



## Conversion from calcineurin inhibitors to sirolimus of recipients with chronic kidney graft disease grade III for a period 2003–2011

Konverzija sa kalcineurinskih inhibitora na sirolimus kod primalaca sa hroničnom insuficijencijom bubrežnog grafta trećeg stepena u periodu 2003–2011.

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### Abstract

**Background/Aim.** Tremendous breakthrough in solid organ transplantation was made with the introduction of calcineurin inhibitors (CNI). At the same time, they are potentially nephrotoxic drugs with influence on onset and progression of renal graft failure. The aim of this study was to evaluate the outcome of a conversion from CNI-based immunosuppressive protocol to sirolimus (SRL) in recipients with graft in chronic kidney disease (CKD) grade III and proteinuria below 500 mg/day. **Methods.** In the period 2003–2011 24 patients (6 female and 18 male), mean age  $41 \pm 12.2$  years, on triple immunosuppressive therapy: steroids, antiproliferative drug [mycophenolate mofetil (MMF) or azathiopirine (AZA)] and CNI were switched from CNI to SRL and follow-up for  $76 \pm 13$  months. Nine patients (the group I) had early posttransplant conversion after  $4 \pm 3$  months and 15 patients (the group II) late conversion after  $46 \pm 29$  months. During the regular outpatient controls we followed graft function through the serum creatinine and glomerular filtration rate (GFR), proteinuria, lipidemia and side effects. **Results.** Thirty days after conversion, in all the patients GFR, proteinuria and lipidemia were insignificantly increased. In the first two post-conversion months all the patients had at least one urinary or respiratory infection, and 10 patients reactivated cytomegalovirus (CMV) infection or disease, and they were successfully treated with standard therapy. After  $21 \pm 11$  months 15 patients from both groups discontinued SRL therapy due to reconversion to CNI (10 patients) and double immunosuppressive therapy (3 patients), return to hemodialysis (1 patient) and death (1 patient). Nine patients were still on SRL therapy. By the end

of the follow-up they significantly improved GFR (from  $53.2 \pm 12.7$  to  $69 \pm 15$  mL/min), while the increase in proteinuria (from  $265 \pm 239$  to  $530.6 \pm 416.7$  mg/day) and lipidemia (cholesterol from  $4.71 \pm 0.98$  to  $5.61 \pm 1.6$  mmol/L and triglycerides from  $2.04 \pm 1.18$  to  $2.1 \pm 0.72$  mmol/L) were not significant. They were stable during the whole follow-up period. Ten patients were reconverted from SRL to CNI due to the abrupt increase of proteinuria (from  $298 \pm 232$  to  $1639 \pm 1641$  mg/day in 7 patients), rapid growth of multiple ovarian cysts (2 patients) and operative treatment of persisted hematoma (1 patient). Thirty days after reconversion they were stable with an insignificant decrease in GFR (from  $56.10 \pm 28.09$  to  $47 \pm 21$  mL/min) and significantly improved proteinuria (from  $1639 \pm 1641$  to  $529 \pm 688$  mg/day). By the end of the follow-up these patients showed nonsignificant increase in the serum creatinine (from  $172 \pm 88$  to  $202 \pm 91$  mmol/L), decrease in GFR (from  $56.10 \pm 28.09$  to  $47 \pm 21$  mL/day) and increased proteinuria (from  $528.9 \pm 688$  to  $850 \pm 1083$  mg/min). **Conclusion.** In this small descriptive study, conversion from CNI to SRL was followed by an increased incidence of infections and consecutive 25–50% dose reduction in the second antiproliferative agent (AZA, MMF), with a possible influence on the development of glomerulopathy in some patients, which was the major reason for discontinuation of SRL therapy in the 7 (29%) patients. Nine (37.5%) of the patients experienced the greatest benefit of CNI to SRL conversion without serious post-conversion complications.

