Chapter 11

Renin-Angiotensin System and Renal Allograft Long-Term Outcome: A Review

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67082

Abstract

Recent developments in immunosuppressive therapy have reduced the loss of allografts from acute rejection, with a significant improvement in the one-year allograft survival. However, the introduction of more potent and selective new drug, had no effect on the development of chronic allograft dysfunction and the long-term outcome remains unchanged. Several and repeated different types of allograft insults such as delayed graft function, rejection episodes, drug nephrotoxicity, hypertension, dislipidemia determines a progressive damage with graft failure within a decade. There is no established maintenance immunosuppressive therapy that decreases chronic allograft dysfunction. The renin-angiotensin system is an important mediator in the pathogenesis of chronic progressive kidney diseases. Although the pathogenesis of chronic allograft nephropathy (CAN) is poorly understood, a reduced nephron function with hemodynamic changes associated with a cascade of inflammatory mediators, result in a chronic inflammatory process, progressive fibrosis and tissue remodeling. Recent evidence has shown beneficial effects of renin-angiotensin system blockade in the posttransplant with a decrease of blood pressure, proteinuria and inflammatory process.

Keywords: renal transplant, chronic allograft nephropathy, renin-angiotensin system, allograft survival

1. Introduction

The renin-angiotensin system (RAS) was described in the 1980s, and since then studies have focused on its role in the hemodynamic control [1]. The RAS is classically associated with blood pressure regulation and electrolyte balance. The system main peptide angiotensin II acts through two major receptors termed type 1 and type 2. They are widely distributed in the tissues, and have different functions; hemodynamic changes such as vasoconstriction and cellular proliferation are related to type 1 receptor and vasodilation and anti-cellular proliferation to type 2 [2].

All components of the RAS, including the receptors, are present very early in the human development (24–35 days of gestation), suggesting a role for angiotensin II in the organogenesis [3].

The RAS components are present in many tissues, and there are evidences for a tecidual angiotensin II biosynthesis with high concentrations in the kidneys (intrarenal RAS) [4, 5]. They are synthesized by different cells and interact locally with autocrine and paracrine effects. It has been suggested that the plasma RAS is important for acute regulatory mechanisms, whereas the tissue RAS may be more involved in chronic cardiovascular and renal regulation [6, 7].

Therefore, RAS maintains hemodynamic homeostasis and controls tecidual growth.

Pathologic consequences can result in overactivity of this cascade with an involvement of the RAS in several renal diseases. Regardless of the initial type of injury, all chronic renal diseases develop glomerular and vascular sclerosis, tubular atrophy and interstitial fibrosis, with progressive nephron loss and chronic renal failure. Adaptative changes in the remaining nephrons after initial injury cause more scarring and nephron loss, thus perpetuating a vicious cycle that results in the end-stage kidney. Chronic RAS activation is involved in these maladaptive mechanisms of progressive renal damage. Angiotensin II-mediated effects such as haemodynamics changes, glomerular and tubular hypertrophy and hyperplasia, infiltration of mononuclear cells and fibrogenesis were observed [8].

The system hyperactivity leads to progressive lesions presenting an important role in the pathophysiology of chronic cardiovascular and renal diseases. The RAS activation has been demonstrated in various kidney diseases, in both experimental and clinical studies [9, 10]. The system blockade, with inhibitors of angiotensin converting enzyme (ACE) of angiotensin II and angiotensin II-receptor blockers, shows large benefits in the treatment of chronic kidney diseases [11].

Thus, the classical approach of Angiotensin II as a vasoactive agent that participates in the systemic hemodynamic changes was expanded to recognize its role as a growth factor that modulates cell proliferation, synthesis and degradation of extracellular matrix.

A significant complication on renal transplantation is the chronic and progressive allograft dysfunction that develops months or years after transplantation. Recent advances with new immunosuppressive drugs did not improve the long-term allograft survival. Despite the well established knowledge of the ability of renin-angiotensin system blockade to control blood pressure and urinary protein excretion, the use of RAS inhibitors and blockers in renal transplant has been limited [12, 13].

