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Research Article

Effect of cyclosporin and tacrolimus on kidney function in liver recipients

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Abstract

Introduction. Chronic renal failure is a significant issue regarding treatment of patients after liver transplantation. One of the factors determining the impaired renal function after liver transplantation is a long-term immunosuppressive therapy based on calcineurin inhibitors. The objective of the study was to evaluate the dynamics of renal function, depending on the use of various calcineurin inhibitors in the long-term postoperative period in liver recipients in real clinical practice.

Materials and methods. A retrospective analysis of the renal function in patients operated in the State Public Health Budget Institution "Scientific Research Institute – S.V. Ochapovsky Regional Clinic Hospital № 1", Krasnodar Region, was carried out. This article describes dynamics of creatinine level and glomerular filtration rate (GFR) in patients before liver transplant, as well as 6 months, 1, 2 and 3 years after surgery. GFR was calculated using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration). Statistical processing of the results was carried out using the Statistica 10 software package.

Results and discussion. Before transplantation, the level of creatinine in the blood plasma was 82.9±19.8 mmol/l, 6 months later a20.4% increase in creatinine was registered (p=0.004), 12, 24 and 36 months later – it increased by 24.8% (p=0.00001), 24.4% (p=0.0004), and 26.0% (p=0.0005), respectively. Both cyclosporine and tacrolimus caused an increase in the level of creatinine. Baseline GFR was 83.4±25.9, the reduction in GFR occurred in comparison with the baseline by 14.2% (p=0.0005), 18.8% (p=0.00001), 20.2% (p=0.00003), 22.6% % (p=0.00006) 6, 12, 24 and 36 months later, respectively. The degree of the decrease in GFR against the background of tacrolimus therapy did not differ significantly from that in case of cyclosporine. Verification of chronic kidney disease and the administration of statins were recorded in isolated cases.

Conclusions. In liver recipients, the level of creatinine rises and GFR decreases. Reduction of kidney function occurs against the background of both inhibitors of calcineurin, in connection with which it is necessary to increase the doctors' alertness for early detection of a decrease in glomerular filtration rate with further verification of chronic kidney disease.

Keywords

liver transplant, creatinine, glomerular filtration rate, chronic kidney diseases, cyclosporine, tacrolimus, statins.

Introduction

Chronic renal failure is a significant risk factor for the deterioration in the prognosis of patients after liver transplantation. With the development of chronic kidney disease (CKD), the risk of death of the liver recipient increases 4.48 times within a year (Gautier et al. 2013). It is known that renal insufficiency can be present before liver transplantation; it can also develop or worsen during transplantation or occur in the early and late postoperative period. One of the reasons determining the impaired renal function after liver transplantation is a long-term immunosuppressive therapy based on calcineurin inhibitors. Calcineurin inhibitors are considered responsible for more than 70% of CKD cases after liver transplantation (Gonwa et al. 2001). In transplantology, this clinic-pharmacological group is represented by tacrolimus and cyclosporine. An analysis of foreign literature showed conflicting data on the severity of nephrotoxicity of these drugs in liver recipients (LaMattina et al. 2011, Naesens et al. 2009, Reich et al. 2005, DuBay et al. 2008).

The objective of the study was to evaluate the dynamics of renal function depending on the use of various calcineurin inhibitors in the long-term postoperative period in liver recipients, as well as to analyze the compliance of the diagnosis and treatment of CKD with the reference documents in real clinical practice.

Materials and methods

A retrospective analysis of the patient data (n = 89), who had been operated on in the State Public Health Budget Institution "Scientific Research Institute – S.V. Ochapovsky Regional Clinic Hospital № 1", Krasnodar Region, Ministry of Public Healthcare was carried out within the framework of the register study of liver recipients "Complex Assessment of Co-Morbid Pathology after Liver Transplantation (KOMPAS-RAN)". This article analyzes the data of the patients before liver transplantation, as well as 6 months, 1, 2 and 3 years after surgery. The results of the laboratory tests was copied out of the primary medical documentation (outpatient medical records [Form No. 025/y-87], in-patient medical record [medical history, form No. 003/y-80]). The main one is glomerular filtration rate (GFR). The level of creatinine and GFR were analyzed as the main parameter characterizing the functional state of the kidneys in accordance with the current "Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease" (KDIGO 2012). The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula was used as more prognostically valid than the Cockcroft-Gold and MDRD formulas (KDIGO 2012).

