Transplant International ISSN 0934-0874

REVIEW

The renin angiotensin system blockade in kidney transplantation: pros and cons

Josep M. Cruzado,[1] Jorge Rico[2] and Josep M. Grinyó[1]

1 Servei de Nefrologia, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
2 Nephrology Department, Universidad de Antioquía, Hospital Universitario San Vicente de Paúl, Medellín, Colombia

Keywords
angiotensin converting enzyme inhibitors, angiotensin receptor blockers, kidney transplantation, renin-angiotensin system.

Correspondence
Josep M. Cruzado, Servei de Nefrologia, Hospital Universitari de Bellvitge, Feixa Llarga s/n. 08907 L'Hospitalet de Llobregat, Barcelona, Spain. Tel.: +34932607602; fax: +34932607607; e-mail: 27541jcg@comb.es

Received: 10 November 2007
Revision requested: 10 December 2007
Accepted: 2 January 2008

doi:10.1111/j.1432-2277.2008.00638.x

Summary

Besides the immunological mediated damage on the graft, the intrarenal renin-angiotensin system (RAS) is viewed as an additional mechanism in the development and progression of chronic allograft injury. RAS blocking agents efficiently control post-transplant hypertension and are useful to reduce proteinuria and for treating post-transplant erythrocytosis. However, RAS blockade is associated with some potentially relevant adverse events as hyperkalemia, anemia, and even to a decline in renal function. There are consistent experimental data showing that RAS blockade has a therapeutic effect on chronic allograft injury. Some clinical studies have shown that RAS blockade reduces transforming growth factor-β1 and other markers of fibrosis but, up to now, there is not convincing evidence supporting that RAS blockade has further benefit on the progression of chronic allograft injury in comparison with other antihypertensive interventions. Theoretically, RAS blockade may also improve cardiovascular disease, which constitutes the main cause of mortality and morbidity in renal allograft recipients. Nevertheless, to date there is lack of evidence for supporting that RAS blockade improves neither graft nor patient survival in comparison with other antihypertensive drugs. Randomized, prospective, double blind, placebo-controlled trials with enough sample size and follow-up are needed to address the potential role of RAS blockade to improve graft and patient outcome. Meanwhile, we should empirically balance case to case the pros and cons of RAS blockade in renal transplantation.

Introduction

Renal transplantation is the best therapeutic option for the majority of patients having end-stage renal disease [1]. However, the degree of renal function achieved after transplantation is sometimes far to be optimal [2] and eventually declines overtime because of the concurrence of immunological and nonimmunologic factors [3]. On the other hand, many renal allografts prematurely fail because of patient's death from cardiovascular origin [4]. There were some attempts to improve graft and patient survival after transplantation by treating typical cardiovascular risk factors as dyslipidemia and hypertension. The assessment of Lescol in renal transplantation (ALERT) study showed that statins could reduce cardiovascular events in renal allograft recipients but were unsuccessful to prolong allograft survival [5–7]. Hypertension is a very common condition after transplantation and is an important risk factor for graft and patient survival [3,4]. Cosio *et al.* [8] suggested that elevated blood pressure acts as an independent risk factor for acute rejection and showed that treatment with calcium channel blockers but no other antihypertensive medications were associated with a lower incidence of acute rejection. On the other hand, Dragun *et al.* [9] reported the presence of agonistic antibodies against the angiotensin II receptor type 1 (AT_1) in renal allograft recipients who had severe vascular rejection and malignant hypertension and suggested that the

addition of the AT_1 receptor blocker losartan to the standard treatment of humoral rejection could improve outcome. More importantly, intrarenal renin-angiotensin system (RAS) activation is a well-known mechanism involved in the progression of chronic nephropaties [10]. Some experimental [11] and clinical [12] studies do suggest that RAS blockade can be a strategy capable to slow down progression of chronic allograft injury. However, to date whether RAS blockade can increase graft and patient survival is not known. Observational studies have conflicting results, randomized trials are small and with a short follow-up enough to determine differences between treatment groups and furthermore, it is very difficult to ascertain whether RAS blockade effect is independent of its inherent blood pressure lowering effect. Therefore, we review the RAS system with special emphasis in the renal hemodynamic consequences of its blockade, the current indications of RSA blockade in renal transplantation, side-effects and the controversial findings regarding patient and graft survival.

Case report of RAS blockade in a renal allograft recipient

A 40 year-old woman suffering from end-stage renal disease secondary to chronic pyelonephritis received a renal allograft in 1990 in our Institution. Immunosupression was OKT3 induction therapy, cyclosporine, and steroids. Prednisone was withdrawn in 1998 after introduction of mycophenolate mofetil (MMF). In 2002, hypertension was diagnosed and treated with a β-blocker agent. In 2003 a renal biopsy was performed because of increase in serum creatinine and proteinuria, showing grade 2 chronic allograft injury. At this time, ramipril was prescribed (Fig. 1). The response to ramipril was excellent in terms of control of hypertension (120/70 mmHg) and reduction of proteinuria although the patient developed anemia that was treated with subcutaneous darbepoetin. Three years later ramipril was discontinued because of hyperkalemia. One-month later serum potassium was within normal range but the patient displayed severe hypertension (162/101 mmHg), increase of serum creatinine, hypoalbuminemia, and nephrotic range proteinuria. Ramipril was reintroduced with excellent clinical response (120/70 mmHg) (Fig. 2). Hyperkalemia was avoided by taking sodium polystyrene sulfonate.