We review our own observations and recent reports from the literature about the important role of RAS in the pathogenesis of chronic inflammatory process and local tecidual growth, in the chronic allograft dysfunction.

2. Case description

LAR, a 20-year-old woman with chronic renal failure due to focal and segmental glomerulosclerosis (FSGS) was admitted at the Clinical Hospital of Faculdade de Medicina de Botucatu

http://dx.doi.org/10.5772/67082

(UNESP) to receive a renal transplant. She underwent an HLA—haploidentical living donor transplant from a 50-year-old woman in 17 March 1993. Panel reactivity (PRA) against HLA class I and II antibodies was negative. Induction therapy has not been done. Maintenance therapy was performed with a triple immune suppressive regimen with prednisone (1 mg/kg/day), azathioprine (4 mg/kg/day) and cyclosporin (8 mg/kg/day). In the early follow-up, without a significant ischemic exposure, the patient had an episode of acute cellular rejection that was adequately treated. At hospital discharge her serum creatinine level was 1.2 mg/dl (eGFR = 60 ml/min) which remained up to 1 year post transplant. The patient started presenting mild proteinuria (0.28 g/24 h) and progressive deterioration of renal function over the years reaching creatinine of 1.8 mg/dl (eGFR = 39 mL/min) after 14 years of transplant (**Figure 1**). Immunosuppression at that time consisted of azathioprine (1.5 mg/kg/day), prednisone (10 mg) and cyclosporin in order to reach a serum level of 100–150 ng/ml. The renal biopsy diagnosis at this time (February 2007) was "chronic allograft nephropathy (CAN)" characterized by mild interstitial fibrosis and tubular atrophy, and intense arteriolar hyalin deposits observed in more than one arteriole, some with circumferential involvement (Banff grade I). A mild mononuclear inflammatory infiltrate was observed in scarred areas. The glomeruli and the small arteries were unremarkable (**Figures 2** and **3**). Tests for C1q, C3, IgG, IgA, IgM and C4d were all negative by immunofluorescence. Losartan was introduced (50 mg/day) and there was a gradual improvement of renal function over time (**Figures 1** and **4**).

