Influence of cyclosporin, tacrolimus and rapamycin on renal function and arterial hypertension after renal transplantation

José M. Morales, Amado Andres, Manuel Renget and José L. Rodicio

Renal Transplant Unit, Nephrology Department, Hospital 12 de Octubre and Nephrology Department, Hospital Gregorio Marañón, Madrid, Spain

Abstract
Cyclosporin and tacrolimus have improved survival figures in organ transplantation. However, both drugs are potentially nephrotoxic. The immunosuppressive and nephrotoxic effects of both drugs appear to depend on the inhibition of calcineurin. Cyclosporin and tacrolimus cause acute (functional changes) and chronic nephrotoxicity (structural lesions in the kidney). These last important lesions include arteriolar hyalinosis, stripped interstitial fibrosis and tubular atrophy. It is possible that repeated episodes of renal ischaemia contribute to the development of chronic nephrotoxicity and then chronic allograft nephropathy. Cyclosporin and tacrolimus also induce arterial hypertension. Therefore, the beneficial effects of immunosuppression have been limited due to nephrotoxicity and arterial hypertension. Rapamycin, a novel immunosuppressive agent, that does not inhibit calcineurin, provides immunosuppression without nephrotoxicity. In fact, in the trials performed in Europe, sirolimus-treated immunosuppression patients exhibited a much better renal function than cyclosporin-treated patients. However, sirolimus can potentiate the nephrotoxic effect of cyclosporin. Therefore, when cyclosporin and sirolimus are used in combination, a reduction of the cyclosporin dose is desirable.

Cyclosporin and tacrolimus
It is well known that the nephrotoxic and immunosuppressive effects of cyclosporin and tacrolimus appear to depend on the inhibition of calcineurin, a protein phosphatase with important regulatory effects blocking expression of T-cell activation genes [1,2]. Both cyclosporin and tacrolimus cause acute and chronic nephrotoxicity [1–3].

Acute nephrotoxicity
Acute nephrotoxicity induced by anticalcineurin drugs is characterized by dose-dependent functional changes of the kidney, which are reversible with a decrease in the dose or drug withdrawal. Cyclosporin and tacrolimus induce renal vasoconstriction of the afferent pre-glomerular arterioles that is followed by a decrease in renal blood flow and glomerular filtration rate [4]. This reversible alteration is mediated by endothelin, an imbalance between vasoconstrictory and vasodilatory prostaglandins (thromboxane A₂ and prostaglandin E₂), nitric oxide synthase inhibition, increased sympathetic tone and activation of the renin–angiotensin system [5]. Several clinical forms of acute nephrotoxicity have been reported: prolonged acute tubular necrosis delaying the renal function recovery time; transient episodes of increases of serum creatinine; and de novo or recurrent haemolytic uraemic syndrome [6]. The most frequent clinical form consists of a transitory elevation of serum creatine that improves after cyclosporin/tacrolimus doses are reduced. In renal transplant patients, this problem sometimes makes the diagnosis of rejection difficult.

Introduction
Cyclosporin and, more recently, tacrolimus have improved patient and graft survival rates in organ transplantation [1,2]. However, these beneficial effects of immunosuppression have been limited because both drugs can induce nephrotoxicity and arterial hypertension [3]. Here we review the most important effects of these agents on renal function and arterial hypertension together with the new experimental and clinical data obtained with rapamycin, a new immunosuppressive agent with a different mechanism of action.

Correspondence and offprint requests to: José M. Morales, MD, Associate Professor of Medicine, Renal Transplant Unit, Nephrology Department, Hospital 12 de Octubre, Carretera de Andalucía Km 5.400, 28041 Madrid, Spain.

© 2001 European Renal Association–European Dialysis and Transplant Association
Chronic nephrotoxicity

Chronic cyclosporin and tacrolimus nephrotoxicity are characterized by the presence of structural lesions in the kidney. These alterations include afferent arteriolar hyalinosis, stripped interstitial fibrosis and tubular atrophy. Chronic nephrotoxicity is the major side effect of cyclosporin and tacrolimus. Chronic cyclosporin and tacrolimus nephrotoxicity is manifested by renal insufficiency and arterial hypertension. Pathogenetic factors for chronic nephrotoxicity are not well understood, although it is possible that repeated episodes of renal ischaemia contribute to the development of chronic nephrotoxicity. Interstitial fibrosis is associated with increased expression of osteopontin, chemokines and, particularly, transforming growth factor-β1 (TGF-β1) [1]. It has also been reported that accelerated apoptosis characterizes interstitial fibrosis induced by cyclosporin. Clinically, Mourad et al. reported that in up to 6% of the total renal transplant population, chronic renal allograft dysfunction may be caused only by chronic cyclosporin nephrotoxicity [8].

