Renal function as a predictor of long-term graft survival in renal transplant patients

M. Roy First

Research and Development, Fujisawa Healthcare, Inc., Deerfield, IL 60015, USA

Abstract

Acute rejection is a major risk factor for kidney graft failure. However, as acute rejection has been progressively reduced by recent immunosuppressive regimens, other risk factors are becoming increasingly important. Evidence is accumulating that early renal function predicts long-term outcome. A recent registry survey of more than 100,000 kidney transplants found that 6- and 12-month serum creatinine levels, as well as the change between 6 and 12 months, are strongly associated with long-term graft survival. A survey of paediatric renal transplant recipients showed that poor creatinine clearance (<50 ml/min) as early as 30 days post-transplant predicted an annual rate of graft loss of 13% compared with <3% in patients with 30-day clearance >50 ml/min. This association between early renal function and long-term outcome was confirmed in multicentre studies. Renal transplant recipients (n=572) with 6-month serum creatinine levels >1.5 mg/dl suffered 3-year graft loss of 19.3% compared with only 8.5% in patients with levels <1.6 mg/dl (P<0.001). Significantly fewer patients receiving tacrolimus had 12-month serum creatinine levels >1.5 mg/dl compared with ciclosporin (42 versus 54%, P<0.05). Interestingly, a single-centre study (n=436) found that while glomerular filtration rate (GFR) at 6 months post-transplant had remained stable over the last decade, the rate of loss of renal function had decreased. A lower rate of GFR loss was associated with absence of rejection, use of mycophenolate mofetil rather than azathioprine and use of tacrolimus rather than ciclosporin (P<0.01). In conclusion, early measures of renal function allow identification of those patients at highest risk of graft failure and provide an invaluable tool for improving outcomes by tailored immunosuppression. The choice of such immunosuppression should be guided not only by its ability to prevent rejection, but also by its impact on renal function.

Keywords: rejection; renal function; renal transplantation; survival; tacrolimus

Introduction

Both immunological and non-immunological factors contribute to the development of chronic allograft nephropathy (CAN), the leading cause of graft loss after the first year post-transplantation. Early identification of those patients at greatest risk of graft loss and subsequent timely therapeutic intervention is necessary to improve outcomes in the renal transplant population. The parameters of renal function—mainly serum creatinine, creatinine clearance and glomerular filtration rate (GFR)—are valuable indicators of long-term outcome, as will be discussed in this article.

Risk factors for CAN

The current annual rate of graft loss, although lower than in earlier years, is 3–5% [1]. CAN has a multifactorial aetiology, with acute rejection being one of the major risk factors. However, with the development of modern immunosuppressive regimens, the incidence of acute rejection after renal transplantation has declined considerably in recent years.

In a large study reported by Mayer et al. in 1997 [2], a total of 448 patients received triple immunosuppressive therapy of either tacrolimus or ciclosporin plus corticosteroids and azathioprine. The 12-month incidence of acute rejection was 24.1% with the tacrolimus-based regimen and 43.4% with ciclosporin (P<0.001). More recently, Margreiter [3] compared triple regimens based on tacrolimus or ciclosporin microemulsion, both in combination with corticosteroids and azathioprine, in a 6-month study of 560 patients in 50 European centres. Acute rejection occurred in 19.6%
of tacrolimus-treated patients and in 37.3% of patients receiving ciclosporin microemulsion (P < 0.0001). Still lower 12-month incidences of acute rejection were reported by Johnson et al. [4] with regimens of tacrolimus and corticosteroids in combination with either azathioprine (17.1%) or mycophenolate mofetil (MMF; 15.3%), compared with 20.0% for ciclosporin microemulsion, corticosteroids plus MMF. In a recent study comprising 266 renal transplant patients, 3-month incidences of acute rejection were only 11.1% with a tacrolimus, steroids plus MMF regimen and 13.0% with a tacrolimus, steroids plus sirolimus regimen [5].

The progress in the prevention of acute rejection in recent years has been paralleled by an improvement in graft survival. A retrospective analysis of 93 934 renal transplantations in the USA from 1988 to 1996 showed that 1-year survival rates increased during this period from 88.8 to 93.9% for grafts from living donors and from 75.7 to 87.7% for cadaveric grafts [6]. Moreover, the calculated half-life for grafts from living donors and from cadaveric donors increased from 12.7 to 21.6 years, and from 7.9 to 13.8 years, respectively. The impact of acute rejection on the long-term outcome was demonstrated by the fact that the average yearly reduction in the relative risk of renal graft failure was significantly higher for patients without acute rejection episodes compared with those who suffered acute rejection (6.3 versus 0.4%, P < 0.001).

Poor HLA matching and previous sensitization, as well as delayed graft function, are the major risk factors for the onset of acute rejection. Suboptimal immunosuppression and non-compliance may also result in subacute chronic alloimmune responses. Both processes may cause immunological injuries ultimately leading to CAN. Long-term graft survival also depends on non-immunological risk factors including donor age, graft quality and graft damage before and during transplantation. Moreover, post-transplantation factors such as hypertension, hyperlipidaemia and the potential toxicity of long-term treatment with ciclosporin or tacrolimus also contribute to CAN [1].

