Long-Term Kidney Allograft Function and Survival in Prednisone-Free Regimens: Tacrolimus/Mycophenolate Mofetil versus Tacrolimus/Sirolimus

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Summary

Background and objectives The optimal maintenance immunosuppressive regimen to improve long-term renal allograft function and graft survival is yet to be determined.

Design, setting, participants, & measurements This observational study prospectively compared tacrolimus/sirolimus with tacrolimus/mycophenolate mofetil in renal transplant recipients using a prednisone-free regimen with over 8.5 years of follow-up. Patients received methylprednisolone and anti-IL2 receptor antagonist (Basiliximab) induction and were blindly randomized to either the tacrolimus/mycophenolate mofetil (n=45) or tacrolimus/sirolimus (n=37) groups. Outcome measures included patient and renal allograft survival, incidence of acute rejection, and estimated GFR.

Results The tacrolimus/mycophenolate mofetil group compared with the tacrolimus/sirolimus group had overall better renal allograft survival (91% versus 70%, P=0.02); 13 patients (35.1%) in the tacrolimus/sirolimus group and 8 patients (17.8%) in the tacrolimus/mycophenolate mofetil group experienced biopsy-proven acute cellular rejection (P=0.07). By 3 months post-transplant, estimated GFR was significantly lower in the tacrolimus/sirolimus group compared with the tacrolimus/mycophenolate mofetil group (47.7 versus 59.6 ml/min per 1.73 m², P=0.0002), and this trend persisted throughout the follow-up period. Also, the slope of decline in the tacrolimus/sirolimus group was significantly steeper than in the tacrolimus/mycophenolate mofetil group.

Conclusions This study shows that, in a prednisone-free immunosuppressive regimen, long-term renal graft survival and function are significantly worse in the tacrolimus/sirolimus group than the tacrolimus/mycophenolate mofetil group. The synergistic nephrotoxic effect and higher acute rejection rates in the tacrolimus/sirolimus compared with the tacrolimus/mycophenolate mofetil group adversely affect graft survival.


Introduction

There exists tremendous variation among transplant centers in the United States regarding immunosuppressive regimens in an effort to improve patient and graft survival while minimizing toxicity. Newer immunosuppressive agents have improved early acute rejection rates; however, the optimal maintenance immunosuppressive regimen to promote long-term renal allograft function and improve survival is yet to be determined (1).

Calcineurin inhibitors (CNIs) are an important cause of post-transplant renal function decline and graft loss (2–8). Consequently, CNI minimization and withdrawal strategies are being aggressively investigated. Agents such as the mammalian target of rapamycin inhibitor sirolimus (SRL) and purine biosynthesis inhibitor mycophenolate mofetil (MMF) are being used in conjunction with CNIs in an effort to reduce the dose of CNI and related toxicity. Tacrolimus (Tac) seems to be less toxic than cyclosporine (9–11). Scientific Registry of Transplant Recipients data reveal that the Tac/MMF combination is the most common maintenance immunosuppression for renal transplant patients in the United States (12).

Few studies have attempted to delineate which antiproliferative agent (MMF versus SRL, both combined with Tac) is superior. These studies are limited in scope by their retrospective nature, the inadequacy of registry data, and the lack of long-term follow-up (13–15). One multicenter randomized study had a follow-up of only 12 months post-transplant and used a prednisone-based maintenance regimen, limiting, in part, its implications regarding the impact on long-term graft function (16). Our group was the first, to our knowledge, to prospectively compare Tac/SRL with Tac/MMF in renal transplant recipients using a prednisone-free regimen (17). During a 3-year follow-up, we showed that renal graft survival and graft function were significantly lower in the Tac/SRL combination compared with Tac/MMF.

We present here an extended follow-up to our initial study, with over 8.5 years of follow-up.
Materials and Methods
Detailed methods have been outlined previously (17).

Study Design and Aim
This trial is a single-center, randomized trial aimed at evaluating the impact of two Tac-based prednisone-free maintenance immunosuppressive protocols (Tac/SRL versus Tac/MMF) on long-term graft function and survival.

