INFLUENCE OF SOFOSBUVIR BASED THERAPY OF CHRONIC HEPATITIC C ON BLOOD CONCENTRATION OF CALCINEURIN INHIBITORS IN KIDNEY TRANSPLANT PATIENTS

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Background

Interferon-free regimens are now considered as a treatment of choice in patients with kidney transplant recipients (KTR) infected with hepatitis C virus (HCV). Currently recommended therapy with sofosbuvir (SOF) based regiment cures almost 100% patients, however there is no real-life data exploring the influence of SOF-based therapy on blood concentration of tacrolimus (Tc) or cyclosporine A (CyA). The use of new direct acting antivirals (DAAs) may be associated with potential drug interactions leading to increased or decreased plasma concentrations of DAA, but also affect the concentration of concomitant medications (according to the characteristics of the respective medicinal products). It may lead to modify dosage or even stop the use of certain medications (eg. amiodarone or carbamazepine).

The aim of the study was to analyze the potential changes of Tc or CyA blood trough level (Tc0 and CyA0 respectively) during therapy based on SOF in KTR with chronic hepatitis C.

Material and methods

In 35 kidney recipients (clinical characteristics of the patients is presented in the Table 1.) were qualified to antiviral therapy. GT1- and GT4- infected KTR were treated 12 weeks (first eight patients for 24 weeks) with 400 mg of sofosbuvir (SOF) and 90 mg of ledipasvir (LDV), with initial dose of ribavirin (RBV) 0-800 mg depending on the starting blood hemoglobin level. Patients infected with GT2 and GT3 were treated for 24 weeks with 400mg SOF with initial dose of RBV 200-800mg.

Table 1. Clinical characteristics of the patients	N=35
Sex	20M/15K
Age	49,6±6,4
Mean time after transplantation	10,4±7.3 lat
HCV genotype	
1b	26 (79%)
2a	2 (6%)
3	3 (9%)
4	2 (6%)
Viremia	$2,81x10^6$ IU/ml ± 4351,54
Fibrosis	
F0/FI/FII	28 (3/23/2) (71%)
FIII/FIV	7 (5/2) (29%)
ALT	46,51±85,56 U/l
AST	38,41±48,08 U/l
GGT	48,68±66,47 U/l
Creatinine	143,01±27,42 µmol/dl
eGFR	56.2±26,2 ml/min

Before the administration of first doses of antiviral drugs, and after 4, 8 and 12 weeks of therapy Tc0 (in 15 patients) or CyA0 (in 20 patients) was determined. Daily calcineurin inhibitors (CNIs) dosage was adjusted according to the current blood concentration of CyA or Tc.

Results

In KTR a significant decrease ($p<0.001$) of initial Tc blood trough levels (-41,3±15,4%) and initial blood trough levels of CyA (-51.1±14.8%) was found during SOF-based therapy. The mean Tc0 decreased from 7.61±1.72ng/ml at start to 4.56±1.91ng/ml during treatment, mean CyA0 decreased from 111.08±35.17ng/ml at start to 50.75±14.11ng/ml during therapy. The difference of means was -3.05±1.07ng/ml (95%CI: from -3.75 to -2.37) in Tc group and -60.33±31.16ng/ml (95%CI: from -80.1to -40.5) in CyA group. In Figures 1-4, the mean and individual values of Tc0 and CyA0 before and during therapy are presented.

