Comparison of Kidney Transplant Function, Lipid Metabolism Disorders, and Glucose and Hemoglobin Concentration in Transplant Patients Treated With Proliferation Signal Inhibitor (Everolimus) or Calcineurin Inhibitor (Tacrolimus)

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ABSTRACT

Introduction. After kidney transplantation (KTx) in patients with diagnosed cancers, calcineurin inhibitor tacrolimus (TAC) is replaced by sirolimus or everolimus (EV).

Objective. The objective of the study was to compare the lipid metabolism parameters, KTx function, and glucose and hemoglobin (Hgb) levels in patients treated with EV to those on TAC.

Material and Methods. The retrospective study included 114 patients: 54 (17 women and 37 men) aged 57.6 years (18-77 years) treated with EV and 60 (18 women and 42 men) aged 49.6 years (20-77 years) treated with TAC as a control group. Their total cholesterol (TC), triglycerides (TG), fasting glucose (FG), serum creatinine (SCr), Hgb, and estimated glomerular filtration rate (eGFR) were assessed. In the patients treated with EV, the above values were evaluated before conversion, as well as 12 and 24 months following the switch and were evaluated once in the group treated with TAC.

Results. In the EV-treated group, the mean preconversion values after 12 and 24 months were as follows: TC 5.06, 6.59, and 5.98 mmol/L; TG 1.90, 2.48, and 2.20 mmol/L; FG 94.95, 97.85, and 104.05 mg/dL; SCr 1.46, 1.44, and 1.56 mg/dL; Hgb 12.46, 12.83, and 13.36 g/dL; and eGFR 50.3, 50.6, and 50.5 mL/min/1.73 m^2. In the patients on TAC, the authors obtained the following values: TC 4.6 mmol/L; TG 1.87 mmol/L; glucose 104.13 mg/dL; SCr 1.51 mg/dL; Hgb 13.96 g/dL; and eGFR 56.6 mL/min/1.73 m^2.

Conclusions. After conversion from TAC to EV, increased values of TC and TG were observed after 1 year, while the increased values of TC, TG, SCr, Hgb, and FG were observed after 2 years.

PATIENTS with chronic kidney disease (CKD), especially during dialysis, show accelerated atherosclerosis, which is manifested by increased morbidity and mortality rates [1]. After successful kidney transplantation (KTx), cardiovascular mortality decreases, but it continues to be very high. The phenomenon is because most of the changes existing in the cardiovascular system are irreversible; additionally, the employed immunosuppressive therapy may negatively affect the metabolism of the body [2]. In patients after KTx, the calcineurin inhibitor (CNI) cyclosporin A (CyA) or tacrolimus (TAC), mycophenolate mofetil (MMF), and glucocorticosteroids (GS) are most often used

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Table 1. Parameters Values (Average, Standard Deviation, and Range) and Statistical Results in Each Group of Studied Population

Studied Parameters	TAC Patients n = 60 Group I	EV Patients n = 54 Group IIA	Group IIB	Group IIC	Statistical Significance *P* Values	
Age (y)	49.6 ± 15.6 (20-77)	57.6 ± 13.2 (18-76)	58.6 ± 13.2 (19-77)	59.6 ± 13.2 (20-78)	I vs IIA: $P = .004$*	
					I vs IIB: $P = .001$*	
					I vs IIC: $P = .0002$*	
TC (mmol/L)	4.6 ± 5.2 (1.8-7.2)	5.06 ± 0.64 (3.4-6.6)	6.59 ± 1.13 (3.0-10.5)	5.98 ± 0.78 (3.7-8.2)	I vs IIA: $P = .003$*	IIA vs IIB: $P < .0001$‡
					I vs IIB: $P < .0001$*	IIA vs IIC: $P < .0001$‡
					I vs IIC: $P < .0001$*	IIB vs IIC: $P = .0002$‡
TG (mmol/L)	1.87 ± 0.7 (0.6-3.8)	1.90 ± 0.58 (0.91-4.1)	2.48 ± 0.74 (1.15-6.3)	2.20 ± 0.53 (0.68-3.97)	I vs IIA: NS	IIA vs IIB: $P < .0001$‡
					I vs IIB: $P < .0001$*	IIA vs IIC: $P = .003$‡
					I vs IIC: $P < .0001$*	IIB vs IIC: $P < .0001$‡
SCr (mg/dL)	1.51 ± 0.62 (0.76-3.34)	1.46 ± 0.47 (0.74-2.81)	1.44 ± 0.52 (0.60-3.24)	1.56 ± 0.60 (0.70-3.68)	I vs IIC: NS	IIA vs IIB: NS
					I vs IIB: NS	IIA vs IIC: $P = .017$‡
					I vs IIA: NS	IIB vs IIC: $P < .0001$‡
eGFR (mL/min/1.73 m^2)	56.6 ± 20.8 (15-68)	50.3 ± 11.2 (19-72)	50.6 ± 14.5 (16-85)	50.5 ± 16.4 (10-88)	I vs IIA: NS	IIA vs IIB: NS
					I vs IIB: NS	IIA vs IIC: NS
					I vs IIC: NS	IIB vs IIC: NS
Hgb (g/dL)	13.96 ± 1.92 (8.2-17.7)	12.46 ± 1.69 (8.8-16)	12.83 ± 1.60 (9.1-16.4)	13.36 ± 1.49 (9.1-16.6)	I vs IIA: $P < .0001$†	IIA vs IIB: NS
					I vs IIB: $P = .0004$†	IIA vs IIC: $P = .0002$‡
					I vs IIC: $P = .049$†	IIB vs IIC: $P = .0003$‡
FG (mg/dL)	104.13 ± 31.3 (63.8-241.1)	94.95 ± 10.4 (78.0-140.0)	97.85 ± 14.3 (74.0-166.1)	104.05 ± 13.5 (74.4-160.4)	I vs IIA: NS	IIA vs IIB: NS
					I vs IIB: NS	IIA vs IIC: $P = .0004$‡
					I vs IIC: $P = .028$*	IIB vs IIC: $P = .0001$‡

