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Patiromer Does Not Alter Tacrolimus Pharmacokinetics in Kidney Transplant Recipients When Administered Three Hours Post–Tacrolimus

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Background. Hyperkalemia is common in kidney transplant (KTx) recipients. Patiromer, a potassium-binding polymer used to treat acute and chronic hyperkalemia, has the potential to bind charged particles in the gastrointestinal tract and thereby potentially affect the absorption of coadministered drugs. The immunosuppressive drug tacrolimus (Tac) has a narrow therapeutic window, is susceptible to drug-drug interactions (DDIs), and a potential gastrointestinal interaction with patiromer could elevate the risk of allograft rejection. We aimed to investigate the potential DDI between patiromer and Tac pharmacokinetics in KTx with hyperkalemia by sampling capillary blood using volumetric absorptive microsampling (VAMS). **Methods.** Thirteen KTx recipients on Tac twice daily (BID) with plasma potassium levels of >4.6 mmol/L were included. Two 12 h Tac pharmacokinetic investigations were performed with and without 8.4 mg patiromer/d for 1 wk. Oral Tac dose remained unchanged and patiromer was administered 3 h after Tac dose. Tac sampling was self-conducted using VAMS after mastering the technique. **Results.** Ten patients provided 2 evaluable pharmacokinetic profiles. The Tac area under the curve $(AUC)_{0-12}$ ratio ($AUC_{Tac+patiromer}/AUC_{Tac}$) was 0.99 (90% confidence interval [CI], 0.86-1.14), and the C_{max} ratio was 1.01 (90% CI, 0.86-1.19). Tac C_0 and C_{12} fulfilled the bioequivalence criteria with a ratio of 0.98 (90% CI, 0.90-1.07) and 0.93 (90% CI, 0.83-1.04), respectively. **Conclusions.** When administered 3 h after the Tac morning dose, patiromer has no clinically relevant impact on Tac pharmacokinetics. We demonstrate that VAMS is a well-suited sampling method to simplify the execution of DDI studies.

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The calcineurin inhibitor tacrolimus (Tac) is a cornerstone immunosuppressant in most kidney transplant (KTx) protocols worldwide.[1,2] Given its narrow therapeutic window, Tac is vulnerable to drug-drug interactions (DDIs). Accordingly, therapeutic drug monitoring (TDM) of Tac is routinely conducted to tailor the dose and optimize efficacy while reducing toxicity.[3,4]

Due to both pharmacologic and pathophysiological-related mechanisms, KTx recipients are at increased risk of developing hyperkalemia.[5] Notably, among recipients treated with calcineurin inhibitors, hyperkalemia is a frequently occurring side effect, with a reported incidence ranging from 25% to 44%.[6,7] For the management of severe acute hyperkalemia, treatment options include insulin, beta$_2$-adrenergic agonists, and dialysis.[8] In patients experiencing chronic or recurrent hyperkalemia, patiromer (Veltassa) has emerged as a valuable treatment option.[5] Patiromer binds potassium in the gastrointestinal tract, which leads to a reduction in plasma

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potassium levels and an increase in fecal potassium excretion.[9] Patiromer does not enter the systemic circulation, mitigating concerns about DDIs when used in combination with other drugs.[9] However, patiromer has the potential to bind charged particles in the gastrointestinal tract, which could lead to reduced absorption of certain coadministered drugs. Reduced absorption has been observed for some drugs (eg, metformin, metoprolol, trimethoprim) when patiromer is administered concurrently.[10] Consequently, it is recommended to administer patiromer either 3 h before or after other drugs.[11] Due to the narrow therapeutic window of Tac, any potential interaction with patiromer could elevate the risk of allograft rejection, and clinical validation is therefore warranted.

Recent advancements in finger-prick microsampling for TDM have facilitated home-based sampling, offering a patient-friendly method for obtaining multiple blood samples for the proper area under the curve (AUC)-targeted TDM.[12] This methodology may also simplify the execution of pharmacokinetic clinical trials.[13] The current study aimed to investigate the potential pharmacokinetic interaction between patiromer and Tac in KTx recipients with hyperkalemia by sampling capillary blood using volumetric absorptive microsampling (VAMS).