Patient Recruitment
Patients were recruited between October of 2000 and September of 2001. All patients provided written informed consent. The Institutional Review Board of Northwestern University approved the protocol.

Figure 1 shows the Consolidated Standards of Reporting Trials flow diagram (18). In the final analysis, 45 patients were included in the Tac/MMF arm, and 37 patients were included in the Tac/SRL arm. No additional late discontinuations of either immunosuppressive regimen were encountered aside from the early changes described previously (one MMF and seven SRL) (17).

Inclusion Criteria
Consecutive kidney transplant recipients between 30 and 70 years transplanted at Northwestern University between October of 2000 and September of 2001 were included.

Exclusion Criteria
The study excluded pediatric recipients, multiorgan transplants, ABO blood group–incompatible, positive crossmatch, donation after cardiac death donors, and expanded criteria donors. We also excluded patients with a pretransplant fasting serum cholesterol >350 mg/dl, patients with a body mass index >35 kg/m², patients who were pregnant/lactating, patients who were HIV-positive, and patients with a known sensitivity to Tac, SRL, or MMF.

Immunosuppression
All patients were induced with methylprednisolone and the anti-IL2 receptor antagonist Basiliximab with no additional steroids (rapid steroid elimination). Tac (Prograf) and MMF (Cellcept) or SRL (Rapamune) were started on postoperative day 1.

Drug Monitoring
Target 12-h trough levels for Tac were 8–10 ng/ml during the first 3 months, 7–9 ng/ml from 4 to 6 months, and 6–8 ng/ml thereafter. The target 24-h trough levels for SRL were 7–10 ng/ml during the entire study period.

Outcomes
The primary end points of the study were patient and graft survival. The secondary end points were (1) incidence and severity (by histologic grade) of acute renal allograft

Figure 1. | Consolidated Standards of Reporting Trials flow diagram.
rejection, (2) graft function determined by the Modification of Diet in Renal Disease equation, and (3) incidence of hyperlipidemia, infections, hematologic abnormalities, and malignancy.

Data Collection
Recipient demographics included but were not limited to age, race, sex, comorbidities, and need for dialysis pretransplant. Donor characteristics such as donor type (living versus deceased), age, and race were also collected. Post-transplant data included delayed graft function (DGF), episodes of acute rejection, graft loss, patient survival, serial GFRs, new-onset hypertension, diabetes mellitus, incidence of cardiovascular events, anemia, infections, malignancy, and hyperlipidemia.

Rejection Monitoring and Treatment
All rejection episodes were biopsy-proven and graded using the Banff 97 classification. Acute cellular rejections were treated, based on severity, with methylprednisolone followed by a 7-day course of tapered prednisone or antilymphocyte antibody therapy (Thymoglobulin) for up to 14 days. No modification of immunosuppression was made on diagnosis of biopsy-proven chronic allograft nephropathy. Patients who developed acute cellular rejection requiring therapy were maintained on prednisone 5 mg one time per day.

Renal Allograft Function Measurement
GFR was calculated at different time points (1, 3, 6, and every 6 months up to 8.5 years) using the abbreviated Modification of Diet in Renal Disease equation (19).

Statistical Analyses
Data were summarized using descriptive statistics (means and standard deviation for continuous variables; frequency and count for categorical variables). Baseline patient characteristics and postoperative outcomes were compared between the Tac/MMF and Tac/SRL groups. Chi-squared or Fisher exact tests were used to compare categorical variables, whereas the two-sample t or nonparametric Mann–Whitney U tests were used for continuous variables. Patient survival, graft survival, and occurrence of acute rejection were determined using the Kaplan–Meier survival estimates, whereas the cumulative curves were compared between the Tac/MMF and Tac/SRL groups using the log-rank test.

Variables that were found significantly different between the two treatment groups at baseline were included in the risk adjustment model using Cox proportional hazards regression. Finally, a mixed effects model was used to compare estimated GFR (eGFR) slopes over time between the Tac/MMF and Tac/SRL groups. Our power analysis indicated that, using Cox regression of the log hazard ratio with an anticipated patient morality rate and graft failure rate of 5% and 20%, respectively, a sample of 82 patients will achieve 81% power at a two-tailed 0.05 significance level to detect a minimum hazard ratio of 4.33 for any given covariate. Thus, our study is powered to detect any hazard ratios greater than 4.33 or smaller than 0.23 (1/4.33) between the Tac/MMF and Tac/SRL groups. All analyses were conducted using SAS 9.2 (SAS Inc., Cary, NC). All P values were two-sided, and P<0.05 was considered statistically significant.