Group IIA, before conversion; Group IIB, 1 year after conversion; Group IIC, 2 years after conversion.
Abbreviations: eGFR, estimated glomerular filtration rate; EV, everolimus; FG, fasting glucose; Hgb, hemoglobin; NS, not significant; SCr, serum creatinine; TAC, tacrolimus; TC, total cholesterol; TG, triglcerides.
*Mann-Whitney *U* test.
†Student *t* test.
‡Wilcoxon test.

in the immunosuppression regimen. In patients with cancer, CNI is replaced with a proliferation signal inhibitor (PSI), sirolimus (SIR) or everolimus (EV) [3]. In addition to the beneficial antitumor activity, PSIs show side effects, including disturbed lipid metabolism, which may increase the risk of death from cardiovascular causes [4].

The objective of the study was to compare the behavior of lipid metabolism parameters, transplanted kidney function indicators, and glucose and hemoglobin (Hgb) levels in patients treated with TAC and EV after KTx.

MATERIALS AND METHODS

The study was performed in 114 patients after KTx. One group consisted of 54 patients (17 women and 37 male) converted from the CNI to PSI treatment (EV) within the last 5 years who demonstrated maintained graft function for at least 2 years. The reason for conversion was the diagnosis of cancer. The control group included 60 randomly selected patients (18 women and 42 men) treated with CNI (TAC). Apart from PSI or CNI, the immunosuppressive regimen consisted of a combination of mycophenolate mofetil/sodium mycophenolate and steroids. The PSI group was assessed during the ambulatory follow-up visits 2 years after immunosuppressive conversion and the CNI group was assessed in the course of random visits occurring in the same period. Total cholesterol (TC), triglycerides (TG), fasting glucose (FG), serum creatinine (SCr), estimated glomerular filtration rate (eGFR), and Hgb level were compared between the groups. To better explore the changes of the parameters, the analysis was extended retrospectively to include the preconversion, 12 and 24 months postconversion results in the EV group. All the statistical analyses were performed using commercially available software Statistica 13.3 (TIBCO, Palo Alto, Calif, United States). The Mann-Whitney U test, Student t test, and Wilcoxon tests were employed in the statistical analysis. The results were considered to be significant at $P < .05$.

The study was performed according to the Declaration of Helsinki, and the university's Ethical Committee approved its conduction (KBET/100/B/2006 dated June 29, 2006).

RESULTS

The specific results are summarized in Table 1. The patients before the conversion to EV (group IIA) were significantly older ($P = .004$) and characterized by higher mean values of TC ($P = .003$) and lower values of Hgb ($P < .0001$) as compared to the patients using TAC (group I). The mean values of the remaining parameters studied were similar. In the group of patients converted to EV after 1 year, the authors observed a statistically significant increase of TC ($P < .0001$), TG ($P < .0001$) and after 2 years and an increase of TC ($P < .0001$), TG ($P = .003$), SCr ($P = .017$), Hgb ($P = .0002$), and FG ($P = .0004$) as compared with the values obtained before the conversion. The eGFR values were similar in the 2 studied groups and were not significantly changed after the conversion to EV during 2-year follow-up. The mean values of TC and TG determined 1 and 2 years after the conversion to EV were significantly higher when compared with group I ($P < .0001$), whereas the Hgb values were lower after 1 year ($P = .0004$) and 2 years ($P = .049$). Two years after the conversion, the authors observed a significant increase of FG as compared with the preconversion ($P = .0004$) and 1 year after conversion ($P = .0001$) values.