This case, rather than the goodness of ramipril, clearly shows how important is to control hypertension in chronic renal disease patients. Also, it would illustrate how difficult is to differentiate the RAS blockade antihypertensive effect from other favorable effects in terms of renoprotection as reduction of proteinuria, renal inflammation or fibrosis. Further, this case allows us to point

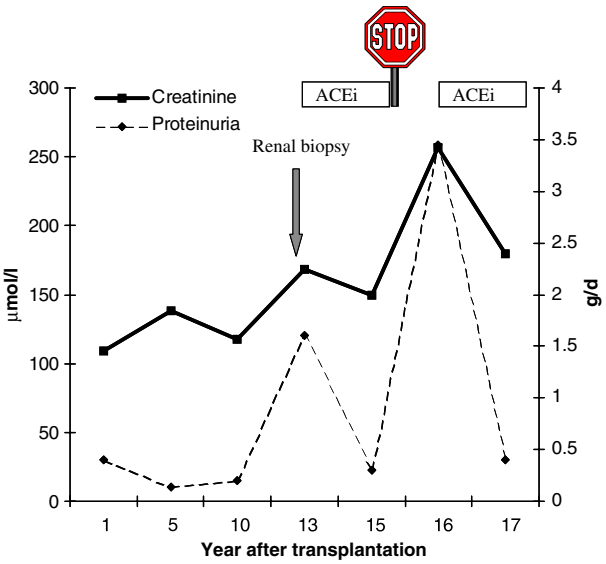

Figure 1 Evolution of serum creatinine and proteinuria. Treatment with angiotensin II converting enzyme inhibitors (ACEi) was introduced 13 years after kidney transplantation because of severe hypertension, proteinuria and histological diagnosis of chronic allograft injury. The response to ramipril was excellent in terms of control of hypertension and reduction of proteinuria although the patient developed anemia that was treated with subcutaneous darbepoetin. Three years later ramipril was discontinued because of hyperkalemia. One-month later serum potassium was within normal range but the patient displayed severe hypertension, increase of serum creatinine, hypoalbuminemia, and nephrotic range proteinuria. Ramipril was reintroduced with excellent clinical response Hyperkalemia was avoided by taking sodium polystyrene sulfonate.

out that the RAS blockade-associated decline of renal function, while usual, can not necessarily be universal. Finally, it would reflect the most frequent adverse events related with the introduction of RAS blockade in renal allografts, that is, anemia and hyperkalemia. All these controversies will be discussed in the present review.

A brief appraisal on the renin angiotensin system

Angiotensin II, the central product on the RAS, is a peptide widely studied in human health and disease (Fig. 2). The classical view of the RAS as a main controller of blood pressure by means its activation in the renal macula densa is currently surmounted. Therefore, the RAS is widespread distributed in many cell types, including endothelial, smooth muscle, mesangial, epithelial cells as well as fibroblasts and macrophages [13]. The angiotensin II exerts its action by binding to AT_1 and AT_2 receptors on cell surface. Despite their similar affinities for angiotensin II, AT_1 and AT_2 are functionally distinct, with a sequence homology of only 30% [14]. The AT_1 subtype mediates the majority of described angiotensin II effects

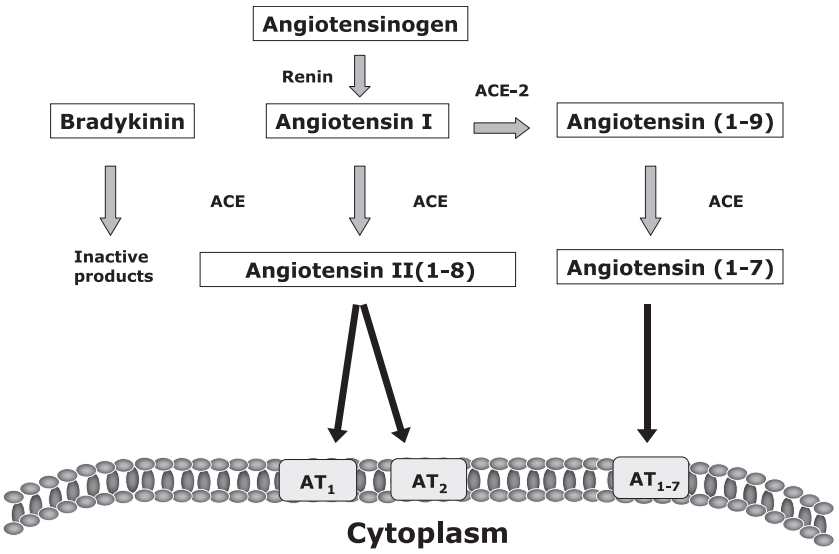

Figure 2 The renin-angiotensin system. Renin is secreted from the macula densa when there is a reduced stretch in the wall of the afferent arteriole or by a reduced sodium in the distal tubule. Renin converts angiotensinogen in angiotensin I. The angiotensin converting enzyme (ACE) is a Zn-dependent metalloprotease that converts angiotensin I in the active form of angiotensin II and, at the same time, inactivates kinins. The angiotensin II binds to its specific receptors angiotensin II receptor type 1 (AT_1) for exerting its better known effects. The effects mediated by AT_2 are not so well understood. The ACE-2 pathway was recently described and may as balancing mechanism.

including vasoconstriction, cardiac hypertrophy, vascular damage, and organ fibrosis. The actions of the AT_2 receptor are less well-understood, although recent investigations suggest that AT_2 receptors act as a counter-regulatory mechanism of the RAS activation [15].

The RAS is involved in many pathologic processes, mainly vascular damage and organ fibrosis. Angiotensin II plays a role in several stages of the atherosclerotic process such as endothelial dysfunction, proliferation and migration of smooth muscle cells, LDL oxidation, inflammatory response, and coagulation [16]. On the other hand, overactivation of the RAS can result in cell hypertrophy and extracellular matrix accumulation through activation of transforming growth factor-β (TGF-β), platelet-derived growth factor, and connective tissue growth factor (CTGF) [16]. Diabetic kidney disease and renal mass ablation are paradigm of renal fibrotic processes in which the angiotensin II is playing a key role [17,18]. In fact, in these pathologic conditions, the RAS blockade has well-established antifibrotic effect [17,19,20].

