Spironolactone in Post-Transplant Proteinuria: A Safe Alternative Therapy

M.V. de Sousa[a,*], J.P. Guida[b], C.F. do Valle[a], L.F. Camargo[a,b], G.G. Rivelli[a], and M. Mazzali[a]

[a]Renal Transplant Unit, Division of Nephrology, Department of Medicine, School of Medical Sciences, University of Campinas, UNICAMP, Campinas-SP, Brazil; and [b]Post Graduate Program, School of Medical Sciences, University of Campinas, Campinas-SP, Brazil

ABSTRACT

Background. Aldosterone is involved in the process of renal allograft fibrosis, clinically manifest by proteinuria and allograft dysfunction, with increased risk for cardiovascular death. The treatment with aldosterone antagonists appears to be effective in controlling proteinuria, with a protective effect on progression of renal fibrosis.

Methods. This retrospective, cohort study included kidney transplant recipients from January 1993 to June 2015. Inclusion criteria were persistent proteinuria >0.5 g/d, longer than 6 months, and spironolactone therapy.

Results. One hundred forty transplant recipients fulfilled the inclusion criteria and were divided into 3 groups, according to proteinuria levels at the beginning of spironolactone therapy: low (<1 g/24 h), intermediate (1–3 g/24 h), and nephrotic (>3 g/24 h). Groups were comparable in demographic data, with a higher incidence of living related donors in the nephrotic group. In patients with proteinuria ≥1 g/d, we observed a significant reduction in proteinuria after 6 months of therapy that persisted over time. Blood pressure and glomerular filtration rate persisted stable over time. Adverse events were not severe to withdrawal therapy.

Conclusions. Spironolactone can be a safe alternative to control post-transplant proteinuria, especially in patients with mild to moderate allograft dysfunction with proteinuria ≥1 g/day.

ALDOSTERONE participates in the process of interstitial fibrosis and endothelial dysfunction in kidney transplantation. Mechanisms include adhesion and infiltration of macrophages to endothelium, activation of circulating lymphocytes, transcription of pro-inflammatory proteins [1], induction of apoptosis of proximal tubular cells, and transformation of epithelial cells into mesenchymal cells, with stimulation of extracellular matrix components synthesis [2], and with increase in collagen synthesis and reduction in metalloproteinases, resulting in glomerular sclerosis, interstitial fibrosis, tubular atrophy, rarefaction of peritubular capillaries, and depletion of podocytes, with complete destruction of the renal parenchyma [3].

In kidney transplant recipients, fibrosis leads to chronic allograft dysfunction, clinically manifest by proteinuria and reduced glomerular filtration rate (GFR) [4]. Prevalence of proteinuria after transplant ranges from 7.5% to 45% and is associated with impaired allograft function and higher mortality rates [5]. Blockade of the renin-angiotensin system is considered the gold standard therapy for proteinuria in non-transplant patients, but data are insufficient to state its effect in kidney transplantation [6]. Blockade of aldosterone receptors appears as a potential treatment for chronic allograft dysfunction and can be effective in controlling proteinuria and glomerular sclerosis in kidney transplantation [7].

*Address correspondence to Marcos Vinícius de Sousa, Renal Transplant Unit, Division of Nephrology–DCM/FCM UNICAMP, School of Medical Sciences, State University of Campinas, Rua Tessália Vieira de Camargo 126, Cidade Universitária Zeferino Vaz, 13083-970-Campinas, São Paulo, Brazil. E-mail: marcosnefro@gmail.com

230 Park Avenue, New York, NY 10169

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Table 1. Demographic and Clinical Characteristics From Groups According Initial Proteinuria

	Low n = 31	Intermediate n = 82	Nephrotic n = 27	*P* Value
Age (y)	51.4 ± 8.8	49.5 ± 13.4	43.7 ± 15.7	.16
Male sex (%)	22 (71%)	59 (71.9%)	23 (85.2%)	.35
Time after transplant (mo)	58.4 ± 60.5	85.6 ± 96.3	74.5 ± 59.5	.27
Etiology of CKD				.65
Glomerulonephritis	11 (34.5%)	22 (26.8%)	10 (37%)	
Pre-transplant hypertension (%)	29 (96.7%)	76 (98.7%)	19 (86.4%)	.02
Pre-transplant diabetes (%)	5 (17.2%)	14 (18.4%)	1 (4.5%)	.28
Deceased donor (%)	26 (83.9%)	68 (82.9%)	16 (59.3%)	.02
Expanded-criteria donor (%)	7 (24.1%)	13 (16.4%)	4 (14.8%)	.65
Cold ischemia time (h)	19.3 ± 5.4	20.9 ± 6.7	20.3 ± 6.3	.57
Calcineurin inhibitor (%)	17 (56.7%)	53 (65.4%)	22 (84.6%)	.07
mTOR inhibitor (%)	13 (43.3%)	15 (19%)	2 (7.4%)	.002
Anti-proliferative (%)	27 (87.1%)	72 (88.9%)	26 (96.3%)	.45
ACEi/ARB pre-spironolactone	9 (32.1%)	17 (23.9%)	7 (33.3%)	.57
Associated ACEi/ARB	5 (16.3%)	11 (14.1%)	7 (26.9%)	.31