MATERIALS AND METHODS

Patients and Study Design

The study was an open, nonrandomized, prospective study performed at Oslo University Hospital, Rikshospitalet, from October 2021 to January 2023. Patients were eligible for inclusion based on the following inclusion criteria: >3 wk post-KTx, age 18 y and older, receiving Tac twice daily (BID) with stabile dose and trough concentration. Patients experiencing hyperkalemia indicated by plasma potassium between 4.6 and 5.6 mmol/L were asked to participate. Patients were not included if they experienced <3 bowel movements per week, had hypomagnesemia (plasma Mg <0.6 mmol/L), were pregnant, or had an allergy to patiromer. In addition, concomitant treatment with potentially Tac-interacting drugs, such as diltiazem, verapamil, phenytoin, carbamazepine, fluconazole, ketoconazole, voriconazole, erythromycin, clarithromycin, calcium resonium, and/or sodium zirconium cyclosilicate led to exclusion.

KTx recipients on Tac BID with hyperkalemia were identified through routine blood test analyses during outpatient follow-up and were started on treatment with patiromer (8.4 mg/d) the same day. The patients were instructed, as specified in the package insert, to administer patiromer 3 h "after" the Tac morning dose. Adherence was assessed by counting empty patiromer bags. Two 12 h pharmacokinetic investigations were performed. The first pharmacokinetic investigation (PK1) was performed after 7 d of patiromer treatment. After PK1, patiromer was discontinued for a washout period of 6–7 d before the second pharmacokinetic investigation (PK2). Tac doses were to be unchanged during the study period. The study was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency (EudraCT: 2020-002621-29). ICH guidelines for Good Clinical Practice and ethical principles originated from the Declaration of Helsinki were followed during the trial, and written informed consents were obtained before study procedures.

Immunosuppression

Maintenance therapy consisted of a combination of Tac BID, mycophenolate mofetil, and steroids. According to center transplant protocol, Tac was initiated on the day of transplantation, administered as a starting dose of 0.04 mg/kg BID for immunological standard-risk patients, and adjusted to maintain a trough concentration (C_0) between 4 and 7 µg/L. Mycophenolate mofetil was administered at a fixed dose of 750 mg BID from the day of transplantation, with dose modifications only in response to side effects. Prednisolone was given according to a fixed tapering dose regimen commencing at 20 mg/d the day after transplantation and tapered to a maintenance dose of 5 mg/d. All patients received induction therapy with basiliximab 20 mg on days 0 and 4 posttransplantation, accompanied by intravenous methylprednisolone 250 mg on day 0.

Pharmacokinetic Investigation

Patients fasted overnight and abstained from taking any medications on the mornings of the pharmacokinetic study days. Twelve microsamples of capillary blood were collected from the fingertip using a Mitra microsampling device (Neoteryx, Torrance, CA). Samples were collected before administration of Tac (and other patient-specific comedication; C_0) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after Tac administration. Patiromer was administered 3 h after Tac at PK1 only. All drug dosing during PK investigations was supervised by study personnel. The first 6 capillary blood samples were collected at the hospital under supervision and as part of patient education on the sampling technique. The remaining samples were collected at home by the patients after proving they mastered the technique. For home-based sampling, patients were provided with a kit containing 6 sampling devices and a log sheet to record exact times and eventual comments for each microsample. Patients delivered all samples and the sampling logs to the laboratory the following day.

Analytical Assay

The concentration of Tac in dried capillary microsamples was determined by a validated liquid chromatography–tandem mass spectrometry method, as previously reported.[13] The measurement range for the dried microsamples was 0.70–65 µg/L with CV of ≤11% and mean accuracy of 88%–98% (for more detailed information, see Vethe et al[13]).