There are several ways for therapeutically interfering RAS, the more usual being angiotensin II converting enzyme inhibitors (ACEi) and AT_1 receptor antagonists (ARB). There are two major differences between the ACEi and ARB (Fig. 2). First, angiotensin II can activate both AT_1 and AT_2 receptors. As a result, inhibition of angiotensin II formation with an ACEi will diminish the activity of both receptor subtypes. In contrast, the ARB only diminishes AT_1 activity. Thus, there is no change in AT_2 receptor-mediated effects. Second, kinins are vasodilators that can reduce renal ischemia induced by angiotensin II and norepinephrine in hypovolemia and also decrease sodium reabsorption in the inner medulla and impair the ability of ADH to increase local water reabsorption [21]. Kinins are metabolized by kininases, one of them is the ACE that converts angiotensin I in angiotensin II. Thus, kinins are not modified by ARB.

On the other hand, the first direct renin inhibitor (DRI), aliskiren, has been recently approved by the USA Food and Drug Administration for the treatment of hypertension [22]. Although there is lack of experience in renal transplantation, the DRI drugs may be of interest on treating chronic allograft injury, as they induce a more complete inhibition of the RAS.

Hemodynamic consequences of blocking the RAS in renal allografts

The renal function achieved after renal transplantation is usually below that is considered normal in general population. In fact, the majority of renal allograft recipients show a glomerular filtration rate (GFR) <60 ml/min/m^2, that is stage 3 of chronic kidney disease [2]. Several factors such as donor characteristics, acute rejection, ischemia reperfusion injury, infections, and immunosuppressive drugs are contributing to this condition. Therefore, some authors suggested that many renal allografts suffer from glomerular hypertension and hyperfiltration because of lack of nephron mass [19]. The clinical consequences are hypertension, proteinuria, and progressive loss of renal function. These [23] and other [24] authors corroborated this hypothesis by demonstrating that supplying additional renal mass of a kidney graft avoided appearance of proteinuria and preserved renal function and structure.

The RAS acts as a regulatory mechanism addressed to maintain GFR when there is renal hypoperfusion. Angiotensin II produces systemic vasoconstriction and sodium and water retention. Angiotensin II can regulate GFR by

producing vasoconstriction of the efferent and afferent glomerular arterioles, although the increase in the efferent resistance is higher than in the afferent one [25]. So, angiotensin II induces a reduction in renal blood flow and maintain GFR when there is renal hypoperfusion, as it happens in renal artery stenosis or severe vasculopathy. Thus, the administration of RAS blockers may reduce GFR by reducing filtration pressure. This is not the case of other antihypertensive drugs as calcium channel blockers as they abolish the afferent vasoconstriction while having no effect on the efferent arteriole. The RAS is activated in renal allografts with chronic renal damage [26] and experimentally ACEi are superior to calcium channel blockers in protecting animals from chronic allograft injury although the GFR at the end of this study was similar between groups [11]. Thus, theoretically RAS blockade in a renal allograft, particularly if there is chronic renal damage, will induce a reduction of GFR. This fact has been recently corroborated by Hiremath *et al.* [27] in a systematic review of randomized trials with RAS blocking agents in renal transplantation.

Potential indications of RAS blockade in renal transplantation: the pros

Renal transplantation is the treatment of choice for end-stage renal disease [1]. However, many organs prematurely fail by progressive renal damage and patient's death of cardiovascular origin [3,4]. In renal allograft recipients, ACEi and ARB are used for the treatment of hypertension, post-transplant erythrocytosis (PTE) and to reduce proteinuria. Nevertheless, conflicting data have been obtained when analyzing the impact of RAS blockade on graft and patient survival [28,29] (Fig. 3).

Hypertension, left ventricular hypertrophy and arterial stiffness

Cardiovascular disease (CVD) is the most important cause of death in renal allograft recipients [4]. The estimated annual risk of death because of CVD is 3.5–5% in renal transplant recipients, which is 50-fold higher than in the general population [30]. Hypertension is the most prevalent CVD risk factor among kidney-transplanted patients. The reported prevalence of hypertension among this population is as high as 75–90% [31–33]. Three recent observational studies suggest that for every 1 mmHg of increase in systolic blood pressure there is a 1–2% increased risk of fatal or nonfatal CVD event [31,34,35]. Several factors are associated with post-transplant hypertension including history of pretransplant hypertension, high-body mass index, primary kidney disease, quality of donor organ, delayed graft function, acute rejection, calcineurin inhibitor therapy, glucocorticoids, transplant renal artery stenosis, and chronic allograft nephropathy [35,36]. Elevated blood pressure can result in decreased allograft survival and left ventricular hypertrophy (LVH), the latter being an independent risk factor for heart failure and death in the general population and renal transplant recipients [37–40]. It has been suggested that long-term renal allograft survival may be negatively influenced by post-transplant hypertension [41,42].

