Abstract. Introduction: Therapeutic approaches directed at reducing proteinuria are under development. The aim of the present study was to prospectively elucidate the impact of losartan treatment in renal transplant recipients with persistent proteinuria. Patients and Methods: Twenty-eight patients with persistent proteinuria or mild hypertension were assigned to receive losartan. Proteinuria was defined as a ratio of urinary protein to urinary creatinine \( (U_p/U_c) >0.5 \) in continual urinary tests in the outpatient setting. Results: All patients with mild hypertension reached target blood pressure (BP) with losartan treatment, but the change was not significant. In twelve patients with proteinuria before initiation of the study, urinary protein excretion was significantly reduced with treatment. No correlation was observed between reductions in proteinuria and mean BP. A significant decrease was identified in the hemoglobin concentration of patients with serum creatinine concentrations >2.0 mg/dl before the study. Discussion: Losartan efficiently reduces proteinuria in renal transplant recipients with adequate tolerance. Multicentric prospective studies are required to confirm its clinical effectiveness.

A dramatic improvement in the survival of renal allografts has occurred over the course of the last few decades, predominantly attributable to the introduction of cyclosporin A (CsA) in the early 1980s. However, chronic renal transplant failure (CRTF), one of the leading causes of terminal renal insufficiency (1), has remained problematic for clinicians. Approximately 20% of renal transplant patients enter maintenance dialysis because of allograft failure. Epidemiological studies have shown that urinary protein excretion represents a strong and independent predictor of renal outcome in patients with chronic native kidney disease (2). This, in some respects at least, shares some remarkable similarities with CRTF (3).

Several studies that have been undertaken using therapeutic strategies have proven beneficial in ameliorating proteinuria in patients with chronic native kidney diseases. One of these strategies has involved blockade of the renin-angiotensin-aldosterone system. In chronic native kidney disease, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) have been shown to slow progression of the disease (4, 5), probably by protecting the remaining nephrons after loss of a critical amount of renal mass (6). CRTF definitely represents a state of reduced numbers of nephrons, and ACE inhibitors might therefore exert positive effects on excretory allograft function. ACE inhibitors reduce proteinuria and similar effects might be expected with the use of ARBs in clinical settings. Losartan is the first of a number of non-peptide selective blockers of angiotensin II binding to type I angiotensin receptors on the cell membrane, thereby inhibiting the action of angiotensin II (7). We investigated whether losartan administration was effective in reducing proteinuria when given following renal transplantation.

Patients and Methods

Patients. A total of 51 renal transplant recipients (31 males, 20 females; mean age, 44 years), receiving CsA- or tacrolimus-based immunosuppression with methylprednisolone, were recruited from our outpatient clinic. All patients had undergone transplantation at least one year earlier and had displayed stable excretory allograft function for at least 6 months. Prior to the initiation of treatment, renal transplant artery stenosis was excluded using three-dimensional computed tomography.

Study design. This study was performed on an outpatient basis. Patients with persistent (>3 months) proteinuria or mild hypertension were assigned to receive losartan 25 or 50 mg for 6 months (ARB group; 20 males, 8 females; mean age, 43 years). Proteinuria was defined as a ratio of urinary protein to urinary creatinine \( (U_p/U_c) >0.5 \) in continual urinary tests in the outpatient setting. These urine samples were provided by patients with persistent proteinuria.
after careful instruction in proper collection methods. Mild hypertension was defined as a systolic blood pressure (BP) between 140 and 159 mmHg and a diastolic BP between 90 and 99 mmHg. To accurately evaluate the additive effects of losartan, all other agents or dietary habits were maintained throughout the study. No patients received concomitant antihypertensive medications. All patients in the ARB group tolerated losartan treatment without adverse effects. By way of comparison, 23 renal transplant recipients (11 males, 12 females; mean age, 44 years) without proteinuria or hypertension were selected and matched according to age, sex, height and body weight. The study was approved by the local human ethics committee and written informed consent was obtained from every patient prior to admission to the study.

Methods. Laboratory parameters were measured before and after treatment phase. Plasma samples were stored at -70°C until further analysis.

Statistical methods. All values are given as mean ± SD. Statistical significance (p<0.05) was determined by paired t-test or Dunnett’s t-test for multiple comparison using StatView Version 4.0 (Abacus Concepts, Berkeley, CA, USA).

Results

All patients with mild hypertension reached target BP (<130/85 mmHg) with losartan treatment, although this reduction was not significant due to the small number of patients. Hypotension was not documented. During the study period, all biochemical parameters (serum sodium, potassium, uric acid, albumin and TP) remained stable. No acute impairment of renal function was observed after initiation of losartan (Figure 1). CsA and tacrolimus trough levels remained stable throughout the course of the study.