**Key words:**  
kidney transplantation; graft survival; kidney failure, chronic; calcineurin; sirolimus; disease progression.

## Apstrakt

**Uvod/Cilj.** Značajan prodor u transplantaciji solidnih organa postignut je uvođenjem kalcineurinskih inhibitora (KNI). Istovremeno, njihovi potencijalno nefrotoksični efekti mogu da doprinesu nastanku i progresiji insuficijencije bubrežnog grafta. Cilj ispitivanja bio je da se utvrdi ishod konverzije sa imunosupresivnih protokola baziranih na KNI na sirolimus (SRL) kod primalaca sa trećim stepenom hronične bubrežne slabosti grafta i proteinurijom manjom od 500 mg/dan. **Metode.** U periodu od 2003. do 2011. 24 bolesnika (6 žena i 18 muškaraca), prosečne starosti  $41 \pm 12,2$  godine, na trostrukoj imunosupresivnoj terapiji: steroidi, antiproliferativni lek [mekofenolat mofetil (MMF)/ azatioprin (AZA)] i KNI prevedeno je sa KNI na SRL i praćeno  $76 \pm 13$  meseci. Devet bolesnika (I grupa) prevedeno je rano, tokom prve postransplantacione godine ( $4 \pm 3$  meseca) i 15 kasno, nakon prve godine ( $46 \pm 29$  meseci). Tokom redovnih ambulantnih kontrola pratili smo funkciju grafta praćenjem vrednosti serumskog kreatinina, jačine glomerulske filtracije (JGF), proteinurije i lipidemije. **Rezultati.** Tridesetog dana nakon konverzije kod svih bolesnika vrednosti JGF, proteinurije i lipidemije bile su neznatno povećane. Tokom prva dva meseca svi bolesnici imali su makar jednu urinarnu ili respiratornu infekciju, a kod 10 bolesnika se reaktivirala citomegalovirusna infekcija/bolest. Bolesnici su uspešno izlečeni standardnom terapijom. U periodu od  $21 \pm 11$  meseci kod 15 bolesnika iz obe grupe obustavljena je terapija SRL zbog: rekonverzije na KNI (10 bolesnika) ili dvostruke imunosupresivne terapije (3 bolesnika), vraćanja na hemodijalizu (1 bolesnik) i smrti (1 bolesnik). Devet bo-

lesnika bilo je i dalje na terapiji SRL. Do kraja praćenja oni su znatno popravili JGF (sa  $53,2 \pm 12,7$  na  $69 \pm 15$  mL/min), a neznatno povećali proteinuriju (sa  $265 \pm 239$  na  $530,6 \pm 416,7$  mg/dan) i lipidemiju (holesterol sa  $4,71 \pm 0,98$  na  $5,61 \pm 1,6$  mmol/L i trigliceride sa  $2,04 \pm 1,18$  na  $2,1 \pm 0,72$  mmol/L). Svi su bili stabilni tokom praćenja. Deset bolesnika vraćeno je na KNI zbog naglog povećanja proteinurije, sa  $298 \pm 232$  na  $1639 \pm 1641$  mg/dan (7 bolesnika), brzog rasta multiplih ovarijalnih cista (2 bolesnika) i operativnog lečenja perzistentnog hematoma (1 bolesnik). Od rekonverzije do kraja praćenja bili su stabilni, ali sa neznatnim sniženjem JGF (sa  $56,10 \pm 28,09$  na  $47 \pm 21$  mL/min) i značajno nižom proteinurijom (sa  $1639 \pm 1641$  na  $529 \pm 688$  mg/dan). Do kraja praćenja kod njih se neznatno povećala vrednost serumskog kreatinina (sa  $172 \pm 88$  na  $202 \pm 91$  mmol/L), smanjila vrednost JGF (sa  $56,10 \pm 28,09$  na  $47 \pm 21$  mL/min) i povećala proteinurija (sa  $528,9 \pm 688$  na  $850 \pm 1083$  mg/dan). **Zaključak.** U ovom malom deskriptivnom ispitivanju prevođenje sa KNI na SRL bilo je praćeno većom incidencijom infektivnih komplikacija, što je uslovalo sniženje doze drugog antiproliferativnog leka (AZA ili MMF) za 25–50% i moguće imalo uticaj na pojavu glomerulopatije, koja je bila razlog za prekid terapije sirolimom kod sedam (29%) bolesnika. Najveću korist od konverzije sa KNI na SRL imalo je devet (37,5%) bolesnika koji nisu ispoljili značajne komplikacije nakon konverzije.