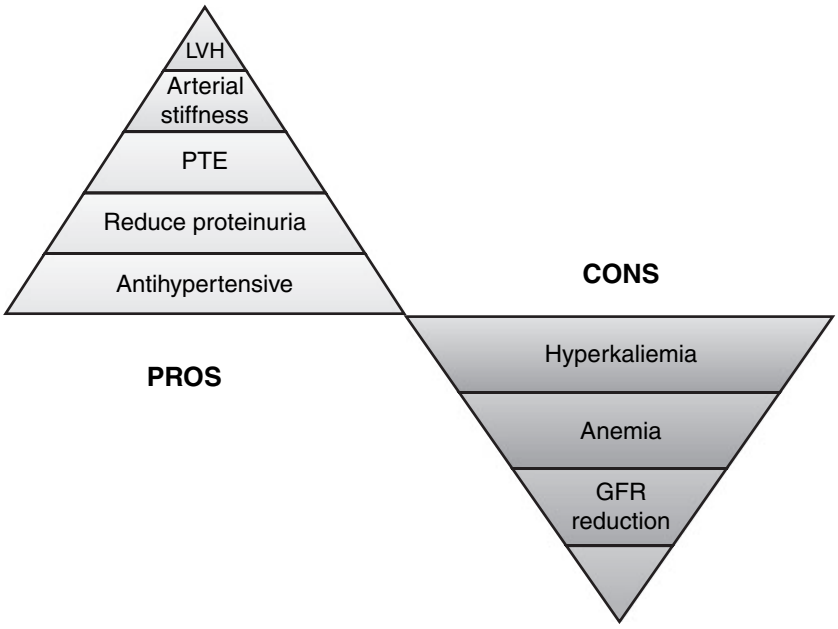

Figure 3 Pros and cons of renin-angiotensin system (RAS) blockade in renal transplant recipients. These drugs are effective in controlling hypertension and post-transplant erythrocytosis (PTE), reduce proteinuria and left ventricular hypertrophy (LVH) and improve arterial stiffness. However, they also reduce glomerular filtration rate (GFR), induce or aggravate anemia and hyperkalemia.

Hence, there is agreement for treating hypertension in renal transplant recipients. However, whether ACEi/ARB drugs are superior to other antihypertensive medications in terms of patient and graft survival is not known. There are some retrospective and prospective studies showing that ACEi and ARB are safe and effective in the treatment of the hypertension in renal transplant recipients [43,44], while others have noted a significant risk of hyperkalemia [42]. In a recent study, Paolleti *et al.* [37] showed that a prolonged course of ACEi therapy is effective in regressing the persistent LVH in renal transplant recipients by mechanisms independent of effects on blood pressure control. However, the use of both ACEi and ARB drugs are associated with anemia in renal allograft recipients [45,46] and anemia is a critical factor associated with LVH [47].

Arterial stiffness is considered a blood pressure-independent cardiovascular risk factor [48]. Large arteries are stiffer in chronic kidney disease patients because of several factors as vascular calcifications, anemia, RAS activation, and volume overload [49]. It has been described that successful renal transplantation improves the progression of arterial stiffness in patients with end-stage kidney disease [50]. Of interest, impaired renal allograft function [51] and some immunosuppressants [52] are associated with increased arterial stiffness in renal transplant recipients. Rather than other antihypertensive drugs ACE and ARB improve arterial stiffness in many patients [49]. Thus, RAS blockade may preferentially reduce arterial stiffness in renal-transplanted patients. However, as RAS blockade can also induce anemia and worsening of renal function in this population, studies are needed to further investigate this issue.

Post-transplant erythrocytosis

The PTE is defined as a hematocrit >51%. It is a multifactorial condition [53] affecting 10–15% of renal transplant recipients, most often within the first 8–24 months after surgery [54–56]. Erythropoiesis appears to be stimulated in many cases by excess erythropoietin release from native kidneys [57]. In a study, serum erythropoietin levels were elevated six of seven patients with PTE [58]. Also, other factors may either enhance the sensitivity to erythropoietin or directly promote erythropoiesis [54,59]. Implicated proteins include insulin-like growth factor-1 (IGF-1) and IGF-binding protein [60]. ACEi and ARB may reduce erythropoiesis either by a direct inhibition of erythropoietin and IGF-1 production or by an indirect mechanism derived from improvement of renal perfusion and subsequent decrease in oxygen consumption [61]. Also, activation of the AT_1 receptor may enhance erythropoietin production in the graft or increase sensitivity of red cell precursor to erythropoietin [62]. Many reports have concluded that ACEi and ARB are safe and effective to treat PTE [54,63–67]. Their effect usually begins within 2–6 weeks and is complete in 3–6 months.

Proteinuria in kidney transplantation

Proteinuria is an excellent marker of poor long-term graft and patient survival in the renal transplant population [68]. Furthermore, in a recent study, Halimi *et al.* [69] showed that microalbuminuria is a risk factor for graft loss even in nonproteinuric patients. Some authors propose that proteinuria by itself contributes to progression of chronic renal damage [70], whereas others believe that it is still unclear whether proteinuria is a cause or only a consequence of progressive renal injury [71]. In renal allografts proteinuria is caused by immunological and nonimmunological factors [72]. The antiproteinuric effect of ACEi and ARB is well documented in experimental models and translated into humans with diabetic and nondiabetic chronic renal disease [73,74]. In a comparison with other antihypertensive agents, the RAS-inhibiting drugs appear to be superior in reducing proteinuria and slowing renal failure progression [11]. Several explanations for such an effect have been offered, including reduction of glomerular hypertension and hyperfiltration, the restoration of altered glomerular filtration barrier with subsequent reduction of proteinuria and reduction of inflammatory response, renal hypertrophy and fibrosis [74]. Some authors suggest that the protective renal effects of the RAS-inhibiting drugs are independent of the reduction in systemic blood pressure [70,73]. However, Casas *et al.* [75] in a recent metanalysis showed that, in comparison with other antihypertensive drugs, the superiority of RAS blockade in terms of renoprotection is related to more pronounced reduction in blood pressure.

Holgado *et al.* [76] showed that treatment with losartan-reduced proteinuria in renal-transplanted patients. Many reports have concluded that the losartan is as effective as enalapril in reduced proteinuria in renal transplant patients [37,40]. Martinez Castelao *et al.* [77], showed higher antiproteinuric effect in patients on ACEi than on calcium channel blockers. Furthermore, no correlation was found between the reduction in proteinuria and control of blood pressure, suggesting that the antiproteinuric effect of ACEi or ARB was independent of blood pressure modification. Montanaro *et al.* [78] showed that ACEi/ARB have renoprotective effects when used in patients with good and stable renal function with mild proteinuria. In a pilot study, Dominguez-Gil *et al.* [79] showed that losartan efficiently reduced proteinuria even in kidney transplant patients with nephrotic range proteinuria. Tylicki *et al.* [80] demonstrated that, rather than

carvedilol, losartan decreases albuminuria with minimal side effects in renal transplant recipients. In a recent metanalysis, Hiremath *et al.* [27] found that in renal allograft recipients RAS blockade is associated with an average reduction of 470 mg/day in proteinuria. Thus, there is strong evidence that RAS blockade reduces 'multifactorial' proteinuria in renal allograft recipients.

