

Cardiorenal benefits of early *versus* late cyclosporine to sirolimus conversion in a rat model

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ABSTRACT

Objective: To compare the cardiorenal effects of early versus late cyclosporine (CsA) to sirolimus (SRL) conversion, using a novel animal model that mimics these protocols used in the clinical practice, and focusing on blood pressure, heart rate (HR), biochemical data and heart and kidney lipid peroxidation.

Materials and Methods: The study had five groups. Six male Wistar rats in each group were used during a 9-week study protocol: control, CsA (5 mg/kg/day), SRL (1 mg/kg/day); early conversion and late conversion. Cardiorenal evaluation was assessed by biochemical data, blood pressure, HR, and heart and kidney lipid peroxidation.

Results: As expected, CsA promoted cardiorenal impairment, viewed by development of hypertension, tachycardia, increased urea, creatine kinase, and glucose levels, as well as heart and kidney oxidative stress. SRL, as expected, promoted less cardiorenal side effects, namely those related with nephrotoxicity. In agreement, both early and late conversions from CsA to SRL produced less side-effects, namely those related to the CsA-induced nephrotoxicity. **Conclusions:** In our model, both early and late CsA to SRL conversion promoted amelioration of the CsA-induced cardiorenal damage. However, early substitution seems to produce more benefits, in particular due to higher improvement of the cardiac profile.

Key words: Cyclosporine, cardiotoxicity, early *versus* late conversion, nephrotoxicity, sirolimus

INTRODUCTION

Cyclosporine A (CsA) has revolutionized kidney transplantation (KTx), in particular due to reduction of rejection and improvement of outcomes, at short-term.^[1] However, CsA has a significant adverse impact on renal function and promotes hypertension and cardiovascular disease (CVD).

^[2,3] Renal dysfunction is an independent risk factor for graft loss and mortality after KTx and CVD disease is the main cause of post-transplant mortality.^[3,4] Thus, extended long-term graft survival has not been achieved. We have already demonstrated that in KTx patients and in animal models, the main components of the renal/cardiovascular side-effects of CsA, include platelet and vascular hyperreactivity, nitric oxide impairment, oxidative stress, renin-angiotensin system, and sympathetic overactivity.^[5-15]

The main strategies used to limit CsA exposure are early and late CsA substitution to sirolimus (SRL), which is an inhibitor of the mammalian target of rapamycin (mTOR) that has been viewed as a therapeutic advance in the prevention of acute renal allograft rejection and chronic allograft nephropathy (CAN).^[16,17] Because SRL does not share the vasomotor renal

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adverse effects exhibited by CNIs,^[18] it has been designated a non-nephrotoxic drug. However, clinical reports suggest that, under some circumstances, SRL is associated with proteinuria and acute renal dysfunction.^[19-23] Although these adverse effects occur in some patients, their occurrence could be minimized by knowledge of the molecular effects on the kidney and its use in appropriate populations. Further long-term analysis of renal allograft studies using CsA conversion to SRL along with clinical and laboratory studies will refine these issues in the future. The clinical practise *per se* cannot clarify these aspects, not only because of the short duration of trials, but also, especially, because of the absence of biomolecular studies. This study intended to compare the cardiorenal effects of early *versus* late CsA to SRL conversion, using a novel animal model.

MATERIALS AND METHODS

Animals

Male Wistar rats (Charles River Lab. Inc, Barcelona, Spain), weighing 310–330g, were maintained in an air conditioned room, subjected to 12 h dark/light cycles and given standard laboratory rat chow (IPM-R20, Letica, Barcelona, Spain) and free access to tap water. Animal experiments were conducted according to the National and European Communities Council Directives on Animal Care.

Chemicals

Cyclosporine (Sandimun Neoral[®]) was obtained from Novartis Farma Produtos Farmacêuticos SA (Sintra, Portugal) and Sirolimus (Rapamune[®]) was obtained from Wyeth Europe Ltd. (Berkshire, UK) through Laboratórios Pfizer Lda (Lisbon, Portugal). All the other chemicals were of analytical grade.