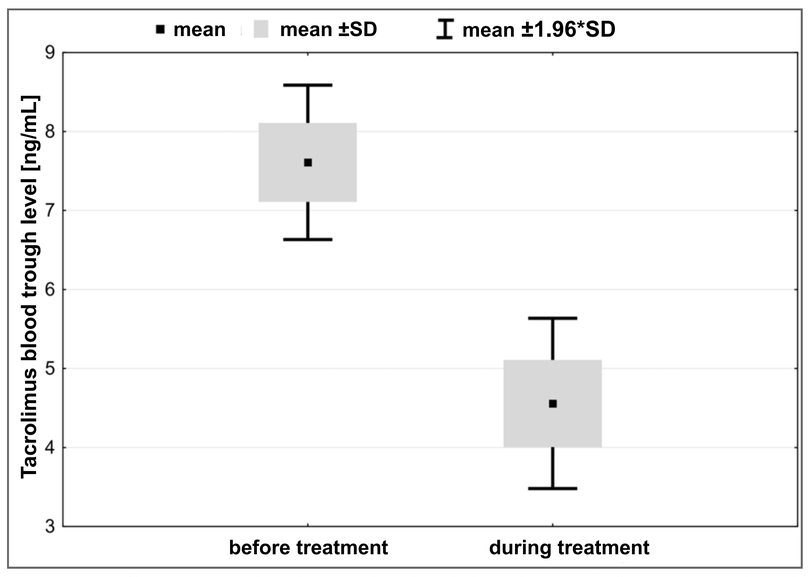

Figure 1. Changes in the lowest levels of tacrolimus (Tc0) during antiviral therapy (mean ± SD).

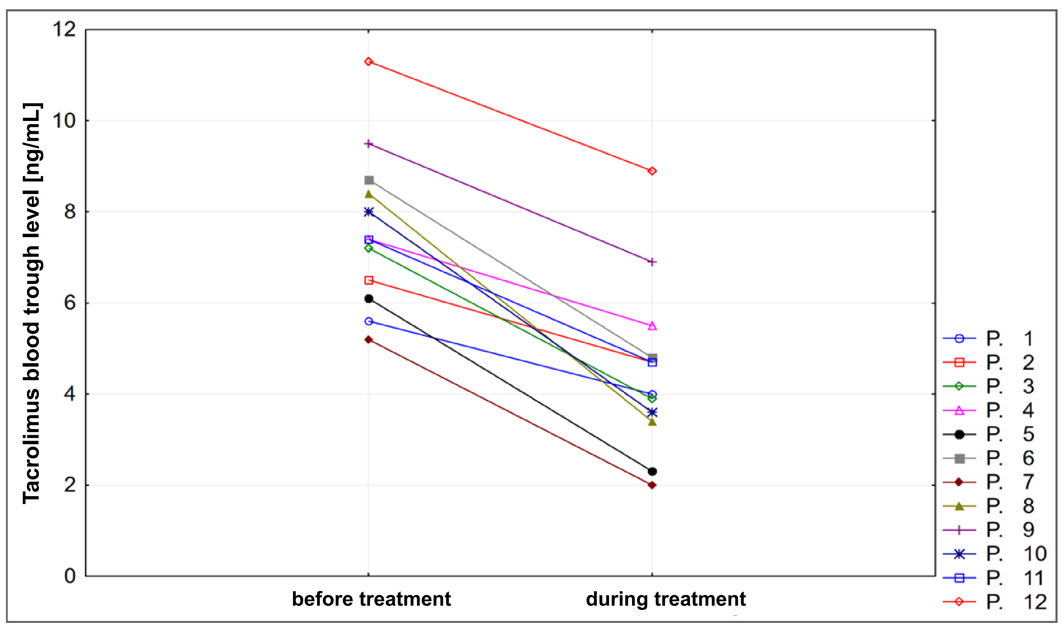

Figure 2. Individual values of lowest tacrolimus (Tc0) before and during antiviral therapy.

