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The effect of the use of omeprazole versus famotidine on the kidney transplant function: a randomized controlled study

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Tacrolimus is metabolized in the liver with the participation of cytochrome P450 isoforms 3A4 and 3A5 (CYP3A4, CYP3A5). Omeprazole, unlike famotidine, is a substrate and inhibitor of CYP2C19, CYP3A4, CYP3A5 enzymes. The aim of the study is to compare the effect of omeprazole and famotidine on the tacrolimus concentration and the kidney transplant function. A randomized study was conducted in 24 adult patients with stable kidney transplant function who received a standard triple immunosuppression regimen. Patients were assigned to the group I (n = 12) additionally receiving omeprazole (20 mg) or the group II (n = 12) receiving famotidine (20 mg). At the time of qualification and during follow-up visits, tacrolimus blood concentration and selected laboratory tests were performed. Statistical analysis was performed using the MedCalc system. The value of tacrolimus concentration in the blood increased after a year in the group I (7.27 ± 2.33 vs 9.20 ± 2.46 ng/mL, p = 0.0478). A reduction in tacrolimus dosage was observed after three years in the group I (3.56 ± 1.75 vs 2.78 ± 1.00 mg, p = 0.0440) and in the group II (2.72 ± 0.84 vs 2.10 ± 0.48 mg, p = 0.0051). There was significant difference in the percentage changes of glomerular filtration rate between the groups after 3 years of the study (– 5.56% vs 9.13%, p = 0.0343). Omeprazole significantly change the concentration of tacrolimus in the blood when administered together with tacrolimus after one year of observation. There was no effect of famotidine or omeprazole on the function of the kidney transplant. ClinicalTrials.gov identifier: NCT05061303.

Keywords Omeprazole, Famotidine, Tacrolimus, Kidney transplantation, Kidney transplant function

It is known that there may be an interaction between omeprazole and tacrolimus. There have written several cases in the past[1–3]. Tacrolimus is metabolized in the liver by the CYP3A4 isoform of cytochrome P450 (CYP3A4). Urinary excretion accounted for less than 3% of total administered dose, therefore the drug dose does not depend on the renal filtration function[4]. The drug is nephrotoxic and has a narrow therapeutic window, therefore pharmacotherapy with tacrolimus require regular therapeutic drug monitoring. CYP3A4 substrates and inhibitors may increase the blood concentration of tacrolimus, which may cause side effects of this drug. The pharmacokinetics of tacrolimus is also influenced by genetic polymorphisms in genes such as CYP3A4, CYP3A5 and ATP-binding cassette sub-family B member 1 (ABCB1). Pharmacogenetic tests allow for individual adjustment of tacrolimus doses for the patient, which increases the effectiveness of treatment and minimizes the risk of adverse effects[5]. Zhao W et al. described the case of a patient who had homozygous mutations (*1/*1) for CYP3A4. The patient also had a homozygous mutation (*3/*3) for CYP3A5, which resulted in a significant reduction of the corresponding CYP3A5 protein. Moreover, the patient had a homozygous mutation [C1236T (T/T), G677T/A (T/T) and C3435T (T/T)] for the ABCB1 transporter, which resulted in a significant reduction in ABCB1 expression. All the above-mentioned mutations lead to an increase in the concentration of tacrolimus in the blood[1].

Proton pump inhibitors (PPIs), such as omeprazole, are administered as standard pharmacotherapy for kidney transplant patients to prevent duodenal and gastric ulcers caused by the pro-inflammatory effects of immunosuppressive drugs or infections. Omeprazole is a substrate and inhibitor of CYP2C19 and CYP3A4 enzymes, as well as an inhibitor of P-glycoprotein and may interact with tacrolimus[3]. Therefore, it seems important to use drugs with a similar preventive effect on the gastrointestinal tract, which, unlike omeprazole,

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are not substrates or inhibitors of the CYP3A4 enzyme, such as famotidine—an H2 receptor antagonist[6]. Due to the potential influence of omeprazole on the pharmacokinetics of tacrolimus, which may impact on kidney transplant function and the toxicity of the drug, it seems important to investigate this hypothesis and to search for medicinal substances neutral to the above process.