The statistical processing of the results was carried out using the Statistica 10 software package. The data are presented as M±σ. The results of the study were processed by nonparametric methods of statistical analysis using the Mann-Whitney test for independent samples and the Wilcoxon test for dependent groups. The differences were considered significant at a significance level of $p<0.05$.

Results

In the local register of liver recipients "Comprehensive Evaluation of Co-Morbid Pathology after Liver Transplantation (KOMPAS-RAN)", 130 patients were included who had undergone orthotopic liver transplantation from 2010 to 2017 in the Research Institute Krai Clinical Hospital No. 1. Eighty-nine patients were included in the group for the analysis of the dynamics of creatinine and GFR at stages of 6, 12, 24 and 36 months, aged 49.6±9.8 years. The gender composition: males – 52.8%, females – 47.2%.

In most cases, terminal hepatic failure, which caused the patient's need for a donor organ, resulted from virus aggression (56.2%), primary biliary cirrhosis (11.2%), autoimmune and toxic hepatitis (6.7%), and in 11.2% of cases, the etiology of the disease that determines severe hepatic failure is not specified. Before transplantation, the level of creatinine in the blood plasma was 82.9±19.8 mmol/l, 6 months afterwasrds an increase in creatinine was registered by 20.4% (p=0.004), 12, 24 and 36 months after – by 24.8% (p=0.00001), 24.4% (p=0.0004), and 26.0% (p=0.0005), respectively.

In the analysis, dividing the recipients' data into the groups of those receiving tacrolimus (group 1) and cyclosporine (group 2) showed that both drugs caused a significant increase in plasma creatinine level. Table 1 shows the results of the analysis of creatinine depending on the basic immunosuppressive therapy with calcineurin inhibitors.

Initially, there were no significant differences in the level of creatinine between the groups of the patients who had been put on cyclosporine or tacrolimus (Table 1). Six moths later, against the background of cyclosporine, creatinine increased by 16.8% (p=0.01), and then by 38.4% (p=0.0001), 35.5% (p=0.001) and 51.9% (p=0.001) in a year, 24 months and 36 months, respectively. In the tacrolimus group, creatinine increased 6 months, 1 year, 2 and 3 years later by 9.2% (p=0.02), 30.7% (p=0.17), 17.8% (p=0.02), 23.2% (p=0.009), respectively. The significance of the difference between the cyclosporine group and the tacrolimus group by the creatinine level was observed at all periods, except for 12 months.

In our retrospective study, an assessment of how adequate GFR calculation by physicians in the actual clinical practice is to the recommended formulas was not possible in view of the fact that practically no primary

Table 1. Dynamics of creatinine against the background of calcineurin inhibitors

Parameter	Period	Tacrolimus		Cyclosporine		p**
		ml/min	p*	ml/min	p*	
Creatinine	Before liver transplantation	78.8±13.1		84.9±21.7		0.28
	6 months	86.1±43.8	0.73	99.2±22.8	0.01	0.03
	12 months	103±25.8	0.01	117.5±27.3	0.0002	0.17
	24 months	92.8±54.3	0.19	115±30.8	0.001	0.03
	36 months	97±24.7	0.02	129±40.1	0.001	0.01