Chronic allograft injury

Chronic allograft injury is characterized by a progressive decline in kidney function and is recognized as the principal cause of late graft loss [81]. Some of the pathogenic factors involved in chronic allograft injury, such as hypertension, atherosclerosis, and cyclosporine nephrotoxicity, are associated with RAS activation. Accordingly, inhibition of RAS either by ACEi and ARB slows down the progression of chronic allograft injury in some experimental models [11,82]. Amuchastegui *et al.* [11] demonstrated that losartan is clearly better than a calcium channel blocker in protecting against chronic allograft injury. In contrast to other antihypertensive drugs, ACEi and ARB reduce systemic and glomerular hypertension, hyperfiltration, and proteinuria [83].

Transforming growth factor β1 (TGF-β1) is involved in the pathogenesis of chronic allograft injury [12,74,84]. Importantly, the production of TGF-β1 may be modulated by the intrarenal RAS [85]. Campistol *et al.* [12] reported that losartan decreases the synthesis and secretion of renal TGF-β1 in patients with chronic allograft injury. Agroudy *et al.* [84] found that RAS blockade significantly decrease the plasma levels of TGF-β1 and the rate of histopathological progression. In a recent double-blind, placebo-controlled and crossover study, Tylicky *et al.* [74] showed that losartan exerts a beneficial effect against tubular injury and graft fibrosis and thus may have role in preventing chronic allograft injury. In this study losartan reduced urinary excretion of TGF-β1 and amino-terminal propeptide of type III procollagen, proteins that are associated with tubular damage and graft fibrosis, respectively.

Thus, although some surrogate markers point at the beneficial effect of ACEi/ARB for treating chronic allograft injury, there is not yet convincing evidence supporting that RAS blockade can prevent or slow down progression chronic renal damage in clinical renal transplantation.

Potential side effects of RAS blockade in renal allografts: the cons

The use of ACEi and ARB is associated with some adverse events that may limit the potential benefits in renal transplantation (Fig. 3). Hiremath *et al.* [27] in a systematic review of randomized trials with RAS-blocking agents in renal transplantation described that these agents are associated with a decline of renal function, anemia, and hyperkalemia. To minimize side effects we recommend performing a Doppler ultrasound examination of the graft to exclude renal artery stenosis before starting RAS blockade, starting these drugs at the low-therapeutic dose and to carry out close monitoring of renal function, hemoglobin, and serum potassium. All these recommendation are particularly important in patients with chronic allograft dysfunction.

Reduction of glomerular filtration rate

Midtvedt *et al.* [86] reported that transplanted patients treated with nifedipine had better renal function that patients treated with lisonopril. This effect was not observed in other studies (reviewed in [27]). However, a recent metanalysis [27] showed that patients receiving ACEi or ARB had on average a reduction of 5.8 ml/min in glomerular filtration. The authors found that this effect is robust and independent of baseline renal function, time after transplantation or duration of follow-up. So far, whether that reduction of GFR is clinically relevant is not known and deserves further investigation. Although RAS blockade is usually associated with a decline of renal function in patients with renal allograft dysfunction, it should be pointed out that in particular situations it may efficiently control hypertension without increasing or even reducing serum creatinine, as the case report presented here illustrates. It would be interesting to analyze whether RAS-blockade-induced increase of serum creatinine depends on maintenance immunosuppression, particularly calcineurin inhibitor drugs.

Hyperkalemia

The RAS blockade in renal allografts is associated with hyperkalemia [45] because of its inhibitory effect on aldosterone. However, in this setting, hyperkalemia is from multifactoral origin. Predisposing factors are treatment with calcineurin inhibitors, betablockers and presence of chronic renal damage, all reducing renal potassium excretion [45,87]. There are some strategies to minimize this life-threatening complication. In patients not receiving calcineurin inhibitors and with good renal function hyperkalemia is unusual. In the rest, RAS blockade should be started at low dose, loop diuretic can be added to enhance potassium excretion and serum potassium should be closely monitored. Low-potassium diet and sodium polystyrene sulfonate can be added in some cases. RAS blockade should be temporally discontinued if serum potassium is >6 mmol/L.

Anemia

The use of both ACEi and ARB drugs are associated with anemia in renal allograft recipients [42,43]. It was recently described that in renal allograft recipients RAS blockade is associated with an average reduction of 3.5% in hematocrit [27]. The same mechanisms useful for controlling post-transplant erythrocytosis can induce anemia. Renal dysfunction, antiproliferative drugs, and iron deficiency are contributing factors. Thus, some patients receiving ACEi or ARB require iron and particularly erythropoiesis-stimulating agents to maintain hemoglobin levels within recommended objective of 10–12 g/dl.

Controversial effects of RAS blockade in graft and patient survival

Observational studies showed conflicting results regarding the impact of RAS blockade on graft and patient survival. Heinze *et al.* [26] in a retrospective analysis of 2031 patients showed that treatment with ACEi or ARB in comparison with patients that did not receive such treatment resulted in 20% and 30% increase of patient and graft survival at 5 years, respectively. These impressive results were not confirmed by Opelz *et al.* [29] in a retrospective study of 17209 kidney transplant recipients from the Collaborative Transplant Study. There have been several small, randomized trials evaluating the use of ACEi/ARB in kidney transplantation, but most of these studies were short of duration and did not examine clinical end-points as graft loss and death. In the nontransplant population, randomized trials evaluating renal outcomes have shown that ACEi/ARB use began to show favorable separation of survival curves at approximately 24 months. These findings suggest that adequately powered randomized controlled trials of sufficient duration are needed to properly assess the impact of RAS blockade on renal transplant population.

