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Tacrolimus Trough Levels and Level-to-Dose Ratio in Stable Renal Transplant Patients Converted to a Once-Daily Regimen

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ABSTRACT

Numerous evidence has been reported to support a safe 1:1 conversion from the twice-daily tacrolimus (Tac-T) to the once-daily tacrolimus regimen (Tac-O), but frequently there is a reduction in drug trough levels, which has been estimated by some authors to be about 20%. The relationship between Tac-O dosage and trough levels after conversion is not clear. The tacrolimus trough levels-to-dose ratio has been applied to better define the wide variability in doses and blood levels of tacrolimus. The aim of this study was to evaluate tacrolimus trough levels, tacrolimus daily dosage, and tacrolimus level-to-dose ratio during 1 year pre-postconversion follow-up in 31 stable kidney transplant patients who had received Tac-T therapy for over 6 months with stable renal function. They were converted to the same dosage of Tac-O. Patients before and after conversion were their own controls. The trough levels of tacrolimus showed a slight albeit significant reduction after conversion, remaining in the therapeutic range. Nineteen percent underwent an adjustment in total daily dosage after conversion versus 39% before conversion with no significant difference. No significant differences were detected in the total daily dose administered either by tacrolimus level-to-dose ratio before or after conversion. Kidney transplant recipients under Tac-O therapy were safely maintained using the same therapeutic monitoring as when receiving Tac-T.

TACROLIMUS (Tac) accounts for more than 67% of immunosuppressants for new kidney transplant patients in the United States.[1,2] Its use has led to acute rejection rates as low as 10% at 1 year after transplantation.[3] Primary adverse mostly dose-dependent effects associated with Tac include hypertension, posttransplant diabetes, dyslipidemia, and nephrotoxicity.[4,5] Tac shows interindividual and intraindividual pharmacokinetic variabilities.[6,7] Indeed, the oral bioavailability of Tac has been evaluated to vary by an average of about 25%. Genetic studies have demonstrated various cytochrome genotypes to influence Tac clearance.[8] However, Tac variability seems largely due to extrahepatic metabolism in the gastrointestinal epithelium, wherein intrapatient variability seems to be low.[9] Several factors are involved in the variability of Tac trough levels, such as fasting assumption, fatty meals, or prendisolone comedications at doses over 10 mg/d.[10] The new extended-release formulation of tacrolimus administered once daily (Tac-O) seems to have less intrasubject variability in exposure versus the twice-daily formulation (Tac-T).[9]

In stable kidney transplant patients, the pharmacokinetics of Tac-O shows equivalent exposure at steady state with similar correlations between area under the curve and trough levels but with substantially reduced peak levels.[4,11] Evidence has been reported to support a safe 1:1 conversion from Tac-T to Tac-O. Monitoring trough levels of Tac-O is considered to be a surrogate of AUC the same as for Tac-T.[11]

A number of studies have indicated that kidney recipients can be safely converted from the Tac-T to the same dose of the Tac-O regimen.[4,11,12] Frequently the reduction in Tac

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trough levels after the conversion from Tac-T to Tac-O has been estimated to be about 20%. Moreover, higher doses of Tac-O, sometimes over 50%, have been required in de novo kidney transplant recipients.[4,13,14] Therefore, the relationship between Tac-O dosage and trough levels after conversion is not clear. The Tac trough levels-to-dose ratio has been applied to better define the wide variability in doses and blood levels of Tac.[15] In a previous study, we described a slight decrease in Tac trough levels with improved graft function after conversion to Tac-O among 31 stable kidney transplant patients.[16] The aim of this study was to evaluate Tac daily dosages and Tac level-to-dose ratios in the same group of patients over 1-year follow-up pre-postconversion.