Note: *p – in comparison with the initial value, **p – comparison between cyclosporine and tacrolimus

medical documentation had any records about the glomerular filtration rate. For the present study, GFR was calculated based on the parameters obtained when copying the data during the compilation of the retrospective part of the KOMPAS-RAN register. The analysis was carried out for five time periods – before transplantation,and 6, 12, 24 and 36 months after liver transplantation. Initially, GFR was 83.4±25.9, 6 months after the operation –71.6±21.5, 12 months later – 67.7±21.6, 24 months and 36 months later – 61.5±20.5, and 64.6±22.6, respectively. Thus, GFR decreased in comparison with the baseline by 14.2% (p=0.0005), 18.8% (p=0.00001), 20.2% (p=0.00003), 22.6% % (p=0.00006) 6, 12, 24 and 36 months later, respectively. In this study, it is impossible to provide the incidence rate of CKD in liver recipients, because according to the up-to-date recommendations, the CKD criteria are a steady decrease in GFR for 3 or more months (GFR<60 ml/min/1.73 m^2 (GFR categories C3a- C5)), as well as a number of other markers of kidney damage, which cannot be systemized in a retrospective study.

The estimation of GFR was carried out in dynamics in the subgroups of patients taking various inhibitors of calcineurin. Initially, GFR in these subgroups did not differ significantly (83.4±22.2 against tacrolimus, 84.8±22.5 against cyclosporine (p<0.91). Figure 1 demonstrates the unidirectionality of the changes in the indicator regardless of the drug taken; the percentages of GFR decrease for the periods in the dynamics and the trend line of the absolute values of GFR against tacrolimus and cyclosporine are presented.

The intensity of the decrease in GFR on tacrolimus did not differ significantly from cyclosporine (Table 2).

At the same time, tacrolimus, unlike cyclosporine, did not reduce kidney function 6 months after the operation in comparison with the initial value. In the patients taking cyclosporine, decreased GFR is proved for all time intervals of the study.

Table 2. Dynamics of GFR against the background of calcineurin inhibitors

Parameter	Period	Tacrolimus		Cyclosporine		P**
		ml/min	p*	ml/min	P*	
Glomerular filtration rate	Before liver transplant	83.4±32.2		84.8±22.5		0.91
	6 months	76.9±25.4	0.34	70.8±15.7	0.04	0.24
	12 months	66.7±23.8	0.02	65.2±20.3	0.00001	0.89
	24 months	68.9±24.2	0.05	64±18.8	0.0004	0.33
	36 months	70.1±23.8	0.03	59.7±22.5	0.0006	0.15

Note: *p – in comparison with the initial value, **p – comparison between tacrolimus and cyclosporine.

Discussion

In the literature, there are conflicting data on the degree of iatrogenic nephrotoxic effect of calcineurin inhibitors. For example, in the study by John C. LaMattina and his co-authors (LaMattina et al. 2011), calcineurin inhibitors were studied in the first post-transplantation year in 724 patients, which was 99% of all the cases sequentially included in the analysis. There were no significant differences in the rate of progression of the CKD stage in patients treated with cyclosporine in comparison with those treated with tacrolimus. Pharmacokinetic analysis showed that the average level of drug concentration in the bloodstream during the first year, as well as the discontinuation of cyclosporine or tacrolimus, did not predict the progression of the CKD stage. It can be assumed that the main reason for the continuing debate about the degree of nephrotoxicity of various calcineurin inhibitors is the difficulty in comparing the data obtained in different laboratories. First, until recently, kidney function was assessed by the level of creatinine, which was reflected in the works and conclusions of the years 1980-2013. Secondly, the authors proposed for analysis any one of the periods after transplantation from the first months to several years, which, too, could undoubtedly affect the result. The authors tried to take into account these nuances and make more frequent analytical sections for three years af-