The importance of renal function in long-term outcome

Renal function within the first year after transplantation has been shown to be an important parameter influencing long-term graft survival [7]. In a retrospective survey of 105 742 renal transplant patients in the USA from 1988 and 1998, renal function was assessed on the basis of serum creatinine levels at 6 months and at 1-year post-transplantation. The survey indicated that there was a distinct relationship between the serum creatinine concentration at both time-points and graft survival at 5-year post-transplantation; for example, 6-month serum creatinine levels ≤ 1.5 mg/dl were associated with a graft survival rate of ~55%, and at > 3.0 mg/dl the graft survival rate fell to ~40%. Recipients with serum creatinine levels of > 1.5 mg/dl and an increase in creatinine concentration of ≥ 0.3 mg/dl between months 6 and 12 post-transplant had a substantially lower projected graft half-life than other groups. It was concluded that processes occurring within the first year post-transplant are critical in determining graft survival. One-year serum creatinine levels and the change in serum creatinine between months 6 and 12 can be used as surrogate markers for renal function and predict long-term renal graft survival.

Results from multicentre studies support this point of view. Fitzsimmons et al. [8] analysed the ability of serum creatinine measurements at 6 and 12 months to predict 3-year graft survival using data from two multicentre clinical studies comparing tacrolimus- and ciclosporin-based immunosuppression. Patients alive with a functioning graft at 6 months (n = 572) and 12 months (n = 535) were included in the analysis. In patients with a serum creatinine level of > 1.5 mg/dl at 6 or 12 months, the rates of graft loss over 3 years were 19.3 and 17.0%, respectively. For patients with serum creatinine values of > 2.0 mg/dl at 6 or 12 months, the 3-year graft losses were 24.6 and 26.5%, respectively. In comparison, 3-year graft losses were significantly lower in patients with serum creatinine < 1.6 mg/dl at 6 or 12 months, being 8.5 and 5.3%, respectively (P < 0.001). Cox regression analysis of predictors of graft loss at 3 years is presented in Table 1. These results indicate that serum creatinine values at both 6 and 12 months post-transplant and the change in serum creatinine level between these times are important predictors of graft loss over 3 years. Patients receiving tacrolimus were at lower risk of graft loss compared with those receiving ciclosporin, but the difference did not reach statistical significance.

Calculated creatinine clearance was assessed retrospectively as a surrogate endpoint for long-term graft survival in 6686 paediatric renal transplant recipients with functioning grafts [9]. Creatinine clearance (ml/min) was calculated at 30 days and at years 1, 2 and 3 post-transplantation and compared with graft survival rates 3 years after sampling (Table 2). It was apparent that regardless of the time of clearance

| Table 1. Regression analysis of predictors of graft loss at 3 years post-transplantation (adapted from Fitzsimmons et al. [8]) |
|------------------|-----------------|----------------|------------------|
| Hazard ratios    | 6-month P       | 12-month P     |
| SCr> 1.5 mg/dl   | 2.44 <0.001     | 3.46 <0.001    |
| SCr> 2.0 mg/dl   | 2.55 <0.001     | 4.61 <0.001    |
| ΔSCr ≥ 0.3 mg/dl | – –             | 3.53 0.001     |
| Tacrolimus       | 1.0 –           | 1.0 –          |
| Ciclosporin      | 1.27 0.299      | 1.21 0.463     |

SCr, serum creatinine.
ΔSCr, change in SCr between months 6 and 12.
determination, patients with clearances < 50 ml/min had more than a one in three chance of graft loss within 3 years, with an annual risk for graft failure of ~13%. The risk of graft failure was substantially lower (<3%) for patients with a clearance of >50 ml/min. Based on a proportional hazards analysis of post-day-30 survival using a flexible regression function and after adjusting for risk factors such as donor source, race, transplant year, acute tubular necrosis and number of prior transplants, the effect of creatinine clearance was highly significant (P < 0.0001).

In 436 cadaveric renal transplant recipients, the GFR at 6 months after transplantation and the change in GFR over time were analysed in a single-centre study [10]. Patients were included if their grafts survived beyond 1 year and if five or more serum creatinine measurements had been taken. While mean 6-month GFR rates were stable between 1990 and 2000 (at ~65 ml/min), the rate of decline of GFR improved over the decade. The authors suggested that this was most likely due to fewer rejection episodes, reflecting improvements in immunosuppressive therapy. The lower rate of GFR deterioration was associated with MMF (versus azathioprine), tacrolimus (versus ciclosporin) and absence of rejection (all P < 0.01). In contrast, a significant reduction in mean 6-month GFR was associated with low donor GFR, older donors, female donors, retransplantation, delayed graft function, rejection, long cold ischaemia time and immunosuppression with azathioprine (as opposed to MMF) and ciclosporin (as opposed to tacrolimus; P < 0.05). GFR values were also lower for female and older recipients.

### Table 2. Renal allograft survival 3 years after creatinine clearance measurement (adapted from Tejani et al. [9])

<table>
<thead>
<tr>
<th>Measurement time post-transplant</th>
<th>&lt; 50 ml/min</th>
<th>50–75 ml/min</th>
<th>&gt; 50 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>65.5</td>
<td>85.2</td>
<td>88.9</td>
</tr>
<tr>
<td>1 year</td>
<td>65.1</td>
<td>88.7</td>
<td>91.3</td>
</tr>
<tr>
<td>2 years</td>
<td>65.5</td>
<td>91.9</td>
<td>93.9</td>
</tr>
<tr>
<td>3 years</td>
<td>63.4</td>
<td>89.5</td>
<td>91.2</td>
</tr>
</tbody>
</table>

### Conclusions

As the incidence of acute rejection has been progressively reduced by recent immunosuppressive regimens, the assessment of other risk factors for graft loss is becoming increasingly important. Renal function in the first year after transplantation can be regarded as a variable predicting long-term renal graft survival, and the assessment of renal function provides a useful tool for predicting long-term outcome. A subset of patients at greater risk of long-term graft loss can be identified by considering serum creatinine levels or creatinine clearance at month 6 or 12, and the deterioration of these values between months 6 and 12. Finally, the choice of immunosuppressive regimen remains critical for prevention of rejection and the maintenance of good renal function.

### References