Improving long-term renal transplant outcomes with tacrolimus: speculation vs evidence

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Abstract
Achieving long-term graft survival and optimal patient health are ultimate clinical goals in renal transplantation. Many factors negatively impact long-term transplant outcomes, including graft rejection, renal dysfunction and increased cardiovascular burden. Additionally, glucose metabolism disturbance, also a cardiovascular risk factor, influences morbidity and mortality. As such, careful consideration of the immunosuppressive strategy and its impact on these factors is critical to optimizing outcomes. Large-scale clinical trials and registry studies conducted over the past decade have demonstrated tacrolimus to be a cornerstone immunosuppressant in renal transplantation. Compared with ciclosporin treatment, tacrolimus has been shown to be associated with decreased acute and chronic rejection, improved renal function over the long term post-transplant, as evidenced by lower serum creatinine concentrations and a slower decline in the glomerular filtration rate, and a superior cardiovascular risk profile, as demonstrated by lower incidences of hyperlipidaemia and hypertension. The incidence of new-onset diabetes in patients receiving tacrolimus is low due to continued refinement of tacrolimus-based regimens and a better understanding of the effects of tacrolimus on metabolic parameters. Together, these findings may translate into improved long-term transplant outcomes with tacrolimus-based immunosuppression. In fact, long-term follow-up results from multicentre trials plus data from registry analyses are already documenting improved survival with this cornerstone immunosuppressant.

Keywords: cardiovascular risk; post-transplant diabetes mellitus; rejection; renal function; renal transplantation; tacrolimus

Introduction
Significant improvements in short-term graft survival have been attained over the last decade, in part due to more effective immunosuppressive regimens, but also as a result of a better understanding of risk factors that impact graft survival. Achieving this success in the long term proves to be a major challenge. The two leading causes of late renal allograft loss are chronic allograft nephropathy and death with a functioning graft [1]. Thus, many factors are implicated in determining long-term transplant outcome, including acute and chronic rejection, renal function and cardiovascular risk factors. The best outcomes after renal transplantation can, therefore, only be achieved after careful consideration of the immunosuppressive regimen and its impact on such factors.

By examining evidence from large-scale clinical trials and registry databases, this paper reviews the factors that influence transplant outcome, namely acute and chronic rejection, renal function, cardiovascular disease and post-transplant diabetes mellitus (PTDM), and assesses the potential of immunosuppressive strategies based on tacrolimus or ciclosporin to improve long-term renal transplant survival.

Importance of preventing graft rejection
It has long been recognized that acute rejection is a significant risk factor for the subsequent development of chronic allograft failure (CAF), a major cause of late graft loss [2–4]. In the majority of cases, acute rejection occurs early post-transplant, normally within the first 3 months post-transplant. While the incidence of acute rejection has decreased in recent years, due in part to the introduction of newer immunosuppressive agents, this trend has not been mirrored by a decline in CAF.

In a study to analyse the relative impact of acute rejection era on the development of CAF, Meier-Kriesche et al. evaluated >63,000 primary renal
transplant patients who had been reported to the US Renal Data System (USRDS) between 1988 and 1997 [4]. CAF was defined as graft loss after 6 months post-transplant, censored for death or graft loss secondary to acute rejection, thrombosis, infection, surgical complications or recurrent disease. The results of the study revealed that an acute rejection episode within the first 6 months of transplantation was the most important risk factor for CAF [relative risk (RR) 2.4]. Although the incidence of acute rejection was seen to decrease, from 31.4% in 1988–1989 to 15.2% in 1996–1997, the risk of developing CAF increased 5-fold (P<0.001). This finding may be explained by a poorer functional status of a minority of kidney grafts that still undergo rejection, which is possibly of a more severe grade. Whatever the reason(s), it has become increasingly important to avoid rejection of grafts that would appear to be at higher risk of failure/loss.