Wijarnpreecha et al. conducted a meta-analysis (n = 536,902) to assess the risk of chronic kidney disease; CKD (a health-important abnormality of kidney structure or function that persists for more than 3 months) in patients receiving PPIs and H2 antagonists (H2RAs). Compared with non-users of PPIs, the pooled risk ratio (RR) for CKD in patients using PPIs was 1.33 (95%CI 1.18–1.51). However, there was no association between H2RAs use and CKD, with a pooled RR of 1.02 (95%CI 0.83–1.25). Compared with people not using PPIs, patients receiving PPIs were observed to have an increased risk of acute kidney injury (AKI) [RR 1.44 ($p < 0.05$), CKD [RR 1.36 ($p < 0.05$), acute interstitial nephritis (AIN) [RR 3.61 ($p < 0.05$) and ESRD [RR 1.42 ($p < 0.05$)[7]. However, the results of another meta-analysis did not show a significant increased risk of CKD associated with the use of PPIs (HR = 1.03, 95%CI: 0.87–1.23)[8]. It is not known whether the use of omeprazole has an impact on the function of a kidney transplant.

Previous studies have assessed the effects of PPIs and H2RAs on kidney transplant function. Ciftci HS et al. studied the effect of PPIs on pharmacokinetics mycophenolate acid concentrations[9]. In one study compared different drugs with different pharmacokinetics, PPIs group consisted of patients taking: pantoprazole, lansoprazole, esomeprazole, omeprazole, dexlansoprazole, rabeprazole and the H2RAs group: famotidine, ranitidine, nizatidine[10]. In the available scientific literature, there are two studies assessing the effect of pantoprazole or omeprazole and ranitidine on the functions of the transplanted kidney[11–13]. However, it is known that ranitidine is an inhibitor of the CYP3A4 and CYP3A5 isoforms, which causes drug-drug interactions with tacrolimus[14]. In the available scientific literature, there is no head-to-head study assessing the effect of omeprazole and famotidine on the function of the transplanted kidney. The aim of our study was to compare the effect of omeprazole and famotidine on the kidney transplant function.

Methods

Study design

The present 3-year study was the second analysis and a randomized controlled trial, which primarily investigated the assessment of omeprazole and famotidine effects on the pharmacokinetics of tacrolimus[3]. We recruited adult patients after kidney transplantation with stable function from 1 to 24 months after transplantation from a tertiary hospital in Poland (Department of Nephrology, Transplantology and Internal Diseases of Poznan University of Medical Sciences) from November 2020 to June 2022. Two individuals withdrew their informed consent and were excluded from the study. The study used the simple randomization method. One of the authors of the study (no the principal researcher) generated a randomized sequence for assigning patients to groups. The random component (computer-generated random numbers) was used in the sequence generation process. Figure 1 presented CONSORT flow chart. No participant changed the group during the study. The patients received orally standard, most commonly used triple immunosuppression regimen: tacrolimus, mycophenolate mofetil, prednisone/methylprednisone/deflazacort and depending on the group orally: omeprazole 20 mg (group I) or famotidine 20 mg (group II). Patients received omeprazole or famotidine with a minimum time interval of 30 min before taking tacrolimus. Patients received tacrolimus once daily in the form of tacrolimus monohydrate prolonged-release tablets (Envarsus®, Chiesi Farmaceutici), registration numbers: EU/1/14/935/00, EU/1/14/935/004, EU/1/14/935/006, EU/1/14/935/007 or in the form of tacrolimus monohydrate prolonged-release hard capsules (Advagraf®, Astellas Pharma Europe), registration numbers: EU/1/07/387/001, EU/1/07/387/003, EU/1/07/387/011, EU/1/07/387/007. Notably, patients were continuously treated with tacrolimus prior to entering the study, but did not take omeprazole or famotidine. On the day of enrollment in the study, the following data were collected: age, gender, weight, height, BMI, living donor / dead donor, cold ischemia time, delayed graft function (hemodialysis), acute rejection process, comorbidities (diabetes, hypertension), cytomegalovirus and BK virus infection. Tacrolimus concentrations were determined using the Chemiluminescent Microparticle Immuno Assay method (CMIA)—instrument Alinity I[15]. As standard, laboratory tests (creatinine concentration, estimated glomerular filtration rate (eGFR), urinalysis, hemoglobin, leukocytes, neutrophils, proteinuria, C-reactive protein (CRP)) were performed during baseline and follow-up visits. In addition, GFR was calculated for each patient using The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation to estimate GFR. No study-related adverse events were reported by patients, physicians, medical staff or others during the study. This study was approved by the Bioethical Commission at the Poznan University of Medical Sciences (No. 687/20). All study procedures adhered to the Declaration of Helsinki. Patients gave written informed consent before study enrollment.