### Ključne reči:

**transplantacija bubrega; graft, preživljavanje; bubreg, hronična insuficijencija; kalcineurin; sirolimus; bolest, progresija.**

## Introduction

Possible beneficial effects of early postransplant conversion from calcineurin inhibitors (CNI) to sirolimus (SRL) in patients with normal renal graft function and proteinuria have been well documented in recently published papers<sup>1-4</sup>. There are only a few papers with a small number of patients dealing with conversion from CNI to SRL-based protocol in patients with graft chronic kidney disease<sup>5-11</sup>. The main idea of this conversion was to prolong the duration of graft chronic kidney disease (CKD) and postpone the dialysis. It is well-known that patients who are on these less toxic protocols are at a higher risk for subclinical, acute and chronic rejection if, through SRL concentration was lower than 10–15 ng/mL in the first 6 months<sup>11</sup>. In the same time the risk for malignancies<sup>12-14</sup> and cardiovascular events should be decreased<sup>15,16</sup>.

The aim of the study was to investigate the outcome of conversion from immunosuppressive protocol based on CNI to SRL, measuring glomerular filtration rate (GFR) estimated by the Cockcroft-Gault equation, proteinuria, lipidemia and resistive index of interlobar arteries, as well as side effects in patients with graft CKD grade III and proteinuria below 500 mg/day.

## Methods

From March 2003 to December 2011, 24 patients (6 females and 18 males) were switched from immunosuppres-

sive protocols based on CNI (15 cyclosporine A and 9 tacrolimus) with steroids and antiproliferative agent [azathioprine (AZA) or mycophenolate mofetil (MMP)] to SRI and prospectively followed  $76 \pm 13$  months.

Before transplantation, all the patients had slowly progressive chronic kidney disease that lasted more than 10 years: chronic glomerulonephritis (21 patients), endemic nephropathy (1 patient) and congenital anomalies (2 patients). The patients with glomerulonephritis presented mostly with daily proteinuria below 1 or 2 gr, some of them with intermittent or persistent microhematuria and mild, easily controlled hypertension (with ACE inhibitor and/or diuretics). Only four patients were histologically verified: three with IgA nephropathy and one with rapidly progressive glomerulonephritis (anti-glomerular basement membrane positive with isolated renal disease).

Eighteen patients received a graft from living related donors, and six from deceased donors. HLA matching was  $50 \pm 12,5\%$ , panel reactive antibody (PRA) was zero and pretransplant lymphocytotoxic cross match was negative. All the patients had increased blood pressure, kept in target range (120–130/70–80 mmHg) with a low dose of beta blocker in combination with an ACE inhibitor or a calcium channel blocker.

Before conversion from CNI to SRL all the patients had graft CKD grade III estimated by the Cockcroft-Gault equation and daily proteinuria below 500 mg. Graft function

in these patients was suboptimal initially, due to older donor age and nephroangiosclerosis, or as a consequence of an ischemic-reperfusion injury. Although most of these patients, as expected, had histology verification for mild or moderate tubulointerstitial fibrosis, the aim of this study was to determine clinical parameters, particularly GFR and proteinuria, as markers of efficient conversion from CNI to SRL.