MATERIALS AND METHODS

We selected 31 patients with stable kidney transplantations who were receiving immunosuppression with Tac, mycophenolate mofetil, and less than 10 mg corticosteroids Eligibility criteria were: patient ages 18 to 70 years; between 3 and 5 years after transplantation; and Tac-T therapy for more than 6 months with stable renal function. All patients were converted from Tac-T to Tac-O at the same dosages (1 mg:1 mg). Tac trough levels and Tac total daily dose, were evaluated monthly for 6 months before and after conversion. Patients before and after conversion were their own controls.

Characteristic of eight female and 23 male have already been described as mean age of 53.8 ± 11.2 years and posttransplant 45.4 ± 22 months with mean values of creatinine and glomerular filtration rate (MDRD) to be 1.6 mg/dL and 53.4 mL/min, respectively.

The trough levels of Tac were maintained in the therapeutic range of 4 to 10 ng/mL. Tac trough levels were measured by the Flex technique (Dimension XPand System) according to the product insert. The accuracy and precision has been evaluated by The International Proficiency Testing Scheme (D.W. Holt, St Georges Hospital Medical School, London, UK).

Statistical Techniques

We preliminarily performed a descriptive analysis consisting of percentages, averages, and standard deviations. Because the data showed normality despite the limited sample size, we employed parametric methods for an inferential approach. The homogeneity of variances was evaluated with the Levene test. Mean variations and total areas of distributions were evaluated with Student *t* test for paired data. Comparisons of values used the chi-square test for discrete variables. All tests were performed using SPSS system 18.0 (SPSS Inc, Chicago, Ill, USA) with a *P* value below .05 considered significant.

RESULTS

The trough levels of Tac showed a slight, albeit significant reduction after conversion ($P = .024$; Fig 1A). Tac dose was adjusted when trough levels were below 4 ng/mL or above 10 ng/mL (therapeutic range). Six of 31 patients (19%) underwent adjustments in total daily dosage after conversion. Of them, 3/6 (50%) had an increase and 3/6 (50%), a decrease. Twelve of 31 (39%) had a dosage adjustment before conversion. We did not observe any significant difference in the number of patients who underwent an adjustment in total daily dosage before and after conversion ($P = .093$; Fig 2). Dose adjustments ranged between 0.5 and 1 mg/d. No significant differences were observed in the total daily dose administered either in Tac level-to-dose ratio before or after conversion (Fig 1B and C).