Calculation and Statistical Analysis

Noncompartmental methods were used to determine the pharmacokinetic variables. The area under the whole blood concentration-time curve from time 0 to 12 (AUC_{0-12}) was calculated using the log-trapezoidal rule, and C_0, C_{12}, and C_{max} represent the actual observed values. All individual pharmacokinetic parameters were ln-transformed before statistical analysis. Using an ANOVA model, which included a fixed factor for treatment and a random factor for subject effect, the geometric mean ratio and its associated 90% confidence interval (CI) were calculated. The 90% CI was back-transformed to the original scale and compared with the specified ranges outlined in the European Medicines Agency guidelines for bioequivalence.[14] Tac has a narrow therapeutic window, and the acceptance interval for AUC is therefore tightened to 90%–111%. A sample size of 11 individuals was

calculated using the 90%–111% acceptance interval for the $AUC_{0–12}$ geometric mean ratio ($AUC_{Tac+patiromer}/AUC_{Tac}$) and a projected SD of the $AUC_{0–12}$ ratio of 0.1 was applied. The difference in potassium levels before and after patiromer treatment was tested using a Wilcoxon signed-rank test. *P* values of <0.05 were deemed statistically significant. Unless stated otherwise, data are presented as mean ± SD. All statistical analyses were conducted in R version 4.3.2.[15]

RESULTS

Patients

Thirteen KTx recipients with plasma potassium levels between 4.6 and 5.6 mmol/L were included. Three patients did not complete the study; 1 experienced adverse events (nausea and hypomagnesemia) after 2 d of patiromer treatment, 1 was infected by SARS-CoV-2, and 1 was excluded because the last 3 samples at PK2 were sampled incorrectly. The final population for determining bioequivalence ultimately included 10 patients. Demographic data and patient characteristics at baseline are presented in Table 1. Treatment with patiromer was initiated 23 ± 5 d after transplantation. PK1 was performed following 7.2 ± 0.8 d on patiromer, and PK2 was performed after a 6.6 ± 0.5 d washout period. After patiromer treatment, plasma potassium levels decreased on average by 0.45 ± 0.32 mmol/L ($P < 0.01$). None of the patients needed additional interventions to lower potassium. All patients were treated with prednisolone, mycophenolate mofetil, pantoprazole (40 mg/d), and sulfamethoxazole/trimethoprim (400/80 mg/d; Table 1). The doses of Tac and concomitant medications remained unchanged from the initiation of patiromer treatment and throughout the study, except for prednisolone. Mean prednisolone dose at PK1 and PK2 were 13.5 ± 2.4 and 11 ± 2.1 mg/d, respectively. In total, 98% of the microsamples were filled satisfactorily.

Pharmacokinetics

Mean whole blood concentration versus time curves are visualized in Figure 1, demonstrating nearly superimposable average Tac profiles regardless of patiromer treatment. There was no statistically significant difference in $AUC_{0–12}$: 136 ± 29 µg·h/L and 137 ± 23 µg·h/L ($P = 0.88$) with and without patiromer, respectively. Of the 10 patients included in the analysis, 4 displayed higher $AUC_{0–12}$ when coadministered with patiromer, with individual changes ranging from 14% to 42%. Four patients showed a decrease in $AUC_{0–12}$ (ranging from –11% to –38%), whereas 2 patients had differences within ±5% (Figure 2A). Tac $AUC_{0–12}$ failed to fulfill the bioequivalence criteria with a ratio of 0.99 (90% CI, 0.86-1.14). Eight of the patients showed a change in C_{max} when cotreated with patiromer (ranging from –35% to 53%), whereas 2 patients had differences within ±5% (Figure 2B). Tac C_{max} fulfilled the bioequivalence criteria with a ratio of 1.01 (90% CI, 0.86-1.19). C_0 and C_{12} both fulfilled the bioequivalence criteria with a ratio of 0.98 (90% CI, 0.90-1.07) and 0.93 (90% CI, 0.83-1.04), respectively (Figure 2C and D). Intrapatient $AUC_{0–12}$ and C_{max} coefficient of variations were 13% and 18%, respectively. Pharmacokinetic data for Tac with and without comedication with patiromer are summarized in **Table S1** (**SDC,** http://links.lww.com/TXD/A716). Data from the analysis with all the patients who completed PK1 and PK2 (including excluded patients) are presented and visualized in **Table S2 and Figures S1 and S2** (**SDC,** http://links.lww.com/TXD/A716).