Conclusion

Besides the immunological mediated damage, the intrarenal RAS represents an additional mechanism in the development and progression of chronic allograft injury. There are consistent experimental data showing that RAS blockade has a therapeutic effect on chronic allograft injury. Some clinical studies have shown that RAS blockade reduces TGF-β1 and other markers of fibrosis but up to now there is not convincing evidence supporting that RAS blockade has further benefit on the progression of chronic allograft injury in comparison with other antihypertensive interventions. On the other hand, RAS blockade may also improve CVD, which constitutes the main cause of mortality in renal allograft recipients. ACEi and ARB efficiently control post-transplant hypertension, reduce proteinuria and arterial stiffness and are useful in treating post-transplant erythrocytosis. However, RAS blockade in renal allograft recipients is associated to adverse events which may limit its success as hyperkalemia, anemia and even to a reduction of GFR. To date there is lack of evidence for supporting that RAS blockade improves neither graft nor patient survival in comparison with other antihypertensive drugs. Randomized, prospective, double blind, placebo-controlled trials as the Canadian ACE-inhibitor trial will probably clarify the precise role of RAS blockade in renal transplantation. Meanwhile, we should empirically balance case to case the pros and cons of RAS blockade in renal transplantation.

Authorship

All three authors contributed to this review by searching published papers, discussing and writing the manuscript.

Funding sources

This work is supported by FIS grant PI 06/0582.

References

1. Wolfe RA, Ashby VB, Milford EL, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
2. Gill JS. Potential advantages and limitations of applying the chronic kidney disease classification to kidney transplant recipients. *Am J Transplant* 2006; **6**: 2821.
3. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med* 2002; **346**: 580.
4. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. *Transplantation* 2006; **82**: 603.
5. Holdaas H, Fellstrom B, Jardine AG, *et al.* Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003; **361**: 2024.
6. Fellstrom B, Holdaas H, Jardine AG, *et al.* Effect of fluvastatin on renal end points in the assessment of Lescol in renal transplant (ALERT) trial. *Kidney Int* 2004; **66**: 1549.
7. Holdaas H, Fellstrom B, Cole E, *et al.* Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant* 2005; **5**: 2929.
8. Cosio FG, Pelletier RP, Pesavento TE, *et al.* Elevated blood pressure predicts the risk of acute rejection in renal allograft recipients. *Kidney Int* 2001; **59**: 1158.

9. Dragun D, Muller DN, Brasen JH, *et al.* Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. *N Engl J Med* 2005; **352**: 558.
10. Fogo AB. Mechanisms of progression of chronic kidney disease. *Pediatr Nephrol* 2007; **22**: 2011.
11. Amuchastegui SC, Azzollini N, Mister M, Pezzotta A, Perico N, Remuzzi G. Chronic allograft nephropathy in the rat is improved by angiotensin II receptor blockade but not by calcium channel antagonism. *J Am Soc Nephrol* 1998; **9**: 1948.
12. Campistol JM, Inigo P, Jimenez W, *et al.* Losartan decreases plasma levels of TGF-beta1 in transplant patients with chronic allograft nephropathy. *Kidney Int* 1999; **56**: 714.
13. Ruiz-Ortega M, Ruperez M, Esteban V, *et al.* Angiotensin II: a key factor in the inflammatory and fibrotic response in kidney diseases. *Nephrol Dial Transplant* 2006; **21**: 16.
14. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996; **334**: 1649.
15. Siragy HM. Angiotensin AT1 and AT2 receptors the battle for health and disease. *Nephrol Dial Transplant* 2007; **22**: 3128.
16. Ruiz-Ortega M, Esteban V, Ruperez M, *et al.* Renal and vascular hypertension-induced inflammation: role of angiotensin II. *Curr Opin Nephrol Hypertens* 2006; **15**: 159.
17. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 1985; **76**: 612.
18. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986; **77**: 1925.
19. Meyer TW, Anderson S, Rennke HG, Brenner BM. Reversing glomerular hypertension stabilizes established glomerular injury in renal ablation. *J Hypertens Suppl* 1986; **4**: S239.
20. Meyer TW, Anderson S, Rennke HG, Brenner BM. Converting enzyme inhibitor therapy limits progressive glomerular injury in rats with renal insufficiency. *Am J Med* 1985; **79**: 31.
21. Madeddu P, Emanueli C, El-Dahr S. Mechanisms of disease: the tissue kallikrein-kinin system in hypertension and vascular remodeling. *Nat Clin Pract Nephrol* 2007; **3**: 208.
22. Segall L, Covic A, Goldsmith DJA. Direct renin inhibitors: the dawn of a new era, or just a variation on a theme? *Nephrol Dial Transplant* 2007; **22**: 2435.
23. Mackenzie HS, Tullius SG, Heemann UW, *et al.* Nephron supply is a major determinant of long-term renal allograft outcome in rats. *J Clin Invest* 1994; **94**: 2148.
24. Cruzado JM, Torras J, Riera M, *et al.* Influence of nephron mass in development of chronic renal failure after prolonged warm renal ischemia. *Am J Physiol Renal Physiol* 2000; **279**: F259.
25. Denton KM, Fennessy PA, Alcorn D, Anderson WP. Morphometric analysis of the actions of angiotensin II on renal arterioles and glomeruli. *Am J Physiol* 1992; **2**: F367.
26. Mas V, Alvarellos T, Giraudo C, Massari P, De Boccardo G. Intragraft messenger RNA expression of angiotensinogen: relationship with transforming growth factor beta-1 and chronic allograft nephropathy in kidney transplant patients. *Transplantation* 2002; **74**: 718.
27. Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. *Am J Transplant* 2007; **7**: 2350.
28. Heinze G, Mitterbauer C, Regele H, *et al.* Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol* 2006; **17**: 889.
29. Opelz G, Zeier M, Laux G, Morath C, Dohler B. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. *J Am Soc Nephrol* 2006; **17**: 3257.
30. Toussaint C, Kinnaert P, Vereerstraeten P. Late mortality and morbidity five to eighteen years after kidney transplantation. *Transplantation* 1988; **45**: 554.
31. Campistol JM, Romero R, Paul J, Gutierrez-Dalmau A. Epidemiology of arterial hypertension in renal transplant patients: changes over the last decade. *Nephrol Dial Transplant* 2004; **19**(Suppl. 3): iii62.
32. Diaz JM, Sainz Z, Guirado LL, *et al.* Risk factors for cardiovascular disease after renal transplantation. *Transplant Proc* 2003; **35**: 1722.
33. First MR, Neylan JF, Rocher LL, Tejani A. Hypertension after renal transplantation. *J Am Soc Nephrol* 1994; **4**(Suppl. 1): S30.
34. Aakhus S, Dahl K, Wideroe TE. Cardiovascular disease in stable renal transplant patients in Norway: morbidity and mortality during a 5-yr follow-up. *Clin Transplant* 2004; **18**: 596.
35. Kasiske BL, Anjum S, Shah R, *et al.* Hypertension after kidney transplantation. *Am J Kidney Dis* 2004; **43**: 1071.
36. Bolad IA, Breen J, Rogers P, Partridge J, Banner NR. Prevalence and significance of renal artery stenosis and abdominal aortic atherosclerosis early after heart transplantation. *Transplant Proc* 2002; **34**: 3236.
37. Paoletti E, Cassottana P, Amidone M, Gherzi M, Rolla D, Cannella G. ACE inhibitors and persistent left ventricular hypertrophy after renal transplantation: a randomized clinical trial. *Am J Kidney Dis* 2007; **50**: 133.
38. Hernandez D. Left ventricular hypertrophy after renal transplantation, new approach to a deadly disorder. *Nephrol Dial Transplant* 2004; **19**: 1682.
39. Mange KC, Feldman HI, Joffe MM, Fa K, Bloom RD. Blood pressure and the survival of renal allografts from living donors. *J Am Soc Nephrol* 2004; **15**: 187.
40. Fernandez-Fresnedo G, Escallada R, Martin de Francisco AL, *et al.* Association between pulse pressure and