Results
Patient Characteristics
Eighty-two kidney transplant recipients (Tac/SRL, n=37; Tac/MMF, n=45) were included. Donor and recipient baseline demographics are depicted in Table 1. There were no differences between the two groups, comparing recipient

| Table 1. Patient and donor characteristics by treatment group: Tac/SRL versus Tac/MMF |
|----------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics                       | Tac/SRL (n=37)  | Tac/MMF (n=45)  | P Value<sup>a</sup> |
| Age in years (mean±SD)                | 45.7±13.4       | 42.3±11.9       | 0.24            |
| Race                                  |                 |                 | 0.87            |
| white                                 | 25              | 30              |                 |
| African American                      | 10              | 11              |                 |
| Hispanic                              | 1               | 1               |                 |
| Asian                                 | 1               | 3               |                 |
| Sex                                    |                 |                 | 0.80            |
| male                                  | 22              | 28              |                 |
| female                                | 15              | 17              |                 |
| Diabetes                              |                 |                 | 0.21            |
| yes                                   | 7               | 4               |                 |
| no                                    | 30              | 41              |                 |
| Degree of mismatch in number of Ags (mean±SD) | 3.1±2.0        | 3.6±1.8         | 0.25            |
| PRA (percent) >25%                    | 3               | 8               | 0.99            |
| Donor type                            |                 |                 | 0.77            |
| deceased                              | 10              | 15              |                 |
| living                                | 20              | 21              |                 |
| living (unrelated)                    | 7               | 9               |                 |
| Donor age in years (mean±SD)          | 39.7±13.3       | 33.3±11.5       | 0.03            |
| DGF                                   | 4               | 0               | 0.02            |

<sup>a</sup> test for continuous variables; chi-squared or Fisher exact test for categorical variables.}

Tac, tacrolimus; SRL, sirolimus; MMF, mycophenolate mofetil; Ags, antigens; PRA, Panel reactive antibody; DGF, delayed graft function.
Similarly, the rate of DGF in the Tac/SRL group was higher (39.7 ± 13.3 versus 33.3 ± 11.5 years, P=0.03). Similarly, the rate of DGF in the Tac/SRL group was higher (10.8% versus 0%, P=0.02).

Patient and Graft Survival

Median follow-up in the Tac/SRL and Tac/MMF groups was 8.5 years (interquartile range 8.1–9.1) and 8.6 years (interquartile range 4.3–9.1), respectively (Table 2). Patient survival at 8.5 years post-transplant tended to be worse among Tac/SRL- compared with Tac/MMF-treated recipients, but it failed to achieve statistical significance (P=0.05) (Figure 2A). Similarly, there were fewer deaths in the Tac/MMF group compared with the Tac/SRL group (0/45 versus 3/37, P=0.09, respectively) (Table 2). Causes of death included leukemia (n=1), lung adenocarcinoma (n=1; patient expired less than 1 year post-transplantation), and myocardial infarction (n=1; patient with known coronary artery disease pretransplant).

Graft survival was significantly worse in the Tac/SRL group compared with the Tac/MMF group (P=0.01) (Figure 2B). Similarly, there were significantly greater graft losses in the Tac/SRL group compared with the Tac/MMF group (11/37 versus 4/45, P=0.02, respectively) (Table 2). Causes of graft loss in the Tac/MMF group included chronic allograft nephropathy (n=8) and death with a functioning graft (n=3). In the Tac/MMF group, the causes of graft loss were acute rejection in the setting of nonadherence (n=1) and chronic allograft nephropathy (n=3). After excluding death with a functioning graft, the difference in graft survival between the Tac/SRL and Tac/MMF groups was 24% versus 9%, respectively, but it failed to achieve statistical significance (P=0.11).