Tacrolimus metabolism

In order to establish the tacrolimus metabolism rate in the patients, the blood concentration normalized by the dose (C/D ratio) was calculated. The C0/D ratio can be calculated by dividing the tacrolimus pre-dose concentration (C0) by the corresponding daily tacrolimus dose (D). In the presented study, the authors used the scale suggested by Thölking G. et al.[16] If the C/D ratio was 1.05–1.54 ng/mL*1/mg, the patients were classified as intermediate metabolizers. The ultra-rapid metabolizers group included patients with a C/D ratio of < 1.05 ng/mL*1/mg, whereas if the aforementioned ratio was ≥ 1.55 ng/mL*1/mg, the participants were described as poor metabolizers. The results are presented in Table 1.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (inter-quartile range (IQR)). The Shapiro–Wilk test was used to verify whether the results of differences in pairs of parameters were normally

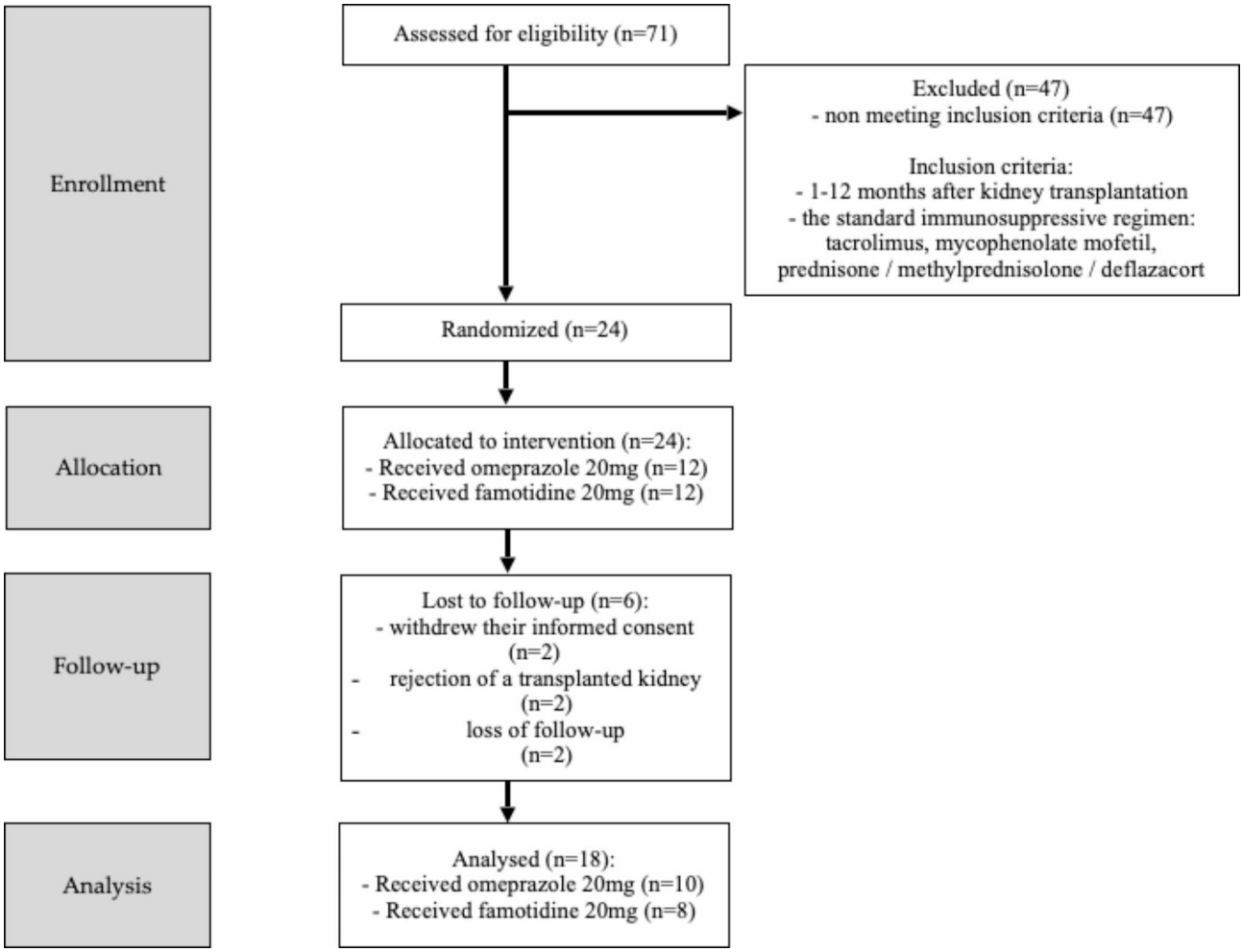

Fig. 1. CONSORT flow chart.

