DOI: 10.15825/1995-1191-2023-1-52-61

PERSONALIZED DOSING PROTOCOL FOR EXTENDED-RELEASE TACROLIMUS IN KIDNEY TRANSPLANT RECIPIENTS IN THE EARLY POSTOPERATIVE PERIOD

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Objective: to develop a personalized algorithm for extended-release tacrolimus in kidney recipients and to analyze its early outcomes in comparison with a retrospective control group. **Materials and methods.** The first (I) control group "Standard Protocol" included 228 patients operated on at Botkin City Clinical Hospital from June 2018 to November 2021; tacrolimus was administered postoperatively in a starting standard dosage of 0.2 mg/kg. The second group (II) consisted of 75 patients operated from December 2021 to November 2022, whose postoperative treatment involved a personalized extended-release tacrolimus dosing protocol. Induction immunosuppression was similar in both groups. The target tacrolimus level in the early postoperative period was considered to be 10–12 ng/ml for all patients. The comparison criteria included incidence of Over-immunosuppression (tacrolimus C_0 >15 ng/ml), incidence of acute rejection and infectious complications in the first month after surgery, incidence and duration of delayed graft function (DGF), and length of stay at the hospital. **Results.** Over-immunosuppression was statistically significantly lower in the personalized protocol group, with 36.7% in group I and 87.5% in group II ($p < 0.001$). There was also a lower incidence of early infectious complications in group II: 5.4% vs. 13.2%, however, without reaching a level of statistical significance ($p = 0.088$). DGF incidence in group I and group II were 25.4% (58/228) and 22.7% (17/75), respectively. The length of stay at the hospital in group II was also statistically significantly lower: 13 versus 19 bed days ($p = 0.033$). In both subgroups, no patient developed acute rejection in the first month after surgery ($p = 1$). **Conclusion.** The personalized dosing protocol that was developed for extended-release tacrolimus in kidney recipients achieves the target levels of the drug recommended for the early postoperative period with low risk of under-immunosuppression and associated acute graft rejection, with a significantly lower incidence of over-immunosuppression.

Keywords: tacrolimus, kidney transplantation, immunosuppressive therapy, DGF.

INTRODUCTION

Kidney transplantation (KTx) is currently regarded as the optimal treatment method for renal replacement therapy for patients without absolute contraindications. The discovery and introduction of calcineurin inhibitors (CNIs) into immunosuppression regimens was the breakthrough in clinical transplantology that made KTx the gold standard treatment for end-stage kidney disease. Introduction of cyclosporine A (CsA) in the early 1980s saw the one-year survival rate of renal transplants rise from 60% to over 80%. Tacrolimus (Tac), on the other hand, as an alternative to cyclosporine, was introduced into clinical practice in the early 1990s, and to date, its advantage over cyclosporine has been proven by many authors. Tac is much more effective in preventing acute rejection and it generally has comparable side effects with CsA [1–2]. That is why since 2009, the KDIGO guidelines have proposed Tac as the basis for most immunosuppressive maintenance therapy regimens [3].

Despite the proven superiority of Tac, its side effects not only worsen renal graft function gradually, but also cause serious diseases such as diabetes mellitus and arterial hypertension in the late post-transplant period. In the early post-transplant period, when the recommended doses and concentrations of the drug are highest, acute nephrotoxicity is the most common and undesirable effect in renal transplant recipients [4–5]. It is based on changes in hemodynamics at the microcirculatory level, endothelial cell dysfunction, tubular damage, development of thrombotic microangiopathy and impaired ion exchange, leading to reduced glomerular filtration rate (GFR) and increased plasma creatinine levels. In addition to increased vasoconstrictor synthesis, CNIs cause endothelial dysfunction by reducing NO synthesis. There is also an increase in the formation of free radicals and

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superoxides, probably due to hypoxia associated with efferent arteriolar vasoconstriction [6].