Acute Rejection Rate

Thirteen patients (35.1%) in the Tac/SRL group experienced acute cellular rejection compared with eight patients (17.8%) in the Tac/MMF group (Table 2) (P=0.07), which corresponded with a similar trend in rejection-free survival for the Tac/MMF group (P=0.08) (Figure 2C).

Renal Allograft Function
eGFR was consistently lower in the Tac/SRL group compared with the Tac/MMF group throughout the entire long-term follow-up period (Figure 2A, Table 3). At 1 month post-transplantation, eGFR was similar in the two groups (45.7 ml/min per 1.73 m² in the SRL group compared with 51.4 ml/min per 1.73 m² in the Tac/MMF group, P=0.14). From 3 months on, graft function was significantly worse in the Tac/SRL group (Table 3). At 3, 5, and 8.5 years of follow-up, eGFR in the Tac/MMF group was 36.9 versus 58.3, 30.3 versus 55.3, and 23.5 versus 54.1 ml/min per 1.73 m², respectively (Table 3). Moreover, the slope of decline in the SRL group was significantly steeper than in the MMF group (significant group×time interaction effect, P=0.02; data not shown).

Adverse Events

There was no significant difference between the two groups with regard to anemia (hemoglobin<11 g/dl), infections, malignancy, new-onset diabetes after transplantation, hypertension, heart disease, or hyperlipidemia (Table 2); 9 of 37 patients (24.3%) in the Tac/SRL group developed >1 g/day proteinuria, and only 3 of 37 patients in the Tac/MMF group developed >3.5 g/day (one with active crescents and recurrent IgA nephropathy and another with chronic allograft nephropathy). In the Tac/MMF group, five patients (11.1%) developed >1 g/day proteinuria, and three patients developed >3.5 g/day (one patient with focal segmental glomerulosclerosis, one patient with recurrent focal segmental glomerulosclerosis, and one patient with recurrent membranoproliferative glomerulonephritis).

<p>| Table 2. Comparison of outcomes between the two groups: Tac/SRL versus Tac/MMF |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient Outcome</th>
<th>Tac/SRL (n=37)</th>
<th>Tac/MMF (n=45)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of follow-up (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD median (range)</td>
<td>8.5±0.3</td>
<td>8.5±0.7</td>
<td>0.99</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>8</td>
<td>8.1</td>
</tr>
<tr>
<td>Kidney loss</td>
<td>11</td>
<td>11</td>
<td>29.7</td>
</tr>
<tr>
<td>Rejection</td>
<td>13</td>
<td>13</td>
<td>35.1</td>
</tr>
<tr>
<td>Infection</td>
<td>9</td>
<td>9</td>
<td>24.3</td>
</tr>
<tr>
<td>Post-Tx CAD</td>
<td>1</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>CAN</td>
<td>8</td>
<td>8</td>
<td>21.6</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36</td>
<td>36</td>
<td>97.3</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>19</td>
<td>19</td>
<td>51.4</td>
</tr>
<tr>
<td>Anemia (Hgb&lt;11)</td>
<td>18</td>
<td>18</td>
<td>48.6</td>
</tr>
<tr>
<td>NODAT</td>
<td>9</td>
<td>9</td>
<td>24.3</td>
</tr>
</tbody>
</table>

<sup>a</sup><sup>test or Mann–Whitney U test for continuous variables; chi-squared or Fisher exact test for categorical variables.</sup>
Drug Monitoring

Dosing and trough blood levels of Tac during the entire follow-up post-transplantation were similar in the two groups (Figure 3B). SRL levels were between 6 and 10 ng/ml throughout follow-up.

