Angiotensin II type 1 (AT\(_1\)) receptor antagonists in the treatment of hypertension after renal transplantation

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**Abstract**

Hypertension is highly prevalent after renal transplantation and has been associated with lower graft survival. Optimum management of post-transplant hypertension remains to be defined. Losartan, a potent, orally active and selective non-peptide blocker of the angiotensin subtype 1 receptor, could represent a useful drug for treating post-transplant hypertension. Recently, a prospective study of 12 weeks treatment with losartan has showed a satisfactory control of arterial hypertension associated with a decrease in proteinuria in this high-risk group of renal transplant patients. A retrospective study was performed to review the role of losartan as a renoprotective agent (evaluating blood pressure and proteinuria) in renal transplant recipients in a long-term follow-up. A total of 150 transplant recipients were included in the study. None of the patients had a serum creatinine >3 mg/dl, or suspected renal artery stenosis, or other severe concomitant diseases. The indication for losartan therapy was hypertension, proteinuria and/or post-transplant erythrocytosis. The values of blood pressure, results of fasting haematology, blood chemistry and total proteinuria in 24-h urine samples were recorded at the time of initiation of losartan therapy, 6 and 3 months before the start, and at 3, 6, 12, 18 and 24 months thereafter. A tendency analysis by linear regression comparing two slopes before and after treatment was realized. A decrease in mean blood pressure and proteinuria, from 106.7±0.9 to 98.2±2.1 mmHg and from 1253.9±188 to 91.2±33.7 mg/24 h, \(P<0.05\), respectively, was observed after introduction of losartan. A progressive increase in creatinine clearance was observed after the third month of losartan treatment. No significant changes were seen in haematocrit or serum potassium levels. We can conclude that a progressive decrease in mean arterial pressure associated with a decrease in proteinuria was observed during long-term follow-up. Based on the capacity of losartan to improve renal function, this drug could be decisive for the treatment and prevention of chronic allograft nephropathy.

**Keywords:** chronic allograft nephropathy; hypertension; proteinuria; renal transplantation

**Introduction**

A significant improvement in the short-term survival of renal allografts and patients has occurred in the last two decades. This improvement is due mainly to improved immunosuppressive regimens, especially with the introduction of cyclosporin A (CyA) in the early 1980s [1]. However, the rate of late renal allograft failure has remained relatively unchanged. Cardiovascular risk factors, such as high blood pressure, and chronic allograft nephropathy are considered important causes of graft loss after the first year of transplant [2].

In most of the published series, the prevalence of hypertension after renal transplant is consistently ~50% [3]. Acute and chronic rejection immunosuppressive therapy, renal artery stenosis, native kidney diseases and recurrent renal diseases have been implicated in causing post-transplant arterial hypertension [4]. The generalized use of calcineurin inhibitors (CyA and tacrolimus) as basic immunosuppressive therapy has aggravated the problem of hypertension. With the use of CyA therapy, the prevalence of hypertension is consistently ~75%, and the prevalence of severe hypertension has been reported to be 20% [5].

Hypertension is associated with poor patient survival and lower graft survival, although the nature of this relationship has not been clearly defined. Recently, Opelz et al. [6] have shown a striking association between systolic and diastolic blood pressure and kidney graft survival, post-transplant blood pressure being a highly significant predictor of long-term graft survival.

**Practical considerations**

Several studies have demonstrated that treatment with angiotensin-converting enzyme (ACE) inhibitors
lowers blood pressure, reduces proteinuria and slows the rate of progression of renal disease [7,8]. In experimental animal models, the ACE inhibitors have been shown to slow the progression of chronic renal allograft nephropathy [9].

Different renoprotective mechanisms of treatment with ACE inhibitors have been proposed. These possible mechanisms include a decrease in systemic and intraglomerular blood pressure, reduction of proteinuria and increase in renal functional reserve probably secondary to the decrease in glomerular capillary hydrostatic pressure, and inhibition of angiotensin II-mediated glomerulosclerosis [10–13]. In renal transplant recipients, glomerular capillary hypertension may occur due to an increase in systemic blood pressure, reduced nephron mass, immunosuppressive therapy (calcineurin inhibitors) and chronic graft rejection [14]. On the basis of these renoprotective mechanisms, treatment with ACE inhibitors has been recommended, although many physicians avoid this kind of drug due to a functional decrease of renal perfusion when administered with CyA [15].

