Effect of Angiotensin II Type-1 Receptor Blockers on Stable Allograft Kidneys: Prospective Randomized Study

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ABSTRACT

Objective. Is assess the effects of angiotensin II type-I receptor blockers on outcomes in renal transplant recipients without proteinuria or posttransplantation erythrocytosis.

Patients and Methods. Fifty renal transplant recipients (30 men and 20 women, with a mean [SD] age of 40 [13] years) were randomized into 2 groups of 25 patients each; 1 group was treated with losartan for 1 year, and the other was not (control group). Blood pressure and other biochemical parameters were measured at baseline and at 6 and 12 months posttransplantation.

Results. After 1 year, the losartan group had significantly lower systolic blood pressure (113 [22] mm Hg vs 126 [18] mm Hg; $P = .04$) and hemoglobin concentration (12.8 [1.9] g/dL vs 14.5 [2.1] g/dL; $P = .006$) and significantly higher serum high-density lipoprotein cholesterol concentration (58 [22] mg/dL vs 47 [10] mg/dL; $P = .03$) compared with the control group; however the incidence of anemia did not differ (37% vs 20%; $P = .20$). In the losartan group, there were significant changes in hemoglobin concentration between baseline and 6 months (14.5 [1.6] g/dL vs 12.9 [1.49] g/dL; $P < .001$), but not between 6 and 12 months (12.9 [1.49] g/dL vs 12.8 [1.96] g/dL; $P = .43$). After 1 year, there were no significant between-group differences in diastolic hypertension, serum creatinine concentration, creatinine clearance, and serum potassium, low-density lipoprotein cholesterol, triglyceride, and uric acid concentrations.

Conclusion. Losartan significantly increased high-density lipoprotein concentration and significantly decreased systolic hypertension. Although losartan decreased the hemoglobin concentration during the first 6 months, its effect did not progress with longer use. To determine the effect of losartan on renal function, additional studies with longer follow-up are needed.

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ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs) are used in renal transplant recipients[1–3] to treat hypertension,[2–6] proteinuria and chronic rejection,[7–9] and posttransplantation erythrocytosis.[10,11] We assessed the effects of ARBs on stable allograft kidney recipients without proteinuria or erythrocytosis and without considering existing hypertension.

MATERIALS AND METHODS

Patients and Study Design

Between February and May 2006, we evaluated all consecutive unrelated living donor renal transplant recipients older than 18 years who had received transplants at least 6 months earlier. Exclusion criteria included a history of taking angiotensin-converting enzyme (ACE) inhibitors or ARBs, serum creatinine concentration greater than 2.5 mg/dL, serum potassium concentration greater than 5.5 mEq/L, and renal transplant artery stenosis. No patient had proteinuria, erythrocytosis (hematocrit >51%), or a history of smoking. All patients were taking cyclosporine and prednisolone, and some were taking mycophenolate mofetil (n = 39) or azathioprine (n = 9). The study protocol was approved by the ethics committee of our institution, and informed consent was obtained from each patient.

Patients were randomized to receive losartan, 50 mg/d, or no losartan. Patients with hypertension were allowed medication except for ACE inhibitors and ARBs. Blood pressure, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) creatinine clearance (CCr), and other biochemical profiles were evaluated at baseline and after 6 and 12 months of treatment. Anemia was defined as a hemoglobin concentration less than 13.5 g/dL in men and less than 12 g/dL in women. Creatinine clearance was calculated for men using the Cockcroft-Gault equation (CCr [mL/min] = [140 − age) × lean body weight [kg]/Cr [mg/dL] × 72), and was multiplied by 0.85 for women. Serum creatinine, potassium, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglyceride, HGB, and uric acid concentrations were measured by standard methods. Serum samples were drawn after 12-hour fasting. Cyclosporine trough levels were measured using automated clinical chemistry analysis.

Statistical Analysis

The paired or unpaired *t* test was used for continuous variables with normal distribution, and the χ^2 or Fisher exact test was used for categorical variables. Statistical significance was established at $P < .05$. All data were analyzed with commercially available software (SPSS version 13 for Windows; SPSS Inc., Chicago, Ill).

RESULTS

At 1 year, there were no between-group differences in mean number and class (type) of blood pressure medications and use of hydroxymethylglutaryl CoA reductase inhibitors, fibric acid derivatives, allopurinol, folic acid, and ferrous sulfate. No the patients received nicotinic acid. Immunosuppression was also similar in both groups. Age, sex, BMI, time since transplantation, episodes of acute rejection before study, frequency of hypertension and diabetes, and cyclosporine trough levels did not differ significantly between the 2 groups (data not shown). During follow-up, there were no acute rejection episodes and no graft losses.