cardiovascular disease in renal transplant patients. *Am J Transplant* 2005; **5**: 394.
41. Sanders CE, Curtis JJ. Role of hypertension in chronic renal allograft dysfunction. *Kidney Int* 1995; **52**: S43.
42. Cheigh JS, Haschemeyer RH, Wang JC, *et al.* Hypertension in kidney transplant recipients. Effect on long-term renal allograft survival. *Am J Hypertens* 1989; **1**: 341.
43. Stigant CE, Cohen J, Vivera M, *et al.* ACE inhibitors and angiotensin II antagonist in renal transplantation: an analysis of safety and efficacy. *Am J Kidney Dis* 2000; **35**: 58.
44. Martinez-Castelao A, Hueso M, Sanz V, *et al.* Double-blind, crossover, comparative study of doxazosin and enalapril in the treatment of hypertension in renal transplant patients under cyclosporine immunosuppression. *Transplant Proc* 2002; **34**: 403.
45. Formica Jr RN, Friedman AL, Lorber MI, Smith JD, Eisen T, Bia MJ. A randomized trial comparing losartan with amlodipine as initial therapy for hypertension in the early post-transplant period. *Nephrol Dial Transplant* 2006; **21**: 1389.
46. Ersoy A, Kahvecioglu S, Ersoy C, Cift A, Dilek K. Anemia due to losartan in hypertensive renal transplant recipients without posttransplant erythrocytosis. *Transplant Proc* 2005; **37**: 2148.
47. London GM, Fabiani F, Marchais SJ, *et al.* Uremic cardiomyopathy: an inadequate left ventricular hypertrophy. *Kidney Int* 1987; **31**: 973.
48. London GM, Marchais SJ, Guerin AP, Pannier B. Arterial stiffness: pathophysiology and clinical impact. *Clin Exp Hypertension* 2004; **26**: 689.
49. Agarwal R. Antihypertensive agents and arterial stiffness: relevance to reducing cardiovascular risk in the chronic kidney disease patient. *Curr Opin Nephrol Hypertens* 2007; **16**: 409.
50. Covic A, Goldsmith DJ, Gusbeth-Tatomir P, Buhaescu I, Covic M. Successful renal transplantation decreases aortic stiffness and increases vascular reactivity in dialysis patients. *Transplantation* 2003; **76**: 1573.
51. Kneifel M, Scholze A, Burkert A, *et al.* Impaired renal allograft function is associated with increased arterial stiffness in renal transplant recipients. *Am J Transplant* 2006; **6**: 1624.
52. Martínez-Castelao A, Sarrias X, Bestard O, *et al.* Arterial elasticity measurement in renal transplant patients under anticalcineurin immunosuppression. *Transplant Proc* 2005; **37**: 3788.
53. Nankivell BJ, Allen RD, O'Connell PJ, Chapman JR. Erythrocytosis after renal transplantation: risk factors and relationship with GFR. *Clin Transplant* 1995; **9**: 375.
54. Gaston RS, Julian BA, Curtis JJ. Posttrasplant erythrocytosis: an enigma revisited. *Am J Kidney Dis* 1994; **24**: 1.
55. Vlahakos DV, Marathias KP, Agroyannis B, Madias NE. Posttransplant erythrocytosis. *Kidney Int* 2003; **63**: 1187.
56. Augustine JJ, Knauss TC, Schulak JA, Bodziak KA, Siegel C, Hricik DE. Comparative effects of sirolimus and mycophenolate mofetil on erythropoiesis in kidney transplant patients. *Am J Transplant* 2004; **4**: 2001.
57. Aeberhard JM, Schneider PA, Vallotton MB, Kurtz A, Leski M. Multiple site estimates of erythropoietin and renin in polycythemic kidney transplant patients. *Transplantation* 1990; **50**: 613.
58. Dagher FJ, Ramos E, Erslev AJ, Alongi SV, Karmi SA, Caro J. Are the native kidneys responsible for erythrocytosis in renal allorecipients? *Transplantation* 1979; **28**: 496.
59. Ilan Y, Dranitzki-Elhallel M, Rubinger D, Silver J, Popovtzer MM. Erythrocytosis after renal transplantation. The response to theophylline treatment. *Transplantation* 1994; **57**: 661.
60. Wang AY, Yu AW, Lam CW, *et al.* Effects of losartan or enalapril on hemoglobin, circulating erythropoietin, and insulin-like growth factor-1 in patients with and without posttransplant erythrocytosis. *Am J Kidney Dis* 2002; **39**: 600.
61. Morrone LF, Di Paolo S, Logoluso F, *et al.* Interference of angiotensin-converting enzyme inhibitors on erythropoiesis in kidney transplant recipients: role of growth factors and cytokines. *Transplantation* 1997; **64**: 913.
62. Glicklich D, Kapoian T, Mian H, Gilman J, Tellis V, Croizat H. Effects of erythropoietin, angiotensin II, and angiotensin-converting enzyme inhibitor on erythroid precursors in patients with posttransplantation erythrocytosis. *Transplantation* 1999; **1**: 62.
63. Inigo P, Torregrosa JV, Campistol JM, Oppenheimer F. Treatment with losartan in kidney transplant recipients with posttransplant erythrocytosis. *Transplant Proc* 1999; **31**: 2321.
64. Ducloux D, Fournier V, Bresson-Vautrin C, Chalopin JM. Long-term follow-up of renal transplant recipients treated with losartan for post-transplant erythrosis. *Transpl Int* 1998; **11**: 312.
65. 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* 2001; **3**: 542.
66. Klaassen RJ, van Gelder T, Rischen-Vos J, Deinum J, Man in't Veld AJ, Weimar W. Losartan, and angiotensin-II receptor antagonist, reduces hematocrits in kidney transplant recipients with posttrasplant erythrocytosis. *Transplantation* 1997; **64**: 780.
67. Vlahakos DV, Canzanello VJ, Madaio MP, Madias NE. Enalapril-associated anemia in renal transplant recipients treated for hypertension. *Am J Kidney Dis* 1991; **72**: 199.
68. Fernández-Fresnedo G, Plaza JJ, Sánchez-Plumed J, Sanz-Guajardo A, Palomar-Fontanet R, Arias M. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. *Nephrol Dial Transplant* 2004; **19**(Suppl. 3): iii47.
69. Halimi JM, Buchler M, Al-Najjar A, *et al.* Urinary albumin excretion and the risk of graft loss and death in