Evidence from a European multicentre study indicates that the cumulative incidence of acute rejection is lower with tacrolimus than with ciclosporin [original (oil-based) formulation] [5]. After the first year post-transplant, there was just one late episode of acute rejection in the tacrolimus treatment group compared with seven episodes in the ciclosporin group. This difference was preserved when the cumulative incidence of chronic rejection (at 5 years: tacrolimus 6.6%, ciclosporin 15.3%; P<0.01) and graft loss associated with chronic rejection was accounted for in the analysis (Figure 1). The projected graft half-life also favoured tacrolimus therapy (15.8 vs 10.8 years for ciclosporin). In the recent comparison of tacrolimus and ciclosporin microemulsion in renal transplant recipients, the incidence of acute rejection at 6 months post-transplant was significantly lower in patients receiving tacrolimus (19.6 vs 37.3%, respectively; P<0.0001) [6]. However, longer term data are required to assess whether this difference will impact on chronic rejection and graft loss rates.

**Importance of preserving renal function**

Registry data indicate that renal function within the first year of transplantation is a strong predictor of long-term kidney graft survival [7]. Therefore, a serum creatinine concentration of >1.5 mg/dl at 6 or 12 months post-transplant is associated with a decline in long-term graft survival.

As per the European study described previously, the phase III, US multicentre trial of tacrolimus in kidney transplant patients demonstrated that tacrolimus was more effective than ciclosporin (oil-based formulation) in preventing acute rejection during the first year post-transplant [8]. Importantly, long-term follow-up data showed that preservation of renal function, determined by monitoring serum creatinine levels over a 5 year period, was better in patients treated with tacrolimus than in those receiving ciclosporin [9]. On an intent to treat basis, median serum creatinine levels at the end of the evaluation period were 1.4 mg/dl among patients maintained on a tacrolimus regimen compared with 1.7 mg/dl among those maintained on ciclosporin (P = 0.0014). Furthermore, significantly fewer tacrolimus-treated patients had a serum creatinine level >1.5 mg/dl (40.4%) than was the case among those who received ciclosporin (62.0%; P = 0.0017). Evaluation of crossover data in this study indicated that more transplant recipients crossed over from ciclosporin treatment to tacrolimus (>25% of the patient population initially randomized to receive ciclosporin compared with <10% of those patients initially randomized to receive tacrolimus; P<0.001). Additional analysis, in which crossover for rejection was counted as graft failure, demonstrated a 10% better graft survival at 5 years post-transplant in tacrolimus-treated patients compared with ciclosporin-treated patients (63.8 vs 53.8%, P = 0.014). These findings are pertinent since they offer a clinically relevant perspective that mimics ‘real life’ therapeutic strategies that are frequently implemented during a 5 year post-transplant period to prevent rejection. The study concluded that therapeutic strategies employing tacrolimus have the potential to enhance long-term graft survival.

The finding of better preserved renal function with tacrolimus therapy is supported by the results of a study that compared the annualized change in glomerular filtration rate (GFR) among >40000 USRDS primary kidney recipients transplanted between 1987 and 1996 who had graft survival of at least 2 years [10]. Compared with patients receiving ciclosporin microemulsion (used as a base reference point, i.e. the change in GFR with ciclosporin microemulsion = 0), there was a slower decline in GFR among tacrolimus-treated patients (+1.60 ml/min/1.73 m²/year, P < 0.001); in contrast, patients receiving the oil-based formulation of ciclosporin had a faster decline in GFR compared with those receiving...
cyclosporin microemulsion (−0.16 ml/min/1.73 m²/year, \( P = 0.04 \)). Similar results were obtained when the analysis was restricted to patients who were transplanted after 1993, i.e. a slower decline in GFR was observed among tacrolimus-treated patients compared with those receiving cyclosporin microemulsion (±1.64 ml/min/1.73 m²/year, \( P < 0.001 \)). Accordingly, this study demonstrates that in comparison with cyclosporin microemulsion, tacrolimus is associated with the most favourable effects on rates of change in renal function.

Other registry data have shown benefits with respect to renal function with tacrolimus therapy. Using the Scientific Registry of Transplant Recipients database, Kaplan et al. compared long-term renal function in paired deceased donor kidneys (where one kidney was allocated to a patient receiving cyclosporin microemulsion and the other in the pair was allocated to a patient receiving tacrolimus) [11]. The results of this paired kidney analysis, which was conducted to minimize donor variability and bias, showed superior renal function, as assessed by mean serum creatinine measurements, for tacrolimus at all time points during a 5 year follow-up (tacrolimus vs cyclosporin microemulsion: 1.55 vs 1.67 mg/dl, respectively, at month 6; 1.54 vs 1.79 mg/dl at 5 years).

