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Impact of Conversion From Advagraf to Twice-Daily Generic Tacrolimus in Kidney Transplant Recipients: A Single-Center Study—A 3-Year Follow-Up

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Tacrolimus is a key immunosuppression drug in solid organ transplantation with a narrow therapeutic index. Twice-daily brand tacrolimus Prograf to once-daily brand tacrolimus Advagraf conversion was proven to be safe as was Prograf to twice-daily generic tacrolimus (Sandoz).[1,2] Our group previously published the first study comparing the clinical outcomes of renal transplant patients switched from Advagraf to generic tacrolimus with good results at 9-month follow-up.[3] We sought to find if the conversion was still considered safe at 36 months.

We included patients with stable renal function, serum creatinine less than 2.0 mg/dL, transplanted for 6 months or longer. Tacrolimus conversion was performed on a 1 mg:1 mg basis. Thereafter, doses were adjusted to maintain target trough levels between 5 and 10 ng/mL. Our main endpoints were patient and graft survival at 12, 24, and 36 months. Secondary endpoints included evolution of serum creatinine levels 36 months after conversion and biopsy-proven acute rejection episodes.

From the 109 included patients, there were 99 active on tacrolimus at 36 months. Graft and patient survival was 100% at 12- and 24-month follow-up. At 36 months, death-censored graft survival was 93% and patient survival was 97%. There were 3 deaths with a functioning graft, 1 infectious, 1 neoplastic, and 1 cardiovascular, and 4 patients were transferred to hemodialysis due to chronic allograft dysfunction. Two patients transited to cyclosporine, for diabetes and posterior reversible encephalopathy syndrome, and 1 to sirolimus due to Kaposi syndrome. The serum creatinine levels were not statistically different at conversion and 36 months follow-up ($P = 0.737$). There were no episodes of acute rejection. Doses were statistically different between conversion and 3 months ($P < 0.001$) and between 3 and 36 months ($P < 0.001$). Trough levels were not statistically different at conversion and 3 months ($P = 0.595$) but were between 3 and 36 months ($P < 0.001$) (Table 1).

In our study, the twice-daily generic formulation proved to be safe, with serum creatinine levels stable at conversion and at 36 months follow-up. The patients that transited to hemodialysis had been transplanted 10 years previously and were probably on a process of chronic allograft dysfunction at conversion. One third of our patients needed dose reduction at 14 days or 1 month after conversion to avoid toxicity, meaning that conversion was not on a strict 1 mg:1 mg basis in all patients, as suggested. On the other hand, this represented a great increase in the number of outpatient visits.[3] Statistically significant differences between tacrolimus doses and levels at 3-month and 36-month follow-up probably reflect a clinical tendency to lower trough levels of tacrolimus in renal transplantation that influenced our practice (trough tacrolimus levels 3-7 ng/mL).[4,5] Additionally, our study was limited by the small sample size, and the fact that it is a single-center study.

In conclusion, the twice-daily generic tacrolimus seems to provide similar efficacy and safety to Advagraf at 36-month follow-up. Additional drug monitoring postconversion should be recommended because 1 of every 3 patients may require dose titration to avoid toxicity.

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TABLE 1.

Summary of tacrolimus dose and trough levels and serum creatinine over the study period

Variables	T0	T0.5	T1	T3	T6	T36
Dose, mg/d	5.0 (2.0-18.0)	5.0 (2.0-18.0)	4.0 (2.0-16.0)	4.0 (1.5-15.0)	4.0 (1.5-15.0)	3.0 (1.5-12.0)
Dose, mg/kg per day	0.07 (0.02-0.34)	0.07 (0.02-0.34)	0.06 (0.02-0.30)	0.06 (0.02-0.26)	0.06 (0.02-0.26)	0.05 (0.02-0.23)
Trough level, ng/mL	7.7 ± 2.1	8.7 (4.4-17.6)	7.9 (3.2-17.1)	7.8 ± 1.7	7.8 ± 1.7	6.8 ± 1.7
Serum creatinine, mg/dL	1.2 ± 0.3	—	1.2 (0.5-2.1)	1.41 ± 0.52	1.2 (0.3-2.5)	1.2 (0.5-4.3)

Summary of tacrolimus dose (mg/d and mg/kg per day), tacrolimus trough levels (ng/mL) and serum creatinine (mg/dL) over the study period. Normal variables are described as mean and standard deviation and variables without a normal distribution are described as median and range.

T0, before conversion; T0.5, 14-day visit; T1, 1-month visit; T3, 3-month visit; T6, 6-month visit; T36, 36-month visit.

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