Losartan is a potent, orally active and selective non-peptide blocker of the angiotensin subtype 1 (AT$_1$) receptor. It is the first of a new class of drugs recently introduced for clinical use in hypertension. Losartan clearance is primarily non-renal, whereas clearance of its active metabolite, E-3174, occurs through both renal and non-renal routes. Plasma concentrations of E-3174, however, are not significantly altered in patients with renal impairment or undergoing dialysis [16].

In patients with essential hypertension, losartan has been shown to lower blood pressure effectively and to be well tolerated [17]. In patients with renal impairment, the blood pressure-lowering effect of losartan is accompanied by a significant reduction in proteinuria. No significant change was seen in serum potassium or creatinine level nor in the creatinine clearance after treatment with losartan in patients with renal impairment, including patients on haemodialysis [18].

**Clinical experiences**

Recently a multicentre study has been published to evaluate the efficacy and safety of losartan in the treatment of hypertension in renal transplant recipients [19]. This prospective study of 12 weeks treatment with losartan clearly showed a satisfactory control of arterial hypertension in this high-risk group of renal transplant patients (baseline mean BP vs week 12 mean BP, 113.96 ± 0.5 vs 102.19 ± 9.9, $P < 0.01$). After 12 weeks of treatment, proteinuria significantly decreased in the whole group (from 1.5 ± 2.2 to 0.54 ± 1.1 g/24 h, $P = 0.04$), constituting a promising effect of losartan on proteinuria.

The tolerability of losartan was excellent, and no serious side effects were recorded. Although this study lasted only 12 weeks, the mean serum creatinine showed a slight, non-clinically significant increase at week 4, and then remained stable during the whole period. Serum potassium also increased slightly at week 4 without any clinical relevance, but after week 8 the serum potassium level remained stable. In the whole group, haemoglobin levels and haematocrit decreased slightly, but without clinical significance.

Similar results have been published recently by Calviño *et al.* [20] who documented that the use of losartan had a satisfactory antihypertensive effect and produced a significant reduction in proteinuria without adversely affecting graft function.

Based on these promising preliminary results, losartan could represent a useful and effective drug for treating hypertension and, through its ability to ameliorate proteinuria, it could also prevent renal failure.

In addition, a retrospective multicentre study was performed to review the role of losartan as a renoprotective agent in renal transplant recipients in long-term follow-up [21]. The aim of this trial was to test the efficacy and safety of long-term use of losartan as a renoprotective drug, evaluating blood pressure and the evolution of proteinuria in renal transplant recipients.

In this study, the renal transplanted patients recruited had no suspected or documented renal artery stenosis. None of the patients had a serum creatinine >3 mg/dl, or other severe concomitant diseases or suspected active infections. The indication for losartan therapy was hypertension, proteinuria and/or post-transplant erythrocytosis. A total of 150 renal transplant recipients were included in the study. The values of blood pressure, heart rate and the results of fasting haematology, blood chemistry and total proteinuria in 24-h urine sample were recorded at the time of initiation of losartan therapy (time 0), at 6 and 3 months before the start, and at 3, 6, 12, 18 and 24 months thereafter. The quantitative results are expressed as mean ± SEM, and a tendency analysis by linear regression comparing two slopes before and after treatment was realized.

A decrease in mean blood pressure from 106.7 ± 0.9 to 98.2 ± 2.1 mmHg, $P < 0.05$, was observed after the introduction of losartan. A strong positive effect was observed on proteinuria after losartan treatment, with a progressive decrease from 1253.9 ± 188 to 91.2 ± 33.7 mg/24 h, $P < 0.05$. A progressive decline in renal function was observed before and after introduction of losartan in the treatment until the third month of follow-up. After this period, the creatinine clearance increased significantly till the end of study period at 24 months. No significant changes were seen in haematocrit or in serum potassium and uric acid levels.