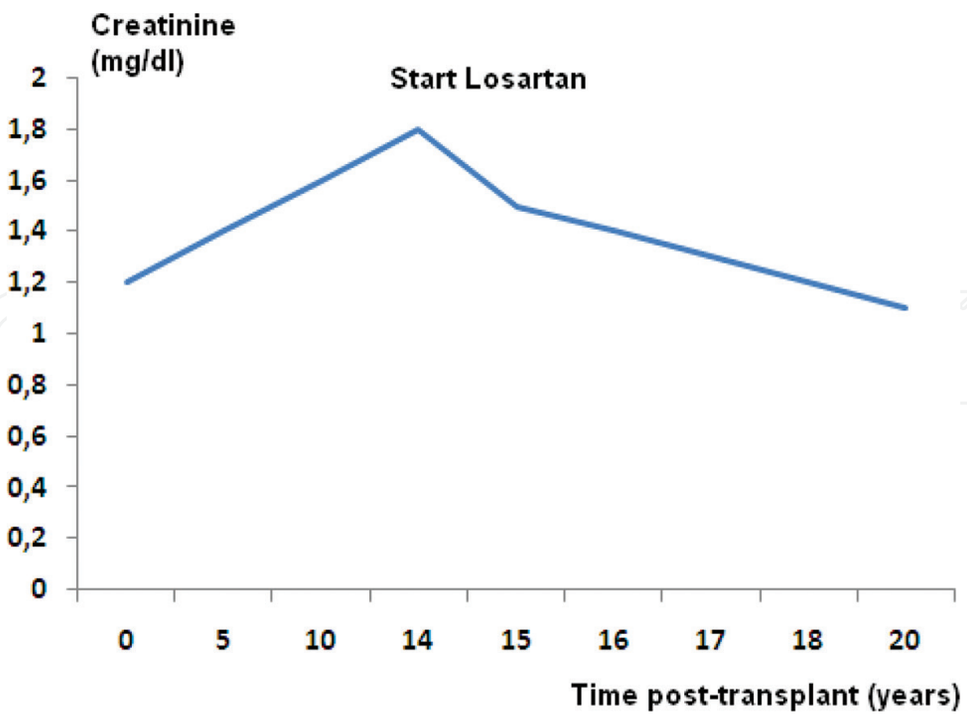

Figure 1. Serum creatinine levels after transplantation. Renal biopsy with chronic allograft nephropathy (CAN) and introduction of losartan 14 years after transplant.

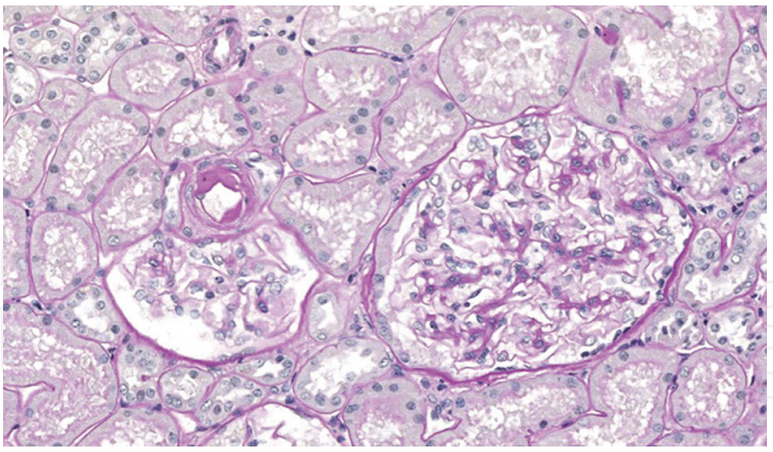

Figure 2. Renal allograft biopsy with arteriolar hyalin deposits. PAS-200×.

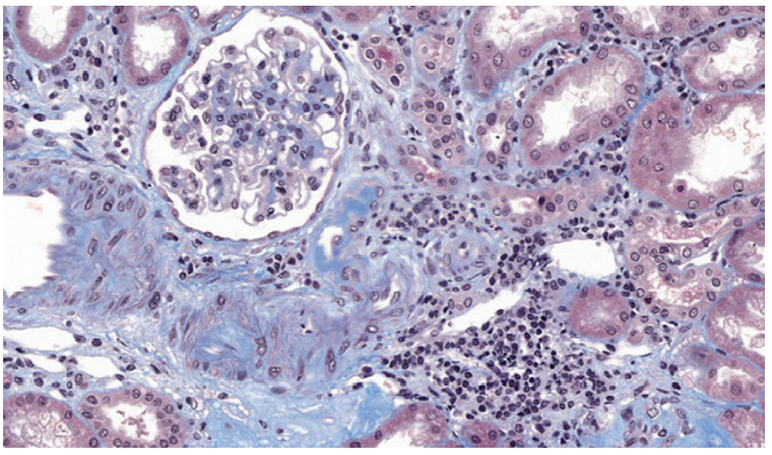

Figure 3. Renal allograft biopsy with focal area with tubulointerstitial fibrosis, tubular atrophy and mononuclear infiltrate. Arteriolar hyalinosis. Masson Trichrome-200×.