One of the most common early postoperative complications is delayed graft function (DGF). It is commonly defined as the need for hemodialysis within 7 days following a KTx; its pathogenesis is based on kidney graft damage during cold preservation and reperfusion [7]. Development of CNI-induced acute nephrotoxicity with the need for hemodialysis in the first week after KTx, according to the classical definition, may be the cause of DGF [8]. This side effect of Tac is usually dose-dependent and completely reversible after correction; however, performing hemodialysis sessions in the early postoperative period may be a risk factor for more serious complications.

In our previous study on the search for DGF risk factors, DGF was found to have a statistically significant association with increased incidence of early postoperative complications and decreased long-term graft survival [9]. According to multivariate analysis, increased Tac zero levels in the first 4 days >23 ng/ml was statistically significant and was an independent risk factor for DGF ($p = 0.025$). This prompted a revision of the then-existing protocol for immunosuppressive therapy after kidney transplantation in our clinic and the development of a personalized dosing algorithm for extended-release Tac. The purpose of this study was to analyze the initial outcomes of the use of this protocol in comparison with a retrospective control group.

MATERIALS AND METHODS

From June 2018 through November 2022, 337 isolated kidney transplants from deceased donors were performed at Botkin City Clinical Hospital. Organ explantation from the donor, cold preservation, and surgical technique were performed according to the standard protocols of the National Clinical Guidelines. For immunosuppression in the early postoperative period, a triple regimen consisting of extended-release Tac, mycophenolic acid derivatives and methylprednisolone was used as standard. Basiliximab (20 mg) was given as induction therapy intraoperatively and on day 4; methylprednisolone (10 mg/kg) was administered intraoperatively and on days 3 and 5 intravenously. The starting Tac dose that the patient received before surgery was determined at 0.2 mg/kg from 2018 to 2021, and thereafter (2021–2022) according to the personalized protocol developed. The target Tac level in the early postoperative period was considered to be 10–12 ng/ml for all patients.

Group characteristics

The first control group of the "Standard IST Protocol" included 228 patients operated on at Botkin City Clinical Hospital from June 2018 to November 2021. There were 83 (36.5%) women and 145 (63.5%) men in this group. The mean age was 47 ± 11 (IQR: 39–55) years, mean recipient BMI was 25.5 (IQR: 23.0–29.0) kg/m^2, residual diuresis was 300 (IQR: 100–600) ml, donor age was 49 (IQR: 44–54) years, donor BMI was 26.0 (IQR: 24.2–30.0) kg/m^2, cold preservation time was 625 (IQR: 515–740) minutes, secondary warm ischemia time was 40 (IQR: 30–50) minutes, and intraoperative blood loss was 100 (IQR: 50–150) ml. The most common causes of end-stage renal disease in group 1 were chronic glomerulonephritis (61%), chronic pyelonephritis (9%), polycystic disease (9%), diabetic nephropathy (9%), chronic tubulointerstitial nephritis (5%), etc. In 225/228 cases, the kidney graft was obtained from brain-dead donors, and in 3 cases, the graft was procured from a donor with effective circulatory arrest.

The second group consisted of 75 patients operated on at Botkin City Clinical Hospital between December 2021 and November 2022, whose postoperative treatment involved a personalized dosing protocol for extended-release Tac developed at the Department of Organ and Tissue Transplantation, Botkin City Clinical Hospital. There were 33 (36.5%) women and 42 (63.5%) men in this group. Median age was 46 (IQR: 38–54) years, median recipient BMI was 26.0 (IQR: 24.0–27.3) kg/m^2, residual diuresis was 300 (IQR: 0–700) ml, donor age was 51 (IQR: 48–52) years, donor BMI was 31.5 (IQR: 27.4–34.0) kg/m^2, cold preservation time was 710 (IQR: 640–780) minutes, secondary warm ischemia time was 40 (IQR: 30–47) minutes, and intraoperative blood loss was 100 (IQR: 100–200) ml. The most common causes of end-stage renal disease in group II were chronic glomerulonephritis (54%), chronic pyelonephritis (9%), polycystic disease (8%), diabetic nephropathy (15%), chronic tubulointerstitial nephritis (5%), etc. In 73/75 cases, the renal transplant was obtained from brain-dead donors, and in 2 cases from donors with effective circulatory arrest. Primary graft nonfunction (PNF), a need for revision and graftectomy within the first week after transplantation, and the use of hypothermic oxygenated machine perfusion during graft preservation were the exclusion criteria. The characteristics of the groups are presented in Table 1.