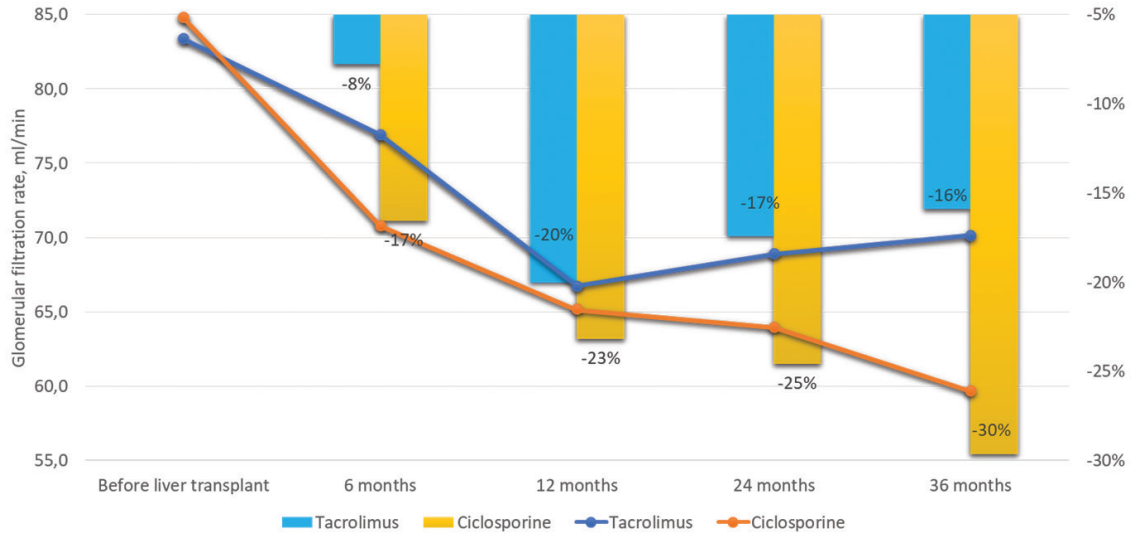

Figure 1. Dynamics of glomerular filtration rate when taking cyclosporine and tacrolimus

ter the operation, with the data being copied step by step at intervals of 6, 12, 24 and 36 months. In addition, assessing the function of the kidneys, the current criteria for assessing the function of the kidneys, formulated by the experts of the Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease (KDIGO 2012). According to the modern concepts, the main parameter characterizing the functional state of the kidneys is the glomerular filtration rate, and not the level of creatinine. It is the evaluation of GFR that is of considerable significance, because in addition to the objective indicator of the functional capacity of the kidneys, it is also a predictor of various pathological conditions, including cardiovascular complications (Rabelink 2004, Bibbins-Domingo et al. 2006, Sarnak 2000, Kobalava 2007, Mukhin, Moiseev 2003, Clinical recommendations 2014, Smirnov et al. 2005). At the same time, in the world for the last 15-20 years, several different formulas have been used to calculate GFR, which is the third weighty reason why it is difficul to compare the results and conclusions from different laboratories. Since 2012 to the present, the formula for calculating GFR has been generally accepted due to its high prognostic role, not only the level of creatinine, but also a number of other indicators. The obtained results demonstrated a difference in the manifestation of nephrotoxicity of tacrolimus and cyclosporine in three post-transplantation periods out of four, if only creatinine is used for the analysis of renal function. At the same time, evaluation of kidney function by means of GFR did not reveal any significant differences in the nephrotoxic effect of different calcineurin inhibitors among themselves at any period. However, the tendency to better tolerability of tacrolimus is present at a 6-month interval, where a decline in GFR did not differ significantly from the baseline. In addition, absolute values and degrees of negative growth also indirectly testify in favour of tacrolimus, as a less nephrotoxic drug. Final conclusions should be made after prospective well-planned studies. Currently, the promise of cyclosporine replacement with tacrolimus is possible with manifestations of nephrotoxicity; however, the protocols for minimizing the doses of both calcineurin inhibitors are more intensively studied in an attempt to stabilize and even improve kidney function and the outcome in recipients (Farkas et al. 2009, Moreno et al. 2003, Cantarovich et al. 2003, Creput et al. 2007, Koch et al. 2004, Reich et al. 2005, Pageaux et al. 2006, Pillebout et al. 2005, Siddharth 2012). It is proposed to replace calcineurin inhibitors with less nephrotoxic drugsб such as azathioprine, mycophenolic acid and inhibitors of the proliferative signal (Sirolimus and Everolimus), or a decrease in the dose of calcineurin inhibitors against the background of the inclusion of different pharmacological subgroups into the immunosuppressant regimen. The transplant center solves the issues of reducing the dose of calcineurin inhibitors, combining low doses of calcineurin with mycophenolate mofetil with or without concomitant glucocorticosteroids (GCS), which is safer for the kidneys state. The complete withdrawal of calcineurin inhibitors and the use of mycophenolate mofetil and GCS are associated with a significant risk of graft dysfunction. Transition from Sirolimus immunosuppression has a beneficial effect on kidney function if performed 1-2 years before the onset of proteinuria, otherwise the kidney function in patients with liver transplant will not improve. On the other hand, the results were obtained that indicated the development of nephrotoxicity and a number of other side effects when taking immunosuppressants not belonging to the group of calcineurin inhibitors (Simone et al. 2009, Campbell et al. 2007, Castroagudin et al. 2009, Nair et al. 2003, Shenoy et al. 2007, DuBay et al. 2008). A greater rejection rate is recorded with the exclusion or minimization of calcineurin inhibitors (Burroughs et al. 2009, De Simone et al. 2009, Campbell et al. 2007, Jensen et al. 2008, Castroagudin et al. 2009, Fairbanks, Thuluvath 2004, Bahirwani, Reddy 2009, Shenoy et al. 2007, DuBay et al. 2008).

