Renal function: defining long-term success

Julio Pascual, Roberto Marcén and Joaquín Ortuno

Department of Nephrology, Ramón y Cajal Hospital, Madrid, Spain

Abstract
One of the leading causes of late graft loss is chronic allograft nephropathy, characterized in part by deteriorating renal function. Registry data have demonstrated that renal function within the first year post-transplant is an important predictor of long-term transplant outcome, with serum creatinine concentrations ≤1.5 mg/dl at 6 or 12 months being associated with the highest rate of 5 year graft survival. These findings are supported by a retrospective, pooled analysis of two multicentre trials in the USA, as well as by our own data showing that serum creatinine concentrations may be predictive of long-term survival as early as 1 month post-transplant. Analysis of 216 renal transplantsations carried out at our centre (1996–2000) using immunosuppressive therapy based on tacrolimus, corticosteroids and azathioprine (n = 51) or mycophenolate mofetil (MMF; n = 70) vs ciclosporin microemulsion, azathioprine and corticosteroids (n = 95) showed that the best 3 year graft survival was achieved with tacrolimus/MMF therapy. While serum creatinine concentrations at this time point were similar for the tacrolimus and ciclosporin treatment groups (1.69 and 1.65 mg/dl, respectively), the proportion of patients with functioning grafts was significantly higher in the tacrolimus group (84% vs 67%, P = 0.007). Similar findings of improved renal function or graft outcomes with tacrolimus- vs ciclosporin-based therapy have been reported in other single-centre and multicentre trials and a USRDS registry survey. Accumulating data suggest that renal function compares well between tacrolimus-based and calcineurin inhibitor (CNI)-sparing regimens. Consequently, the vast majority of renal transplant recipients maintain good long-term renal function with tacrolimus cornerstone immunosuppression without adopting CNI minimization or withdrawal strategies.

Keywords: chronic allograft nephropathy; calcineurin inhibitor elimination; graft survival; rejection; renal function; tacrolimus

Introduction
In recent years, renal transplant recipients have benefited from improved short-term graft survival [1]. This is partly due to the introduction of the primary immunosuppressants ciclosporin and tacrolimus, which heralded enormous improvements in terms of acute rejection. Despite this, there remains a steady decline in graft survival beyond the first year post-transplantation, due predominantly to chronic allograft nephropathy (CAN) and death with a functioning graft [2,3].

CAN manifests clinically as a gradual reduction in renal function, accompanied by hypertension and low-grade proteinuria, and usually occurs months or years after transplantation [3]. Histopathological findings generally include transplant arteriopathy, chronic transplant glomerulopathy, tubular atrophy and interstitial fibrosis. Antigen-specific cellular mechanisms and humoral immune mechanisms both play a role in the pathogenesis of CAN. The production of alloantibodies against class I or II human leukocyte antigens (HLAs) of the donor has been shown to be associated with chronic rejection, and recent studies have found complement C4d deposits in peritubular capillaries of biopsy samples from patients with CAN, suggesting the presence of an ongoing immunological process. Non-immunological factors involved in the pathogenesis of CAN include the contribution of acute peritransplantational injury to delayed graft function and accelerated senescence. Also, the age of the donor, the quality of the graft and the number of nephrons in the donor organ are important predictors of graft survival.

Prevention or reversal of CAN would greatly enhance the long-term success of renal transplantation. One of the most challenging and important issues.
in this regard is to attempt to identify patients at risk of developing CAN, thus enabling appropriate strategies to be used for those at high risk.

**Causes of CAN**

A retrospective analysis of >105 000 renal transplantations undertaken between 1988 and 1998 identified renal function during the first year post-transplant as being one of the most important variables influencing long-term graft survival [1]. Serum creatinine concentrations >1.5 mg/dl at 6 or 12 months post-transplant and a change in serum creatinine of ≥0.3 mg/dl between 6 and 12 months were associated with a decline in 5 year graft survival. At 1 year, the hazard ratio (HR) for graft failure was estimated at 1.63 (95% confidence interval 1.61–1.65) for each 1.0 mg/dl increment in serum creatinine; this increased further when the change in serum creatinine between 6 and 12 months increased to 0.5 mg/dl [2.26 (2.20–2.31)].