In creating a personalized dosing protocol for extended-release Tac at the first stage, we determined the really necessary doses of the drug per kg of each patient's weight, which they received 3 weeks after surgery (at the time of discharge). Calculation of the optimal dose included group 1 patients who received a triple immunosuppressive regimen (extended-release Tac + mycophenolic acid preparations + methylprednisolone), provided they achieved the target concentration consistently required for the appropriate postoperative period. After that, for 204 patients selected from the retrospective group, we evaluated the significance of the influence of several quantitative and qualitative characteristics of the recipient on the required Tac dose: volume of residual diuresis, sex, age, weight, body mass index, history of kidney

transplantation, etiology of chronic kidney disease, product and sum of recipient age and weight.

After developing and implementing a personalized immunosuppressive therapy protocol into clinical practice, we evaluated its safety and efficacy in a comparative study. The following parameters were analyzed: incidence of over-immunosuppression (Tac pre-dose concentration C_0 >15 ng/mL), incidence of acute rejection and infectious complications in the first month after surgery, incidence of DGF and its duration, and length of stay at the hospital. DGF was defined as the requirement for hemodialysis within the first 7 days following renal transplantation.

Statistical analysis

Statistical processing and data analysis were performed using SPSS Statistics for Microsoft Windows version 26 (USA). Student's t-test or Welch's t-test was used to compare two groups of quantitative indicators with normal distribution (depending on equality of variance). For distributions other than normal, the Mann–Whitney U test was used to compare two groups of quantitative data, while the Kruskal–Wallis H test was used to compare three or more groups. Qualitative indicators were compared using Pearson's chi-squared test or Fisher's exact test, with the determination of the odds ratio (OR) and closeness of correlation between the characteristics under study. Correlation analysis was performed by the Spearman method with determination of rank correlation coefficient ρ and closeness of correlation according to Cheddock's scale. The dependence of changes in quantitative indicators on each other was assessed in a linear regression model. Pseudorandomization was performed in SPSS Statistics v. 26 using the PSM method with a fit tolerance of 0.1. Statistically significant differences were considered at $p < 0.05$, the trend towards statistical significance was defined as $p < 0.1$.

RESULTS

Development of a personalized dosing protocol for extended-release tacrolimus

Among the 204 patients selected from the retrospective group, 34 (17%) had a calculated Tac dose of less than 0.1 mg/kg at discharge, 121 (59%) were in the range of 0.1–0.19 mg/kg, and only 49 (24%) patients needed a dose of 0.2 mg/kg or more. In the analysis of factors influencing the required drug dose 3 weeks after KTx, such parameters as age ($p = 0.012$), weight and BMI ($p = 0.009$ and $p = 0.021$), product and sum of recipient age and weight ($p = 0.005$ and $p = 0.0023$), achieved statistical significance. At the same time, the inverse correlation of the highest closeness on the Cheddock's scale was demonstrated precisely for the sum of the patient's age and weight ($\rho = –0.706$). Analysis of the effect of various recipient characteristics on the required dose of extended-release Tac at the time of discharge is shown in Table 2.

