ELSEVIER

Renin-Angiotensin System Dual Blockade Using Angiotensin Receptor Plus Aliskiren Decreases Severe Proteinuria in Kidney Transplant Recipients

V. López, M. Martin, C. Cobelo, P. Aranda, M. Cabello, E. Sola, C. Gutierrez, D. Burgos, D. Martínez, and D. Hernandez

ABSTRACT

Background. Renin-angiotensin system (RAS) blockade has cardioprotective and renoprotective effects in the general population; however, whether dual blockade using angiotensin-receptor blockade (ARB) plus a renin inhibitor, aliskiren, can minimize severe proteinuria in kidney transplant recipients remains undetermined.

Objective. To analyze the efficacy and safety of dual blockade of the RAS with an ARB and aliskiren in kidney transplant recipients with severe proteinuria and creatinine concentration 2.5 mg/dL or less.

Patients and Methods. This prospective study included 16 patients (mean age 56 years; 10 men [62%] who had undergone cadaveric renal transplantation between 1992 and 2004. Immunosuppression therapy included a calcineurin inhibitor in 9 patients (56%) or mammalian target of rapamycin inhibitor in 7 (44%), and mycophenolate mofetil in 15 (94%). All received high-dose ARB II (1.0–3.5 g/24 h) because of marked proteinuria, with poor response. Accordingly, 11 patients also received aliskiren, and in 5 who were receiving an angiotensin-converting enzyme inhibitor, therapy was changed to aliskiren. Mean (range) follow-up was 11 (3–18) months.

Results. At 3 months, proteinuria decreased by 40%, and at 6 months by 60%. In addition, mean blood pressure was decreased significantly. Renal function remained stable, as did the serum potassium concentration. A slight but significant decrease in hemoglobin concentration was observed, with no clinical repercussions.

Conclusions. Dual blockade of the RAS with ARB II plus aliskiren therapy demonstrated an additive effect to decrease severe proteinuria and blood pressure in kidney transplant recipients. Neither relevant adverse effects in renal function nor anemia or hyperkalemia were observed. These findings might contribute to prolonging long-term kidney graft survival.

COMBINED THERAPY with angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria and delays progression of both diabetes-associated[1] and nondiabetes-associated[2] chronic kidney disease in the general patient population. Several trials have documented their effectiveness in preventing cardiovascular morbidity and mortality.[3] Renin-angiotensin system (RAS) blockade may decrease blood pressure, proteinuria, and polycythemia in kidney transplant recipients.[4] However, there is controversy insofar as the beneficial effect of RAS blockade on recipient survival.

Aliskiren, a direct inhibitor of plasma renin, decreases blood pressure and other angiotensin-related adverse effects such as proteinuria and cardiac enlargement.[5] A recent clinical trial demonstrated that aliskiren, 300 mg, decreased proteinuria in both patients with hypertension

From the Nephrology Department, Hospital Universitario Carlos Haya, Malaga, Spain.

Address reprint requests to Verónica López, MD, Nephrology Department, Hospital Universitario Carlos Haya, Malaga 29010, Andalucia, Spain.

0041-1345/–see front matter
doi:10.1016/j.transproceed.2010.07.053

Table 1. Effect of Aliskiren on Renal Function and Laboratory Values*

Variable	Baseline	Time Posttransplantation			
		3 Months	*P* Value	6 Months	*P* Value
MDRD4 equation, mL/min/1.73 m^2	48.1 (15.1)	49.3 (17.7)	.70	47.5 (13.8)	.50
Creatinine, mg/dL	1.68 (0.5)	1.66 (0.5)	.70	1.7 (0.5)	.20
Proteinuria, g/24 h	1.89 (0.8)	1.03 (0.6)	.005	0.82 (0.58)	.09
Blood pressure, mm Hg	99.7 (16.7)	77.4 (9.5)	.003	75.1 (8.9)	.005
Potassium, mEq/L	4.4 (0.6)	4.6 (0.7)	.30	4.6 (0.6)	.50
Hemoglobin, g/dL	12.3 (1.3)	11.8 (1.3)	.04	11.9 (0.8)	.02

MDRD, Modified Diet in Renal Disease.
*Values are given as mean (SD).

and those with diabetes mellitus who previously had received losartan therapy.[6] In addition, aliskiren may also decrease left ventricular hypertrophy in patients with hypertension.[7] However, the potential beneficial effects on severe proteinuria in kidney transplant recipients has not yet been elucidated. This preliminary study assessed the efficacy and safety of combined aliskiren plus ARB therapy in patients with proteinuria who had previously exhibited an inadequate response to ARB therapy.

PATIENTS AND METHODS

This observational prospective study included 16 patients (mean age, 56 years; 62% men) who had undergone kidney transplantation between 1992 and 2004. Immunosuppression therapy included a calcineurin inhibitor (CNI) in 9 patients (56%) or mammalian target of rapamycin (mTOR) inhibitor in 7 (44%), and mycophenolate mofetil in 15 (94%). In 6 of the 7 patients receiving mTOR, therapy was converted from a CNI, in 4 patients because of tumor, and in 2 because of CNI toxicity; only 1 patient had been receiving mTOR de novo.

All 16 patients had hypertension and proteinuria (1.0–3.5 g/24 h), for which they were treated, with poor response, with a high-dose ARB II: losartan (100 mg/24 h in 5 patients [31.3%] and 200 mg/24 h in 7 [43.8%]) or valsartan (320 mg/24 h in 3 patients [18.8%] or 640 mg/24 h in 1 [6.3%]). In 11 patients, aliskiren, 300 mg, was added, and the other 5 were also receiving an angiotensin-converter enzyme inhibitor, enalapril (20 mg/24 h), with poor response. Enalapril was changed to aliskiren, 300 mg. Blood pressure control was attempted with other medications including a β-blocker in 3 patients (19%), a calcium channel blocker in 6 (37%), an α-blocker in 25% (4), and a diuretic in 3 (19%). Mean (range) follow-up was 11 (3–18) months.