In support of these findings are data from a smaller, pooled analysis of two US multicentre trials comparing tacrolimus with ciclosporin or ciclosporin microemulsion, which showed that serum creatinine concentrations >1.5 mg/dl at 6 months (HR 2.44, \( P < 0.001 \)) or 12 months (HR 3.46, \( P < 0.001 \)) are associated with poorer 3 year renal graft survival than serum creatinine concentrations ≤1.5 mg/dl [4]. Interestingly, data obtained from our own centre between 1996 and 2000 show that serum creatinine concentrations may be predictive of long-term outcome as early as 1 month post-transplant, with values >2 mg/dl at this time point being associated with significantly (\( P < 0.01 \)) worse 3 year graft survival vs serum creatinine concentrations ≤2 mg/dl (Figure 1).

A number of additional recipient, donor and peritransplant factors have also been shown to determine success in renal transplantation. The UNOS (United Network for Organ Sharing) population registry database indicates that older age, female sex, black race, pre-transplant diabetes mellitus, previously failed transplants and panel-reactive antibody >80% are important recipient factors associated with long-term kidney graft failure (Table 1) [1]. The same analysis also highlighted black donor race and older donor age (age >50 years), delayed graft function and HLA mismatch as being associated with poor outcomes.

**Calcineurin inhibitors and maintenance of renal function**

**Evidence from single-centre studies**

The contribution of calcineurin inhibitors to the evolution of CAN is controversial and is probably overestimated. Our own experience comes from a non-randomized, retrospective study, undertaken between 1996 and 2000, of 216 renal transplant recipients. In this study, 95 patients were treated with ciclosporin microemulsion and corticosteroids ± azathioprine, 51 were treated with tacrolimus and corticosteroids ± azathioprine, and 70 were treated with tacrolimus, mycophenolate mofetil (MMF) and corticosteroids. All patients were followed for 3 years or until graft loss. The study showed a trend towards improved 3 year, non-censored, Kaplan–Meier estimated graft survival with tacrolimus- vs ciclosporin-based therapy (\( P = 0.074 \), Figure 2). The best survival was achieved with tacrolimus, MMF and corticosteroids (91% at 3 years). Although mean serum creatinine was not significantly different at 3 years between tacrolimus- and ciclosporin microemulsion-treated patients (1.69 and 1.65 mg/dl, respectively), the proportion of patients with functioning grafts was significantly higher with tacrolimus treatment (84 vs 67%, \( P = 0.007 \)). The reason for failure to show any

<table>
<thead>
<tr>
<th>Recipient variables</th>
<th>Relative hazard</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 53 vs 43 years</td>
<td>1.07</td>
<td>1.06–1.08</td>
</tr>
<tr>
<td>Female</td>
<td>1.10</td>
<td>1.07–1.13</td>
</tr>
<tr>
<td>Black</td>
<td>1.41</td>
<td>1.36–1.46</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.59</td>
<td>1.54–1.65</td>
</tr>
<tr>
<td>Previous transplant</td>
<td>1.38</td>
<td>1.32–1.43</td>
</tr>
<tr>
<td>Recent PRA 80%+</td>
<td>1.17</td>
<td>1.06–1.28</td>
</tr>
<tr>
<td>Donor variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living</td>
<td>0.80</td>
<td>0.77–0.83</td>
</tr>
<tr>
<td>Black</td>
<td>1.15</td>
<td>1.10–1.20</td>
</tr>
<tr>
<td>Age &gt;50 years</td>
<td>1.23</td>
<td>1.14–1.34</td>
</tr>
<tr>
<td>Transplant variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>1.16</td>
<td>1.12–1.20</td>
</tr>
<tr>
<td>HLA mismatch</td>
<td>1.05</td>
<td>1.04–1.06</td>
</tr>
</tbody>
</table>

PRA = panel-reactive antibody.

Cox proportional hazard model: \( P < 0.001 \) for all variables except for recent PRA, which is \( P = 0.0010 \).
difference in serum creatinine concentrations between the treatment arms was that more patients in the ciclosporin group lost their graft during the early phases of follow-up, resulting in poorly functioning grafts being excluded from the data pool.

Data from the Cardiff group support our own findings, showing 5 year renal graft function, as assessed by measuring median glomerular filtration rates (GFRs), to be superior in patients treated with tacrolimus, azathioprine and corticosteroids than in those treated with ciclosporin microemulsion, azathioprine and corticosteroids (62 vs 43 ml/min, respectively; $P = 0.017$) [5].