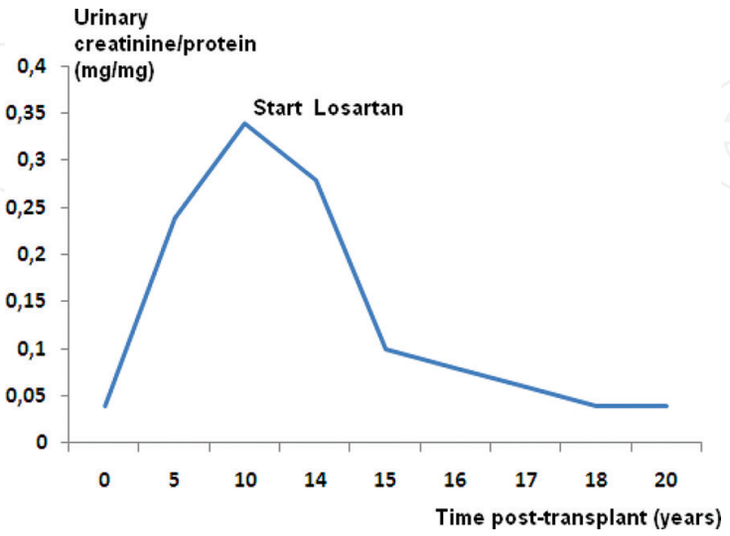

Figure 4. Proteinuria after transplantation. Renal biopsy with chronic allograft nephropathy (CAN) and introduction of losartan 14 years after transplant.

http://dx.doi.org/10.5772/67082

3. Case discussion and review of the literature

In our case, a young woman that received a successful renal transplant 14 years ago, now exhibited clinical evidences of chronic and slow progressive kidney injury manifested mainly by deterioration of renal function.

There were no morphological evidences of recurrence of her native kidney disease, the focal and segmental glomerulosclerosis (FSGS). The recurrent rate of primary FSGS is very high but, usually manifests with nephrotic syndrome much earlier in the posttransplant and have a lower graft survival. The degree of proteinuria of this patient was very mild and started after a long period of well functioning allograft.

There was also no morphological evidences of chronic rejection. Chronic allograft glomerulopathy and arteriopathy, Banff's morphological criteria for chronic rejection, were absent and C4d was negative.

Our diagnosis of renal biopsy was chronic allograft nephropathy.

3.1. Chronic allograft nephropathy and chronic allograft dysfunction

Chronic allograft nephropathy (CAN) is the major cause of late allograft loss. This is a heterogeneous and complex process caused by immunologic and non-immunologic factors including glomerular hyperfiltration, hypertension, dyslipidemia, delayed graft function, drug toxicity and recurrent or the novo nephropathy. Clinically, there is a gradual and progressive deterioration of renal function in association with hypertension and proteinuria [14, 15].

Similar to what occurs in the native chronic renal diseases, repeated injury of the renal allograft determines activation of adaptative mechanisms to maintain homeostasis, but also induces a reparative process with deposition of large quantities of an extra cellular matrix with formation of a connective scar. CAN is characterized histologically by glomerulosclerosis, arterial fibroelastic intimal hyperplasia, tubular atrophy and interstitial fibrosis. The extension of tubulointerstitial fibrosis correlates closely to the extent of renal allograft dysfunction [16–18].

However, CAN is a generic and a misleading term used for all causes of chronic allograft dysfunction with fibrosis, inhibiting the accurate diagnosis and appropriate therapy. These non-specific morphological findings make it difficult to recognize the causes. The 8th Banff Conference [19] proposed replacing CAN for an appropriate classification of chronic allograft dysfunction that enables the diagnosis of specific causes of chronic allograft dysfunction in order to treat adequately. Protection against complications and pathogenetic investigations of late graft deterioration have become important. Nevertheless, chronic allograft dysfunction remains an unresolved problem.

Thus, what should be a more specific diagnosis for our patient?

Histologic findings showed a non-specific parenchymal scarring characterized by interstitial fibrosis and tubular atrophy associated to arteriolosclerosis and a mononuclear inflammatory infiltrate.

Although the biopsy showed a mononuclear inflammatory infiltrate, there were no clinical and morphological criteria for late acute rejection; the inflammatory cells were observed only in areas of fibrosis and the decline of renal function was gradual over the years.