**Discussion**

Although optimum management of post-transplant hypertension remains to be defined, this action requires
individualization of treatment and particular consideration of safety and tolerability. In fact, hypertension is a frequent complication after renal transplantation and may result in an increased risk of cardiovascular morbidity and mortality [22]. High blood pressure, which is both a cause and a consequence of renal disease, is an important risk factor contributing to the progression of renal failure. Calcium channel blockers have been proven to control hypertension, reverse cyclosporin-induced renal vasoconstriction and prevent post-transplant acute tubular necrosis [23]. These are the most commonly used drugs for the treatment of post-transplant hypertension, and are generally administered to antagonize cyclosporin vasoconstriction [22,24], because they may reduce the long-term cyclosporin nephrotoxicity. However, the glomerular haemodynamic effects of calcium antagonists and the recently described proteinuria-enhancing effect of some of them could damage the long-term renal function of the transplant, especially in patients with chronic graft nephropathy and hyperfiltration syndrome.

The intrarenal renin–angiotensin system has been strongly implicated in the progression of renal injury [11]. This influence has been attributed to its role in the regulation of glomerular haemodynamics and, recently, to its participation in the regulation and expression of potentially damaging cytokines, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β [13]. Elevated glomerular capillary hydrostatic pressure is maintained, in part, by increased local angiotensin II activity. Interruption of the renin–angiotensin system with ACE inhibitors or angiotensin II type 1 receptor antagonists has been shown to reduce the renal injury in animal models of chronic renal failure [25,26]. However, in addition to the haemodynamic effects, angiotensin II stimulates extracellular matrix protein synthesis in rat glomerular mesangial cells through increased TGF-β synthesis and conversion from the latent to the active form [13]. TGF-β is known to be a key fibrogenic cytokine implicated in the fibrosis of a number of chronic diseases of the kidney and other organs [27]. Macrophages have been implicated as important contributors to graft injury in rat models. Angiotensin II-stimulated transcriptional activation of ICAM-1, RANTES and MCP-1 leads to an enhanced recruitment, activation and intragraft retention of macrophages. Recently, Ziai et al. have demonstrated in animal models that losartan treatment reduces glomerular capillary hydraulic pressure and proteinuria, and these effects are associated with a reduction in allograft macrophage infiltration and attenuated expression of molecules involved in macrophage recruitment [28]. There is also evidence to suggest that the renin–angiotensin system is activated in chronic cyclosporin nephrotoxicity and chronic graft nephropathy [29]. In different animal experimental models, the ACE inhibitors and angiotensin II receptor antagonists have been proven to limit proteinuria, and to decrease glomerulosclerosis and improve graft survival [9,30,31].

The studies previously commented on demonstrated the capacity of losartan to control blood pressure with safety and good tolerability in the high-risk group of renal transplant patients. A progressive decrease in mean arterial pressure was observed during the short- and long-term follow-up without serious effects. The degree of proteinuria may be a function of intra-glomerular haemodynamics and can be considered as an indicator of glomerular injury [32]. In the last mentioned study, we observed, in association with the decrease in blood pressure, a decrease in proteinuria and improvement of renal function after 24 months of follow-up. Based on losartan’s antifibrotic effect and capacity to reduce glomerulosclerosis in rat models, and based on our preliminary results in humans, we can propose the use of losartan for the treatment and prevention of chronic nephropathy, although a randomized long-term study to confirm this positive effect is warranted.

References

5. Pochet JM, Pinson Y, van Ypersele de Strihou C. Is post renal transplantation hypertension more severe or more frequent on Cs than on conventional therapy. Nephrol Dial Transplant 1989; 4: 507–510
14. Curtis JJ, Luke RG, Wikelch JD, Diethelm AG, Jones P, Dustan HP. Inhibition of angiotensin converting enzyme in
17. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. Am J Cardiol 1995; 75: 793–795