Table 1

Characteristics of the study groups

	Group I Standard ISx protocol (2018–2021) n = 228	Group II Modified ISx protocol (2021–2022) n = 75	p
Recipient age (years)	47 (IQR: 39–55)	46 (IQR: 38–54)	0.867
Recipient BMI (kg/m^2)	25.5 (IQR: 23.0–29.0)	26.0 (IQR: 24.0–27.3)	0.65
Residual diuresis (ml)	300 (IQR: 100–600)	300 (IQR: 0–700)	0.756
Donor age (years)	49 (IQR: 44–54)	51 (IQR: 48–52)	0.15
Donor BMI (kg/m^2)	26.0 (IQR: 24.2–30.0)	31.5 (IQR: 27.4–34.0)	0.03
Cold preservation time (min)	625 (IQR: 515–740)	710 (IQR: 640–780)	0.015
Secondary warm ischemia time (min)	40 (IQR: 30–50)	40 (IQR: 30–47)	0.83
Intraoperative blood loss (ml)	100 (IQR: 50–150)	100 (IQR: 100–200)	0.73
Donor type: – *SD* – *ECD* – *DCD*	 115 (50.4%) 109 (47.8%) 4 (1.8%)	 38 (50.6%) 34 (45.3%) 3 (4.1%)	>0.05
Etiology of CKD: – *Chronic glomerulonephritis* – *Chronic pyelonephritis* – *Diabetic nephropathy* – *Polycystic kidney disease* – *crTIN* – *Others*	 139 (61%) 21 (9%) 21 (9%) 21 (9%) 11 (5%) 15 (7%)	 40 (54%) 6 (8%) 11 (15%) 6 (8%) 8 (9%) 4 (6%)	>0.05

Note: SD, standard donor; ECD, expanded criteria donor; DCD, donor after cardiac death; CrTIN, chronic tubulointerstitial nephritis.

Based on the identified statistically significant and closest inverse correlation between the required Tac dose per kg of body weight and the sum of the recipient's age and weight, a predictive linear regression model was built. The observed dependence is described by the equation:

$$Y_{dose} = 0.285 - 0.001 \times X_{age + weight},$$

where Y_{dose} is the extended-release Tac dose and $X_{age + weight}$ is the sum of the recipient's age and weight. A graphical representation of the linear regression model is shown in Fig. 1.

The significance level was $p < 0.001$. Based on the value of the coefficient of determination (R^2), the factors included in the model determined 28.5% of variance. To categorize patients into groups according to the extended-release Tac dose administered, cut-off points were determined by the sum of the recipient's age and weight by a combined analysis of median, quartiles (25% and 75%), most sensitive and specific cutoff points from ROC analysis, and applicability in clinical practice. Thus, patients whose sum of age and weight was less than 105 were given extended-release Tac at 0.2 mg/kg of recipient body weight; those with a sum of 105 to 134 got 0.15 mg/kg, and patients with a sum of more than 134 got 0.1 mg/kg. The personalized dosing protocol for extended-release Tac is shown in Fig. 2.

Comparative analysis of the safety and efficacy of the personalized dosing protocol for extended-release tacrolimus with respect to the standard regimen

The incidence of over-immunosuppression (Tac predose concentration C_0 >15 ng/mL) in Group I was 87.5% of patients (199/228), in the personalized immunosuppression (ISx) protocol group this rate was 34.7% (26/75) ($p < 0.001$). No episodes of under-immunosuppression were reported in any case of the personalized Tac dosing

Table 2

Influence of various indicators on the required extended-release tacrolimus dose

Indicator	p value	Spearman's rank correlation coefficient ρ (for quantitative indicators)	Strength of correlation according to the Cheddock's scale
Recipient residual diuresis	0.73	–	–
Recipient gender	0.321	–	–
Recipient age	**0.012**	–0.352	Moderate
CKD etiology	0.41	–	–
Repeat kidney transplantation	0.512	–	–
Recipient weight	**0.009**	–0.413	Moderate
Recipient BMI	**0.021**	–0.248	Weak
Product of recipient age and weight	**0.005**	–0.678	Moderate
Sum of recipient age and weight	**0.0023**	–0.706	Strong