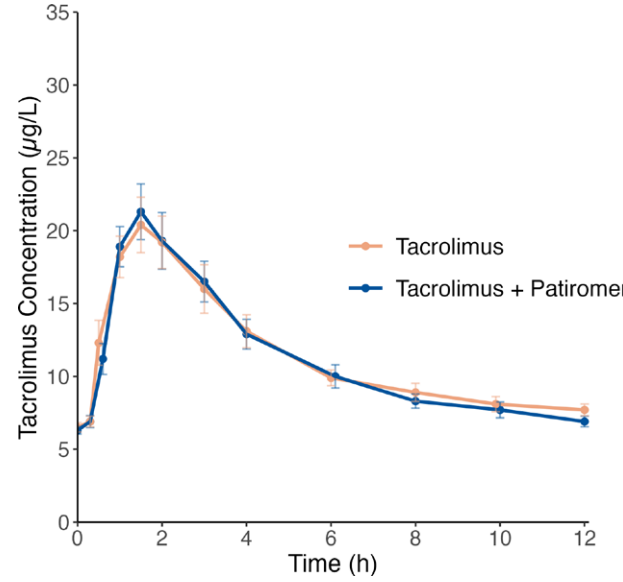

FIGURE 1. Mean (±SEM) tacrolimus whole blood concentration-time profiles with and without comedication with patiromer.

TABLE 1.

Demographic data and patient characteristics at baseline

Characteristics	N = 10
Age, y	63 ± 14
Sex (female/male), n/N	3/7
BMI, kg/m^2	27 ± 4
Tac dose, mg/d	6.2 ± 2.0
Tac C_0, µg/L	7.4 ± 1.1
Treated with prednisolone, n	10
Treated with mycophenolate (750 mg ×2), n	10
Treated with pantoprazole (40 mg ×1), n	10
Treated with sulfamethoxazole/trimethoprim (400/80 mg ×1), n	10
P-Creatinine, µmol/L	132 ± 28
P-Potassium, mmol/L	5.0 ± 0.3
Time after Tx to study start, d	23 ± 5

Data are presented as mean ± SD or number of patients.
BMI, body mass index; C_0, concentration before the dose; Tac, tacrolimus; Tx, transplantation.

DISCUSSION

This is the first prospective study to in detail investigate the pharmacokinetic interaction between patiromer and Tac in a relevant clinical setting in KTx recipients. The main findings indicate that concomitant treatment with patiromer does not change Tac pharmacokinetics to any clinically relevant degree when administered 3 h after the morning dose of Tac. It is well recognized that the pharmacokinetics of Tac is characterized by a significant degree of intrapatient variability.[16,17] The intrapatient variability in Tac $AUC_{0–12}$ in this study (CV of 13%) corresponds to what we normally see at our center.[18,19] Looking at individual changes, an equal number of patients show an increased AUC and C_{max} as those who show a decrease. Given the potential mechanism for an interaction with patiromer, increases in Tac levels are not expected.