In the patients with overt proteinuria before beginning the study (8 males, 4 females), urinary protein excretion was significantly reduced with treatment. Mean U_p/U_Cr decreased by 1.25, from 1.83 ± 1.04 to 0.58 ± 0.64 after 6 months of treatment (Figure 2), representing a significant difference (p<0.05). A reduction was already evident after 3 months on losartan. Moreover, new onset of proteinuria was not documented during the period on losartan in any non-proteinuric cases. No correlation was observed between reductions in proteinuria and mean BP (data not shown).

In the control group, the hemoglobin concentration did not change during the study. Moreover, no significant difference in hemoglobin concentration was observed between the ARB and control groups, either before or after treatment. However, when the ARB group was divided according to pre-treatment serum creatinine, a significant decrease in hemoglobin concentration was identified in patients with pretreatment serum creatinine >2.0 mg/dl. Hemoglobin levels after losartan treatment in patients with pre-treatment serum creatinine concentrations ≤ and >2.0 mg/dl were 12.66 ± 1.82 and 9.97 ± 0.49, respectively (Table I).

Discussion

The negative impact of proteinuria in native kidney diseases and transplanted kidneys is well known. Some approaches aimed at reducing proteinuria are evaluated. ACE inhibitors have been shown to reduce urinary protein excretion in these patients, and ARBs are known to reduce proteinuria, at least in native kidney diseases (8). The present study demonstrated that losartan was
highly effective in controlling proteinuria in renal transplant recipients with normal renal function or mild renal dysfunction. Favorable data for losartan in terms of an antiproteinuric effect are consistent with Calvino’s report (9). Several mechanisms may explain these effects. Although no glomerular hemodynamic parameters were analyzed in the present study, we consider that the attenuation of proteinuria reflects an improvement in the glomerular function. In renal transplantation, intraglomerular hypertension can contribute to the development of renal failure. This increase in pressure may result from increased systemic blood pressure in conjunction with a reduction in functioning renal mass secondary to repeated renal rejection episodes, CsA nephrotoxicity, small renal size or glomerulonephritis (10). ARBs are supposed to reduce both systemic BP and intraglomerular pressure by inhibiting the contraction of efferent arterioles. Moreover, losartan has been shown to reduce proteinuria by improving glomerular basement membrane characteristics (11). Losartan may therefore improve overall glomerular function.

CsA represents a critical part of the current immunosuppressive approach in renal transplant patients. Unfortunately, this drug has well-recognized nephrotoxic effects and chronic use of CsA may be associated with progressive renal dysfunction. One of the leading possibilities implicated in causing renal injury is the effect of CsA on the renin-angiotensin-transforming growth factor-beta (TGF-β) axis. Clinical studies have demonstrated that ARBs can normalize plasma levels of TGF-β in renal transplant patients receiving CsA (12, 13). Moreover, animal experiments suggest that ARBs may exert a beneficial effect against chronic CsA nephrotoxicity (14). Pharmacological targeting of the renin-angiotensin-aldosterone system may therefore represent an important strategy in reducing graft exposure to CsA-induced production of TGF-β. This study is of interest since hypertension, which can also stimulate production of TGF-β, was similarly reduced with losartan administration. The evidence presented strongly suggests that hypertension has a relationship with the renin-angiotensin-aldosterone system in the development of CsA nephropathy.

Another possibility for the renoprotective effects of ARBs involves prevention of glomerular phenotypic modulation following glomerular injury (15). Glomerular phenotypic changes have been detected in 5/6-nephrectomized rats, in contrast to negligible glomerular changes in sham-operated rats. However, a selective ARB, TCV-116, inhibited these changes. Glomerulosclerosis involves hyperplasia of phenotypically modified mesangial cells. Losartan may inhibit or prevent this modulation.

In renal transplantation, recent reports have documented decreases in hemoglobin concentration with ARBs (16, 17). In fact, the present study revealed a decrease in hemoglobin concentration in patients with renal dysfunction. Morrone et al. (18) suggested either direct inhibition of ARBs in erythropoietin production or an indirect mechanism through the insulin-like growth factor-I system. However, our study revealed almost identical erythropoietin levels in all groups. Although the mechanism remains unclear, losartan may inhibit angiotensin II binding to receptors on the cell membranes of erythroid progenitors, thus inducing anemia.

These findings may provide new strategies for treating persistent proteinuria in renal transplant recipients, although the size of the present study is quite small. Further prospective studies of whether ARBs can reduce or even prevent the development of chronic allograft nephropathy in renal transplant patients are needed.

References


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