DISCUSSION

Patients with CKD show an increased risk of developing atherosclerosis and cardiovascular complications depending on the stage of renal conditions. KTx frees the patient from dialysis but does not eliminate existing exposures [2], and the employed immunosuppression therapy may intensify lipid metabolism disorders and contribute to the increase of infectious complications of viral, bacterial, and fungal etiology, as well as increase the risk of cancer, especially nonmelanoma skin cancers [5,6]. The currently recommended first-line drug from the CNI group is TAC, which is usually used with MMF and steroids [7]. It has been shown that the conversion from CNI to PSI (mammalian target of rapamycin [mTOR] inhibitors) reduces the risk of developing tumors after transplantation [8] and, in some cases, such as Kaposi sarcoma, the conversion may lead to their regression [9]. SIR was the first immunosuppressive drug from the group of PSI introduced in the treatment of patients in 2000, and 10 years later treatment with EV commenced. As shown by the phase I studies, the addition of increasing doses of SIR to CyA and prednisone enhances the immunosuppressive effect without increasing the nephrotoxicity. The side effects of the drug, such as reversible reduction of platelet and leukocyte counts, and a significant increase in cholesterol levels as compared to placebo have also been observed [10]. Further studies have shown that the use of PSI allows for the CNI dose reduction or their complete withdrawal [11,12]. It has been observed that a decrease in exposure to CyA or TAC after the addition of PSI is manifested by a good immunosuppressive effect and less susceptibility to BKV and cytomegalovirus infections, as well as by improved kidney transplant function [13-15]. SIR and EV, kinase inhibitors, block mTOR kinase complex I and mTOR, which plays a role in regulating lymphocyte proliferation. By affecting the mTOR pathways, they play a key role in regulation, proliferation, growth, differentiation, and cell migration [15].

Comparing the effect of SIR and EV on hematological parameters and lipid metabolism [16] in heart recipients with kidney failure, it has been shown that EV is a safer drug than SIR.

Despite the adverse effect on lipid metabolism, PSIs are recommended as prophylactic agents for the development of skin cancers in patients who have had a kidney transplant; they also represent the best therapeutic option for people diagnosed with cancer [17,18].

Liu et al [19], assessing the efficacy and safety of EV in chronic immunosuppression in KTx patients, performed a meta-analysis of 11 randomized clinical trials involving 1633 patients; the investigators showed that patients converted to

EV demonstrated a better kidney function after 1 year with eGFR higher by 5.63 mL/min/1.73 m^2 than patients remaining on CNI ($P = .005$). In longer follow-up (>1 year), the kidney function was stable. There was no significant difference in graft loss, mortality, adverse events, and serious adverse events prevalence. However, the risk of acute rejection and termination of the study because of AE was 1.82 and 2.63 times higher than in patients remaining on CNI 1 year after transplantation ($P = .02$ and $P = .03$). Moreover, patients converted to EV showed a significantly higher risk of anemia, hyperlipidemia, hypercholesterolemia, hypokalemia, proteinuria, stomatitis, mouth ulceration, and acne.

In the present study, the patients received EV for vital reasons. The conversion to this preparation was made after cancer diagnosis. Considering the pros and cons, it should be emphasized that the action of EV increases the risk of lipid disorders in the absence of a significant impact on the occurrence or progression of diabetes, but, nevertheless, an improvement in safety is noted (ie, the risk of cancer recurrence is reduced) [20].

Ying et al [21] assessed the 10-year prognosis of patients after KTx based on 5 randomized clinical trials of patients with immunosuppression receiving EV. The investigators assessed the 10-year risk of graft loss, mortality, and deterioration of the graft function in 349 patients, 243 of whom received EV and 107 of whom were on standard immunosuppressive treatment. There was no significant difference in the risk of transplant loss, death, or eGFR decline.

Kahan et al [22] found a low incidence of tumors in a group of 1008 patients after KTx treated in a single center with SIR + CyA + prednisone. During 62.3 ± 26.1 months of follow-up, the investigators found 36 cancers in 35 patients (3.6%).

On the other hand, based on the meta-analysis data, we must remember that in addition to the reduction in the risk of malignancy and nonmelanoma skin cancers as compared to the controls, PSI can increase the risk of death, especially associated with cardiovascular causes [23].

In the analyzed group of patients treated for cancer after KTx, during treatment with EV, an increase in cholesterol and TG was observed in comparison to the group of patients treated with TAC, despite continuing hypolipemic treatment. It was shown that the lipid-lowering drug, rosuvastatin, shows the most beneficial effect in stable transplant recipients receiving EV [24].

CONCLUSION

After conversion from TAC to EV, the present authors observed increased values of TC and TG after 1 year, while after 2 years an increase of TC, TG, SCr, Hgb, and FG was shown as compared with to the values before conversion. A significant increase of TC and TG in both studied periods, despite the use of lipid-lowering drugs, imposes the need for regular monitoring of lipid parameters and intensification of dietary and pharmacological treatment.

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