**Importance of reducing cardiovascular disease risk**

Cardiovascular disease is a leading cause of death among renal transplant patients with a functioning graft [1,12]. Given this, there has been increasing emphasis in recent years on reducing the cardiovascular burden by targeting key risk factors such as hypertension and hyperlipidaemia. Of note, it has been suggested that patients with hypercholesterolaemia (cholesterol >250 mg/dl) are at increased risk of late graft loss, particularly if they also experience at least one episode of acute rejection [13].

The previously cited US multicentre kidney trial evaluated the cardiovascular risk status of transplant recipients by determining serum lipid levels and use of lipid-lowering or antihypertensive agents [9]. Throughout the 5 year follow-up period, serum total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels were lower in patients receiving tacrolimus than in those on cyclosporin. However, evaluation at 5 years showed that the previously observed differences between tacrolimus and cyclosporin in terms of mean serum total cholesterol (198 vs 210 mg/dl, respectively; \( P = 0.07 \)) and LDL cholesterol (115 vs 118 mg/dl, \( P = 0.98 \)) were no longer statistically significant. Nevertheless, significantly fewer tacrolimus-treated patients required concomitant antihypertensives for control of blood pressure (81 vs 91%, \( P = 0.047 \)) or antihyperlipidaemic medication to control lipid levels (20 vs 59%, \( P < 0.001 \)), than was the case among patients receiving immunosuppression with cyclosporin. Importantly, the study showed that significantly fewer patients maintained on tacrolimus therapy developed hypercholesterolaemia and at least one episode of acute rejection compared with patients maintained on a cyclosporin-based regimen (4.7 vs 17.4%, \( P = 0.0008 \)).

The results of a European analysis comparing tacrolimus and cyclosporin microemulsion in renal transplant recipients showed that the two immunosuppressive agents have differential effects on cardiovascular risk factors and the estimated risk for coronary artery disease (CAD) [14]. Not only was tacrolimus-based immunosuppression associated with significantly lower time-weighted averages for total serum cholesterol (5.34 vs 6.03 mmol/l, \( P = 0.0004 \)) and mean arterial blood pressure (100.2 vs 102.4 mmHg, \( P = 0.0156 \)) compared with cyclosporin microemulsion, but it was also associated with a significantly lower mean 10 year CAD risk in male patients (Table 1). While the risk of CAD was numerically lower in females receiving tacrolimus, the difference did not achieve statistical significance (Table 1).

Cardiovascular risk factors are often one reason necessitating a switch in primary immunosuppression from cyclosporin to tacrolimus. A large, prospective, European multicentre study has confirmed the beneficial effect on cardiovascular risk status when renal transplant recipients are converted from cyclosporin microemulsion to tacrolimus [15]. In 78 patients converted for hyperlipidaemia (total cholesterol >180 mg/dl), there were substantial reductions in total cholesterol and LDL cholesterol at 6 months post-conversion, while high-density lipoprotein (HDL) cholesterol remained constant throughout the study (Figure 2a). Furthermore, the LDL/HDL ratio improved over this period, from 2.9 at baseline to 2.5 at month 6. Similar improvements in triglyceride levels were noted after conversion to tacrolimus. Of the 75 patients who were switched for hypertension, defined as a systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg, a progressive improvement in blood pressure was observed from the time therapies were switched throughout the 6 month study period (Figure 2b).

**Table 1.** Mean 10 year coronary artery disease risk: comparison of tacrolimus- and ciclosporin microemulsion (ME)-based therapy in renal transplant recipients enrolled in a European multicentre study

<table>
<thead>
<tr>
<th></th>
<th>Males Tacrolimus</th>
<th>Ciclosporin-ME</th>
<th>Females Tacrolimus</th>
<th>Ciclosporin-ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 141)</td>
<td>(n = 89)</td>
<td>(n = 56)</td>
<td>(n = 58)</td>
<td></td>
</tr>
<tr>
<td>Mean CAD risk (%)</td>
<td>10.0</td>
<td>13.2</td>
<td>4.7</td>
<td>7.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.7–11.0</td>
<td>10.3–16.0</td>
<td>2.4–8.3</td>
<td>4.2–9.0</td>
</tr>
<tr>
<td>( P )-value</td>
<td>0.0032</td>
<td>0.2602</td>
<td></td>
<td></td>
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Reproduced from Krämer et al. [14], with kind permission. aFramingham risk algorithm. CAD = coronary artery disease; CI = confidence interval.
Post-transplant diabetes mellitus (PTDM)

PTDM, the incidence of which has increased in recent years, is a serious complication that may adversely impact both patient and graft survival [12,16]. It is also recognized as a key atherosclerotic risk factor for the development of cardiovascular disease [16]. It is likely that the development of PTDM is preventable, and this should be an important goal in the management of the transplant recipient [17].