distributed. Statistical evaluation of parameters such as tacrolimus concentration, creatinine concentration, GFR and tacrolimus dosage was performed separately in group I and group II. The parameters that were assessed separately in group I and separately in group II were analyzed using the following statistical tests. For normal distribution variables ($p > 0.05$), the paired Student's t-test was applied to estimate the significance of differences between the two analysed groups. The parameters which were significantly different from the normal distribution ($p < 0.05$) were analysed using the paired Wilcoxon signed-rank test. In addition, creatinine concentration and baseline values were analysed between the groups. Baseline characteristics and parameters such as tacrolimus concentration normalized by dose, creatinine concentration and GFR were compared between the study groups using the following statistical tests. For normal distribution variables ($p > 0.05$), the non-paired Student's t-test was applied to estimate the significance of differences between the two analysed groups. The parameters which were significantly different from the normal distribution ($p < 0.05$) were analysed using the Mann–Whitney U test. For normal distribution variables ($p > 0.05$), the Welch's t-test was applied to estimate the significance of differences between the analysed groups for unequal variances. F test was used to compare the variances between study groups. The correlations between two variables with normal distribution were calculated using the Pearson's correlation and with non-normal distribution were calculated using the Spearman's rank correlation. All statistical analyses were performed by MedCalc Statistical Software version 20.106.

Results

Baseline characteristics

A total of 18 patients with stable kidney transplant function were included in the study and then assigned to the group I ($n = 10$) receiving omeprazole (20 mg) or the group II ($n = 8$) receiving famotidine (20 mg). All patients received a kidney from a deceased donor. The general data were analyzed before the study in both groups and compared as presented in Table 1. Patients in both groups showed no significant differences in terms of gender, age, BMI, systolic and diastolic blood pressure, creatinine level, GFR and daily dose of tacrolimus ($p > 0.05$). In one patient in the group I and in one patient in the group II, the kidney transplant was rejected due to infection and both patients started hemodialysis treatment.

Characteristic parameter	Group I	Group II	p-value
Gender (n; men/women)	7/3	6/2	-
Age (years)	51 ± 12	47 ± 8	p = 0.3750
Body Mass Index (kg/m^2)	25.19 ± 5.31	26.13 ± 5.21	p = 0.7107
systolic/diastolic blood pressure (SBP/DBP) (mmHg) arterial hypertension	147.00 ± 22.76 / 90.80 ± 11.72 (n = 7)	145.13 ± 21.98 / 92.25 ± 15.25 (n = 4)	SBP p = 0.8623 DBP p = 0.8221
Creatinine concentration (mg/dL)	1.53 ± 0.50	1.54 ± 0.25	p = 0.9448
Glomerular Filtration Rate [The Chronic Kidney Disease—Epidemiology Collaboration] (mL/min/1,73 m^2)	56.10 ± 21.97	53.13 ± 9.91	p = 0.7093[1]
Tacrolimus daily dose (mg/kg)	0.0408 (0.0331–0.0549)	0.0324 (0.0247–0.0458)	p = 0.2031[2]
Proteinuria (n)	3	2	-
Erythrocyturia (n)	0	1	-
Cytomegalovirus (n)	3	0	-
BK virus (n)	1	1	-
Anaemia (n)	0	0	-
the mean C_0/D ratio (ng/mL*1/mg)	2.44 ± 1.30	3.04 ± 0.70	p = 0.2579
poor metabolizers (n)	9	8	-
intermediate metabolizers (n)	0	0	-
ultra-rapid metabolizers (n)	1	0	-

Table 1. The baseline characteristics of the study groups. Baseline is the day before starting omeprazole or famotidine in the study. The values are provided as the number of patients (n), as mean ± SD or median (interquartile range (IQR)). [1]The Welch's t-test. [2]The Mann–Whitney U test.