Two groups of patients were formed based on timing of conversion: the early and the late. The early converted group had 9 patients converted before the end of the first posttransplant year (mean  $4 \pm 3$  months post-transplant), with proteinuria below 150 mg/day in two patients and from 150–500 mg/day ( $379 \pm 232$  mg/day) in seven patients. The late converted group included 15 patients that were switched after the first posttransplant year (mean  $46 \pm 26$  months), with proteinuria below 150 mg/day in eight patients and 150–500 mg/day in remaining seven patients (mean  $215 \pm 207$  mg/day).

Before switching to SRL, basic clinical examination was performed. It consisted of physical examination and evaluation of morphology and hemodynamics of renal graft by color Doppler sonography in the level of interlobar arteries. Basic laboratory analysis, blood cell count and standard biochemical parameters were checked (serum creatinine, cholesterol and triglycerides). Graft function was evaluated by serum creatinine and GFR estimated by the Cockcroft – Gault equation. Proteinuria was measured in daily urine samples using the biuret method.

Conversion from CNI to SRL was abrupt. After a night dose of CNI, next morning the first dose of SRL was introduced. First C0 SRL concentration was monitored the third day with target levels of 7–10 ng/mL from 6th to 12th post-transplant months and 5–10 ng/mL after first post transplant year. When SRL reached the target range, the doses of antiproliferative drugs were decreased by 25–50% (MMF from 2

hypertension, lipidemia and proteinuria, new episodes of acute rejection, infections, acute cardiovascular incidents, patients and graft survival and new onset of malignancies). Worsening of proteinuria above 1 g/day was a marker of glomerulopathy development in the course of graft CKD.

All blood analyses were done in our central laboratory using standard procedures. Hematologic analyses were performed on autoanalyzer (Bayer). Creatinine concentration was measured colorimetrically with alkaline picrate (Dimension RXL Dade Behring).

The Cockcroft–Gault equation allows creatinine clearance to be estimated from the serum creatinine:

$$\text{CCr (mL/min)} = \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{\text{CrS [mg/dL]} \times 72} \times 0.85 \text{ (if female)}$$

SRL C0 concentration was measured with Imx Sirolimus Assay based on MEIA (micro particular enzyme immunoassay) technology (Abbot). Reactivation of cytomegalovirus infection was detected with PCR method on Amplicor Hoffman La Roche with positive test above 400 copies/L.

For statistical analysis we used *t*-test in Excel on standard personal computers. The results of analysis were presented in tables as mean value  $\pm 1$  SD (standard deviation) and probability was considered significant if  $p < 0.05$ .

## Results

Initially, all the patients showed a benefit of conversion from CNI to SRL. One month after conversion, the patients from both groups improved graft function and increased lipidemia and proteinuria. Graft hemodynamics, expressed as measured resistive index in interlobar arteries, although significantly increased in the early group, stayed within the referent range (Tables 1 and 2).

**Table 1**  
The results of early conversion from calcineurin inhibitors (CNI) to sirolimus (SRL) in 9 patients

Parameters	CNI ( $\bar{x} \pm \text{SD}$ )	SRL (30th day) ( $\bar{x} \pm \text{SD}$ )	<i>P</i>
Creatinine S ( $\mu\text{mol/L}$ )	$204 \pm 74$	$166 \pm 74$	ns
GFR (mL/min)	$48.9 \pm 16$	$65.6 \pm 23.5$	ns
Proteinuria 24 h (mg)	$379 \pm 22$	$979 \pm 1956$	ns
Cholesterol (mmol/L)	$4.8 \pm 1.5$	$7.63 \pm 0.84$	0.001
Triglycerides (mmol/L)	$2.63 \pm 1.1$	$4.8 \pm 1.74$	ns
RI ILA	$0.63 \pm 0.05$	$0.68 \pm 0.03$	0.038

S – serum; GFR – glomerular filtration rate; RI ILA – resistive index in interlobar arteries; ns – non significant.

g to maximum 1.5 g, and AZA from 125 or 150 mg to maximum 100 mg). Steroids were kept at maintenance doses (5–10 mg daily).

