Early Sirolimus Use With Cyclosporine Elimination Does Not Induce Progressive Proteinuria

J.C. Ruiz, J.M. Campistol, A. Sanchez-Fructuoso, A. Mota, J.M. Grinyo, J. Paul, A. Castro-Henriques, J. Reimao-Pinto, J. Garcia, J.M. Morales, E. Granados, and M. Arias

ABSTRACT

Proteinuria has been reported in several papers after conversion from calcineurin inhibitors to Sirolimus (SRL), but this complication has not been analyzed in randomized clinical trials using de novo SRL. It is not known whether de novo use of SRL is a risk factor for proteinuria. We analyzed a series of patients included in a big multicenter randomized trial (RMR trial) corresponding to all patients in Spain and Portugal with respect to this issue. We retrospectively evaluated 24-hour proteinuria in all the patients during the study period (5 years postransplant) for comparison between treatment arms group A, continuous cyclosporine (CyA) + SRL and group B SRL with CyA elimination at 3 months postransplant. The elimination of CyA after the third month was not followed by significant changes in proteinuria. Nevertheless, during the last year of follow-up (between 48 and 60 months postransplant) an impressive increase in proteinuria was observed in group A. This surprising finding seemed to be a consequence of a protocol amendment that recommended CyA elimination in patients of group A, due to poorer results in the intermediate analysis of the trial. This fact suggests that the hemodynamic changes induced by elimination of the vasoconstrictor CyA might be responsible for the proteinuria but only in the long term probably when significant pathological lesions are already present. This finding argues for earlier conversion.

SIROLIMUS (SRL) conversion after the initial postransplant phase has been frequently associated with increasing proteinuria (PU) in a significant number of patients either in the case of renal transplant recipients or in the recipients of other solid organs.[1–3] The mechanism of appearance of this complication is unclear. Various hypotheses have been proposed, namely, a direct tubular toxicity and especially hemodynamic effects derived from calcineurin inhibitor (CNI) elimination, ie. increased glomerular pressure due to afferent vasodilatation.[4] This complication is reversible in most cases and PU returns to preconversion values after SRL elimination and CNI reintroduction.[3] This complication was surprisingly not reported in de novo trials using SRL before approval for clinical use, but the reason for that was that this parameter was not evaluated in those trials. Especially the Rapamune Maintenance Regimen (RMR) trial demonstrated a significant improvement in renal function after early cyclosporine (CyA) elimination in a regimen including SRL, a better pathological profile at 3 years postransplant and better graft survival at 4 years postransplant[5–8] when compared with the control group who maintained CyA treatment. The objective of this work was to analyze the evolution of PU after early CyA withdrawal in a combination of CyA + SRL compared with a control arm with continuous CyA + SRL.

From the Nephrology Department (J.C.R., M.A.), Valdecilla Hospital, University of Cantabria, Santander, Spain; Unidad de Trasplante Renal (J.M.C.), Hospital Clinic, Barcelona, Spain; Servicio de Nefrología (A.S.-F.), Hospital Clínico Universitario, Madrid, Spain; Unidad de Trasplante Renal (A.M.), Hospital da Universidade de Coimbra, Coimbra, Portugal; Servicio de Nefrología (J.M.G.), Hospital Bellvitge, Barcelona, Spain; Servicio de Nefrología (J.P.), Hospital Miguel Server, Zaragoza, Spain; Servicio de Nefrología (A.C.-H.), Hospital Geral Santo Antonio, Porto, Portugal; Servicio de Nefrología (J.R.-P.), Hospital Curry Cabral, Lisboa, Portugal; Servicio de Nefrología (J.G.), Hospital La Fe, Valencia, Spain; Servicio de Nefrología (J.M.M.), Hospital Doce de Octubre, Madrid, Spain; and Wyeth-Farma (E.G.), Madrid, Spain.

Address reprint requests to Dr. Juan Carlos Ruiz, Nephrology Department, Valdecilla Hospital, 39008 Santander, Spain.

0041-1345/07/$–see front matter
doi:10.1016/j.transproceed.2007.06.054

Table 1. Median PU at Different Time Intervals (in g/d)

	Months Posttransplantation					
	3	12	24	36	48	60
Group A: CsA + SRL	0.30	0.36	0.27	0.27	0.32	0.74
n	33	34	33	27	25	27
Group B: SRL	0.20	0.34	0.36	0.38	0.30	0.36
n	35	36	36	36	27	30
p	.945	.711	.546	.753	.963	.103

Abbreviations: CsA, cyclosporine; PU, proteinuria; SRL, sirolimus.

