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*Original article*

## Conversion from Twice-Daily to Once-Daily Tacrolimus Improves Graft Function but has no Influence on Proteinuria in Renal Transplant Recipients

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### Abstract

**Introduction.** Tacrolimus extended-release formulation enables once-daily use. Although an increasing number of patients have been converted from twice-daily (Tac-BID) to once-daily (Tac-QD) formulation, the available information regarding the initiation and follow-up of Tac-QD is sparse. In the present study we investigated influence of switch from Tac-BID or cyclosporine to Tac-QD on renal allograft function, proteinuria and protein-creatinine (P/C) ratio.

**Methods.** Between October 2012 and October 2014, the switch from Tac-BID or cyclosporine to tacrolimus extended-release formulation was done in 129(38% female, mean age 49 years) renal transplant recipients at different time after transplantation. The analysis focused on markers of graft function (GFR, serum creatinine, proteinuria, P/C ratio), liver function (AST, ALT,  $\gamma$ GT, alkaline phosphatase) and blood glucose. Clinical data were obtained at baseline (before conversion), 1 month (V1), 6 months (V6) and 12 months (V12) after conversion.

**Results.** Both serum creatinine and GFR showed a statistically significant improvement. With GFR, significant improvement was observed as early as V1 and it continued to increase throughout the study period up to V12 (all between-visit changes were statistically significant). With serum creatinine, mean levels were numerically decreasing throughout the follow-up period, but a significant improvement occurred at V6 and remained significant at V12 (both vs. V0 values). Proteinuria and P/C ratio did not show any significant change through the observation period. In the majority of patients, the baseline values of AST, ALT, GGT, AIP and glucose were within normal limits and did not change significantly through the observation period. Analysis of tacrolimus C0 showed a significant decrease throughout the follow-up period, at practically all visit. This finding was paralleled by a significant tacrolimus dose decrease

from baseline to V6 and V12, as well as by a significant decrease of tacrolimus dose/body weight.

**Conclusions.** Conversion from cyclosporine or Tac-BID to extended-release Tac-QD improves graft function in renal transplant recipients, without influence on proteinuria or P/C ratio.

**Keywords:** once-daily, twice-daily, tacrolimus, proteinuria, kidney transplant

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### Introduction

Once-daily tacrolimus (Tac-QD) has the same active component and metabolism as twice-daily tacrolimus (Tac-BID), but is released more distally in the gastrointestinal tract. Pharmacokinetic study performed on 40 kidney transplant recipients converted from Tac-BID to Tac-QD revealed that conversion to the QD formulation decreased inpatient variability [1]. Additionally, Tac-QD could offer the potential benefit of improved medication compliance by decreasing pill burden and thereby simplifying dosing schedule. Although an increasing number of patients has been converted from Tac-BID to Tac-QD formulation, the available information regarding the initiation and follow-up of Tac-QD is sparse [2-6]. Observational data are useful adjuncts to randomized, controlled trials, which clarify whether efficacy under controlled conditions translates into effective treatment in everyday practice. Thus, we investigated influence of switch from Tac-BID or cyclosporine to Tac-QD on renal allograft function, proteinuria and protein-creatinine (P/C) ratio in the routine clinical practice.

### Materials and methods

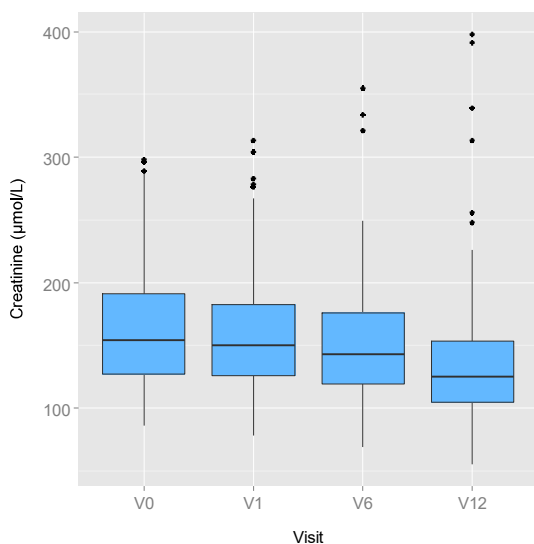
The analysis included 129 kidney transplant patients [49 (38%) female] who were at different times after trans

plantation switched from either regular release of tacrolimus based on individual decision of the attending nephrologist (Prograf® [n=110] or Tacrocel® [n=11]) or cyclosporine (Sandimmune Neoral® (n=8) to prolonged release of tacrolimus (Advagraf®) as part of their immunosuppressive therapy. Switching from Tac-BID to Tac-QD was made on a 1mg: 1mg basis, except in cases of increased trough levels which required dose-reduction. The analysis aimed to assess the dynamics of markers of graft function (serum creatinine, GFR, proteinuria, P/C ratio), liver function (AST, ALT, GGT, AP) and glucose metabolism (blood glucose) as well as the relationship of these variables with other characteristics/variables (including previous immunosuppressive therapy, underlying disease, tacrolimus C<sub>0</sub>, mycophenolate mofetil (MM) dose, tacrolimus and MM dose, tacrolimus and steroid dose) at baseline (V0) and at follow-up visits after 1, 6 and 12 months (V1, V6, V12). Study was approved by the Ethics Committee of the University Hospital Centre Zagreb, and was performed as a part of a project of the Ministry of Sciences.