The effects of losartan on serum creatinine concentration, CCr, systolic and diastolic hypertension, and other biochemical findings at baseline and after 6 and 12 months are given in Table 1. After 1 year, the losartan group had significantly lower mean (SD) systolic pressure compared with the control group (113 [17.6] mm Hg vs 126 [22] mm Hg; $P = .04$); however, the 2 groups did not differ significantly in diastolic hypertension (Table 1). Although the losartan group had lower CCr than the control group at 1 year, the difference was not significant (71 [24.8] mL/min vs 80 [23.6] mL/min; $P = .22$) (Table 1). At 1 year, the losartan group had significantly higher serum HDL (58 [22.4] mg/dL vs 46 [10.6] mg/dL; $P = .03$) (Table 1) and significantly

Table 1. Clinical and Laboratory Data*

Variable	Baseline	6 Months	12 Months
Blood pressure, mm Hg			
Systolic			
Losartan group	129 (16.3)	117 (21.4)	113 (17.6)
Control group	126 (12.3)	119 (28.6)	126 (22)
P value	.40	.80	.03
Diastolic			
Losartan group	85 (9.3)	77 (12.5)	78 (11)
Control group	82 (10)	79 (11.4)	71 (25.4)
P value	.30	.50	.20
Creatinine, mg/dL			
Losartan group	1.2 (0.34)	1.1 (0.33)	1.2 (0.34)
Control group	1.2 (0.31)	1.1 (0.33)	1.1 (0.23)
P value	.90	.90	.38
CCr, mL/min			
Losartan group	71 (16.4)	71 (16.4)	71 (24.8)
Control group	78 (30.4)	78 (30.4)	80 (23.6)
P value	.20	.20	.20
HGB, g/dL			
Losartan group	14.5 (1.6)	12.9 (1.49)	12.8 (1.96)
Control group	14.7 (2.17)	14.6 (2.27)	14.5 (2.17)
P value	.70	.003	.006
Serum potassium, mEq/L			
Losartan group	4.4 (0.5)	4.6 (0.49)	4.4 (0.43)
Control group	4.5 (0.42)	4.5 (0.42)	4.6 (0.44)
P value	.30	.40	.10
LDL, mg/dL			
Losartan group	103 (35.2)	102 (36.1)	94 (49.2)
Control group	115 (42.3)	120 (46.2)	114 (41.4)
P value	.30	.10	.10
HDL, mg/dL			
Losartan group	50 (9.3)	49 (13.4)	58 (22.4)
Control group	47 (6.6)	46 (12.3)	46 (10.6)
P value	.20	.37	.03
Triglycerides, mg/dL			
Losartan group	163 (74.1)	178 (93.5)	172 (89.4)
Control group	165 (68.9)	178 (78.1)	180 (71.2)
P value	.80	.90	.70
Uric acid, mg/dL			
Losartan group	6.2 (2.13)	5.2 (1.43)	6 (1.7)
Control group	6.8 (1.3)	5.8 (1.02)	6.4 (1.17)
P value	.20	.10	.30

CCr, creatinine clearance; HGB, hemoglobin concentration; HDL, high-density lipoprotein; LDL, low density lipoprotein.
*Values are given as mean (SD).

lower HGB (12.8 [1.96] g/dL vs 14.5 [2.1] g/dL; $P = .006$) than the control group. Within the losartan group, there were significant changes in HGB between baseline and 6 months (14.5 [1.6] g/dL vs 12.9 [1.49] g/dL; $P < .001$) and between baseline and 12 months (14.5 [1.6] g/dL vs 12.8 [1.96] g/dL; $P < .001$); however, the difference between 6 and 12 months was not significant (12.9 [1.49] g/dL vs 12.8 [1.96] g/dL; $P = .43$). At the end of the study, the frequency of anemia was higher in the losartan group than in the control group (9 patients [37%] vs 5 patients [20%]; $P = .20$); however, the difference was not significant. Other biochemical profiles did not differ between the 2 groups after 1 year (Table 1). Adverse effects of losartan included hypotension, hyperkalemia, and muscle spasm in 1 patient each.

DISCUSSION

We evaluated the effect of losartan on renal transplant recipients who had no proteinuria or posttransplantation erythrocytosis (PTE), with only 50% having hypertension. We found that HGB concentration decreased 6 months after transplantation but did not progress during the next 6 months. Although the losartan group had lower HGB concentrations, the incidence of anemia was not higher.

Previous studies have shown that losartan decreases HGB concentration in patients with PTE.[11–13] Moreover, Ersoy et al[3] showed that 43% of renal transplant recipients without PTE developed anemia with losartan treatment; however, the patients were followed up for only 3 weeks. To our knowledge, the present study is the first to report that losartan increased HDL concentration in renal transplant recipients. However, there were no between-group differences in the use of statins or fibrates. We also found that losartan did not alter LDL or triglyceride concentrations after 1 year. A previous study[14] showed that losartan did not affect the lipid profile in renal transplant recipients; in that study, however, follow-up was short (8 weeks) and fibrate and statin use was not compared.