The USRDS has been used as a resource to investigate the incidence, risk factors and outcomes for patients who develop PTDM [17]. This evaluation, which involved >11,000 patients who underwent kidney transplantation between 1996 and 2000, estimated the cumulative incidence of PTDM to be 9.1, 16.0 and 24.0% at 3, 12 and 36 months post-transplant, respectively. Among the risk factors identified for the development of PTDM were: African-American ethnicity (RR 1.68); Hispanic ethnicity (RR 1.35); body mass index at time of transplant >30 kg/m² (RR 1.73); and use of tacrolimus (RR 1.53) (all P<0.0001). Independent of the risk factors associated with PTDM development, PTDM itself was associated with increased graft failure (RR 1.63), death-censored graft failure (RR 1.46) and mortality (RR 1.87) (all P<0.0001). Paradoxically though, while the use of tacrolimus was correlated with an increased risk for PTDM and while PTDM was associated with an increased risk of graft failure, tacrolimus was associated with a significantly reduced risk for graft failure (RR 0.70, P<0.0001) compared with no tacrolimus treatment. Similarly, tacrolimus was associated with a reduced risk for death-censored graft failure and mortality (RR 0.72 and 0.65, respectively). Therefore, it is important to assess all risk factors in order to arrive at the most appropriate regimen for each patient.

A US single-centre study also assessed the incidence of PTDM and the factors associated with its development [16]. Among the 2078 non-diabetic patients treated with ciclosporin between 1993 and 1998, the cumulative incidence of PTDM was 7, 10, 13, 21 and 30% at 1, 3, 5, 10 and 15 years, respectively. The study identified older age, African-American ethnicity, higher body mass index and transplantation after 1995 as risk factors for PTDM [16]; as with other studies, PTDM was associated with significantly increased mortality (RR 1.8, P<0.001) [18]. Of note, the introduction of the microemulsion formulation of ciclosporin in 1995 resulted in a higher incidence of PTDM compared with the use of the oil-based formulation prior to 1995 [16]. This may be due to higher exposure to ciclosporin with the improved bioavailability of the new formulation.

Together, these observations show that ciclosporin and tacrolimus potentially increase the risk for PTDM, and that the risk appears to be related to the degree of drug exposure.

The results of a recent meta-analysis, which included >3000 patients, indicated that the reported incidence of new-onset diabetes mellitus after solid organ transplantation was significantly higher among patients receiving tacrolimus than ciclosporin (P<0.00001) [19]. However, using a more stringent subanalysis of seven prospective, randomized, kidney transplant studies employing identical immunosuppressive therapies, including corticosteroid dosage, the odds ratio was ‘not estimable’ in two of the studies and no difference was noted in one study (published in 2002). Notably, all of the reported statistical difference resulted from the four, more dated studies (one published in 1996 and three published in 1997). The omission of more recent studies from this type of analysis has been commented upon previously [20].

In fact, recent clinical trials with tacrolimus indicate that, in contrast to early studies, the incidence of PTDM in tacrolimus-treated patients is comparable with that seen in patients maintained on ciclosporin-based regimens (Table 2) [6,21–23]. Moreover, findings from a retrospective review [24] of data from five US transplant centres involving kidney recipients (n=245 tacrolimus; n=121 ciclosporin) with at least 6 months of follow-up corroborate these data, showing no significant difference in the incidence of PTDM (defined as the need for insulin in patients with...
no previous history of diabetes) between tacrolimus-treated patients (3.3%) and ciclosporin-treated patients (5.7%).

