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Angiotensin-II receptor antagonist losartan reduces microalbuminuria in hypertensive renal transplant recipients

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Abstract: In recent years, it has been demonstrated that losartan lowers macroproteinuria in diabetic or non-diabetic renal transplant recipients (RTx) similar to angiotensin converting enzyme (ACE) inhibitors. Microalbuminuria (MAU) may reflect subclinical hyperfiltration damage of the glomerulus. It could be a marker of kidney dysfunction in renal transplantation. The aim of the study was to assess the efficacy of losartan in hypertensive RTx with MAU. This study was conducted in 17 (M/F: 4/13) stable RTx. No change was made in the medical treatment of the patients. All cases received 50 mg/day losartan therapy for 12 wk. Renal functions and MAU were determined 12 and 6 wk and just before the treatment as well as sixth and twelfth week of the treatment in all patients. Losartan satisfactorily lowered systemic blood pressure. A significant reduction in MAU was observed from 103 ± 53 μg/min at the beginning to 59 ± 25 μg/min in the sixth week and 47 ± 24 μg/min in the twelfth week ($p = 0.0007$ and 0.0005, respectively). From the sixth week of the treatment, the therapy significantly decreased hemoglobin, hematocrit and erythrocyte levels but did not change mean leukocyte and platelet counts, urea, creatinine levels and creatinine clearances. No serious side-effect was observed during the study.
In conclusion, we found that losartan decreased MAU in hypertensive RTx. For that reason, it might be considered as the first choise antihypertensive agent for the renoprotection in selected patients.

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Hypertension is a frequently observed condition after renal transplantation (1). The presence of hypertension, particularly, raised systolic blood pressure has a striking effect on long-term graft survival besides its effect on cardiovascular and cerebrovascular morbidity (2). In addition, proteinuria, developing after renal transplantation may influence allograft and patient outcomes. In a recent study, it has been demonstrated that the type of post-transplant proteinuria had a stronger effect on allograft outcome than its severity (3). However, there are few studies regarding microalbuminuria (MAU), subclinical albumin excretion >20 μg/min, in this population (4–7). It has been suggested that MAU could be a marker of kidney dysfunction in renal transplantation (7).

In our previous study, we demonstrated that angiotensin II antagonist losartan decreased proteinuria in patients with primary glomerulopathy as the angiotensin converting enzyme (ACE) inhibitors (8–10). Although there are studies dealing with the effects of losartan on prominent proteinuria in renal transplant cases, we did not come over a study investigating the relationship between MAU and losartan treatment in the literature (11, 12). Therefore, we aimed to investigate the effect of losartan on renal functions, MAU, blood pressure and hematologic parameters in this patient group.

Patients and methods

Non-diabetic and non-nephrectomized, hypertensive renal transplant recipients (RTx) who were treated in our transplantation outpatient clinic for more than 1 yr after transplantation were evaluated. Their clinical statuses, all routine biochemical and hematologic parameters were studied. Patients who had urinary tract infection, leukocyturia, a positive determination of total urinary protein, hyperpotassemia, a creatinine clearance < 30 mL/min, smoking, taking diuretic or ACE inhibitors and suspected renal artery stenosis were excluded from the study.

After this evaluation, 17 (4 male, 13 female) RTxs with MAU were included in the study. Five of them had been transplanted from cadaveric donors while the rest from living donors. The mean age of all cases was 34 ± 7.5 yr (16–50). The mean duration of transplantation was 62.8 ± 39.0 months (15–136). The average body mass index was 24.8 ± 3.0 kg/m^2. The diagnosis of the cases were as follows: 11 chronic glomerulonephritis, two chronic pyelonephritis and four unknown. Their average urinary albumin excretions were 111 ± 75 μg/min. The average hemoglobin values of all cases were higher than 12 g/dL, serum creatinine levels were lower than 2 mg/dL and creatinine clearances were higher than 30 mL/min.