On the other hand, serology tests and stains for infectious agents were negative.

However, the presence of inflammatory cells even in the scarred areas of CAN should be considered a risk factor for a progressive lost of renal function decreasing the allograft survival [18, 20, 21]. The persistence of chronic active inflammation may be responsible for the progression of CAN [20].

In addition, long-term administration of the calcineurin inhibitors such as cyclosporin and tacrolimus, produce many allograft side-effects. The most important histological lesion in cyclosporine nephrotoxicity is the structural changes with hyalin deposits in the arterioles that is present in the patient biopsy [22]. On the other hand, these drugs induce hyperlipidaemia and hypertension, important risk factors for CAN development [23, 24]. There is also an interaction between cyclosporine-induced nephrotoxicity and the activation of the RAS. Shang et al. [25] reported an increased expression of renin and angiotensin II in the allograft with a diagnosis of cyclosporin nephrotoxicity, that was significantly higher in specimens with CAN than in those without CAN. The authors concluded that tissue RAS has an important role in the development of adverse effects of cyclosporin on the kidney.

Although the arteriolar hyalin deposits are mostly subendothelial, this morphological finding in the patient's biopsy are highly suggestive of cyclosporine nephotoxicity as a cause of CAN in our patient.

Although the main problem of this patient was renal insufficiency, she presented a mild proteinuria at the normal limit. We do not identify significant glomerular changes in the biopsy. Proteinuria and nephrotic syndrome is a frequent finding in CAN. The glomeruli displayed a spectrum of lesions, mostly non-specific glomerular changes, including global and segmental sclerosis, collapse of the glomerular capillaries and focal and segmental mesangial sclerosis. The degree of proteinuria closely correlated with the severity of renal injury in the CAN [26].

Several studies have suggested an implication of RAS in the pathogenesis of progressive allograft dysfunction and renin-angiotensin system inhibition provide an important strategy for therapeutic intervention [14, 16].

3.2. Renin-angiotensin system and chronic inflammatory process

Besides the action in the circulation, RAS components have an important role in the inflammatory process, acting directly or indirectly by various mechanisms. Increases vascular permeability by mechanical action in the vessels, cell skeletal rearrangement and release of mediators such as prostaglandins and leukotrienes [27].

It stimulates the synthesis and release of cytokines and chemokines such as *interleukin-6* (IL-6), *interleukin-8* (IL-8), *regulated upon activation normal T cell expressed and secreted*

(RANTES), *macrophage inflammatory protein-1 and 2* (MIP-1; MIP-2), *chemokine monocyte chemoattractant protein-1* (MCP-1) and adhesion molecules represented by the *integrins*, *selectins*, *intercellular adhesion molecule-1* (ICAM-1) and *vascular cell adhesion molecule-1* (VCAM-1). The stimulation for these mediator substances results in increased influx of cells to the tissue with proliferation and activation of mononuclear cells, mainly macrophages. Mononuclear cell infiltration and proliferation determine continuing tissue destruction and healing by fibrosis [27, 28].

Several studies have also demonstrated the role of angiotensin II in tissue repair by inducing growth factors such as *transforming growth factor β1* (TGFβ1), *platelet-derived growth factor* (PDGF), *fibroblastic growth factor* (FGF), *vascular endothelial growth factor* (VEGF), *tumor necrosis factor α* (TNFα) and *plasminogen activator inhibitor-1* (PAI-1) [10–12]. Excess extracellular matrix deposition is due to the increased synthesis by the activation of growth factors and by decreased degradation by inhibition of metalloproteinases. TGFβ1 is an important growth factor modulated by RAS activation, with a close connection with this system. It is involved with complex effects on cell growth and differentiation, expression of extracellular matrix, angiogenesis and tissue repair [29–31].

It has been demonstrated increased gene expression of components of the RAS and growth factors into tubular cells and interstitial fibroblasts. These data indicate local activation of the system that correlated with mediators associated with deposition of a matrix in areas of chronic injury and fibrosis [32, 33].