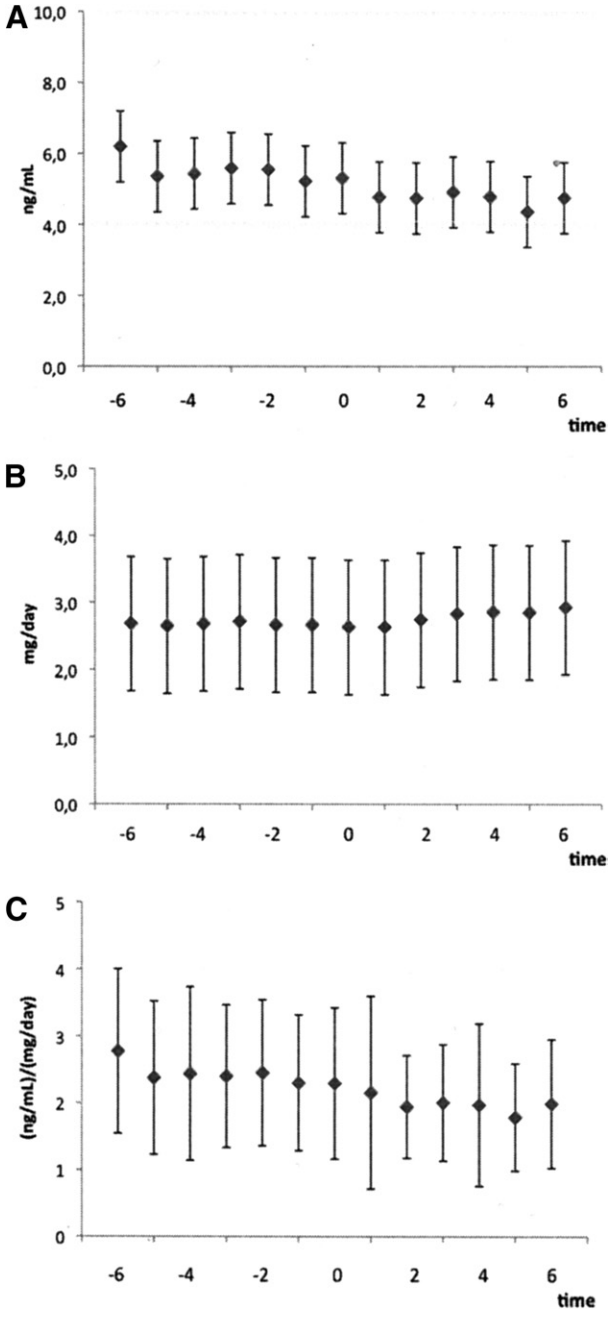

Fig 1. Follow-up monitoring. **(A)** Tacrolimus trough levels. **(B)** Total daily dosage. **(C)** Level-to-dose ratio evaluated in 31 kidney transplanted patients 6 months before and after conversion from twice- to once-daily tacrolimus. 0, time of conversion.

DISCUSSION

A number of studies have shown that kidney recipients can be safely converted from the Tac-T to the same dose of

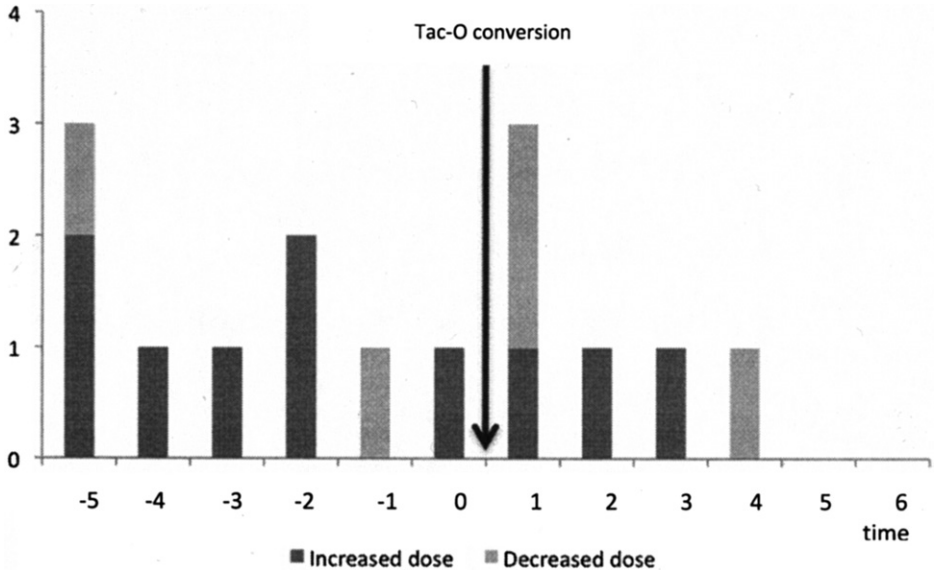

Fig 2. Dose adjustment. Number of patients receiving a dose adjustment before and after conversion. No patients required dose adjustment at 5 and 6 months after conversion.

Tac-O formulation. Conversion from Tac-T to Tac-O is commonly followed by a reduction in Tac trough levels[4,13] estimated by some authors to be about 20%. Moreover, some de novo kidney transplant recipients have required higher doses of Tac-O sometimes as much as over 50% of the dosage.[14] In all of these studies, no modifications of graft function parameters were observed either in converted and in de novo patients.

The clinical meaning of Tac alterations is not clear. They may reflect inter- and intraindividual variability in Tac clearance linked to Tac pharmacokinetics rather than to the formulation.[8] In a previous study, we observed a slight reduction in Tac trough levels among converted renal transplant patients, with improved renal function after conversion to Tac-O.[16] In this study, we described no differences in Tac levels-to-dose ratios or dosage adjustments in the same group of patients.