proteinuric and non-proteinuric renal transplant recipients. *Am J Transplant* 2007; **7**: 618.
70. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med* 1998; **339**: 1448.
71. Zandi-Nejad K, Eddy AA, Glassock RJ, Brenner BM. Why is proteinuria an ominous biomarker of progressive kidney disease? *Kidney Int Suppl* 2004; **92**: S76.
72. Sancho A, Gavela E, Avila A, *et al.* Risk factors and prognosis for proteinuria in renal transplant recipients. *Transplant Proc* 2007; **39**: 2145.
73. Tylicki L, Larczynski W, Rutkowski B. Renal protective effects of the renin-angiotensin-aldosterone system blockade: from evidence-based approach to perspectives. *Kidney Blood Press Res* 2005; **28**: 230.
74. Tylicki L, Biedunkiewicz B, Chamienia A, *et al.* Renal allograft protection with angiotensin II type 1 receptor antagonists. *Am J Transplant* 2007; **7**: 243.
75. Casas JP, Chua W, Loukogeorgakis S, *et al.* Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; **366**: 2026.
76. 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* 2001; **16**(Suppl. 1): 117.
77. Martinez-Castelao A, Hueso M, Sanz V, Rejas J, Alsina J, Grinyo JM. Treatment of hypertension after renal transplantation: long-term efficacy of verapamil, enalapril, and doxazosin. *Kidney Int Suppl* 1998; **68**: S130.
78. Montanaro D, Gropuzzo M, Tulissi P, *et al.* Renoprotective effect of early inhibition of the renin-angiotensin system in renal transplant recipients. *Transplant Proc* 2005; **37**: 991.
79. Dominguez-Gil B, Ortiz M, Sierra MP, *et al.* Losartan reduces massive proteinuria in kidney transplant patients: a pilot study. *Transplant Proc* 2002; **34**: 368.
80. Tylicki L, Biedunkiewicz B, Chamienia A, Wojnarowski K, Zdrojewski Z, Rutkowski B. Randomized placebo-controlled study on the effects of losartan and carvedilol on albuminuria in renal transplant recipients. *Transplantation* 2006; **81**: 52.
81. Paul LC. Chronic allograft nephropathy. An update. *Kidney Int* 1999; **56**: 783.
82. Lutz J, Risch K, Liu S, *et al.* Angiotensin type 1 and type 2 receptor blockade in chronic allograft nephropathy. *Kidney Int* 2006; **70**: 1080.
83. Inigo P, Campistol JM, Lario S, *et al.* Effects of losartan and amlodipine on intrarenal hemodynamics and TGF-beta(1) plasma levels in a crossover trial in renal transplant recipients. *J Am Soc Nephrol* 2001; **12**: 822.
84. 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* 2003; **23**: 300.
85. August P, Suthanthiran M. Transforming growth factor beta and progression of renal disease. *Kidney Int* 2003; **87**(Suppl.): s99.
86. Midtvedt K, Hartmann A, Foss A, *et al.* Sustained improvement of renal graft function for two years in hypertensive renal transplant recipients treated with nifedipine as compared to lisinopril. *Transplantation* 2001; **72**: 1787.
87. Kamel KS, Ethier JH, Quaggin S, *et al.* Studies to determine the basis for hyperkalemia in recipients of a renal transplant who are treated with cyclosporine. *J Am Soc Nephrol* 1992; **2**: 1279.

