Influence of Renin-Angiotensin System Blockers on Graft Function in Retrospective Analysis of Pairs of Renal Transplant Recipients From the Same Donor

A. Zakrzewska[a], L. Tylicki[b,*], and A. Debska-Slizien[a]

[a]Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland; and [b]Unit of Clinical Pharmacology in the Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland

ABSTRACT

Background. Renin-angiotensin system (RAS) blocking agents efficiently control hypertension in renal transplant recipients (RTRs), and reduce proteinuria and post-transplant erythrocytosis. A beneficial effect on the retardation of the long-term decline in renal function has not yet been demonstrated. The aim of the study was to evaluate the effects of RAS blockade on allograft function.

Methods. In order to minimize donor variability and bias, 33 pairs of RTRs receiving grafts from the same donor were included into the retrospective analysis. A total of 66 RTRs were enrolled in which 1 patient from the pair used an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for a minimum period of 60 months (RAS[+]) and the second one did not use it at all (RAS[-]).

Results. There were no differences between RAS(+) and RAS(-) subjects in terms of age, body mass index, mismatches number, duration of total ischemia, episodes of cytomegalovirus infections, acute rejections, or immunosuppressive treatment. Significantly, more RAS(+) patients presented with diabetes and cardiovascular complications. Among RAS(+) patients, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were used in 28 (84.84%) and 5 (15.15%) patients in a mean dose of 23.03 ± 16.83% and 30 ± 11.18% of their maximum doses, respectively. There were no significant differences in estimated glomerular filtration rate changes (−0.37 ± 12.68 vs 2.54 ± 20.76 mL/min) and serum creatinine changes (0.05 ± 0.39 vs 0.14 ± 0.79 mg/dL) between RAS(+) and RAS(-) patients during the 60 months follow-up.

Conclusion. Agents inhibiting the RAS did not significantly affect graft function in RTRs during 60 months of observation.

RENIN-ANGIOTENSIN SYSTEM (RAS) blocking agents efficiently control post-transplant hypertension and are useful to reduce proteinuria and for treating post-transplant erythrocytosis in renal transplant recipients (RTRs). There is, however, still considerable controversy over the benefits of RAS blockade in long-term graft survival [1,2]. Although a beneficial effect on the retardation of the long-term decline in renal function has not yet been demonstrated, it is reasonable to assume that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) display in RTRs properties at least similar to those seen in non-transplanted patients with renal diseases of native kidneys [3]. There is evidence suggesting that RAS plays a role in the development of progressive chronic allograft injury [4,5]. The intrarenal RAS

The paper was supported by educational grant ST 02-0004/07/122 of the Medical University of Gdansk.

*Address correspondence to Prof. Leszek Tylicki, MD, PhD, Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, 80-952 Gdansk, Debinki 7, Poland. Phone and Fax: +48 58 349 25 05. E-mail: leszek.tylicki@gumed.edu.pl

0041-1345/18
https://doi.org/10.1016/j.transproceed.2018.02.113

has been recognized as a growth promoter that contributes to renal fibrosis and arteriosclerosis with deterioration of graft function. Angiotensin II, a locally renal-produced growth factor, regulates recruitment and activation of inflammatory and resident cells with increased synthesis of extracellular matrix [6]. There is also evidence that chronic cyclosporine nephrotoxicity is mediated by RAS [7]. To shed more light on this subject, we performed a retrospective analysis on the effects of RAS blockade on graft function in pairs of RTRs receiving grafts from the same donor.

METHODS

A retrospective analysis was carried out between March 2014 and December 2015. The data was collected from the patients' database of the Outpatient Transplantation Unit of Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland. The study population consisted of pairs of RTRs receiving grafts from the same donor between 2002 and 2012 who were under the supervision of our unit. Patients were included in the study when 1 recipient from the pair used an ACEI or ARB for a minimum period of 60 months (RAS [+]) and the second one did not use either (RAS[-]). The objective of the study was to establish the impact of RAS blockade on the change of glomerular filtration rate and serum creatinine from the baseline during the course of follow-up [$T_{(5)}$-$T_{(0)}$]. The estimated glomerular filtration rate (eGFR) was calculated according to the chronic kidney disease epidemiology collaboration (CKD-EPI) equation using data at baseline [$T_{(0)}$] and at visit after 60 months [$T_{(5)}$].