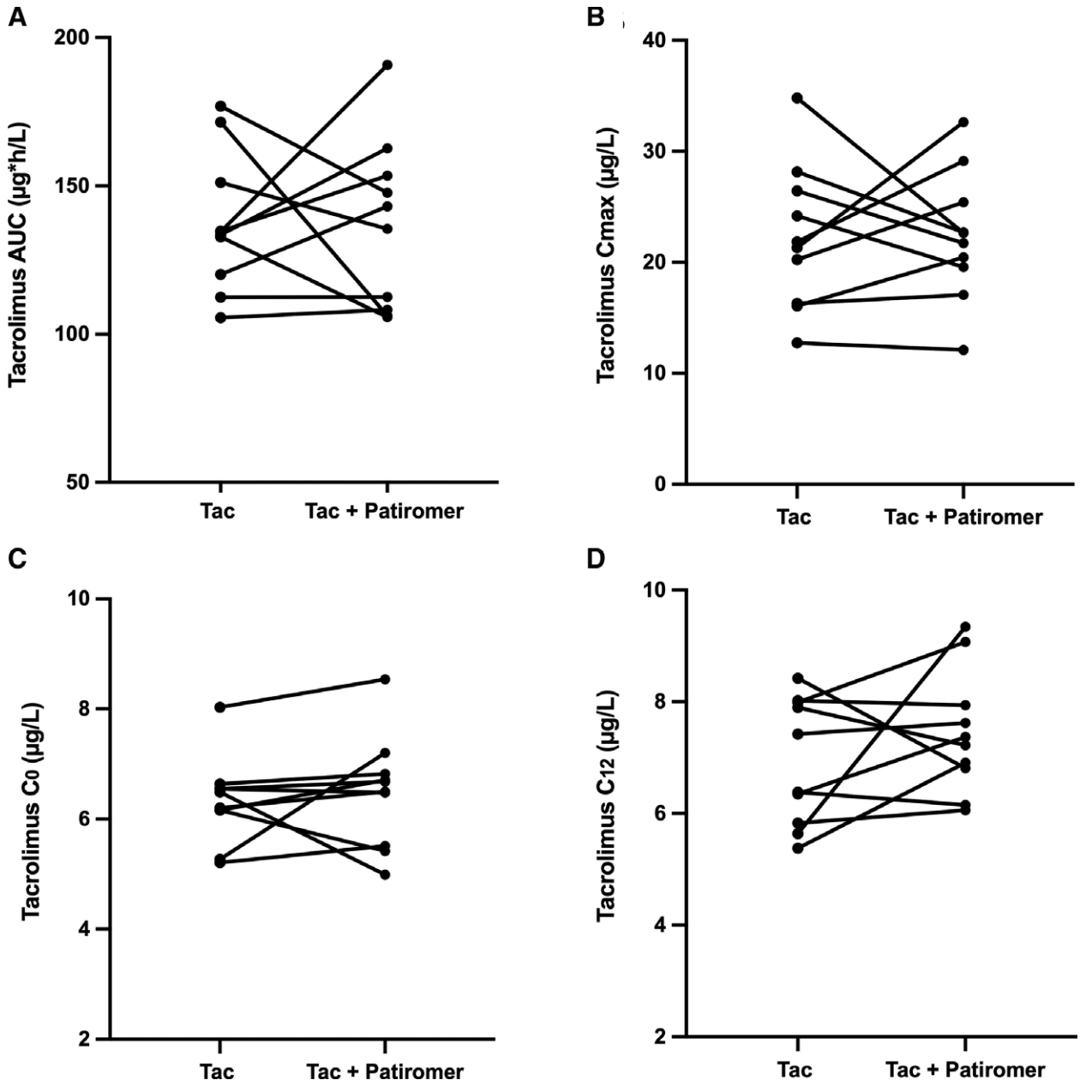

FIGURE 2. Individual change in AUC (A), C_{max} (B), morning trough concentrations (C_0) (C), and evening trough concentrations (C_{12}) (D), with and without comedication with patiromer. AUC, area under the curve; C_0, concentration before the dose; C_{12}, 12 h trough concentration; C_{max}, maximum concentration; Tac, tacrolimus.

Although the standards of the $AUC_{0–12}$ geometric mean ratio ($AUC_{Tac+patiromer}/AUC_{Tac}$) were not fulfilled in this study, this could potentially be due to inadequate sample size. None of the patients experienced Tac adverse events during the study either, further substantiating that the variability seen is due to "normal" Tac variability. Patients were investigated during the early posttransplant phase, when Tac pharmacokinetics changes continuously, further increasing the source of variability.[20-22] A sample size of at least 11 patients was calculated to ensure that the noninferiority hypothesis for Tac $AUC_{0–12}$ and C_{max} with and without patiromer could be adequately tested, with the full 90% CI falling within the bioequivalence acceptance interval. Due to exclusions during the study, the final analysis was unfortunately conducted with data from only 10 patients.