They were using calcium channel blockers as antihypertensive agents. The mean systolic blood pressures of the cases were 131.1 ± 11.8 mmHg and diastolic blood pressures were 91.6 ± 9.2 mmHg. No change was made in the medical treatment of the patients. The combination protocols of the immunosuppressive treatment of cases were: prednisolone (PRD) + azothiopyrine (AZO) + cyclosporin A (CyA) in 13 cases, PRD + AZO in three cases and PRD + CyA in one case. Their average dosages were as follows: 10 ± 2.6 mg/day PRD, 78 ± 25 mg/day AZO and 84 ± 25 mg/day CyA.

All cases received 50 mg/day losartan for 12 wk. After cases had a rest for 15 min, two blood pressure measurements were obtained in supine position twice with 5-min intervals and their average was taken. Hemoglobin, hematocrit and leukocyte counts, serum urea, creatinine, uric acid, natrium, potassium, chloride, calcium, phosphorus, total protein, albumin levels, creatinine clearance and MAU levels were determined 12 and 6 wk, just before the treatment. The tests were repeated in the sixth and twelfth week of the treatment in all patients. The MAU was determined with radioimmunoassay method using albumin double antibody (Diagnostic Products Corporation, Los Angeles, CA, USA) kit. The expected range of the values were 20–200 μg/min. Hematologic and biochemical parameters were measured with Sysmex 2000 and Technicon (Technicon Instruments Corp., Tarrytown, NY, USA) otoanalyser machines, respectively. Creatinine clearance was studied in 24-h urine collection. It was corrected according to body surface area.

Statistical analysis for numerical variables was performed using paired Student's *t*-test and Wilcoxon signed test, when necessary. The correlation analysis was performed with Pearson *r* correlation test. All numerical variables were given as mean ± standart deviation (SD) and p-values < 0.05 were considered to be significant.

Results

Starting from the sixth week of the treatment, losartan therapy decreased MAU which was statistically significant but did not change serum urea, creatinine and creatinine clearance levels (Table 1). No acute renal function impairment was observed after the initiation of losartan therapy. Six weeks after the treatment, the uric acid, total protein, natrium and phosphorus levels of the patients were found to be decreased. The changes occurred in the twelfth wk of losartan therapy were not statistically significant.

Table 1. The changes in MAU, creatinine clearance (CrCl), serum urea and creatinine values of cases

	−Twelfth week	−Sixth week	Pre-T	+Sixth week	+Twelfth week
MAU (μg/min)	107 ± 61[a]	108 ± 62[a]	103 ± 53	59 ± 25[b]	47 ± 24[c]
CrCl (mL/min)		67 ± 18[a]	68 ± 19	64 ± 16[a]	66 ± 17[a]
Urea (mg/dL)		36 ± 7[a]	39 ± 10	37 ± 8[a]	38 ± 8[a]
Creatinine (mg/dL)		1.24 ± 0.21[a]	1.20 ± 0.28	1.2 ± 0.25[a]	1.24 ± 0.23[a]

[a] $p > 0.05$, compared with the pre-treatment values.
[b] $p = 0.0007$, compared with the pre-treatment values.
[c] $p = 0.0005$, compared with the pre-treatment values.

Table 2. The changes in serum levels of other renal parameters of cases

	–Sixth week	Pre-T	+Sixth week	+Twelfth week
Uric acid (mg/dL)	5.8 ± 1.6[a]	5.6 ± 1.9	4.8 ± 1.3[b]	5.1 ± 1.7[a]
T.protein (g/dL)	7.3 ± 0.5[a]	7.1 ± 0.4	6.9 ± 0.4[b]	6.9 ± 0.3[a]
Albumin (mg/dL)	4.4 ± 0.42[a]	4.3 ± 0.3	4.3 ± 0.4[a]	4.2 ± 0.2[a]
Natrium (mEq/L)	142 ± 3.0[a]	142.3 ± 2.8	140.8 ± 2.4[b]	141.2 ± 2.9[a]
Potassium (mEq/L)	3.9 ± 0.53[a]	3.9 ± 0.54	4.12 ± 0.45[a]	4.0 ± 0.43[a]
Chloride (mEq/L)	104.2 ± 3.9[a]	104.8 ± 2.2	103.6 ± 3.9[a]	104.1 ± 4.4[a]
Phosphorus (mg/dL)	3.54 ± 0.41[a]	3.52 ± 0.28	3.24 ± 0.32[b]	3.46 ± 0.36[a]
Calcium (mg/dL)	9.88 ± 0.46[a]	9.82 ± 0.44	9.72 ± 0.60[a]	9.80 ± 0.47[a]

[a] $p > 0.05$, compared with the pre-treatment values.
[b] $p < 0.05$, compared with the pre-treatment values.