Evidence from multicentre studies

Perhaps more meaningful information on long-term renal graft function can be gleaned from randomized, multicentre trials. The 5 year results of a European multicentre trial comparing tacrolimus ($n = 303$) with the original formulation of ciclosporin ($n = 145$) in kidney transplant recipients indicated that renal function was similar in the tacrolimus and ciclosporin groups (median serum creatinine: 1.70 and 1.74 mg/dl, respectively), as was graft survival (67.9 and 65.9%) [6]. However, tacrolimus-based therapy was associated with a significantly lower incidence of chronic rejection at 5 years post-transplant than ciclosporin-based therapy (6.6 vs 15.3%, $P < 0.01$), and the projected graft half-life was 5 years longer for tacrolimus-treated patients (15.8 vs 10.8 years).

The long-term evaluation of renal transplant patients ($n = 412$) enrolled in a similar trial conducted in the USA also revealed some important benefits of tacrolimus over ciclosporin [7]. In this study, median serum creatinine at 5 years post-transplant was significantly lower with tacrolimus (1.4 mg/dl) than with ciclosporin (1.7 mg/dl, $P = 0.0014$). In addition, when crossover for rejection was counted as graft failure, there was a significant improvement in 5 year graft survival with tacrolimus- vs ciclosporin-based therapy (63.8 vs 53.8%, $P = 0.014$).

The 3 year results of a comparative study of tacrolimus ($n = 286$) and ciclosporin microemulsion ($n = 271$) were not substantially different from those observed with the original ciclosporin formulation reported previously [8]. The data demonstrated not only a lower incidence of acute renal graft rejection during the first 6 months post-transplant with tacrolimus vs ciclosporin microemulsion (19.6 vs 37.3%, $P < 0.0001$), but also numerically better graft survival (91.2 vs 88.2%, $P = 0.01$) and improved renal function (median calculated creatinine clearance: 64.5 vs 60.3 ml/min, $P = 0.01$) in the tacrolimus group. In addition, 18% of ciclosporin microemulsion-treated patients required a switch in baseline immunosuppression, compared with just 3% in the tacrolimus group ($P < 0.01$).

Further data supporting the use of tacrolimus comes from a prospective, US multicentre study of 223 kidney transplant recipients, which demonstrated that the median 3 year serum creatinine concentration was lower in patients receiving tacrolimus, azathioprine plus corticosteroids (1.4 mg/dl) or tacrolimus, MMF and corticosteroids (1.4 mg/dl) than in those maintained on ciclosporin microemulsion, MMF plus corticosteroid immunosuppression (1.6 mg/dl) [9].

Graft function achieved with tacrolimus-based immunosuppression in multicentre trials not directly comparing outcomes with ciclosporin is also very encouraging. In a dual vs triple, Spanish–Italian trial, excellent graft function was achieved with tacrolimus plus corticosteroids (dual therapy, $n = 239$) and tacrolimus, corticosteroids plus azathioprine (triple therapy, $n = 236$), even in patients who experienced delayed graft function and received tacrolimus, MMF and corticosteroid therapy (84.1 vs 49.9% in the ciclosporin microemulsion treatment group, $P = 0.02$).

Graft function achieved with tacrolimus-based immunosuppression in multicentre trials not directly comparing outcomes with ciclosporin is also very encouraging. In a dual vs triple, Spanish–Italian trial, excellent graft function was achieved with tacrolimus plus corticosteroids (dual therapy, $n = 239$) and tacrolimus, corticosteroids plus azathioprine (triple therapy, $n = 236$), even in patients who experienced delayed graft function and received tacrolimus, MMF and corticosteroid therapy (84.1 vs 49.9% in the ciclosporin microemulsion treatment group, $P = 0.02$).

Minimizing immunosuppression

Minimization of immunosuppression is not itself a primary goal in organ transplantation. However, minimizing the use of immunosuppressive agents is appropriate when it helps to reduce the risk of drug toxicity, as long as there is no compromise of immunosuppressive efficacy.