Nineteen percent of patients required an adjustment in Tac daily dosage after conversion, but the percentage was similar to that observed during the 6 months before conversion. In fact, small modifications in drug dosage are usual in the routine management of immunosuppressive therapy of stable transplant patients. In our study, we started the follow-up at 6 months before conversion, so that it was possible to evaluate the same patients undergoing therapy with Tac-T first and then with Tac-O with every patient as his own control before and after conversion.

In conclusion, Tac-O seems to be a good therapeutic option in renal transplantation. Kidney transplant recipients under Tac-O therapy can be safely maintained using the same therapeutic monitoring as patients receiving Tac-T.

REFERENCES

1. Butler JA, Roderick P, Mullee M, et al: Frequency and impact of nonadherence to immunosuppressants after transplantation: a systematic review. Transplantation 77:769, 2004

2. Williams MC, Creger JH, Belton Am, et al: The organ center of the United Network for Organ Sharing and twenty years of organ sharing in the United States. Transplantation 77:641, 2004

3. Solez K, Vincenti F, Filo RS: Histopathologic findings from 2-year protocol biopsies from a U.S. multicenter kidney transplant trial comparing tacrolimus versus cyclosporine: a report of the FK506 Kidney Transplant Study Group. Transplantation 66:1736, 1998

4. Wlodarczyk Z, Squifflet JP, Ostrowski M, et al: Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo kidney transplantation: a randomized, open-label trial. Am J Transplant 9:2505, 2009

5. Kramer BK, Charpentier B, Backman L, et al: Tacrolimus once daily (ADVAGRAFT) versus twice daily (PROGRAF) in de novo renal transplantation: a randomized phase III study. Am J Transplant 10:2632, 2010

6. Borra LC, Roodnat JI, Kal JA, et al: High within-patient variability in the clearance of tacrolimus is a risk factor for poor long term outcome after kidney transplantation. Nephrol Dial Transplant 25:2757, 2010

7. Staatz CE, Tett SE: Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet 43:623, 2004

8. Wang J, Zeevi A, McCurry K, et al: Impact of ABCB1 (MDR1) haplotypes on tacrolimus dosing in adult lung transplant patients who are CYP3A5 *3/*3 nonexpressors. Transpl Immunol 15:235, 2006

9. Undre NA: Pharmacokinetics of tacrolimus-based combination therapies. Nephrol Dial Transplant 18(suppl 1):i12, 2003

10. Press RR, Pharm D, Ploeger BA, et al: Explaining variability in tacrolimus pharmacokinetics to optimize early exposure in adult kidney transplant recipients. Ther Drug Monit 31:187, 2009

11. Alloway R, Steinberg S, Khahil K, et al: Conversion of stable kidney transplant recipients from a twice-daily Prograf-based regimen to a once-daily modified-release tacrolimus-based regimen. Transplant Proc 37:867, 2005

12. Crespo M, Mir M, Marin M, et al: De novo kidney transplant recipients need higher doses of Advagraf compared with Prograf to get therapeutic levels. Transplant Proc 41:2115, 2009

13. Mecule A, Poli L, Nofroni I, et al: Once daily tacrolimus formulation: monitoring of plasma levels, graft function, and cardiovascular risk factors. Transplant Proc 42:1317, 2010

14. De Jonge H, Kuypers DR, Verbeke K, et al: Reduced C_0 concentration and increased dose requirement in renal allograft recipients converted to the novel once-daily tacrolimus formulation. Transplantation 90:523, 2010

15. Calvo-Turrubiartes M, Romano-Moreno S, García-Hernández M, et al: Quantitative analysis of regulatory T cells in kidney graft recipients: a relationship with calcineurin inhibitor level. Transpl Immunol 21:43, 2009

16. Tinti F, Meçule A, Poli L, et al: Improvement of graft function after conversion to once daily tacrolimus of stable kidney transplant patients. Transplant Proc 42:4047, 2010