**Registry data on transplant outcomes**

Registry data provide useful information from large patient populations that are necessary to provide sufficient statistical power to identify the differences between treatments in a clinical environment where kidney graft survival is high irrespective of the treatment regimen used. Analysis of such data, therefore, provides the best chance of making meaningful recommendations concerning optimal immunosuppressive regimens to employ in different situations.

Using data from the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) database, Cherikh and colleagues evaluated the risk for graft loss by treatment regimen in 19,246 patients who received a primary cadaveric kidney transplant between 1995 and 1998 [25]. In patients without delayed graft function or early acute rejection, there were significant reductions in the risk of long-term graft loss with both ciclosporin + MMF (10% reduced risk, $P < 0.001$; RR 0.90) and tacrolimus + MMF (20% reduced risk, $P < 0.001$; RR 0.80) compared with a traditional ciclosporin + azathioprine regimen (RR 1.0). The risk of mortality was also lower with these regimens (ciclosporin + MMF, RR 0.86; tacrolimus + MMF, RR 0.71). Although the tacrolimus + azathioprine combination effectively decreased the risk of graft loss (RR 0.80), fewer patients were maintained on this regimen and, therefore, statistical significance was not achieved. These results help to identify therapeutic regimens that potentially improve graft survival, so reducing the need for dialysis or retransplantation.

A more recent analysis of the same database reviewed all kidney transplants reported to the UNOS/OPTN registry from 1995 to 2000 on the basis of the primary immunosuppressant in use at discharge (tacrolimus, $n = 13,026$; ciclosporin, $n = 46,128$) in an attempt to evaluate the impact of modern immunosuppressive therapies on outcome [26]. In this evaluation, tacrolimus was found to be associated with significant gains in graft survival (in cadaveric recipients) compared with ciclosporin at 1, 3 and 5 years post-transplant ($P < 0.0001$). Significant odds ratios for tacrolimus at 1 year post-transplant revealed less acute rejection, fewer patients with serum creatinine levels $>1.5$ mg/dl, fewer grafts lost and a reduction in the composite end-point, defined as combination of at least one of the 1 year end-points (Table 3). Conversely, a separate analysis from the UNOS/OPTN registry of patients ($n = 7,079$) receiving living donor renal transplants in 1998–1999 concluded that the 2 year graft survival was significantly ($P = 0.0006$) higher with ciclosporin microemulsion + MMF than with tacrolimus + MMF [27]. However, the difference in graft survival over 2 years between the two regimens was only 2.1% (94.3 vs 92.1%, respectively).

The UNOS/OPTN results are substantiated by the collaborative transplant study (1995–2001), which showed that renal graft survival is high ($>80%$) at 3 years post-transplant irrespective of the treatment regimen employed [28]. Of note, in this analysis, graft survival was highest in patients maintained on tacrolimus + MMF, followed by tacrolimus + azathioprine, ciclosporin + MMF and, lastly, ciclosporin + azathioprine.

**Conclusions**

The data reviewed indicate that the choice of immunosuppressive regimen is critical to achieving optimal long-term graft survival. Risk factors implicated in reduced graft survival and poor transplant outcome include acute graft rejection and poor renal function during the first year post-transplantation. Other factors, such as co-existing cardiovascular disease or glucose metabolism disturbance, or an underlying risk for these complications, may impact patient morbidity and mortality. Moreover, it has been demonstrated that patients who develop both hypercholesterolaemia and acute graft rejection are particularly vulnerable as they...
have a 2-fold greater risk of graft loss than patients who are rejection free and do not suffer from hypercholesterolaemia [13]. Thus, the current strategy is to select immunosuppressive regimens based not only on evidence showing effective prevention of acute rejection and optimal renal function, but also on evidence of the side effect profiles, including cardiovascular risk.

Tacrolimus is the cornerstone immunosuppressant of choice for renal transplantation. Not only is it associated with a lower incidence of acute rejection compared with ciclosporin, but it has also been shown to be favourable with respect to chronic rejection, a key risk factor for subsequent graft loss [2]. Furthermore, data have shown that patients receiving maintenance immunosuppression with tacrolimus as opposed to ciclosporin have better renal function over the long term and reduced cardiovascular risk. Together, these findings may translate into improved long-term transplant outcomes with tacrolimus, as already being documented by registry analyses.

Conflict of interest statement. M. R. First is a full-time employee of Fujisawa Healthcare, Inc.

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