After conversion, check-ups were on day 3, 6 and 30, then switched to weekly between 3 to 6 months, bi-weekly between 6 to 9 months, monthly between 9 to 12 months and every three months after one year. Follow-up on each visit included serum creatinine, GFR calculated using the Cockcroft–Gault equation and side effects (worsening of

During the 8-year follow-up, 15 patients (out of 24) discontinued sirolimus therapy for different reasons (Table 3).

Nine patients that remained on sirolimus therapy, followed for  $65 \pm 20$  months, significantly improved hemoglobin and graft function. Proteinuria and lipidemia increased insignificantly and hemodynamic parameters of renal allograft were unchanged (Table 4).

Ten patients were reconverted to CNI after  $21 \pm 11$  months. Initially, upon conversion they insignificantly im-

**Table 2**  
**The results of late conversion from calcineurin inhibitors (CNI) to sirolimus (SRL) in 15 patients**

Parameters	CNI ( $\bar{x} \pm SD$ )	SRL (30th day) ( $\bar{x} \pm SD$ )	<i>P</i>
Creatinine S ( $\mu\text{mol/L}$ )	202 $\pm$ 45	167 $\pm$ 35	ns
GFR (mL/min)	52.4 $\pm$ 11.4	61.8 $\pm$ 19	ns
Proteinuria 24 h (mg)	215 $\pm$ 207	1051 $\pm$ 1920	ns
Cholesterol (mmol/L)	6.25 $\pm$ 4.2	5.63 $\pm$ 3.12	ns
Triglycerides (mmol/L)	2.24 $\pm$ 1.32	3.18 $\pm$ 1.57	ns
RI ILA	0.68 $\pm$ 0.06	0.68 $\pm$ 0.05	ns

S – serum; GFR – glomerular filtration rate; RI ILA – resistive index in interlobar arteries; ns – non significant.

**Table 3**  
**The outcome of conversion from calcineurin inhibitors (CNI) to sirolimus (SRL)**

Group	SRL	reCNI	ST + AP	Hd	Death
I	3	4	1	0	1
II	6	6	2	1	0
Total	9	10	3	1	1

The group I – converted from CIN to SRL before the end of the first posttransplant years; the group II – converted from CIN to SRL after the first post-transplant years; reCNI – reversion to calcineurin inhibitors; ST – steroids; AP – antiproliferative agent; Hd-hemodialysis.

**Table 4**  
**The patients with sirolimus (SRL) therapy – initial (start) and final (end) results**

Parameters	CNI start ( $\bar{x} \pm SD$ )	SRL end ( $\bar{x} \pm SD$ )	<i>P</i>
Creatinine S ( $\mu\text{mol/L}$ )	203 $\pm$ 31	167 $\pm$ 28	0.01
GFR (mL/min)	53.2 $\pm$ 12.7	69 $\pm$ 15	0.014
Proteinuria (mg/day)	265 $\pm$ 239	530.6 $\pm$ 416.7	0.061
Cholesterol (mmol/L)	4.71 $\pm$ 0.98	5.6 $\pm$ 1.6	0.116
Triglycerides (mmol/L)	2.04 $\pm$ 1.18	2.1 $\pm$ 0.72	0.45
Hemoglobin (g/L)	124.2 $\pm$ 13.1	140.4 $\pm$ 14.7	0.013
RI ILA	0.66 $\pm$ 0.05	0.66 $\pm$ 0.05	0.37

CNI – calcineurine inhibitors; S – Serum; GFR – glomerular filtration rate; RI ILA – resistive index in interlobar arteries.

proved graft function, but later showed a considerable increase in proteinuria, lipidemia and worsened hemodynamic parameters in the level of kidney interlobar arteries. They were reconverted to CNI due to development of glomerulopathy, which presented with abrupt onset and progressive increase in proteinuria, mostly in subnephrotic range (7 patients), newly formed multiple ovarian cysts with consecutive serious lower extremity edema (2 patients) and an operative treatment (1 patient). The result of reversion was a nonsignificant decrease in proteinuria and worsening of renal function, lipidemia and resistive index without hemodynamic consequences (Table 5). By the end of the total follow-up, 76  $\pm$  13 months, these patients were still in renal failure grade III, with slowly progressive nonsignificant increase in serum creatinine, proteinuria and decrease in glomerular filtration rate.