METHODS

We evaluated PU levels in all RMR patients included in Spain and Portugal ($n = 96$): group A, CyA + SRL; and group B, SRL maintenance with CyA suspension at 3 months postaltransplant. Twenty-four-hour PU retrospectively evaluated during the 5-year follow-up period of the study was compared between both arms. Analysis included median values in g/d and patients were considered in an intention-to-treat analysis. Statistical analysis consisted of the Mann-Whitney test. Additionally, a multivariate analysis was performed to find factors related to the appearance of PU greater than 1 g/d at 12 months postransplant, including baseline proteinuria and glomerular filtration rate (GFR), treatment arm, donor age, sex, baseline angiontensin-converting enzyme inhibitor (ACE), or angiotensin-receptor blockers (ARB-II) use, recipient age, the presence of delayed graft function (DGF), and cold ischemia time.

It is important to consider that treatment arms were not maintained unchanged during the study period. Due to the intermediate results after analysis of 36-month data, a protocol amendment during the fifth year after transplantation recommended a change of immunosuppression in the control arm due to poorer results, namely, CyA withdrawal. This was performed in all but one patient in the months following the protocol amendment.

RESULTS

As this was a subanalysis of a randomized trial, both treatment arms were comparable with respect to demographic data at the moment of transplantation: there were no differences in recipient or donor age, gender distribution, percentage of cold ischemia time, and percentage of delayed graft function. Renal function was comparable in both groups at the moment of randomization at three months postransplant (55 vs 56 mL/min, respectively, using the Cockcroft-Gault formula) and the percentage of patients under treatment with ACEi or ARBs was 27% and 25% respectively (P = NS).

Table 1 shows the median values of PU in both treatment arms during the entire study period from randomization at 3 months to 60 months postransplant. PU remained at low levels and stable (with no significant changes) during the first 48 months in both groups. During the fifth year, a marked increase in PU was observed in group A (0.74 vs 0.36; $P = .1$), whereas in group B it remained unchanged until the end of the study period.

Multivariate analysis failed to demonstrate a correlation between the treatment arm and appearance of proteinuria and only recipient age (.01) and the presence of DGF (.01) showed correlation.

DISCUSSION

SRL use with early CyA elimination was not followed by a significant increase in PU, in contrast to what has sometimes been described in late conversions. Surprisingly, when CyA was eliminated in a later phase (without major modifications in SRL doses), PU seemed to increase secondarily. This difference in PU evolution seemed to be dependent of the moment of CyA elimination, and might reflect the severity of the underlying graft damage that would probably be slight at the third month postransplant, but considerably more severe after 4 years of transplantation. The influence of the hemodynamic effects of CyA withdrawal on the renal vasculature of a kidney with underlying chronic damage might probably be the origin of PU. This fact should be considered as another argument to advocate earlier conversion to SRL, when renal damage is still not too extensive.

REFERENCES

1. Ruiz JC, Campistol JM, Sanchez-Fructuoso A, et al: Increase of proteinuria after conversion from calcineurin inhibitor to sirolimus-based treatment in kidney transplant patients with chronic allograft dysfunction. Nephrol Dial Transplant 21:3252, 2006

2. Aliabadi AZ, Kammerstätter DP, Seebacher G, et al: Development of proteinuria after switch to sirolimus based immunosuppression in long-term cardiac transplant patients. Transplantation 82(suppl 3):562, 2006

3. Letavernier E, Pe'raldi MN, Pariente A, et al: Proteinuria following a switch from calcineurin inhibitors to sirolimus. Transplantation 80:1198, 2005

4. Saurina A, Campistol JM, Piera C, et al: Conversion from calcineurin inhibitors to sirolimus in chronic allograft dysfunction: changes in glomerular haemodynamics and proteinuria. Nephrol Dial Transplant 21:488, 2006

5. Johnson RW, Kreis H, Oberbauer R, et al: Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. Transplantation 72:777, 2001.

6. Oberbauer R, Kreis H, Johnson RW, et al: Long-term improvement in renal function with sirolimus after early cyclosporine withdrawal in renal transplant recipients: 2-year results of the Rapamune Maintenance Regimen Study. Transplantation 76:364, 2003

7. Oberbauer R, Segoloni G, Campistol JM, et al: Early cyclosporine withdrawal from a sirolimus-based regimen results in better renal allograft survival and renal function at 48 months after transplantation. Transpl Int 18:22, 2005

8. Mota A, Arias M, Taskinen EI, et al: Sirolimus-based therapy following early cyclosporine withdrawal provides significantly improved renal histology and function at 3 years. Am J Transplant 4:953, 2004