We found that losartan significantly decreased systolic but not diastolic hypertension. Although 50% of these patients were normotensive, only 1 had hypotension. The more pronounced effect of losartan on hypertension compared with other hypertension drugs has been observed in hypertensive transplant recipients.[2,5]

Similar to previous studies,[6,15] we found that losartan had no effect on allograft function. Longer follow-up studies, however, are needed to confirm the effects of ARBs on renal function. Although ARBs increase secretion of uric acid in urine and hyperkalemia, and decrease serum uric acid concentration,[16,17] we found that losartan had no effect on serum uric acid concentration. Moreover, only 1 of our losartan-treated patients developed hyperkalemia.

In conclusion, we found that treatment with ARBs is safe and effective in stable allograft kidney recipients without proteinuria or PTE and without considering existing hypertension. Losartan significantly increased HDL concentration and significantly decreased systolic hypertension. Although losartan decreased HGB during the first 6 months, a further effect was not observed with longer use. No patient developed anemia after ARB treatment. To determine the effect of losartan on renal function, further studies with longer follow-up are needed.

REFERENCES

1. Tylicki L, Biedunkiewicz B, Chamienia A, et al: Renal allograft protection with angiotensin II type 1 receptor antagonists. Am J Transplant 7:243, 2007

2. Formica RN Jr, Friedman AL, Lorber MI, et al: A randomized trial comparing losartan with amlodipine as initial therapy for hypertension in the early post-transplant period. Nephrol Dial Transplant 21:1389, 2006

3. Ersoy A, Kahvecioglu S, Ersoy C, et al: Anemia due to losartan in hypertensive renal transplant recipients without post-transplant erythrocytosis. Transplant Proc 37:2148, 2005

4. Holgado R, Anaya F, Del Castillo D: Angiotensin II type 1 (AT1) receptor antagonists in the treatment of hypertension after renal transplantation. Nephrol Dial Transplant Suppl 1:117, 2001

5. El-Agroudy AE, Hassan NA, Foda MA, et al: Effect of angiotensin II receptor blocker on plasma levels of TGF-beta 1 and interstitial fibrosis in hypertensive kidney transplant patients. Am J Nephrol 23:300, 2003

6. Ersoy A, Dilek K, Usta M, et al: Angiotensin-II receptor antagonist losartan reduces microalbuminuria in hypertensive renal transplant recipients. Clin Transplant 16:202, 2002

7. Montanaro D, Gropuzzo M, Tulissi P, et al: Renoprotective effect of early inhibition of the renin-angiotensin system in renal transplant recipients. Transplant Proc 37:991, 2005

8. Tanji N, Ohoka H, Shimamoto K, et al: Effects of angiotensin II receptor blocker on proteinuria in renal transplant recipients. In Vivo 18:433, 2004

9. Wang PX, Fan MQ, Huang CB, et al: Effect of losartan on slowing progression of chronic allograft nephropathy. Chin Med Sci 20:231, 2005

10. Yildiz A, Cine N, Akkaya V, et al: Comparison of the effects of enalapril and losartan on posttransplantation erythrocytosis in renal transplant recipients: prospective randomized study. Transplantation 72:542, 2001

11. Celik A, Ok E, Unsal A, et al: Comparison of enalapril and losartan in the treatment of posttransplant erythrocytosis. Nephron 86:394, 2000

12. Iñigo P, Torregrosa JV, Campistol JM, et al: Treatment with losartan in kidney transplant recipients with posttransplant erythrocytosis. Transplant Proc 31:2321, 1999

13. Julian BA, Brantley RR Jr, Barker CV, et al: Losartan, an angiotensin II type 1 receptor antagonist, lowers hematocrit in posttransplant erythrocytosis. J Am Soc Nephrol 9:1104, 1998

14. Noroozianavval M, Argani H, Aghaeishahsavari M, et al: Renin-angiotensin system polymorphisms and hemoglobin level in renal allografts: a comparative study between losartan and enalapril. Transplant Proc 39:1018, 2007

15. Kim W, Lee S, Kang SK, et al: Effects of angiotensin converting enzyme inhibitor and angiotensin II receptor antagonist therapy in hypertensive renal transplant recipients. Transplant Proc 34:3223, 2002

16. Schmidt A, Gruber U, Böhmig G, et al: The effect of ACE inhibitor and angiotensin II receptor antagonist therapy on serum uric acid levels and potassium homeostasis in hypertensive renal transplant recipients treated with CsA. Nephrol Dial Transplant 16:1034, 2001

17. Bakris GL, Siomos M, Richardson D, et al: VAL-K Study Group: ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. Kidney Int 58:2084, 2000