Cox Proportional Hazard Model

After risk adjustment, the Tac/MMF group remained protective against graft failure compared with the Tac/SRL group (hazard ratio=0.20, 95% confidence interval [CI]=0.05–0.77, \( P=0.02 \)) (Table 4). There were no deaths in the Tac/MMF group compared with three deaths in the Tac/SRL group (0/45 versus 3/37, respectively, \( P=0.09 \)). There was a tendency to a lower hazard of acute rejection (HR=0.37, 95% CI=0.13–1.01, \( P=0.05 \)) for the Tac/MMF group after adjusting for donor age and DGF (significant baseline differences were observed for these two variables between the groups).
Discussion

The impact of MMF versus SRL combined with Tac on renal allograft function over the longer term remains poorly characterized. Tac/MMF and Tac/SRL are commonly used immunosuppressive maintenance regimens. Herein, we describe the long-term follow-up of kidney transplant recipients showing that, in steroid-free maintenance immunosuppressive regimens, Tac/SRL was associated with poorer graft survival and poorer renal allograft function compared with Tac/MMF. This finding might be explained on the basis of a trend to a higher acute rejection rate in the Tac/SRL group compared with the Tac/MMF group. The lack of statistical significance observed in our study may be because of insufficient power and a limited sample size. These data are consistent with our previous early observations after limited follow-up (17). Extended follow-up of cohorts is important, because it is often difficult to extrapolate long-term outcomes based on trends from early data (1). Moreover, improvements in short-term outcomes do not seem to translate into improved long-term survival.

Similarly, in a retrospective analysis of adult renal transplant patients from the Scientific Registry of Transplant Recipients between 2000 and 2004, Meier-Kriesche et al. (13) showed that Tac/SRL was associated with significantly worse graft survival compared with Tac/MMF. However, registry data, often lacking in granularity, might not adequately capture changes in immunosuppression, complicating interpretation of studies employing this data source. In another retrospective study of patients treated with Tac or cyclosporine combined with SRL, withdrawal of SRL and substitution with MMF led to improvement of graft function, suggesting a possible synergistic toxicity between SRL and CNIs (20). However, this work was a small, uncontrolled observational study with only 17 patients. The work by Gralla and Wiseman (15) analyzed 518 primary renal recipients transplanted between 2000 and 2006. All patients were maintained on prednisone; 211 patients received Tac/MMF, and 307 patients received Tac/SRL. In addition to the immunosuppressive regimen, outcomes were compared for two eras (2000–2002 and 2003–2006). The Tac/SRL 2000–2002 group had significantly lower 3-year patient and graft survival compared with the Tac/MMF group (57.6 versus 63.1 mL/min per 1.73 m², P < 0.01) during the 2003–2006 period, which further supports the theory of synergistic nephrotoxicity for the Tac/SRL combination.

The work by Mendez et al. (16) compared Tac/SRL (n=185) and Tac/MMF (n=176) combined with prednisone in renal transplant patients in a multicenter randomized study. Despite only a short term of follow-up, at 12 months post-transplantation, renal function was significantly lower in the SRL group compared with the MMF group. These data and our own data support the notion that the nephrotoxic effect of Tac can be augmented by concurrent use of SRL. Decline in renal allograft function is rapid and persistent when Tac and SRL are used together. In our experience, the reduction in GFR became apparent as early as 3 months post-transplant and persisted throughout the
The absence of a normal physiologic compensatory hyperfiltration among the Tac/SRL patients indicated by the early flattening of the Tac/SRL eGFR curve (Figure 3A). This finding was closely coupled with a steeper decline in eGFR thereafter. Short-term allograft function has been shown to correlate with long-term graft survival (21–23). CKD has been associated with higher risk of cardiovascular disease, stroke, and subsequent mortality (24–26). However, in our study, we did not observe a greater number of cardiovascular events or cardiac-related mortality in the Tac/SRL group. This finding may be because of the relatively small sample size in our study.

In another multicenter trial, 318 patients were randomized to Tac/SRL, and 316 patients were randomized to Tac/MMF. Renal function at 6 months of follow-up was comparable; however, the study was limited by short follow-up (27). The Edmonton protocol for islet cell transplantation consists of Tac/SRL maintenance and has been associated with nephrotoxicity (28). The mechanism by which the Tac/SRL combination is potentially more nephrotoxic is unclear. The mechanism implicated includes a complex cascade of events leading to perturbation of glomerular hemodynamics in the setting of Tac/SRL combination therapy (29).

In both animal studies and in humans, SRL has been shown to prolong DGF by impairing recovery from ischemia reperfusion injury (30,31). Although there were not a large number of deceased donor kidney transplants in our analysis, we did observe a higher incidence of DGF in the Tac/SRL group compared with the Tac/MMF group (10.8% versus 0%, P=0.02).