The aim of this study was to evaluate safety and efficacy of aldosterone blockade, with spironolactone, in post-transplant proteinuria.

METHODS

This report describes a retrospective cohort, single-center study. Kidney transplant recipients, from 1993 to 2015, at Clinics Hospital of the State University of Campinas-UNICAMP with persistent proteinuria, were considered for the study. Inclusion criteria included persistent post-transplant proteinuria ≥0.5 g/d, longer than 6 months, serum creatinine ≤3 mg/dL, and therapy with spironolactone. Exclusion criteria included hyperkalemia, known sensitivity to medication, graft dysfunction (serum creatinine >3 mg/dL), and refractory hypertension (mean arterial pressure >120 mm Hg). Patients taking spironolactone for heart or hepatic failure were also excluded.

Data were recovered from medical records and included etiology of chronic kidney disease (CKD), length and modality of dialysis, cold ischemia time, donor characteristics, presence of delayed graft function, hospital length of stay, immunosuppression, total amount of anti-hypertensive drugs, previous or current use of angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB), and mean blood pressure. Laboratory data included proteinuria (24-hour proteinuria or urinary protein/creatinine ratio), serum creatinine, estimated GFR (eGFR, calculated with CKD-Epi formula), potassium, hemoglobin, and hematocrit.

Clinical and laboratorial data were registered at baseline (beginning of the treatment) and at every 3 months. Data were analyzed with the use of EpiInfo 7 (Centers for Disease Control, Atlanta, Ga); categorical data were compared by means of Bartlett test and numerical data by means of Student *t* test. Statistical significance was considered at a value of $P < .05$.

RESULTS

One hundred forty transplant recipients fulfilled the inclusion criteria. The majority (74.3%) were male, mean age was 48.8 ± 13.2 years, and previous dialysis therapy time was 42.6 ± 32.5 months. The majority of patients received a kidney from a deceased donor (78.6%), 18.7% of which were from an expanded criteria donor. A history of hypertension was observed in 96.1%, and diabetes in 15.7% of patients. Therapy with spironolactone was started 77.4 ± 83.5 months after transplant. Because of the large range of post-transplant proteinuria, patients were divided into 3 groups, according to proteinuria levels at the beginning of spironolactone therapy: low (proteinuria <1 g/24 h; n = 2 7), intermediate (proteinuria ≥1 and <3 g/24 h; n = 82), and nephrotic (proteinuria ≥3 g/24 h; n = 27). The 3 groups were comparable for demographic data, including primary renal disease. The nephrotic group had a lower incidence of kidneys received from deceased donors and a lower incidence of mTOR inhibitor therapy. The higher use of mTOR inhibitors was observed in the low proteinuria group ($P < .05$) (Table 1).

In patients with proteinuria ≥1 g/d (intermediate and nephrotic groups), we observed a significant reduction in proteinuria after 6 months of therapy, and this effect persisted as long as 12 months. Half of patients from the intermediate group and a third from the nephrotic group had proteinuria ≤1 g/d after 12 months of therapy (Fig 1).

The nephrotic group presented a lower eGFR at baseline. During the 12 months of follow-up, we observed a subtle reduction in eGFR in all groups that was not statistically significant. Blood pressure remained stable during the 1-year period (Fig 2). Adverse events, such as hyperkalemia and/or hypotension, were not observed in these patients, with no need for therapy withdrawal.

DISCUSSION

Spironolactone can be a safe alternative therapy for post-transplant proteinuria. In this series, after 12 months of therapy, no drug withdrawal caused by adverse events was observed. The best effects were observed in proteinuria ≥1 g/d, without renal function deterioration. In patients with