Switch From Twice-daily Tacrolimus to Once-daily, Prolonged-release Tacrolimus in Kidney Transplantation: Long-term Outcome

D. Sforza*, G. Iaria, L. Petagna, A. Parente, A. Anselmo, F. Sergi, S. Marzio, F. Corrado, S. Telli, T.M. Manzia, and G. Tisone

Hepatobiliary and Transplant Unit, Department of Surgery, Tor Vergata University, Rome, Italy

ABSTRACT

Background. One daily dose of tacrolimus (QDT) improves adherence in kidney transplant (KT) recipients. A switch from twice-daily tacrolimus (BDT) to QDT showed similar efficacy and safety.

Methods. The aim of our study was to demonstrate the long-term efficacy and safety of switching from BDT to QDT in KT recipients. Preliminary results have already been published. Forty-one patients (34 men and 7 women), mean age at KT of 43.9 ± 12.7 years, underwent a 1:1 dose switch from BDT to QDT; the mean time from KT to switch was 36.6 ± 16.1 months. In our study population, 4 patients received a living donor KT and 2 received a second allograft.

Results. The mean follow-up was 86.8 ± 13 months from the switch and 126.2 ± 22.3 months from KT. Graft and patient survival rates were 90.2% and 95.1%, respectively. All patients maintained stable renal function during follow-up. During the first 3 months after the switch we observed a significant decrease in tacrolimus blood level ($P = .0001$). No significant differences were observed regarding tacrolimus dose before and after QDT introduction (P = not significant [NS]). Fourteen patients who stopped steroids under BDT treatment and 16 patients who stopped steroids after the switch are currently steroid-free.

Conclusion. Our study showed safety and efficacy in switching from BDT to QDT. After early (<1 year) dose adjustment, tacrolimus blood levels remained stable throughout follow-up. Moreover, QDT represented a valid alternative for patients showing steroid side effects.

LATE rejection in kidney transplantation (KT), primarily associated with donor-specific antibodies, is a major challenge for all physicians. Adherence to immunosuppressive therapy, together with younger age and class 2 human leukocyte antigen (HLA) mismatching, are leading causes of late rejection [1,2].

In this setting, once-daily, prolonged-release tacrolimus (Advagraf, Astellas Pharma US, Inc.) (QDT), could improve patient compliance to reach effective immunosuppression status [3]. The goal of this study is to demonstrate the safety and efficacy in long-term follow-up after switching from twice-daily tacrolimus (Prograf, Astellas Pharma US, Inc.) (BDT) to QDT, in terms of graft and patient survival and renal function measured with serum creatinine (mg/dL) levels.

MATERIALS AND METHODS

Forty-one (34 men and 7 women) KT recipients (4 had received living donor kidneys and 2 received second allografts), with an overall age at transplantation of 43.9 ± 12.7 (mean ± SD) years, were enrolled in our study from April 2009 to November 2010; patients were switched, with a 1:1 dose ratio, from BDT to QDT. The time from KT to switch was 36.6 ± 16.1 months. Before the switch (at baseline), 1 patient was on immunosuppressive monotherapy with Prograf; 13 patients were on a dual immunosuppression regimen with mycophenolate mofetil and Prograf; and 27 were on

*Address correspondence to Daniele Sforza, MD, UOC Chirurgia dei Trapianti, Policlinico Tor Vergata–Tor Vergata University, Viale Oxford 81, 00133 Rome, Italy. E-mail: dsforza@gmail.com

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triple immunosuppression therapy with mycophenolate mofetil, steroids, and Prograf.

Statistical results are expressed as mean ± SEM. $P < .05$ was considered significant. SPSS version 13.0 for Windows (IBM Corp, Armonk, NY) was used for statistical analysis. All data were handled with a prospective database (Microsoft Access 2.0, Microsoft Corp, Redmond, WA). Normally distributed continuous data were analyzed by a parametric test (Student's t test). Early follow-up data for our cohort from the switch to 19 months have already been published [4]. Herein we report our long-term outcome follow-up.

RESULTS

Mean follow-up was 86.8 ± 13 months from the switch and 126.2 ± 22.3 months from KT. Overall graft and patient survival rates were 85.4% and 95.2%, respectively. One recipient died due to a simultaneous kidney-lung carcinoma and 1 due to sepsis related to colonic diverticulitis, both with graft function. Four patients had graft loss: chronic rejection in 3 cases and BK virus nephropathy in 1 case.