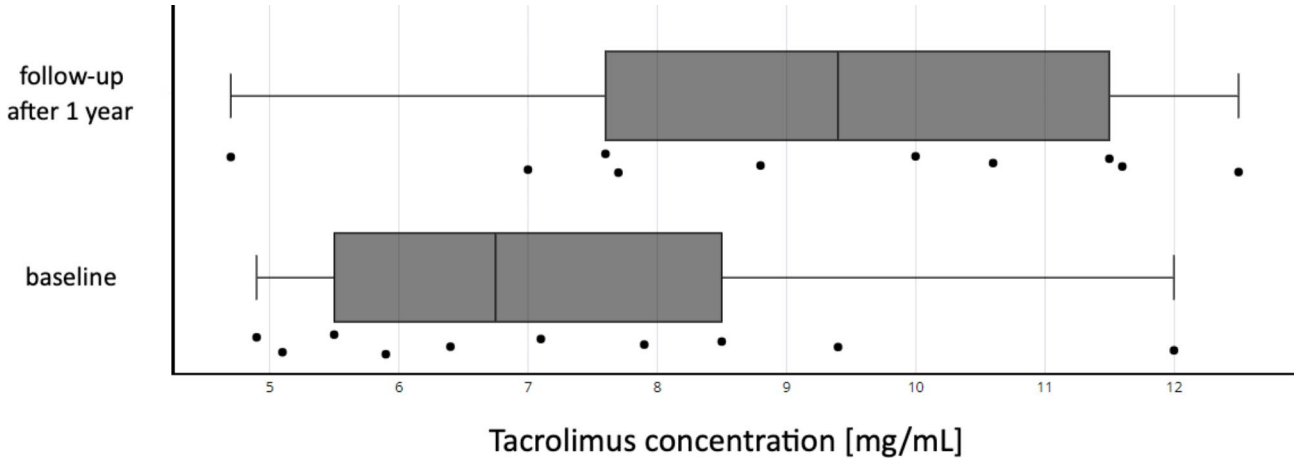

Fig. 2. The value of blood tacrolimus concentration normalized by dose after 1 year in the group. I (OM). The left side of the box is defined by the first quartile, the right side by the third quartile. The vertical line inside the box represents the median value. The right end of the line is the highest value in the group, while the left end to the line is the lowest value. Baseline is the day before starting omeprazole or famotidine in the study.

Tacrolimus concentrations

We compared changes in tacrolimus concentration during the study period in both groups separately. The average values of tacrolimus blood concentration over three years in group II were within the reference range of 5.0–9.0 ng/mL. In the group I the blood tacrolimus concentration was significantly higher than baseline value only after the first year of observation (7.27 ± 2.33 vs 9.20 ± 2.46 ng/mL, p = 0.0478) (Fig. 2, Tables 2 and 3) but the value of blood tacrolimus concentration normalized by dose was higher than baseline value after first year and two years, respectively (179.57 ± 104.65 vs 251.05 ± 102.43 (ng/mL)/(mg/kg), p = 0.0105, 179.57 ± 104.65 vs 220.53 ± 104.13 (ng/mL)/(mg/kg), p = 0.0285). In the group II no significant differences in blood tacrolimus concentrations were observed during the study follow-up. The tacrolimus dosage was lower after two and three years of observation in both groups compared to the baseline, in the group I (3.56 ± 1.75 vs 2.88 ± 1.04 mg, p = 0.0304, 3.56 ± 1.75 vs 2.78 ± 1.00 mg, p = 0.0440) and in the group II (2.72 ± 0.84 vs 2.13 ± 0.50 mg, p = 0.0101, 2.72 ± 0.84 vs 2.10 ± 0.48 mg, p = 0.0051), respectively (Tables 2 and 3).

Parameter	Baseline#	After 1 year	After 2 year	After 3 year
$C_{tacrolimus}$ (ng/mL)	7.27 ± 2.23	9.2 ± 2.46	7.71 ± 2.36	6.76 ± 1.34
p-value	-	**0.0478**	0.6503	0.5833
$C_{tacrolimus}$* ((ng/mL)/(mg/kg))	179.57 ± 104.65	251.05 ± 102.43	220.53 ± 104.13	194.64 ± 60.92
p-value	-	**0.0105**	**0.0285**	0.5445
$C_{creatinine}$ (mg/dL)	1.53 ± 0.50	1.55 ± 0.44	1.69 ± 0.61	1.70 ± 0.72
p-value	-	0.9188	0.4413[1]	0.5071[1]
GFR (mL/min/1,73m^2)	56.10 ± 21.97	53.70 ± 20.80	50.70 ± 22.95	52.30 ± 23.93
p-value	-	0.5787	0.2057	0.4147
Tacrolimus dose (mg)	3.56 ± 1.75	3.09 ± 1.62	2.88 ± 1.04	2.78 ± 1.00
p-value	-	0.0679[1]	**0.0304**	**0.0440**[1]

Table 2. The comparison of serum tacrolimus concentration, serum creatinine concentration and tacrolimus doses in the group I (OM) baseline vs follow-up after 1, 2 and 3 years. The values are provided as the mean ± SD. #The day before starting omeprazole or famotidine in the study. *Tacrolimus concentration normalized by the dose. [1]The paired Wilcoxon signed-rank test. Significant are in value [bold].