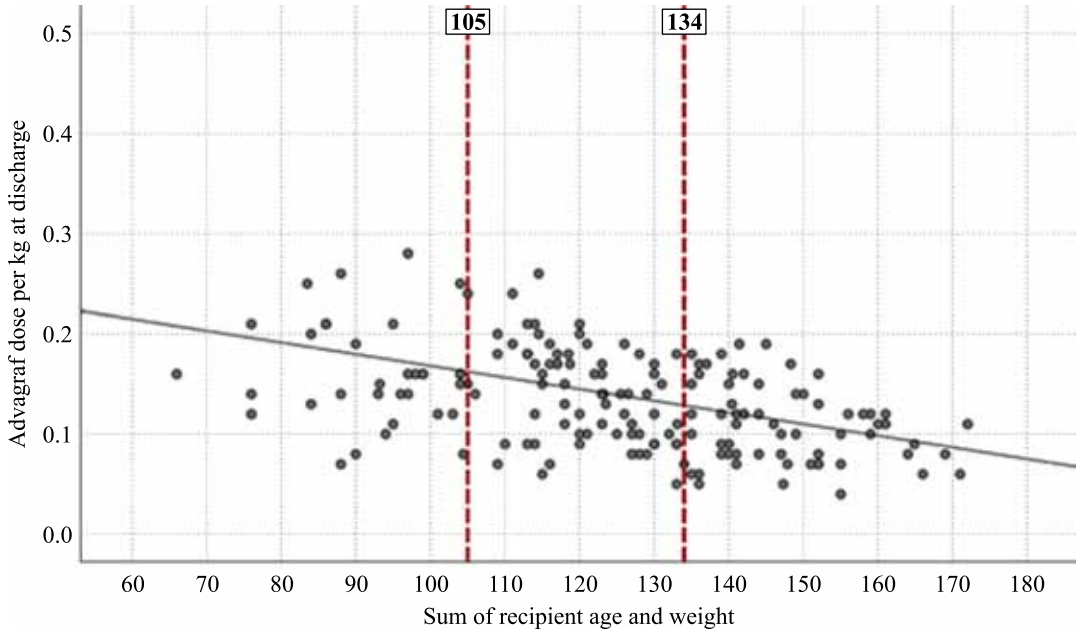

Fig. 1. Dependence of extended-release tacrolimus dose on the sum of recipient age and weight (linear regression)

protocol, and in both subgroups, no patient developed acute rejection in the first month after surgery (p = 1). In group II, there was also a decreased incidence of early infectious complications: 5.4% versus 13.2%, but without reaching the level of statistical significance (p = 0.088). The incidence of delayed renal graft function was 25.4% (58/228) in retrospective group I and 22.7% (17/75) in group II. There were no statistically significant differences in this indicator between the groups (p = 0.629). The groups were also comparable in terms of DGF duration and length of stay at the hospital (p = 0.238 and p = 0.521, respectively).

However, given the presence of statistically significant differences between the groups in terms of donor BMI and static cold preservation time (p = 0.03 and p = 0.015, respectively), we performed pseudorandomization by PSM method for these factors. This resulted in new groups comparable in terms of the above parameters (p = 0.745 and p = 0.612, respectively), with 38 patients in each. DGF incidence in the group using the standard ISx protocol after PSM was 12/38 (31.6%), while in group II it was 4/38 (10.8%). The differences were statistically significant (p = 0.047) and there was a moderate strength relationship between the traits (V = 0.258). The odds of developing DGF with the personalized ISx protocol were 3.9 times lower than in the control group (95% CI: 1.1–13.6). The median duration of DGF in the personalized protocol group was 8 (IQR: 7–11) days, and 15 (IQR: 9–15) days in the control group (p = 0.016). The length of hospital stay in the personalized protocol group was also statistically significantly lower: 13 (IQR: 8–19) versus 19 (IQR: 15–24) bed-days (p = 0.033). The results of the efficacy and safety study of the developed personalized protocol compared with the standard protocol for extended-release Tac before and after pseudorandomization are presented in Table 3.