Several agents have been tested to prevent and to minimize chronic cyclosporin nephrotoxicity, such as calcium channel blockers, fish oil, thromboxane synthesis inhibitors and pentoxifylline. None of them is clearly effective, although several trials demonstrated that patients treated with calcium antagonists such as nifedipine can improve renal function in the long-term follow-up [9]. New approaches are the addition of mycophenolate mofetil [3] or rapamycin, and decreasing or stopping anticalcineurin drugs in patients with deterioration of renal function and biopsy-proven chronic nephrotoxicity.

Differences between cyclosporin and tacrolimus nephrotoxicity

It has been demonstrated that tacrolimus is as nephrotoxic as cyclosporin [2]. Nevertheless, tacrolimus has been associated with less systemic vasoconstriction and less arterial hypertension that cyclosporin (10). In the most important European [11] and American [2] trials comparing tacrolimus vs cyclosporin in renal transplantation, patients on tacrolimus exhibit similar serum creatinine but there was a tendency to present less arterial hypertension than patients on cyclosporin. Also, in the European study at 4 years, serum creatinine exhibited a tendency to be lower in tacrolimus patients. On the other hand, patients who were switched from cyclosporin to tacrolimus (for cosmetic effects or for hypercholesterolaemia) showed an improvement in blood pressure control with less need for antihypertensive drugs and, in some cases, normalization of blood pressure [12].

Cyclosporin- and tacrolimus-induced arterial hypertension

Cyclosporin and tacrolimus can also induce arterial hypertension. Both drugs act by increasing systemic and renal vascular resistance, affecting the afferent arterioles, as mentioned above. Endothelin seems to play an important pathogenetic role in the development of arterial hypertension [13]. In fact, it has been demonstrated experimentally that the administration of an endothelin receptor antagonist controlled cyclosporin-induced arterial hypertension [14]. Clinically, between 40 and 70% of renal transplant patients have arterial hypertension in association with cyclosporin or tacrolimus immunosuppression. Although other causes of hypertension contribute to this frequency, it is clear that these immunosuppressive agents are one of the most frequent causes of post-transplant arterial hypertension [15].

How should post-transplant arterial hypertension induced by cyclosporin and tacrolimus be managed?

The treatment of post-transplant hypertension is mandatory to protect graft function [16] and to protect against cardiovascular disease, the most frequent cause of death in renal transplant patients. General measures should firstly be instigated such as avoidance of an increase of body weight, salt restriction and a reduction of the maintenance corticosteroid dose. In the late 1980s and early 1990s, calcium channel blockers were the elective drugs for post-transplant hypertension [15]. Currently, it is well known that in patients undergoing cyclosporin or tacrolimus immunosuppression, calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors could be useful to control blood pressure [17]. Because it has not been demonstrated that calcium channel blockers have a clear benefit over placebo or lisinopril on plasma creatinine and long-term graft survival, the choice of drug could depend on the presence of proteinuria [18]. In patients without proteinuria, a calcium channel blocker could be used but in proteinuric patients an ACE inhibitor (because of its antiproteinuric effect) could be indicated. Both drugs can also be administered together if blood pressure is not controlled. Before ACE therapy, renal artery stenosis by duplex Doppler should be excluded. It is advisable to monitor the serum potassium after the start of ACE therapy.

Angiotensin II receptor antagonists could be used to control post-transplant arterial hypertension [19]. In addition to this antihypertensive effect, losartan can decrease the serum levels of TGF-β1 and endothelin in patients with chronic allograft nephropathy [20]. Therefore, the use of these promising agents could be useful not only to treat post-transplant arterial hypertension but also to prevent or minimize chronic allograft nephropathy.

Rapamycin

Rapamycin (sirolimus), a novel immunosuppressive agent, targets a different stage of the immune response from that of cyclosporin and tacrolimus. Rapamycin
Cyclosporin, tacrolimus and rapamycin after renal transplantation

123

does not inhibit calcineurin; therefore, it provides immunosuppression without the accompanying side effect of nephrotoxicity. Sirolimus also acts synergistically with cyclosporin [21].