RESULTS

Clinical characteristics of the patients before and after treatment with aliskiren plus ARB are given in Table 1. Proteinuria was decreased by 40% at 3 months, and by 60% at 6 months. In addition, there was a significant decrease in mean blood pressure. Renal function, estimated from the glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD4) equation, compared with the worsening that had occurred during the 12 months before initiation of aliskiren therapy (Fig 1). The serum potassium concentration remained stable. There was a slight but significant decrease in hemoglobin concentration, with no clinical repercussions. In 1 patient, the drug was withdrawn because of symptoms related to decreased blood pressure.

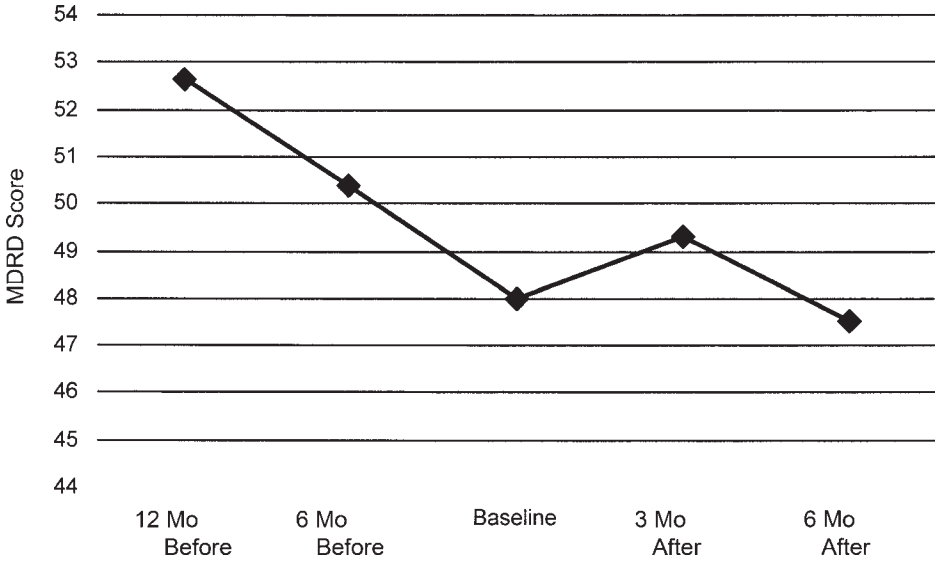

Fig 1. Changes in renal function from 12 months before to 6 months after initiation of aliskiren therapy. MDRD, Modification of Diet in Renal Disease.

DISCUSSION

Results of the present study demonstrate that combination therapy with aliskiren plus high-dose ARB reduced proteinuria in kidney transplant recipients. The benefit of RAS blockade on blood pressure and proteinuria in transplant recipients has been demonstrated previously; however, few data are available about dual blockade to decrease severe proteinuria. Proteinuria is a first-order risk factor for graft and patient survival. Thus, it is important to curb this factor with dual blockade when other strategies fail.

The most effective method of blocking the RAS is to prevent the effects of renin on angiotensinogen because this is the limiting step in the system. In addition, by acting on the initial point of activation, it reduces formation of both angiotensin I and angiotensin II without affecting kinin metabolism or producing increased plasma renin activity as a consequence of the angiotensin II escape phenomenon. Dual blockade of the RAS with aliskiren could produce more complete blockade of the system because it inhibits not only the actions mediated by angiotensin II but also those exerted by prorenin and renin via their receptor stimulation. These effects could result in greater protective effects on various target organs and greater reduction in cardiovascular and renal morbidity and mortality.

Dual blockade of the RAS may produce undesirable adverse effects including hyperkalemia, anemia, and decreased glomerular filtration. Although patients in the present study did not exhibit these adverse effects, close monitoring is vital, in particular in patients with moderate to severe renal dysfunction.

The present study has certain limitations: it was not randomized, and the sample size was small. Nevertheless, it substantially adds to the single case report.[8] in the literature. Randomized studies with more patients will be necessary to corroborate the present findings.

In conclusion, dual blockade of the RAS with an ARB plus aliskiren has additive effects to decrease severe proteinuria and elevated blood pressure in kidney transplant recipients. Neither relevant adverse effects on renal function nor anemia or hyperkalemia were observed. This effect could contribute to prolongation of graft survival.

REFERENCES

1. Lewia E, Hunsicker L, Bain R, et al: The effect of angiotensin-enzyme inhibition on diabetic nephropathy. N Engl J Med 329: 1456, 1993
2. Jafar T, Schmid C, Landa M, et al: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: a meta-analysis of patient-level in high-risk patients. N Engl J Med 342:145, 2000
3. Yusuf S, Sleight P, Pogue J, et al; Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 343:145, 2000
4. Cruzado M, Rico J, Grinyo M, et al: The renin angiotensin system blockade in kidney transplantation: pros and cons. Transp Int 21:304, 2008
5. Muller D, Derer W, Dechend R, et al: Aliskiren: mode of action and preclinical data. J Mol Med 86:659, 2008
6. Parving H, Persson F, Lewis J, et al; for the AVOID Study Investigators: Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 358:2433, 2008
7. Solomon S, Appelbaum E, Manning W; for the Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial Investigators: Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. Circulation 119:530, 2009
8. Freiberger V, Amann K, Heemann U, et al: Effect of a triple blockade of the renin-angiotensin system in recurrent focal segmental glomerulosclerosis after kidney transplantation. Transp Int 22:1110, 2009