Figure 4 shows serum creatinine concentrations obtained 6–12 months post-transplantation in four recent studies evaluating withdrawal of ciclosporin or tacrolimus [11–14]. Also illustrated are the serum creatinine concentrations reported in various studies...
of tacrolimus-based maintenance therapy in renal transplant recipients [15–18]. Patients assigned to the ciclosporin or tacrolimus withdrawal groups, receiving maintenance therapy with sirolimus or MMF and corticosteroids, achieved serum creatinine concentrations in the range 1.30–1.64 mg/dl [11–14], which is comparable with the range of 6–12 month serum creatinine concentrations achieved with tacrolimus-based combination therapy (Figure 4) [15–18]. Thus, these findings suggest that withdrawal of calcineurin inhibitors exposes an initially low-risk population to increased risk of acute and, possibly, chronic graft rejection.

Corticosteroid withdrawal or avoidance has been shown to have no significant impact on maintenance of renal graft function. The THOMAS study, the largest study performed with tacrolimus therapy in renal transplant patients to date, investigated the effect of corticosteroid or MMF withdrawal after 3 months of triple therapy [17]. The results at 6 months demonstrated that good graft function was maintained after corticosteroid or MMF withdrawal (serum creatinine <1.5 mg/dl). Data from this study are supported by a steroid avoidance trial, which demonstrated good graft function at 6 months irrespective of whether or not corticosteroids were administered; median serum creatinine values at 6 months post-transplant were 1.4 mg/dl in the corticosteroid maintenance group and 1.5 mg/dl in the corticosteroid avoidance group [15].

**Evidence from registry studies**

Analysis of registry data can be useful in evaluating the long-term effects of immunosuppressive regimens employed in routine clinical practice. Preliminary evidence was obtained from the US Renal Data System comparing the annualized change in GFR among >40 000 kidney transplant recipients with graft survival of at least 2 years and receiving primary immunosuppression with tacrolimus or ciclosporin [original (oil-based) and microemulsion formulations] [19,20]. During a mean follow-up of 5.7 years, GFR was shown to decrease at an average rate of 1.7 ml/min/1.73 m²/year overall [19]. However, there was a clear difference between patients receiving tacrolimus and ciclosporin [20]. Results of a multiple linear regression analysis showed that compared with patients receiving the microemulsion formulation of ciclosporin, tacrolimus-treated patients had a less rapid decline in GFR.
Renal function: defining long-term success

(1.60 ml/min/1.73 m²/year, P < 0.001); those patients receiving the oil-based formulation of ciclosporin had a faster decline in GFR than ciclosporin microemulsion-treated patients (−0.16 ml/min/1.73 m²/year, P = 0.04). Thus, in this study, tacrolimus was associated with the most favourable effects on rates of change in renal function.

Conclusions

CAN, which manifests clinically as a gradual reduction in renal function, is recognized as a major cause of late renal allograft loss. Early graft function, determined by measurements of serum creatinine, creatinine clearance and GFR, has been shown to predict long-term graft survival. In particular, maintaining 6 or 12 month serum creatinine values ≤1.5 mg/dl is associated with superior 5 year graft survival compared with serum creatinine levels >1.5 mg/dl [1]. Our own data support this observation, showing that patients with serum creatinine ≤2 mg/dl during the first month post-transplant have a significantly higher graft survival rate at 3 years than those with 1 month serum creatinine values >2 mg/dl.

The data reviewed show that excellent renal function and graft survival have been achieved with different tacrolimus-based regimens. Also, immunosuppressive treatment based on tacrolimus has been shown to be superior to ciclosporin-based regimens in maintaining long-term renal graft function [5,7,20]. Importantly, data so far indicate that renal function following treatment with tacrolimus is comparable with that obtained with calcineurin inhibitor-sparing regimens [11–18]; as such, adoption of tacrolimus minimization or withdrawal strategies is probably not warranted in the vast majority of renal transplant recipients administered tacrolimus-based immunosuppression, especially when one considers the possibility of increased risk of acute rejection.

Conflict of interest statement. None declared.

References

14. Grinyo JM, Campistol JM, García J et al. Sirolimus (SIR) and tacrolimus (FK) in renal transplant: results of a randomized trial of a maintenance therapy based in sirolimus versus the combination of sirolimus and tacrolimus. Am J Transplant 2003; 3 [Suppl 5]: 474 [abstract 1256]