Animals and treatments

The animals were divided in five groups ($n = 6$, each), in a 9-week protocol: control group—vehicle (orange juice); Cyclosporine group (CsA)—5 mg/kg/day, dissolved in orange juice; Sirolimus group (SRL)—1 mg/kg/day, dissolved in orange juice; EARLY conversion group—5 mg/kg/day of CsA during 3 weeks and then conversion to 1 mg/kg/day of SRL for additional 6 weeks; LATE conversion group—5 mg/kg/day of CsA during 6 weeks and then conversion to 1 mg/kg/day of SRL for further 3 weeks. Treatments were performed by esophageal gavage during 9 weeks. All the animals, in every group completed 9 weeks of experimental protocol and their body weight (BW) was monitored throughout the study.

Blood pressure, heart rate, and drugs blood concentrations monitoring

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured by the noninvasive “tail cuff” method using a sphygmomanometer (LE 5001 Pressure meter, Letica Scientific Instruments, Spain). CsA

and SRL blood concentrations were assessed by immunoassay using automatic methods (Flex reagent) and equipment (Dimension[®]RxL, Siemens, Germany).

Sample collection and preparation

At the end of treatments, the rats were injected with intraperitoneal anesthesia with 2 mg/kg BW of a 2:1 (v:v) 50 mg/ml Ketamine (Ketalar[®], Parke-Davis, Pfizer Laboratories Lda, Seixal, Portugal) solution in 2.5% chlorpromazine (Largatil[®], Rhône-Poulenc Rorer, Vitória laboratories, Amadora, Portugal). Blood samples were immediately collected by venipuncture from the jugular vein in needles with no anticoagulant (for serum samples collection) or with appropriated anticoagulant (ethylenediamine tetraacid, EDTA) for blood cells analysis. The rats were killed by cervical dislocation, the heart and kidneys were immediately removed, weighted and placed in ice-cold Krebs buffer.

Biochemical data

The following biochemical parameters were assessed in serum through automatic validated methods and equipments (Hitachi 717 analyser, Roche Diagnostics Inc., MA, USA): glucose, urea, creatinine, uric acid, creatine kinase (CK), *aspartate aminotransferase* (AST), *alanine aminotransferase* (ALT), triglycerides (TGs), and total-cholesterol (Total-Chol).

Hematological data

Several hematological parameters were measured in EDTA whole blood by using an automatic Coulter Counter[®] (Beckman Coulter Inc., USA, CA), including: red blood cell (RBC) count, white blood cells (WBC), hematocrit (HCT) and platelet count (PLT). Serum levels of interleukin-2 (IL-2) were measured by using ultrasensitive Quantikine[®] ELISA kit (R&D Systems, Minneapolis, USA).

Tissue lipid peroxidation

Heart and kidney lipid peroxidation were evaluated by the thiobarbituric acid reactive substances (TBARs) method, assessing malondialdehyde (MDA) as previously described.^[24]

Statistical analysis

Results are mean values $\pm$ standard errors of the mean (SEM). Differences between groups were tested by performing analysis of variance (ANOVA), followed by the Bonferroni test and Post-hoc test, using the GraphPad software. Differences were considered to be significant at $P < 0.05$.

RESULTS

Drug blood concentration

The trough blood concentration of CsA and SRL obtained using the doses of 5 mg/kg/day and 1 mg/kg/day in the rat was within the range of those achieved in humans under immunosuppressive regimens of early and late CsA to SRL

conversion. Therefore, trough blood concentration in the rats under CsA treatment was 367.0 ± 45.5 ng/ml and in the rats under SRL treatment of 7.8 ± 1.9 ng/ml.

Body weight monitoring

Body weight was monitored during the 9 weeks of treatments [Figure 1]. CsA-treated rats showed a BW profile similar to that of the control animals. However, SRL-treated groups demonstrated a decrease in BW throughout the treatments, which was notorious when given alone, as well as when CsA was substituted for SRL after 3 or 6 weeks of treatment (early and late conversion, respectively).

Biochemical and hematological data

Concerning the lipid profile, CsA induced a significant ($P < 0.05$) increase in serum TGs levels, which was not evident

in the SRL-treated animals [Table 1]. Total cholesterol also increased in all the treated groups *versus* the control group, although the differences did not reach statistical significance [Table 1]. The CsA-treated rats also demonstrated hyperglycemia ($P < 0.05$), which was less evident in the three SRL-treated animals (alone, early conversion from CsA and late conversion). Similar profiles were encountered for CK and AST activities, demonstrating that CsA is more cardiotoxic and hepatotoxic than SRL [Table 1]. Serum IL-2 levels were significantly reduced in both the CsA- and SRL-treated animals ($P < 0.01$), an effect which was also shown in the early and late CsA to SRL conversion protocols [Table 1].