Fig. 2. Personalized protocol for extended-release tacrolimus based on the sum of recipient age and weight

Table 3

Comparative analysis of the outcomes of standard and personalized dosing protocols for extended-release tacrolimus after kidney transplantation

Indicator	Before PSM			After PSM		
	Group I Standard ISx protocol n = 228	Group II Personalized ISx protocol n = 75	p	Group I Standard ISx protocol n = 38	Group II Personalized ISx protocol n = 38	p
Donor BMI (kg/m^2)	26.0 (IQR: 24.2–30.0)	31.5 (IQR: 27.4–34.0)	**0.03**	28.0 (IQR: 22.5–30.0)	29.5 (IQR: 21.5–31.0)	0.745
Cold preservation time (min)	625 (IQR: 515–740)	710 (IQR: 640–780)	**0.015**	650 (IQR: 620–660)	660 (IQR: 620–670)	0.612
Over-immunosuppression (tacrolimus pre-dose level (C_0) >15 ng/ml)	199 (87.5%)	26 (34.7%)	**<0.001**	34 (89.5%)	15 (39.5%)	**<0.001**
Acute graft rejection in the first month after kidney allotransplantation	0	0	1	0	0	1
Infectious complications in the first month after kidney allotransplantation	29 (12.7%)	4 (5.3%)	0.088	6 (15.8%)	1 (2.6%)	0.108
DGF	58 (25.4%)	17 (22.7%)	0.629	12 (31.6%)	4 (10.5%)	**0.047**
Median duration of DGF (days)	13 (IQR: 8–16)	14 (IQR: 6–16)	0.238	15 (IQR: 9–15)	8 (IQR: 7–11)	**0.016**
Median duration of hospitalization (13 bed days)	16 (IQR: 12–19)	15 (IQR: 10–21)	0.512	19 (IQR: 15–24)	13 (IQR: 8–19)	**0.033**

DISCUSSION

Tacrolimus-associated nephrotoxicity is one of the most important problems of immunosuppressive therapy in kidney transplant recipients. It prompts researchers and clinicians to constantly search for methods to reduce the risk of its development. Acute nephrotoxicity, which develops in the first week after transplantation against the background of increased CNI levels, may be one of the main reasons for DGF. On the other hand, immunological response is maximal during the immediate post-transplant period, which requires higher doses and maintaining higher CNI concentrations than in the long-term period. Therefore, the main challenge in prescribing immunosuppressive therapy during this period is to maintain a balance between adequate prevention of acute rejection and minimization of the risk of side effects.

To solve this problem, many authors propose various strategies to reduce CNI burden in the early post-transplant period. One of them is the administration of low Tac doses (with a target concentration of 3–8 ng/mL) in combination with mTOR inhibitors immediately after transplantation [10–12]. In our opinion, inclusion of these drugs in immunosuppressive regimens in the long-term postoperative period to reduce the effect of CNI-related nephrotoxicity in some cases is certainly justified. However, in the first days after transplantation, the use of mTOR inhibitors may be associated with increased risk of wound infection. Another strategy may be to delay Tac administration, when it is administered on day 4–7 after transplantation. A number of national [13] and foreign [14] studies have found that delayed Tac administration leads to improved long-term survival of kidney transplants, but no statistically significant effect on improvement of initial graft function is demonstrated. At the same time, according to some authors, delayed Tac administration for 4–7 days does not increase the incidence of acute rejection [13–14], while according to other authors, the risk of rejection significantly increases [15]. Thus, the safety and efficacy of this strategy on preventing acute nephrotoxicity in the early postoperative period, in our opinion, is questionable and requires more investigation.