Early after the conversion two of the patients developed serious crural edema and multiple ovarian cysts with oligomenorrhea. After reversion to CNI they lost edema and ovarian cysts and returned to a regular period.

Initially, most of our patients had low C0 SRL concentration (5–7 ng/mL) and showed early infective complications in spite of dose correction of the second anti-

proliferative agent. All the converted patients had acute pyelonephritis caused by *E. coli* or *Enterobacter*, and two of them had pneumonia caused by *Hemophilus influenzae*. Ten patients had symptomatic reactivation of cytomegalovirus (CMV) infection, successfully treated with ganciclovir or valganciclovir. Three of the patients with recurrent bacterial or viral infections stopped SRL therapy, and by the end of the follow-up had double immunosuppressive therapy with steroid and a second antiproliferative agent (AZA or MMF). In these patients GFR and serum creatinine remained in the same range as at the time of SRL discontinuation.

One of the patients during this period progressed to end-stage renal failure and started dialysis. In the meantime he had a second transplantation.

One of the patients with apparently inadequate compliance and blood pressure control died after acute massive intracranial bleeding.

No new onset of malignancies was noticed in any of the followed patients.

In all the followed patients antihypertensive therapy was unchanged, but the dose of hypolipemic agents was increased.



**Table 5**  
**The patients converted from calcineurin inhibitors (CNI) to sirolimus (SRL) and reconverted to CNI (reCNI) on day 30, and at the end of follow-up (after 76 ± 13 months)**

Parameters	CNI start ( $\bar{x} \pm SD$ )	SRL end ( $\bar{x} \pm SD$ )	<i>p</i> CNI start : SRL end	reCNI, 30th day ( $\bar{x} \pm SD$ )	CNI end ( $\bar{x} \pm SD$ )	<i>p</i> reCNI:CNI end
CreatinineS ( $\mu\text{mol/L}$ )	185 ± 76	167 ± 61	0.28	172 ± 88	202 ± 91	
GFR ( $\text{mL/min}$ )	49.45 ± 13,54	55.82 ± 22.67	0.23	56.10 ± 28.09	47 ± 21	
Proteinuria ( $\text{mg/day}$ )	298 ± 232.13	1639 ± 1641*	0.015	528.9 ± 688*	850 ± 1083	ns* / ns
Cholesterol ( $\text{mmol/L}$ )	5.6 ± 1.6	7.22 ± 0.95	0.011			
Triglycerides ( $\text{mmol/L}$ )	2.39 ± 0.68	4.37 ± 1.42	0.001			
RI ILA	0.66 ± 0.06	0.69 ± 0.04	0.177			

\* – Compared values at the end of SRL therapy to those 30 days after reversion to CNI; GFR – glomerular filtration rate; RI ILA – resistive index in interlobar arteries; ns – non significant.

## Discussion

Some authors proposed less toxic immunosuppression for all renal allograft recipients to minimize the risk for development of chronic allograft nephropathy, decrease the incidence of cardiovascular deaths and new onset of malignancies<sup>12–16</sup>. The main idea for patients who already had graft dysfunction was avoiding calcineurine inhibitors and their toxic effects on graft hemodynamics, which potentially could accelerate progression of renal failure<sup>16</sup>. The question remains when the right time is for conversion from CNI to SRL and who should be converted.

