so M1 could be higher in steady state. In conclusion, our study demonstrates the presence of bacterial metabolism of tacrolimus in vivo, suggesting that changes in the gut microbiota could impact tacrolimus trough variability.

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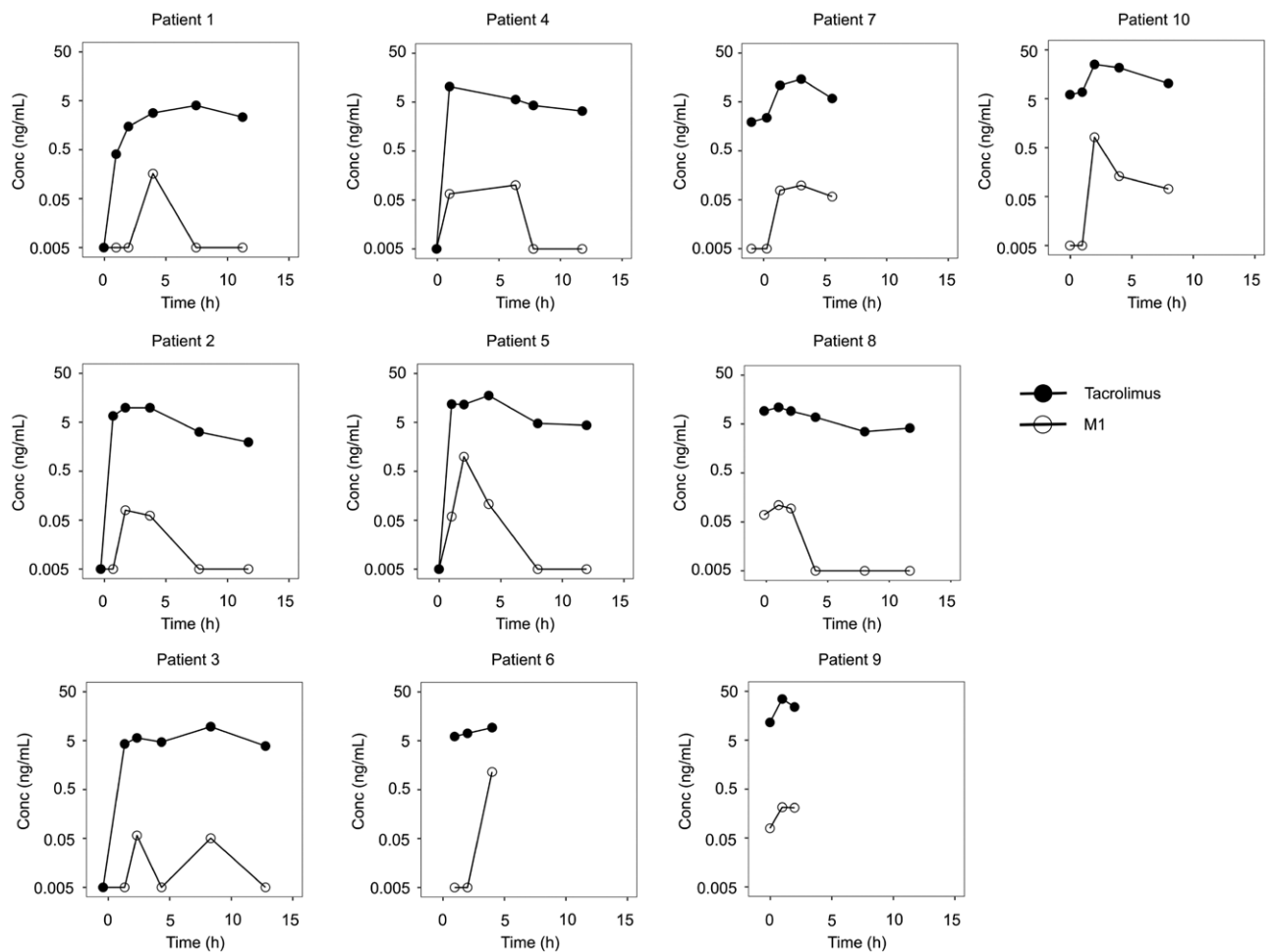


FIGURE 1. Pharmacokinetics of M1 and parent tacrolimus in kidney transplant recipients. Each graph represents a patient with the concentration of either M1 or parent tacrolimus on the y axis (logarithmic scale) and time in h on the x axis. Each point represents a time point when blood was drawn and analyzed for M1 (white points) and parent tacrolimus (black points). M1 values < 0.05, the lower quantification limit of the M1 assay, and tacrolimus values < 0.4, the lower quantification limit of the tacrolimus assay, were represented as 0.005 for plotting purposes on the graphs. Patients 1–6 were tacrolimus-naïve, and patients 7–10 were tacrolimus-exposed. Conc, concentration; ng/mL, nanogram per milliliter.

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