Concerning hematological data, we found no significant differences in RBC, HTC, Hb, PLT, and PCT, but a reduced value of WBC was observed in the group treated with CsA, which was maintained during either the early or late conversion to SRL [Table 1].

Nephrotoxicity and cardiotoxicity

With regard to the markers of nephrotoxicity, we found that CsA promotes significantly ($P < 0.05$) increased levels of urea [Figure 2a] and a trend to higher values of creatinine and uric acid, which was accompanied by significantly ($P < 0.05$) higher values of kidney oxidative stress, viewed by the increased lipid peroxidation [Figure 2b]. These effects were absent in the SRL-treated rats, both alone or after conversion, early or late, demonstrating that SRL is effectively less nephrotoxic in this animal model of early *versus* late conversion.

Together with the increment in CK activity in the CsA-treated group, we found that CsA has also promoted hypertension,

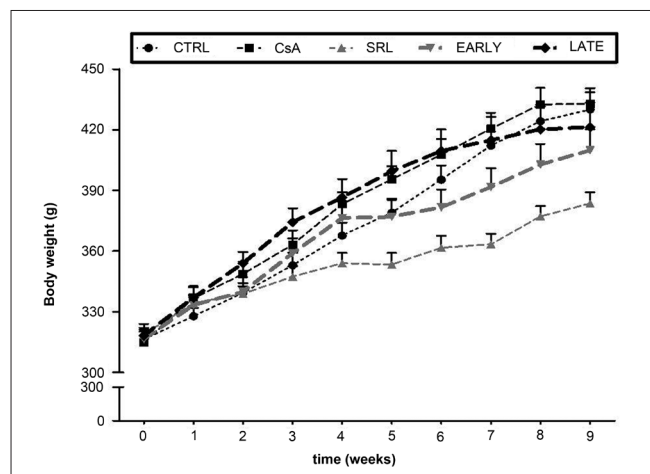


Figure 1: Body weight during the 9-week period of treatment

Table 1: Biochemical and hematological data during 9 weeks of treatment

	Control (vehicle)	CsA (5 mg/kg/day)	SRL (1 mg/kg/day)	Early conversion	Late conversion
Biochemical data					
TGs (mmol/l)	1.13 ± 0.10	$2.22 \pm 0.20^*$	1.48 ± 0.15	$1.22 \pm 0.16^\#$	1.53 ± 0.36
Total-Chol. (mmol/l)	1.27 ± 0.04	1.44 ± 0.05	1.48 ± 0.13	1.43 ± 0.06	1.52 ± 0.08
Glucose (mmol/l)	8.34 ± 1.04	$16.42 \pm 2.19^*$	13.38 ± 1.26	12.50 ± 1.25	11.83 ± 2.09
Creatinine ($\mu\text{mol/l}$)	33.59 ± 1.425	39.12 ± 2.51	40.81 ± 2.16	38.60 ± 2.17	38.54 ± 1.71
Uric Acid ($\mu\text{mol/l}$)	73.36 ± 12.06	97.55 ± 29.42	160.60 ± 21.17	79.70 ± 11.38	57.10 ± 13.25
CK ($\mu\text{mol/l}$)	17342 ± 1452	51094 ± 20221	$28356 \pm 8001^*$	23198 ± 3017	$28254 \pm 11587^\S$
AST (IU/l)	69.67 ± 3.99	118.60 ± 33.62	95.17 ± 14.46	84.33 ± 9.99	87.33 ± 19.91
ALT (IU/l)	38.17 ± 2.40	35.60 ± 3.33	34.83 ± 2.55	32.83 ± 2.06	31.00 ± 2.00
IL-2 (pg/ml)	28.05 ± 4.15	$11.00 \pm 1.17^{**}$	$13.18 \pm 1.18^{**}$	$12.06 \pm 3.38^{**}$	$14.15 \pm 0.89^*$
Hematologic data					
RBC ($\times 10^6/\mu\text{l}$)	7.54 ± 0.12	7.84 ± 0.21	8.30 ± 0.23	8.10 ± 0.18	8.00 ± 0.13
HTC (%)	39.27 ± 0.58	38.85 ± 0.88	41.63 ± 1.30	41.18 ± 0.85	41.00 ± 0.57
Hb (g/dl)	14.15 ± 0.14	14.18 ± 0.30	14.87 ± 0.47	14.87 ± 0.32	14.73 ± 0.17
PLT ($\times 10^3/\mu\text{l}$)	752.30 ± 30.69	711.30 ± 48.18	702.20 ± 57.91	685.50 ± 37.32	797.80 ± 39.48
PCT (%)	0.45 ± 0.01	0.50 ± 0.03	0.45 ± 0.04	0.39 ± 0.02	0.46 ± 0.02
WBC ($\times 10^3/\mu\text{l}$)	7.40 ± 0.71	$3.88 \pm 0.56^*$	$8.35 \pm 1.02^{***}$	$4.73 \pm 0.54^\S$	$4.95 \pm 0.41^\S$