As mentioned above, the first weeks after transplantation are the most critical period, since the recipient's immune response to the allograft is maximally expressed. Excessive minimization of immunosuppression can lead to an unacceptable risk of steroid-resistant rejection and early graft loss. It should be noted that in our study, none of the kidney transplant recipients had acute rejection in the early postoperative period. This can most likely be attributed to the fact that the use of the standard dosing protocol for prolonged-release tacrolimus led to a "balance shift" towards over-immunosuppression in 87.5% of cases, which also worsened the immediate and long-term outcome of KTx. While developing the personalized dosing protocol, we found that a starting Tac dose of 0.2 mg/kg, which was routinely administered to all patients immediately before surgery, was actually needed in less than 25% of patients. Half of the patients required a dose in the range of 0.1–0.2 mg/kg, and 17% required less than 0.1 mg/kg. Our study revealed a statistically significant pattern: the higher the age and weight of the recipient, the lower the Tac dose required ($\rho = -0.706$, $p = 0.0023$). These indicators may be somehow related to the intensity of metabolic processes in the liver, where tacrolimus is metabolized.

A more detailed study of the genetic features of the cytochrome p450 enzyme system could probably help to determine a more accurate starting dose of the drug. Both in the national and world literature, there are works demonstrating the effectiveness of CYP3A5 polymorphism genotyping in transplant candidates for the most accurate selection of Tac dosage after transplantation [16–19]. According to Shuker (2016) and others, CYP3A5-expressing transplant candidates require a dose that is approximately 50% higher than most [20–21] to reach the target concentration. At the same time, despite the promise of determining the CYP3A5 genotype in a patient before KTx for subsequent calculation of the starting Tac dose, this protocol, at present, cannot become the standard for most transplant centers. The medical and cost-effectiveness of this strategy remains to be substantiated and proven by further studies.

Implementation of the developed personalized dosing algorithm for prolonged-release tacrolimus in clinical practice led to a significant decrease in the frequency of over-immunosuppression in the early postoperative period by almost 2.5 times ($p < 0.001$), but episodes of increased Tac concentration (>15 ng/ml) were still recorded in a significant proportion of recipients. Obviously, the recipient's age and weight are not the only factors that can influence the drug dose required to achieve the target concentration, and in 34.7% of cases the administered dose was slightly higher than that actually needed. Nevertheless, we found a significant improvement in early graft function, which was expressed by statistically significant reduction in the frequency and duration of DGF ($p = 0.047$ and $p = 0.016$), as well as the length of hospital stay ($p = 0.033$) in the groups comparable in terms of main characteristics. Decreased CNI burden also resulted in a reduced risk of early infectious complications, but only with a trend toward statistical significance ($p = 0.088$). This is probably due to insufficient number of cases. At the same time, it is important to note that the use of the new protocol did not lead to increased incidence of under-immunosuppression and acute rejection. We also found a significant improvement in early graft function, which was expressed by a statistically significant decrease in the incidence and duration of DGF ($p = 0.047$ and $p = 0.016$), as well as the length of stay at the hospital ($p = 0.033$).

Thus, administration of a starting dose of extended-release Tac according to our protocol based on the patient's individual characteristics – age and body weight – allows both to ensure adequate immunosuppression and minimize the risk of rejection, and to reduce the burden of acute nephrotoxicity and other side effects of calcineurin inhibitors in the early post-transplant period.

CONCLUSIONS

1. The developed personalized dosing protocol for extended-release tacrolimus in patients after KTx allows achieving the recommended target drug concentrations for the early postoperative period with low risk of under-immunosuppression and associated acute graft rejection with significantly lower incidence of over-immunosuppression ($p < 0.001$).
2. Introduction of the personalized dosing protocol in the clinical practice of kidney transplantation allowed to significantly reduce the incidence of DGF from 31.6% to 10.5% ($p = 0.047$) in the groups in terms of the main risk factors of this complication.

The authors declare no conflict of interest.

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The article was submitted to the journal on 17.01.2023