Renal function, as measured by serum creatinine, remained stable during follow-up. Serum creatinine concentration was 1.5 ± 0.4 mg/dL at baseline, 1.5 ± 0.6 mg/dL at 6 months, 1.3 ± 0.5 mg/dL at 12 months, 1.4 ± 0.5 mg/dL at 24 months, 1.5 ± 0.6 mg/dL at 36 months, 1.4 ± 0.5 mg/dL at 60 months, and 1.6 ± 0.8 mg/dL at 84 months. No statistical difference was observed during follow-up for graft function (P = NS). At baseline, the mean blood tacrolimus level was 6.9 ± 2.2 ng/mL vs 4.7 ± 1.8 ng/mL at 3 months, 5.2 ± 1.7 ng/mL at 6 months, 6.2 ± 1.5 ng/mL at 12 months, 5.8 ± 1.9 ng/mL at 24 months, 5.4 ± 1.4 ng/mL at 36 months, 5.5 ± 1.3 ng/mL at 60 months, and 5.8 ± 1.5 ng/mL at 84 months. During the first 3 months after the switch we observed a significant decrease of tacrolimus blood level (P = .0001). After early (<1 year) dose adjustment, Tacrolimus blood levels remained stable throughout follow-up, but differences in tacrolimus dose before and after QDT introduction were not significant (P = NS) (Fig 1).

Among the 14 patients who were steroid-free before the switch, none required steroid readmission. It was possible to withdraw steroids for 16 of 27 (60%) patients when tacrolimus blood trough levels were stable. Among the group with the triple immunosuppressive regimen, 3 of 27 patients (11.1%) developed malignancy (bladder carcinoma, Burkitt lymphoma, and simultaneous kidney-lung carcinoma); these patients were switched to single immunosuppressive therapy with mammalian target-of-rapamycin inhibitors. Moreover, 1 of 27 patients (3.7%) had dizziness and tinnitus requiring reintroduction BDT. Among the same group, 2 of 27 patients (7.4%) had mild acute rejection episodes: the immunosuppressive regimen was managed by adjusting the Advagraf dose, without supplementary treatment.

Fourteen patients who stopped steroids under BDT treatment and 16 patients who stopped steroids after the switch have remained steroid-free.

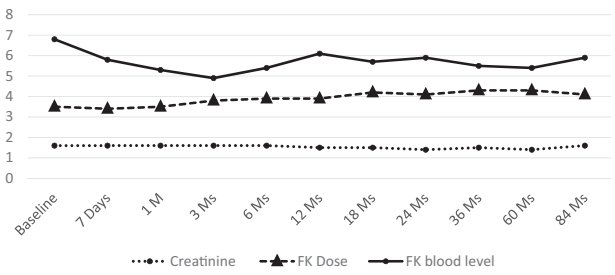

Fig 1. Serum creatinine level (mg/dL), blood tacrolimus level (ng/mL), and tacrolimus dose (mg) data throughout follow-up.

DISCUSSION

Adherence to immunosuppresion therapy is a major issue when dealing with transplanted patients. Nonadherence to treatment has been cited as a major cause of preventable graft loss and rejection [5]. Interventions that improve treatment adherence, such as morning dosing and reducing administration frequency, may also improve long-term outcomes. Improved adherence may result in more stable tacrolimus blood levels, which are less likely to fall below therapeutic levels. QDT offers a great advantage for the quality of life of transplant recipients, allowing for better treatment compliance. QDT showed both efficacy and safety, also observed in liver, kidney, and simultaneous kidney-pancreas transplant patients [6–8]. Moreover, switching from BDT to QDT seems to have ensured better renal function in some studies [9,10].

In this study we have demonstrated the safety and efficacy of conversion from Prograf to Advagraf using a dose-switching ratio of 1:1, with monitoring of tacrolimus blood levels up to 84 months after the conversion. During long-term follow-up, we did not observe any renal damage and both graft and patient survival were satisfactory (85.4% and 95.2%, respectively). Only 2 patients had mild acute rejection episodes that were not treated with high-dose steroids but instead with modification of tacrolimus dose.

Consistent with our previous study from 2011, we confirm that, even after long follow-up, switching from BDT to QDT at a dose ratio of 1:1 in stable KT recipients is safe and may be a feasible option for recipients who require steroid withdrawal due to side effects. In fact, steroid withdrawal was possible in most patients treated with QDT. Moreover, QDT administration in an immunosuppressive regimen is the most cost-effective treatment as it may improve adherence to therapy.

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