Data was evaluated using a Statistica (version 12.0, Stat Soft Inc., Palo Alto, Calif, United States) software package. The variables are expressed as mean value ± standard deviation (SD) or numbers or frequencies (percentages). The χ^2 test was performed to measure the differences between selected categories. The quantitative variables were assessed by Student's t test. $P < .05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

The characteristics of patients are presented in Tables 1 to 3. There were no differences between RAS(+) and RAS(-) subjects in terms of sex, age, body mass index, serum creatinine level and eGFR level, the reasons of end-stage renal disease, methods and time of dialysis before transplantation, or frequency of pre-emptive transplantations. Significantly, more RAS(+) patients presented with diabetes and cardiovascular complications ($P < .05$). RAS(+) and RAS(-) patients did not differ in terms of mismatches number, duration of cold and total ischemia, episodes of cytomegalovirus infections and acute rejections, or immunosuppressive treatment.

Table 1. General Characteristics of Studied Groups of Patients at the Beginning of Observation

Parameter	Patients (RAS[+]) n = 33	Patients (RAS[-]) n = 33	P
Sex, n			
F	10	12	NS
M	23	21	NS
Age (years)	46.45 ± 11.46	44.91 ± 13.72	NS
BMI (kg/m^2)	24.5 ± 3.88	23.87 ± 4.11	NS
Serum creatinine $T_{(0)}$ (mg/dL)	1.42 ± 0.32	1.4 ± 0.45	NS
eGFR $T_{(0)}$ (mL/min/1.73 m^2)	56.70 ± 12.9	60.51 ± 19.85	NS
Time of observation (months)	60		

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; F, female; M, male; NS, not significant; RAS, renin-angiotensin system.

Table 2. Comorbidities in Patients Receiving or Not Receiving Renin-Angiotensin System Blockers

Diagnosis	Patients (RAS[+]) n (%)	Patients (RAS[-]) n (%)	P
Diabetes	12 (36.36%)	5 (15.15%)	.048
Hypertension	33 (100%)	32 (96.97%)	NS
Cardiovascular diseases	11 (33.33%)	3 (9.09%)	.016

Abbreviations: NS, not significant; RAS, renin-angiotensin system.

Usage of RAS Agents and Influence on Graft Function

ACEIs were applied by 28 (84.84%) and ARBs by 5 (15.15%) patients in the RAS(+) group. Patients treated with ARBs were receiving these drugs in 30 ± 11.18% of their maximal doses, whereas ACEIs were given in 23.03 ± 16.83% of their maximal doses. There were no significant differences in eGFR (CKD-EPI) changes and serum creatinine changes between RAS(+) and RAS(-) patients during the course of the follow-up of 60 months (Fig 1).

DISCUSSION

Despite the important physiological role, long-lasting stimulation of RAS also plays a crucial role in processes connected with kidney lesions as well as with progression of chronic kidney diseases. The 2 major ways in which the RAS perpetuates renal impairment are through hemodynamic effects and remodeling. Firstly, the activation of the RAS

Table 3. Characteristics of Transplantation Period in Patients Receiving or Not Receiving Renin Angiotensin System Blockers

Data	Patients (RAS[+]) n = 33	Patients (RAS[-]) n = 33	P
Ischemia time (minutes)			
Cold	665.7 ± 219	684.5 ± 256.3	NS
Total	694.56 ± 218.68	713.33 ± 257.23	NS
Number of HLA mismatches	3.27 ± 1.13	3.21 ± 1.29	NS
Acute rejections, n (%)	11 (33.33%)	5 (15.15%)	NS
CMV infections, n (%)	5 (15.15%)	9 (27.27%)	NS
Immunosuppression, n			
Mycophenolate mofetil	28	27	NS
Mycophenolate sodium	2	4	NS
Tacrolimus	13	13	NS
Cyclosporine	22	24	NS
Everolimus/sirolimus	2	0	NS
Azatioprine	6	6	NS
Antibodies induction	1	2	NS

Abbreviations: CMV, cytomegalovirus; HLA, human leukocyte antigen; NS, not significant; RAS, renin-angiotensin system.