Parameter	Baseline	After 1 year	After 2 year	After 3 year
$C_{tacrolimus}$ (ng/mL)	7.99 ± 2.33	8.4 ± 1.21	8.36 ± 2.37	6.76 ± 0.81
p-value	-	0.6820	0.8025	0.1125
$C_{tacrolimus}$* ((ng/mL)/(mg/kg))	241.42 ± 65.44	278.89 ± 88.44	344.28 ± 159.96	275.89 ± 86.74
p-value	-	0.1437	0.0948	0.1484[1]
$C_{creatinine}$ (mg/dL)	1.54 ± 0.25	1.49 ± 0.33	1.52 ± 0.34	1.51 ± 0.49
p-value	-	0.4062	0.6763	0.1953[1]
GFR (mL/min/1,73m^2)	53.13 ± 9.91	56.38 ± 11.93	54.00 ± 10.14	56.25 ± 12.95
p-value	-	0.3134	0.6882	0.1609[1]
Tacrolimus dose (mg)	2.72 ± 0.84	2.53 ± 0.54	2.13 ± 0.50	2.10 ± 0.48
p-value	-	0.3645	**0.0101**	**0.0051**

Table 3. The comparison of serum tacrolimus concentration, serum creatinine concentration and tacrolimus doses in the group II (FA) baseline vs follow-up after 1, 2 and 3 years. The values are provided as the mean ± SD. #The day before starting omeprazole or famotidine in the study. *Tacrolimus concentration normalized by the dose. [1]The paired Wilcoxon signed-rank test. Significant are in value [bold].

Tacrolimus dosage

Tacrolimus doses were significantly lower after two and three years of the study compared with baseline in the group I (3.56 ± 1.75 vs 2.88 ± 1.04 mg, p = 0.0304 and 3.56 ± 1.75 vs 2.78 ± 1.00 mg, p = 0.0440) and in the group II (2.72 ± 0.84 vs 2.13 ± 0.50 mg, p = 0.0101 and 2.72 ± 0.84 vs 2.10 ± 0.48 mg, p = 0.0051), respectively. The results after one year of the study are available in Tables 2 and 3. We also assessed dosing changes between group I and group II after 1 year (-0.11 ± 0.16 vs -0.03 ± 0.19 mg, p = 0.3454), 2 years (-0.04 ± 0.22 vs -0.16 ± 0.12 mg, p = 0.1805) and 3 years (-0.01 ± 0.12 vs -0.01 ± 0.05 mg, p = 0.6858).

Kidney transplant function-follow-up

The serum creatinine concentration did not differ significantly after a year, after two and three years in group I and separately in group II (Tables 2 and 3) compared to the baseline values. After three years we did not observe a significant difference in the creatinine concentration between group I and group II (1.70 ± 0.72 vs 1.51 ± 0.49 mg/dL, p = 0.6891). There was also no significant difference between percentage changes of groups in creatinine concentration values after 3 years of the study (4.05 (-2.19 to 17.32%) vs -8.08 (-13.58 to -5.26%), p = 0.0545) (Table 4).

The GFR did not differ significantly after a year, after two and three years in group I (56.10 ± 21.97 vs. 52.30 ± 23.93 mL/min/1,73 m^2, p = 0.4147) and in group II compared to baseline values (53.13 ± 9.91 vs. 56.25 ± 12.95 mL/min/1,73 m^2, p = 0.1609) (Tables 2 and 3). We did not observe a significant difference in the GFR between the group I and group II after 3 years of the study (52.30 ± 23.93 vs. 56.25 ± 12.95 mL/min/1,73 m^2), p = 0.6809. However, there was a significant difference between percentage variation of GFR after 3 years of the study (− 5.56% (− 17.24 to 0.00%) vs 9.13% (4.49 to 16.62%), p = 0.0343) (Table 4).

There was a non-significant correlation between the serum creatinine and the blood tacrolimus concentrations or the tacrolimus concentrations normalized by dose in group I (rho = 0.314, p = 0.0914), (rho = -0.066, p = 0.7304) and in group II (r = 0.024, p = 0.9117), (r = 0.036, p = 0.8680), respectively.

Parameter	Group	Baseline	After 1 year	After 2 year	After 3 year
$C_{creatinine}$ (mg/dL)	Group I	1.53 ± 0.50	1.55 ± 0.44	1.69 ± 0.61	1.70 ± 0.72
	Group II	1.54 ± 0.25	1.49 ± 0.33	1.52 ± 0.34	1.51 ± 0.49
p-value		0.9448	0.7571	0.4976	0.6891
$\Delta\%C_{creatinine}$ (%)	Group I	-	9.19 (-11.42 to 14.49)	7.67 (-5.88 to 19.71)	4.05 (-2.19 to 17.32)
	Group II	-	-0.72 (-12.58 to 5.37)	-4.98 (-8.86 to 3.59)	-8.08 (-13.58 to -5.26)
p-value		-	0.3835	0.2743[2]	0.0545[2]
GFR (mL/min/1,73m^2)	Group I	56.10 ± 21.97	53.70 ± 20.80	50.70 ± 22.95	52.30 ± 23.93
	Group II	53.13 ± 9.91	56.38 ± 11.93	54.00 ± 10.14	56.25 ± 12.95
p-value		0.7083[1]	0.2858	0.1962	0.6809
Δ%GFR (%)	Group I	-	-11.46 (-15.38 to 17.24)	-6.03 (-20.59 to 4.26)	-5.56 (-17.24 to 0.00)
	Group II	-	0.79 (-6.18 to 16.80)	4.68 (-5.63 to 9.74)	9.13 (4.49 to 16.62)
p-value		-	0.1728[2]	0.1998	**0.0343**[2]