The interaction of RAS with other vasoactive systems such as aldosterone, nitric oxide, endothelin and kinins can enhance its vasoconstrictor and reparative action but also can stimulate anti-inflammatory effects [11].

3.3. Renin-angiotensin system and chronic allograft nephropathy

Several studies have demonstrated the participation of RAS in the development of lesions in CAN. After transplantation, the system is activated locally [34]. Recent evidences have shown RAS stimulating the secretion of cytokines and growth factors, especially TGFβ1, with increased extracellular matrix deposition [16].

The system determines vasoconstriction of the efferent arterioles increasing glomerular intracapillary pressure and filtration, with consequent proteinuria. Stimulates mesangial cell proliferation with matrix synthesis evolving with glomerular sclerosis. Determines hypoperfusion of the peritubular capillaries and hypoxia in the tubulointerstitial compartment. Proteinuria determines tubular cells injury, stimulates the system locally, which together with the chronic hypoxia leads to apoptosis and epithelial-mesenchymal transdifferentiation with extracellular matrix deposition. Stimulates fibroblast proliferation, transformation into myofibroblasts with deposition of matrix in the tubulointerstitial compartment. It is involved in intimal proliferation of vessels forming a neointima [16].

The studies have focused primarily the correlation of allograft survival with the system blockade by converting enzyme inhibitors and/or angiotensin II receptors blockers. Angiotensin

converting enzyme inhibitors and/or angiotensin receptors blockers therapies are useful in the treatment of hypertension, improvement of the renal function, reduction of erythrocytosis and proteinuria in the posttransplant [35].

Yamada et al. [36] demonstrated that inhibition of angiotensin II converting enzyme determined in transplant patients increased response of plasma renin activity and increased urinary excretion of TGFβ1 in patients who developed chronic allograft nephropathy. The authors suggest that urinary TGFβ1 excretion clinically predicts the future development of chronic allograft dysfunction.

TGFβ1 levels in plasma and urine were increased in overt chronic allograft nephropathy [37, 38]. And a significant correlation between tecidual TGFβ1 and renal interstitial fibrosis has been reported [39].

Montanaro et al. [40] showed a reduction in proteinuria and increased creatinine clearance in patients treated with angiotensin converting enzyme and angiotensin II AT1 receptor blocker. This study suggested that RAS blockade has renoprotective effects when used in patients with good stable renal function and mild proteinuria, and prevent chronic allograft nephropathy.

Artz et al. [41] found that patients who were taking angiotensin converting enzyme inhibitors had overall less severe CAN and longer graft survival. Renal graft survival after treatment with RAS blockade was 6.3 years as opposed to 1.8 years in untreated patients.

Possible mechanisms of the renoprotective effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) include a reduction of intraglomerular capillary pressure due to efferent arteriolar vasodilation and a decreased production and/or expression of TGFβ1 [37]. A reduction of the plasminogen activator inhibitor (*PAI-1*) has also been associated with the rate of CAN progression [42].

Zaltzman et al. [43] studying a group of 40 patients with biopsy-proven CAN that were treated with RAS blockade demonstrated a slow decline in the renal function and 83% of graft survival at 5 years.

Moscoso-Solorzano et al. [44] showed a synergistic effect between ACE inhibition and mycophenolate mofetil (MMF), maintaining serum creatinine stable and decreasing and limiting the progression of proteinuria, as well as histological lesions. The death-censored graft survival analysis was much better for the group treated with ACE inhibition alone, following the group treated with ACE inhibition in combination with MMF.

Heinze et al. [45] studying 2031 patients, found a marked improvement in 10-year graft survival in patients on ACE inhibition or angiotensin II receptor blockers. Ten-year patient survival rates were 74% in the ACEI/ARB group and only 53% in the non-treated group. Ten-year graft survival was 59% in ACEI/ARB patients and 41% in non-users group.