Values are mean $\pm$ SEM of $n = 6$ rats per group; $^*P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ *versus* the control group; $^\#P < 0.05$ and $^{***}P < 0.001$ *versus* the CsA-treated group; $^\S P < 0.05$ and $^{§§}P < 0.01$ *versus* the SRL-treated group, RBC: Red blood cell; WBC: White blood cells; HCT: Hematocrit PLT: Platelet count CK: Creatine kinase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TGs: Triglycerides; Total-Chol: Total-cholesterol

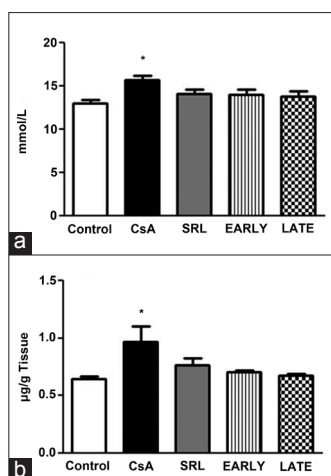


Figure 2: Markers of nephrotoxicity: urea levels (a) and kidney lipid peroxidation—TBARs (b), in the five groups under treatments. Values are mean $\pm$ SEM of six rats per group. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ versus the control group

viewed by the significantly ($P < 0.001$) increased SBP [Figure 3a], as well as heart oxidative stress, expressed by the increment ($P < 0.05$) in cardiac tissue lipid peroxidation [Figure 3a and b]. The SRL-treated animals also demonstrated significant SBP increment, however at lower magnitudes ($P < 0.01$). Early and late conversions were able to reproduce the SRL effects, but the recovery was more pronounced when the substitution was performed earlier, which might be due to the lower SBP and heart lipid peroxidation as compared to those found in the late conversion [Figures 3a and b].

DISCUSSION

Even though the main idea is that timing of sirolimus conversion influences recovery of renal function in transplant recipients,^[25] there is no consensus between the medical/scientific community concerning the choice of combined protocols (early or late replacements) and the real benefits of these protocols, due to the lack of knowledge concerning the biomolecular mechanisms that support the decision.

Previous studies from our group have already elucidated, in KTX patients and in an animal model, the main components of the CV side-effects of CsA, which includes vascular hyperreactivity, NO impairment, oxidative stress, and SNS overactivity.^[5-15] On the other hand, SRL-based immunotherapy is associated with other serious adverse effects, such as lipid abnormalities and thrombocytopenia,^[19] and even the benefits previously reported on renal function and histology have been continuously discussed during the last few years by our group as well as by others, because of the evidence of nephrotoxicity and proteinuria, in particular in an injured kidney previously exposed to CsA.^[19-23,25-29] Furthermore, evidence shows that CsA and SRL potentiate each other's good and adverse effects: CsA augments hyperlipidemia caused by SRL, and

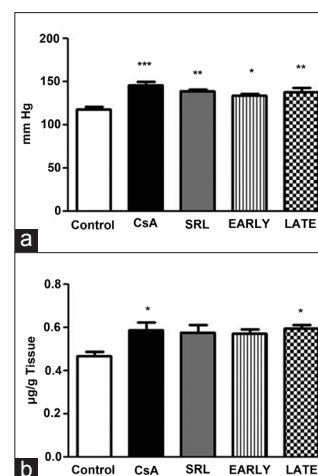


Figure 3: Markers of cardiotoxicity: systolic blood pressure (a) and heart lipid peroxidation—TBARs (b) in the five groups under treatments. Values are mean $\pm$ SEM of six rats per group. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ versus the control group