Table 4. The comparison of values and the percentage variation of values of serum creatinine concentrations and GFR between the study groups. The values are provided as the mean ± SD or median (inter-quartile range (IQR)). #The day before starting omeprazole or famotidine in the study. [1]The Welch's t-test. [2]The Mann–Whitney U test. Significant are in value [bold].

There was a non-significant correlation between the GFR and the blood tacrolimus concentrations or the tacrolimus concentrations normalized by dose in group I (r = -0.147, p = 0.3667), (r = -0.096, p = 0.5540) and in group II (r = -0.117, p = 0.5224), (r = -0.183, p = 0.3160), respectively.

Discussion

Tacrolimus concentrations

In our three-year study, we assessed the effect of omeprazole and famotidine on variability in tacrolimus blood concentrations and on the function of the transplanted kidney. We observed a significantly higher tacrolimus concentrations after one year of the study than baseline in patients administering omeprazole. Moreover, in this group of patients, the average concentration of tacrolimus in the blood after 1 year of study was higher than the recommended norm in the first years after kidney transplantation (9.2 ± 2.46 ng/mL)[17]. In order to exclude the influence of the dose value on the obtained results, we normalized the tested tacrolimus concentrations by dose received by the patient. The value of tacrolimus concentration normalized by dose in the blood increased significantly after a year and two years in the group I. The results after 3 years of follow-up are presented in Table 2. There was no significant increase in tacrolimus concentrations at any point in the study in patients administering famotidine. The results of changes in tacrolimus concentration in both study groups refer to observations from our previous study. At that time, the pharmacokinetics of tacrolimus were assessed after a single administration with omeprazole or famotidine. Omeprazole significantly increased tacrolimus the area under the concentration–time curve from 0 to 6 h (AUC0-6) by 16.30% (p = 0.0295), AUC0-6 normalized by the dose by 12.88% (p = 0.0300), no significant changes in tacrolimus blood concentration were observed for the group II receiving famotidine[3]. The reason for the increase in tacrolimus concentration in patients also administering omeprazole is the risk of drug-drug interactions in which the CYP3A4 isoform plays a key role. Tacrolimus is metabolized by the CYP3A4 isoform like omeprazole, however, the described proton pump inhibitor also acts as an inhibitor of the CYP3A4 isoform. The proposed interaction mechanism is shown in Fig. 3[3].

Tacrolimus dosage

In our study, we observed that tacrolimus dosage was significantly lower in both study groups after two and three years when compared to baseline doses, which we did not observe after one year of the study. Dose reduction in the omeprazole study was also observed by Pascual J et al. in the first months after kidney transplantation[18]. Tacrolimus is a calcineurin inhibitor and has nephrotoxicity which is why in transplant recipients, immunosuppressive treatment regimens with the lowest possible toxic effect are desirable, especially in relation to the risk of transplanted organ rejection. A randomized clinical trial assessed the effect of calcineurin inhibitors on the function of the transplanted kidney. The mean calculated GFR was higher in patients receiving low-dose tacrolimus than in the other study groups. Allograft survival was highest in the low-dose tacrolimus group (94.2%), followed by the low-dose cyclosporine group (93.1%), and the standard-dose cyclosporine group (89.3%)[19]. However, Underdosing or completely discontinuing CNI therapy is not recommended by KDIGO (Kidney Disease: Improving Global Outcomes) because it increases the risk of acute and chronic kidney transplant rejection; CKTR (a graft failure and rejection beyond 1-year post-transplant)[20]. We did not observe any significant difference in the assessment of dosage changes between the study groups after 1, 2 and 3 years of the study. This result allows us to conclude that the change in dosage in both groups did not affect other results of our study.