Consequently, cyclosporine and tacrolimus remain the basic drugs for the prevention of rejection in liver recipients, which makes it urgent to study further in depth the risk factors and predictors of the nephrotoxic iatrogenic effect and the possibilities for its prevention. From the practical point of view, the fact of the deterioration of kidney function in comparison with the pre-transplant period, proved in the present study within the local register of KOMPAS-RAN and practically in all transplant centers, engaged in the systematization of data on recipients in the long-term postoperative period, is important and irrefutable. In the recommendations and instructions on calcineurin inhibitors , the nephrotoxicity of both representatives of the class is mentioned (Siddharth et al. 2012, State register of drug products). The experts formulated the principles of long-term management of kidney function after liver transplantation. In particular, a regular monitoring of serum creatinine and an assessment of the calculated glomerular filtration rate is postulated, at least every 6 months, in combination with successive measurements of proteinuria and hematuria, and in patients without proteinuria, it is necessary to measure microalbuminuria. An attempt may be made to minimize doses of calcineurin inhibitors early (Naesens et al. 2009, Farkas et al. 2009, Siddharth et al. 2012). Collectively with transplantologists, a decision should be made about the possibility of replacing calcineurin inhibitors with less nephrotoxic drugs to prevent donor organ rejection processes. Patients who have renal dysfunction should be followed up by a nephrologist, since a significant reduction in GFR requires the patient to be included in the kidney transplant waiting list, which is a method of selecting renal replacement therapy, improving the long-term survival of patients by 44-60% compared with programmed hemodialysis (Gautier 2013). Doctors responsible for liver recipients should understand the vital importance of timely detection of impaired renal function and timely use non-drug and medicinal options to slow the progression of chronic kidney disease and to improve the quality and life expectancy of liver recipients.

Conclusions

1. The creatinine level was significantly higher after12- and 36-month follow-up in patients taking tacrolimus, compared with the baseline, whereas in the presence of cyclosporine, an increase in creatinine was recorded in all time periods of the study.
2. Tacrolimus and cyclosporine decreased the glomerular filtration rate of the kidneys 12, 24 and 36 months later, compared to the baseline value before liver transplantation. Unlike, tacrolimus, 6 months after the operation, a decrease in GFR was observed in patients taking cyclosporine.
3. The significance of differences in creatinine levels between the groups of patients taking cyclosporine and tacrolimus was recorded 6, 24 and 36 months later, while there were no significant differences in the evaluation of kidney function by GFR.
4. Reduction of kidney function occurs against the background of both inhibitors of calcineurin, in connection with which it is necessary to increase the doctors' alertness for early detection of a decrease in glomerular filtration rate with further verification of chronic kidney disease.

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