It appears that the timing of conversion is not important, while the initial level of renal graft damage is. The CONVERT trial showed that the best results of conversion from calcineurin inhibitors to sirolimus showed patients with GFR above 40 mL/min and urine protein/creatinine ratio less than 0.11<sup>1,2</sup>.

The effect of sirolimus on growth factor inhibition resulted in a specific profile of side effects: increased incidence of postoperative liquid collection, decelerated wound healing and function recovery of primary non-functioning grafts<sup>17,18</sup>. Some authors believe that SRL special profile of side effects is dose-dependent<sup>18</sup>.

Sirolimus should not be introduced immediately in the postoperative period and should be avoided in marginal grafts, patients with long cold ischemia time and high-risk patients. The best results were seen in patients with low immunological risk and without graft dysfunction. Potentially good candidates may also be patients with stent in renal artery and newly discovered skin malignancies.

The conversion can be abrupt, but with good C0 SRL concentration, especially in the first six posttransplant months (10–15 ng/mL) to ensure the minimal risk for subclinical, acute and chronic rejection. Our patients had lower target concentrations in the first six months due to serious and recurrent infective complications. None of our patients in the first post-conversion year had a clinical episode of acute rejection, or worsening of chronic graft dysfunction.

Introducing SRL in immunosuppressive protocol since 2003, we converted all those stable, low-risk graft recipients in grade III renal failure in the first post-transplant year and later, with normal or slightly increased proteinuria, for which we thought that they could benefit from CNI withdrawal.

High doses of two antiproliferative immunosuppressive agents acting in different phases of T and B lymphocyte cell cycles may potentially result in increase in infectious complication, or facilitate myelotoxic effects or digestive symptoms<sup>9</sup>.

Ten (42%) of the patients in the period of 21 ± 11 months after the initial conversion, reconverted to CNI after the increase of 24 h proteinuria above 2 g. The development of glomerulopathy worsened the course of pre-existing chronic graft dysfunction, but without a significant change in urinary sediment, serum creatinine or GFR. Histological examination showed focal and segmental glomerulosclerosis in all the patients. Thirty days after reversion to CNI, proteinuria was below 0.8 g daily and slowly increased to 1.8 g by the end of the follow-up. Graft function was almost the same as at the beginning of the treatment. Color Doppler evaluation of kidney hemodynamics through resistive indices in interlobar arteries of renal graft stayed in the normal range (below 0.7), which additionally confirmed the stability of graft function and good potential for future graft survival. The reason for such increase in proteinuria could be explained partly by low total dose of immunosuppressive therapy (low C0 SRL concentration combined with additional decrease in the dose of the second antiproliferative agent due to serious infectious complications). Notwithstanding with these findings, some authors reported development of glomerulopathy in the patients with high C0 SRL concentrations<sup>19</sup>. An explanation for this could be that it represents the progression of pre-existing disease, or that it is a consequence of specific SRL side-effect profile with impact on podocytopathy<sup>20</sup>.

Almost all the papers about conversion from CNI to SRL stressed the worsening of lipidemia in spite of the correction of hypolipemic therapy. Our patients showed insignificant increase in serum lipids. They were not using hypolipemic therapy regularly because they could not afford or refund this expensive therapy. The patients with SRL therapy, in spite of the persistent dyslipidemia, did not show deteriorating effect on graft function.

## Conclusion

In this small prospective and descriptive study CNI to SRL conversion was followed by the increased incidence of infections and consecutive 25–50% dose reduction of the se-

cond antiproliferative agent (AZA, MMF), with a possible influence on the development of glomerulopathy in some patients, which was the major reason for discontinuation of SRL therapy in 7 (29%) of the patients. Nine (37.5%) of the patients experienced the greatest benefit of CNI to SRL conversion without serious post-conversion complications.

Worsened lipidemia could be corrected with regular use and proper dose of hypolipemic agents and did not influence GFR in patients on SRL therapy. Patients reconverted to cal-

cineurin inhibitors showed slow and progressive chronic kidney graft disease.

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