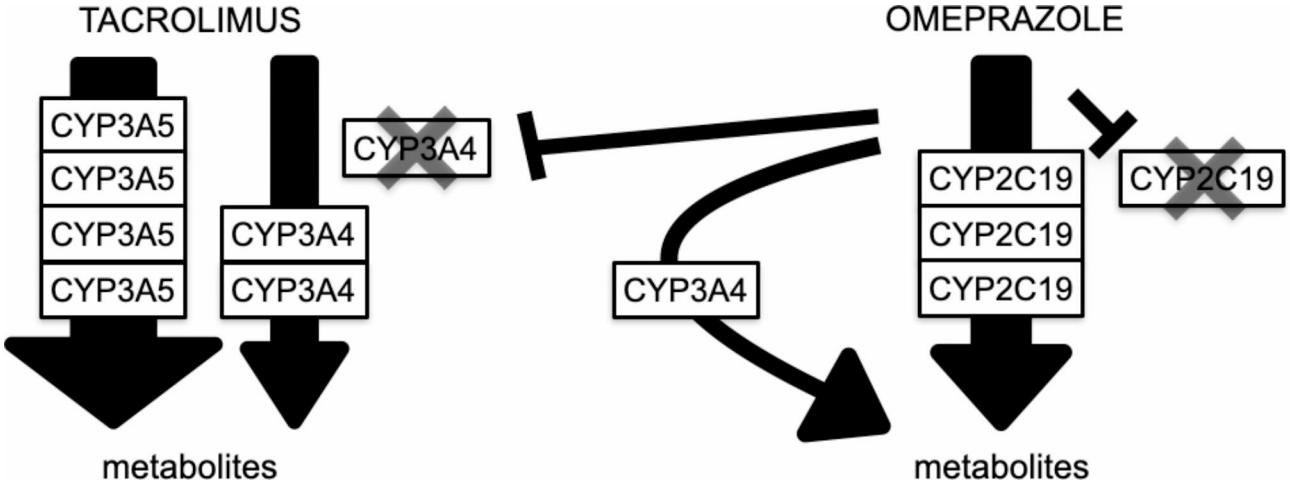

Fig. 3. Drug-drug interaction between tacrolimus and omeprazole in patients – the suggested mechanism[3].

Kidney transplant function

In our study, we observed significant changes in the reduction of GFR values in the group I compared to the group II. Moreover, we observed an increase in creatinine concentration in the group I and a decrease in the group II during the three-year follow-up. The decrease in glomerular filtration rate observed in the group of patients receiving omeprazole in our study refers to previously obtained results in other studies assessing the effect of proton pump inhibitors on the function of the transplanted kidney[13,21,22]. Similar results were observed in patients taking PPIs for the first time. Patients receiving PPIs had a higher risk of reducing the estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 than patients receiving H2 receptor antagonists (H2RA)[23,24]. It should be emphasized that the use of omeprazole is considered a risk factor for elevated creatinine levels[25]. This is the first cohort study assessing the effect of famotidine on transplanted kidney function. Famotidine does not affect the pharmacokinetics of tacrolimus or significant changes in creatinine levels, therefore it may be an alternative to proton pump inhibitors in the prevention of upper gastrointestinal bleeding in patients after kidney transplantation. Moreover, unlike proton pump inhibitors, famotidine does not have a nephrotoxic effect[26].

Limitations

A limitation of our study is the small group of patients. However, despite this limited number of patients, our results were significant. Obtaining significant results, taking into account the number of patients studied, highlights the significant difference between the change in tacrolimus concentration after repeated administration with and without omeprazole. No such change was observed compared to repeated administration of tacrolimus with famotidine.

Conclusion

Omeprazole has significantly influence on the concentration of tacrolimus in the blood when administered together with tacrolimus after one year of observation. No effect of drug-drug interactions, famotidine or omeprazole combined with tacrolimus on kidney transplant function has been observed. Maintaining tacrolimus concentrations within the therapeutic range is more difficult when omeprazole and tacrolimus are co-administered than when famotidine is combined with tacrolimus after one year of combined treatment. The use of famotidine in place of omeprazole have more favorable outcomes of kidney transplant function for renal transplant patients.

Data availability

Data will be made available on request. Requests should be addressed to the author Miłosz Miedziaszczyk (m.miedziaszczyk@wp.pl).

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Author contributions

Miłosz Miedziaszczyk: Conceptualization, Methodology, Validation, Formal analysis, Inves- tigation, Resources, Data curation, Statistical analysis, Visualization, Writing – original draft, Project administration, Funding acquisition. Marek Karczewski: Writing – review & editing, Fund- ing acquisition. Ilona Idasiak-Piechocka: Conceptualization, Formal analysis, Resources, Writing – review & editing, Supervision, Funding acquisition. The final version of the manuscript was approved by all authors.

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Ethics approval and consent to participate

The studies involving humans were approved by The Bioethical Commission at the Poznan University of Medical Sciences (No. 687/20). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

Additional information

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