Potassium concentrations remained statistically unchanged throughout the whole treatment period (Table 2).

The mean hemoglobin and hematocrit values of the cases were found to be decreased (from 13.7 ± 1.7 to 12.4 ± 1.8 g/dL and from 41.7 ± 6.2 to 36.7 ± 5.4%, respectively, $p < 0.01$) while the body weights, mean leukocyte and platelet counts were significantly unchanged.

After losartan therapy, the systolic and diastolic blood pressures of cases were significantly decreased (from 131.1 ± 11.8 to 122.5 ± 9.7 mmHg, $p < 0.0001$ and 91.6 ± 9.2 to 83 ± 8 mmHg, $p < 0.001$, respectively). The percentage changes in systolic and diastolic blood pressures were −7.5 ± 6.4 and −8.1 ± 7.0%, respectively. The percentage changes in MAU levels of the cases were −48.5 ± 24% after losartan treatment. There was no correlation between the decrement in systolic (r: 0.02215, $p > 0.05$) and diastolic (r: −0.04454, $p > 0.05$) blood pressures and the reduction in MAU.

The blood levels of CyA did not significantly change during the study period. No need for CyA dosage change was observed. All cases tolerated losartan therapy well. Adverse effects like hypotension and cough were observed in none of the cases.

Discussion

The prevalence of MAU in patients with essential hypertension varies between 5 and 37% in different studies (13). Microalbuminuria may be a marker of diffuse vascular abnormalities predisposing to cardiovascular disease and/or hypertensive renal disease heralding future renal failure (14, 15). Consequently, MAU is suggested to be a marker of end-organ damage. Some reports state that MAU is a sensitive but not a very specific marker of renal dysfunction in renal transplantation (5, 6). Diamond et al. demonstrated an association between progressive albuminuria and a decrease in glomerular filtration rate with the development of significant glomerulosclerosis in a model of chronic allograft rejection in the rat (16). In another study, it was found that serum creatinine levels were significantly higher in RTxs with positive MAU and correlated with urinary albumin excretion (7). The increase in proteinuria in RTxs might be a manifestation of glomerular injury, with impaired glomerular permselectivity associated with a diminished renal function.

Recently, ACE inhibitors and angiotensin II antagonists have been widely used in the treatment of hypertension and post-transplant erythrocytosis of RTxs. It has been reported that both groups are generally effective antihypertensives and are safe (17). Because of its hemodynamic, metabolic and growth promoting effects, angiotensin II may play an important role in the progression of renal disease (18). Currently, ACE inhibitors and angiotensin II receptor antagonists are commonly used for the renoprotective purpose in non-diabetic or diabetic renal disease. In our study, losartan treatment significantly decreased MAU in RTxs. Indeed, an effective decrement in blood pressures of our cases might result in a substantial decrease in their MAU. But, we demonstrated that there was no significant correlation between the decrements in both parameters.

Transforming growth factor-beta (TGF-β) is the main cytokine involved in the fibrotic process that is involved in chronic rejection. Angiotensin II up-regulates TGF-β production. Experimental data showed a reduction of TGF-β induced fibrosis either with losartan or enalapril in a chronic CyA nephrotoxicity model (19). Inigo et al. compared the effects of losartan and amlodipine on renal hemodynamics, TGF-β and endothelin-1 plasma levels in RTxs who had normal renal function and who were treated with CyA (20). Both of the drugs had opposite effects on renal hemodynamics and only losartan reduced the plasma levels of TGF-β. These

features can be important for the management of chronic allograft nephropathy.

As a result, we came to the conclusion that losartan can be used safely especially in hypertensive RTxs for renoprotective purposes because of its MAU decreasing effect. Whether these effects might protect the graft and, thus, prevent the progression of renal disease requires further long-term investigation in larger groups.

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