Sirolimus is not a nephrotoxic drug, at least not at the doses that are used in human transplantation. Experimentally it has been demonstrated that a high dose induces interstitial changes in the kidney [22]. Currently, information on the influence of sirolimus on renal function and arterial hypertension is reported in the most recent multicentre trials.

Recently, a phase III multicentre, randomized, double-blind, pivotal trial in renal transplant patients comparing the potency of sirolimus vs azathioprine in combination with a baseline cyclosporin microemulsion and prednisone regimen has been published. Use of sirolimus was associated with a statistically significant reduction in the incidence of acute rejection (sirolimus 2 mg, 16.9%; 5 mg, 12%; azathioprine, 29.8%) and the severity of biopsy-proven acute rejection episodes in the first 6 months after transplantation. Nevertheless, at 6 and 12 months, the mean serum creatinine concentrations were significantly higher in patients in the two sirolimus groups than in those in the azathioprine group. Arterial hypertension was also more frequent in sirolimus–cyclosporin combinations than in the control group (sirolimus 2 mg, 38%, 5 mg, 34%; azathioprine, 23%). These unexpected findings could be explained by the potentiation of the nephrotoxic effects of cyclosporin by sirolimus. In fact, Kahan et al. demonstrated that sirolimus augments cyclosporin-induced renal dysfunction due to a pharmacokinetic interaction (Kahan, personal communication). Therefore, special attention should be paid to renal function and arterial hypertension, and cyclosporin doses probably should be reduced when it is administered in combination with sirolimus.

The true effect of sirolimus on renal function can be observed in the trials performed recently in Europe. Sirolimus-based immunosuppression was evaluated as an alternative to cyclosporin-based immunosuppression in cadaver donor renal transplant recipients. In the first study, 83 renal transplant recipients were randomized to receive either sirolimus (n = 41) or cyclosporin (n = 42). All patients also received azathioprine and corticosteroids. In the second study (n = 78), azathioprine was replaced by mycophenolate mofetil in a design similar to that of the previous study: sirolimus (n = 39) vs cyclosporin (n = 39). The results from the two studies subsequently were pooled and showed that patient survival, graft survival and acute rejections were similar at 12 months between patients treated with sirolimus-based therapy (n = 81) and cyclosporin-based therapy (n = 80). Notably, serum creatinine levels were consistently lower in the sirolimus patients, who also exhibited a higher glomerular filtration rate (Nankivell method) from 8 to 52 weeks. The difference in renal function between sirolimus patients and cyclosporin patients was statistically significant at weeks 8–52. The incidence of arterial hypertension in the sirolimus group was 28% vs 40% in the cyclosporin group. Hypokalaemia was more frequent in sirolimus patients (27% vs 8% in cyclosporin patients). Preliminary data regarding hypokalaemia suggest that it can be due to a tubular effect of rapamycin without important clinical implications [27]. Therefore, these trials demonstrated that sirolimus-based therapy may be used as an alternative to cyclosporin as basal therapy in renal transplantation, with a different but less nephrotoxic profile.

The most recent data have been presented in the last Congress of the International Society of Transplantation (Rome, August 2000). Hricik et al. reported that elimination of cyclosporin at 3 months in a procolol with sirolimus is safe (i.e. did not result in a significant increase of acute rejection episodes) and provided improved renal function in patients receiving concentration-controlled rapamycin [28]. Therefore, all available information demonstrates that rapamycin alone is not a nephrotoxic drug and it could therefore be a good immunosuppressive possibility in solid organ transplantation.

In summary, cyclosporin and tacrolimus are excellent immunosuppressive drugs but are potentially nephrotoxic. This important side effect, mainly chronic nephrotoxicity, can favour the development of chronic allograft nephropathy and can therefore limit the therapeutic utility of these agents. These agents also induce arterial hypertension that is considered a risk factor for chronic graft failure. Sirolimus is a new agent with a different mechanism of action and different side effect profile. In fact, sirolimus alone is non-nephrotoxic; nevertheless, sirolimus can potentiate the nephrotoxic effect of cyclosporin. Therefore, when cyclosporin and sirolimus are administered in combination, a reduction in the cyclosporin dose is desirable.

References

3. Takeshi F, Burdmann EA, Bennett WA. Nephrotoxicity of immunosuppressive drugs: experimental and clinical observations. Semin Nephrol 1997; 17: 34–45