Based on these important findings in the Heinze'study [45], Opelz et al. [46] conducted a similar analysis in 17,209 kidney transplant recipients; 33.5% of the patients were on treatment with an ACEI or ARB after 1 year of transplantation. The graft and patient survivals at 6 year were not significantly different between the patients with or without ACEI/ARB treatment.

The different methods to enrolled the patients in the groups that received or not the ACEI/ARB treatment can explain the contrasting results. They did not confirm the higher graft and patient survival rates reported by Heinze et al. [45] and do not recommend a widespread use of ACEI/ARB therapy.

A prospective study of 14 renal transplant patients with CAN, showed that treatment with losartan significantly decreased plasma levels of TGFβ1 by more than 50%. It was observed a significant correlation between the increase of circulating angiotensin II after 2 weeks of treatment and the decrease of plasma TGFβ1 at the end of the study period. The results suggest that the receptor blockade plays a role in the synthesis of TGFβ1 [37].

Some authors have studied gene expression of RAS components and inflammatory mediators in renal biopsies of patients with CAN.

Oka et al. [47] showed an increase in the number of renin positive cells in juxtaglomerular apparatus in CAN. Becker et al. [48] studied the correlation between the AT2 receptor mRNA with the expression of the matrix-modulating genes and histological evidence of chronic rejection. AT2 receptor correlated with TGFβ1, metalloproteinases and inhibitors of metalloproteinases, indicating that the AT2 receptor participates in the modulation of extracellular matrix. Mas et al. [49] also found a correlation between the expression of angiotensinogen and TGFβ1 in the allografts of patients with various degrees of CAN. Some authors [50] observed in CAN correlation between the expression of RAS components and TGFβ1 in the allograft with mRNA levels in the urine. Significant correlation has been observed between TGFβ1 mRNA in the allograft and interstitial fibrosis [39].

In experimental animals, the RAS blockade prevents the increase in mRNA levels of cytokines and growth factors in the allograft, decreases the infiltration of mononuclear cells and attenuates the renal lesions in the chronic rejection models [51–54]. Noris et al. [51] have shown in an experimental study of chronic nephropathy with established lesions decreased MCP-1 expression and inflammatory infiltrate with stabilization of glomerular injury and renal function recovery in animals treated with angiotensin converting enzyme.

There are also some studies investigating the role of RAS gene polymorphisms in the renal transplantation. Circulating and tecidual RAS activity are under genetic control. Genomic variants of the angiotensinogen, ACE, AT1 and AT2 receptors genes have been described. Some authors studied the impact of the various genotypes on renal allograft function. This is a further support about the importance of the RAS in the progression of non-immunological injuries leading to chronic kidney graft failure [55, 56].

In conclusion, the introduction of losartan in the patient under discussion resulted in a significant improvement of renal function.

RAS blockade, with inhibitors of angiotensin converting enzyme of angiotensin II and angiotensin II receptor blockers, shows large benefits in the treatment of chronic kidney diseases. The beneficial effects of RAS blockade in the renal transplant are due to hemodynamic changes lowering blood pressure and reduction of the inflammatory infiltrate ameliorating the renal function. However, there are insufficient data to determine the effect on patient or graft survival.

On the other hand, evidences indicate the existence of an ACE-independent alternative pathway for generation of angiotensin II that is not affected by ACE inhibitors [57]. This explains the different results among the various studies.

While ACE inhibition and angiotensin receptor blockers can reduce progression of chronic renal diseases in humans, they do not achieve full renoprotection, and patients may still progress to end stage renal disease. These findings are consistent with human studies showing that ACE inhibitors slow, but do not halt renal fibrosis. Larger randomized studies are required to assess whether or not angiotensin converting enzyme inhibition and angiotensin II receptor antagonist therapies have beneficial effects after kidney transplantation [16, 58].

Acknowledgements

Financial support by Fundação de Amparo à Pesquisa do Estado de São Paulo/State of São Paulo Research Foundation (FAPESP).

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