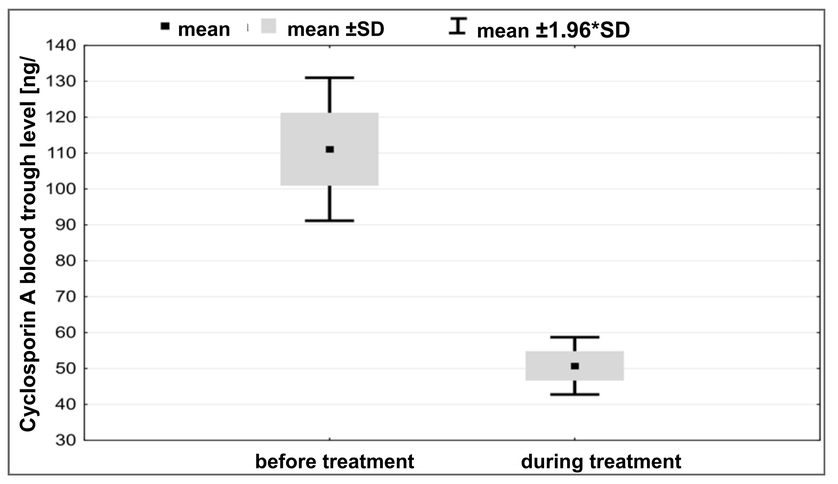

Figure 3. Changes in the lowest levels of cyclosporine (CyA0) during antiviral therapy (mean ± SD).

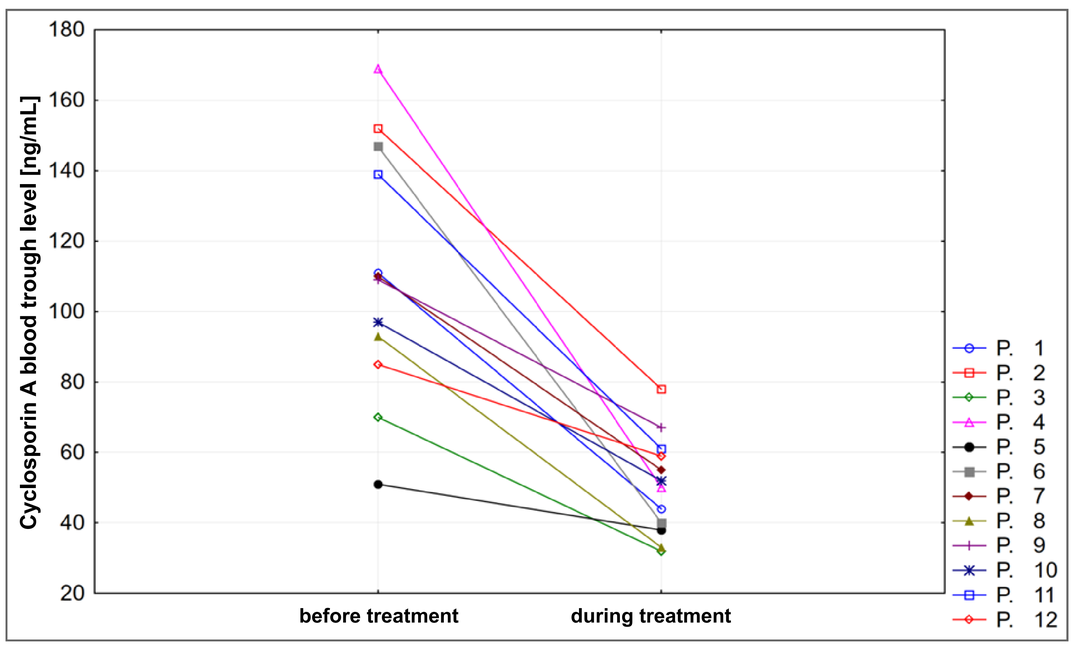

Figure 4. Individual values of lowest cyclosporine (CyA0) before and during antiviral therapy.

In majority of patients, a significant decrease of CNIs blood levels was found after the first month of therapy, in Tc group – 75% (9/12) and CyA group – 58% (7/12).

Conclusions

1. **In majority of KTR, sofosbuvir-based therapy leads to the significant decrease of CyA and Tc blood trough concentration.**
2. **In order to maintain an appropriate blood concentration of CNIs in these patients considerable modification of CyA and Tc dosage is mandatory.**
3. **Close monitoring of CNIs treatment in KTR is especially important during the first month of SOF-based therapy.**

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