SRL augments nephrotoxicity caused by CsA. Thus, despite the extended research already available concerning the effects of each drug (CsA and SRL), per se, the effects of short-term CsA use in higher doses or long-term use in lower-doses before conversion to SRL are expected to be obviously distinct. The main purpose of our studies on this area is to obtain answers to a crucial question in KTx: what are the biomolecular cardiorenal mechanisms and the benefits of the protocols of CsA replacement with SRL (early or late conversion)? Since this cannot be performed in human samples (renal and cardiac tissue), we propose a novel study in a rat model that mimics the protocols of early or late CsA conversion to SRL in clinical practice, and using doses of clinical relevance, which is one key aspect for the significance of data in animal models.

Although no relevant changes on hematological data were found, there was a reduced value of WBC in the group treated with CsA, which was maintained during either the early or late conversion to SRL, suggesting a greater influence of CsA on lymphocytes. However, we found that all the groups treated with CsA and/or SRL were able to significantly reduce serum IL-2 content, whose expression is the main target for both drugs, thus suggesting that the immunosuppressive ability of both drugs was present at the doses used. Our study also showed, as expected, that CsA promotes cardiorenal impairment, viewed by development of hypertension, tachycardia, increased urea, CK and glucose levels, as well as heart and kidney oxidative stress, which is a confirmation of previous studies from us as well as from others.^[1-14] SRL, as expected, promoted less cardiorenal effects, namely those related with nephrotoxicity, and reduced animal growth, which might be due to its anti-proliferative character.^[30] In agreement, both early and late conversion from CsA to SRL produced fewer side effects, namely those related to the CsA-induced nephrotoxicity profile, which is in line with most of the studies.^[31-34] However, we

found that the benefits of CsA to SRL conversion are more pronounced when early performed, in particular for the side-effects related to cardiac impairment, viewed by the higher amelioration of cardiac markers, including blood pressure and kidney lipid peroxidation. He *et al.*^[35] found, using a rat kidney transplantation model, that conversion from CsA to SRL retards the progression of CAN, which is in agreement with our data. Other studies reported beneficial cardiovascular effects of mTOR inhibitors, including a restriction of atherosclerosis pathogenesis in animals^[36] and prevention of glomerular hypertrophy in a model of mass reduction.^[37] However, these data are not consensual values, since in another study, using a remnant kidney model in the rat, the authors found that the mTOR inhibitor everolimus induces proteinuria and renal deterioration.^[38] Furthermore, these aspects are in agreement with the idea that SRL could induce proteinuria in the injured kidney, namely after CsA treatment, as well as with reports of CsA and SRL worsening of nephrotoxicity in a rat model of renal damage induced by reduced nephron mass.^[39] Other reports in animals, which are very few in the literature, have shown SRL-induced damage in podocytes in rats with protein overload nephropathy^[40] and aggravation of the pancreatic islet dysfunction evoked by CsA, which is in agreement with the diabetogenic properties of SRL.^[41]

In our study, in agreement with previous studies from us and from others, we analysed the effects of both immunosuppressive agents without transplantation, reporting only the effects of the agents, *per se*. However, even though our study cannot address influences related with the transplantation process, which obviously could play a role in the organ recovering, this is the first study addressing protocols of early *versus* late CsA to SRL conversion that mimic the clinical practise, which will be crucial for further understanding the molecular mechanisms underlying the effects now observed.

In conclusion, in our model, both early and late CsA to SRL conversion promoted amelioration of the CsA-induced cardiorenal damage *per se*. However, early substitution seems to have even a better benefit, in particular due to higher improvement of the cardiac profile. More studies, namely at the cellular and molecular levels, are now advisory to assess the precise nature of the beneficial cardiorenal profile encountered, in order to help in a judicious choice of the best moment to promote CsA to SRL substitution in distinct situations and patients, as well as of the best anti-hypertensive/renoprotective drugs concerning the effects of the abovementioned protocols on the cardiorenal axis.

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