Previous data on the use of patiromer in KTx recipients are limited to a retrospective study, 1 case report with 2 patients, and 2 small case series.[23-26] Servais et al[23] performed a retrospective study evaluating 32 kidney and liver transplant recipients. No statistically significant changes in 12 h trough concentration (C_{12}) or Tac dosage were observed during the treatment period with patiromer. However, a numerical reduction in the mean C_{12} was observed 1 wk after initiating treatment with patiromer, despite an increase in the mean dosage per day. After patiromer was discontinued, there was an increase in the mean Tac C_{12} without any adjustments in the mean Tac dosage. In contrast to these findings, our results showed no difference in C_{12} levels regardless of patiromer treatment. Considering the extended onset period (4–7 h) of patiromer, a full pharmacokinetic investigation aligned with the evening

Tac dose could have provided additional insights regarding patiromer's prolonged effect on Tac pharmacokinetics.

This DDI study is novel by being the first to use VAMS to determine the drug concentrations. Although we did not assess the correlation between dried capillary microsamples and liquid venous samples in this study, we have previously shown a good correlation between VAMS and venous samples.[13,19] There is a risk for increased bias in single microsampling measurements,[13] which could be due to inadequate sample absorption on the tip or extraction, excess blood on the sample handler, or excessive finger squeezing to obtain a sufficient blood volume.[27,28] Patients received thorough training and guidance on capillary microsampling techniques to mitigate these issues. The patients performed the sampling correctly and at the scheduled times. Remarkably, a total of 98% of the microsamples were filled to the appropriate level, with only a single instance of an overfilled tip noted. The study has confirmed the method's feasibility in a clinical trial context, potentially simplifying the execution of future DDI studies.

The major strengths of this study are the prospective design and the use of capillary microsampling, which allowed for rich sampling throughout the whole Tac dosing interval. There are some limitations. First, the need for immediate intervention of hyperkalemia precluded the use of a randomized crossover design, typically recommended to control for sequence effects and time-dependent variables in DDI studies.[29] Consequently, all patients had to start treatment with patiromer immediately after inclusion. A washout period was introduced to ensure that no carryover effect was present. By having all patients serve as their own controls, we aimed to reduce the impact of the well-known variability in Tac pharmacokinetics between individuals.[4,29] Second, patiromer is also approved for administration 3 h before Tac intake, and this regimen was not explored. This could potentially have a greater impact on Tac pharmacokinetics as the onset of action occurs within 4–7 h after patiromer administration.[11] However, the 3 h post–Tac dose was chosen because this is the most clinically applicable choice of the 2 and also minimized the hospital stay during PK1 and therefore reduced the overall burden on patients. Third, patients were instructed to return empty patiromer packages to validate adherence, but this cannot confirm administration. However, 90% of patients showed reduced plasma potassium levels compared with baseline, and health professionals confirmed the administration of patiromer at PK1. Finally, this investigation did not encompass Tac extended-release formulations. Extended-release formulations are theoretically more exposed to an interaction due to the extended oral absorption profile. Patiromer binds potassium primarily in the colon,[9] whereas Tac BID is mainly absorbed in the small intestines. However, extended-release Tac formulations exhibit increased absorption in the distal small intestines and colon, which supports the possibility of a more considerable DDI potential with patiromer.[30]

In conclusion, this novel prospective study indicates that concomitant treatment with patiromer does not change Tac BID pharmacokinetics to any clinically relevant degree when administered 3 h after the Tac morning dose. In addition, the study has demonstrated that VAMS is a well-suited sampling method to simplify the execution of DDI studies. Considering the large amount of patients experiencing hyperkalemia after transplantation and the few treatment options available, it is of clinical importance to confirm that patiromer is a safe option.

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