Combination of immunosuppressive agents depends on their individual pharmacokinetics and interactions between them (32). SRL increases the bioavailability of cyclosporine, thereby potentially increasing its nephrotoxic effect (33). The impact of SRL on Tac in renal transplant recipients is less consistent (32,34–37). In contrast, MMF has not been shown to impact Tac levels (38). In our study, the trough Tac levels combined with either SRL or MMF were comparable.

SRL has been shown to cause renal tubular collapse, vaculization in the proximal tubules, and nephrocalcinosis in animal models (39). The production of the cytokine TGF-β in the rat kidney increased with SRL administration (40), which may lead to an increase in fibrosis (41). The work by Han et al. (42) showed, in a mouse model, that SRL accelerates the CNI-induced oxidative process by downregulating the renal antioxidant Klotho expression in the kidney.

The work by Andoh et al. (43) showed that SRL combined with cyclosporine enhances the nephrotoxic effects of the CNI after 4 weeks in a rat model (43). However, patients on SRL have a lower incidence of interstitial fibrosis and tubular atrophy compared with patients on cyclosporine (44). In a prospective randomized study using steroid-free maintenance, at 5 years post-transplantation, chronic CNI toxicity was observed more frequently in CNI combinations with SRL (45).

Studies using low-dose CNI with mammalian target of rapamycin inhibitors have yielded favorable results. A randomized study compared 56 patients on everolimus (C0 trough levels=8–12 ng/ml) and low-dose cyclosporine (C2 levels=250–300 ng/ml) with 50 patients with mycophenolate sodium and standard exposure cyclosporine (C2 levels=500–700 ng/ml). Both groups were also maintained on steroids. The everolimus group was associated with lower DGF, better 1-year graft survival, and significantly higher GFR (81.6 versus 62.6 ml/min per 1.73m², P<0.001) (46).

Another recent trial randomized 833 patients to everolimus at 1.5 or 3 mg/day (target C0=3–8 and 6–12 ng/ml, respectively) with reduced exposure cyclosporine or mycophenolic acid with standard exposure cyclosporine (47). All patients received basiliximab ± corticosteroids. At 12 months, eGFR was similar in the everolimus groups versus the mycophenolic acid group. Additional studies with longer follow-up are needed to delineate the optimal immunosuppression regimen and optimal dose.

The randomized nature of the study and the long duration of follow-up contribute to the strengths of our study. However, our study is limited to a single center and a relatively small sample size. Although we presume that the decline in GFR in the Tac/SRL group is likely caused by additive nephrotoxicity, we do not have histologic or mechanistic evidence.

In conclusion, our study shows that, in a prednisone-free immunosuppressive regimen for renal transplant recipients induced with an IL2 receptor antagonist, MMF combined with Tac seems to confer superior allograft function and improved long-term graft survival compared with the Tac/SRL combination. The nephrotoxicity associated with Tac is augmented by combination with SRL in a steroid-free

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### Table 4. Cox proportional hazard model for patient mortality, graft failure, and acute rejection adjusting for donor age and delayed graft function

<table>
<thead>
<tr>
<th></th>
<th>Patient Mortality</th>
<th>Graft Failure</th>
<th>Acute Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI P Value</td>
<td>HR 95% CI P Value</td>
<td>HR 95% CI P Value</td>
</tr>
<tr>
<td>Treatment (MMF vs SRL)</td>
<td>0.00 — 0.08</td>
<td>0.20 0.05–0.77 0.02</td>
<td>0.37 0.13–1.01 0.05</td>
</tr>
<tr>
<td>Donor age</td>
<td>1.71 0.62–4.69 0.29</td>
<td>0.95 0.90–1.01 0.08</td>
<td>0.99 0.95–1.03 0.54</td>
</tr>
<tr>
<td>DGF (no versus yes)</td>
<td>0.12 0.001–10.10 0.35</td>
<td>0.88 0.11–7.29 0.99</td>
<td>1.28 0.16–10.20 0.81</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidential interval; MMF, mycophenolate mofetil; SRL, sirolimus; DGF, delayed graft function.


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