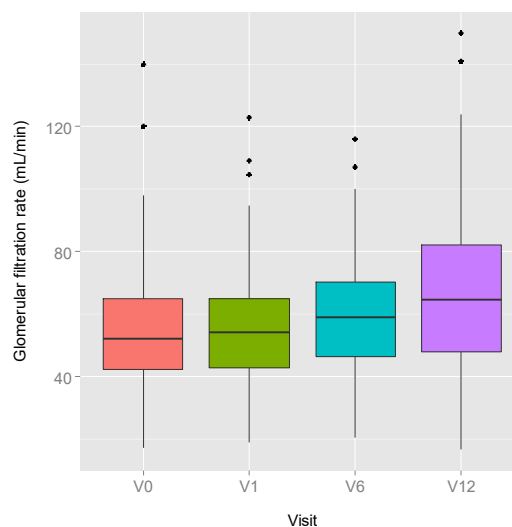
Friedman's non-parametric one-way analysis of variance with repeated measures was used, with a post-hoc Tukey test to investigate between-visits differences. Spearman rank correlation test was used when appropriate. Testing for potential differences between patient groups was performed using the Kruskal-Wallis one-way analysis of variance with Bonferroni correction for multiple comparisons.

## Results

The mean baseline age (at initiation of Tac-QD, V0) (SD; range) was 48.9 (12.6; 19-76) years; the mean age at transplantation was 46.3 (13.4; 14-74) years. The mean duration of dialysis therapy was 54.6 months (54.9



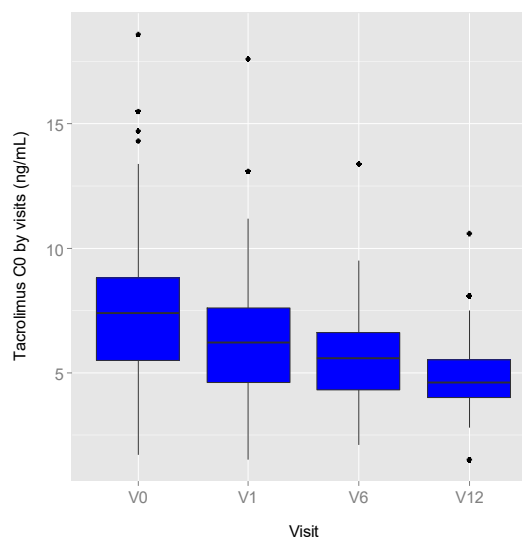
**Fig. 1.** Serum creatinine decreased during the follow-up. Significant differences were observed for V0 vs. V6 ( $p<0.021$ ), V0 vs. V12 ( $p<0.001$ ), V1 vs. V12 ( $p<0.001$ ) and V6 vs. V12 ( $p<0.001$ )



**Fig. 2.** Glomerular filtration rate increased over the observed period

months; 4.1 months-25 years), and the mean time since transplantation to initiation of Tac-QD (i.e. up to V0) was 31.0 months (40.1 months; 13 days-15 years).

A statistically significant serum creatinine level decrease was recorded during the follow-up period ( $p<0.0001$ ). The post-hoc Tukey test showed significant differences for V0 vs. V6 ( $p<0.021$ ), V0 vs. V12 ( $p<0.001$ ), V1 vs. V12 ( $p<0.001$ ) and V6 vs. V12 ( $p<0.001$ ), while differences for V0 vs. V1 and V1 vs. V6 were not significant ( $p=0.75$  and  $p=0.23$ , respectively) (Figure 1). Equally, a statistically significant GFR increase during the follow-up period ( $p<0.0001$ ) (Figure 2) was noted. Significant differences were found for all between-visits differences (except for V0 to V1), with  $p$  values from  $<0.001$  to  $p=0.008$ .

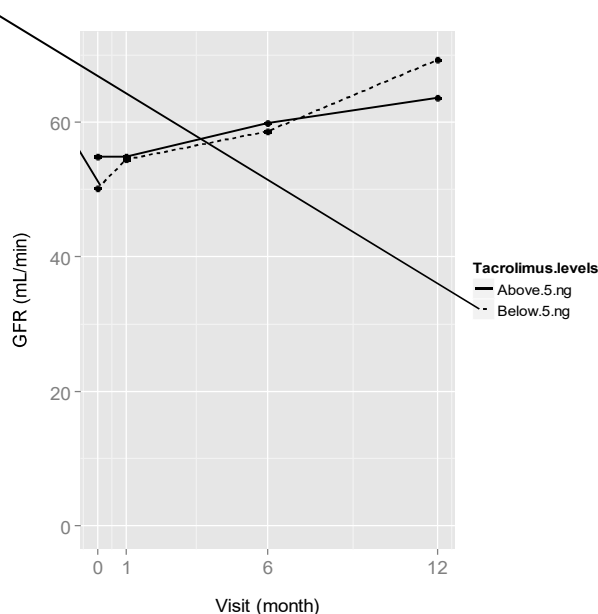


**Fig. 3.** Tacrolimus C<sub>0</sub> trough level decreased throughout the follow-up period

Tacrolimus C0 levels decreased during the follow-up period ( $p < 0.0001$ ). A significant difference was found for V0 vs. V4 ( $p < 0.001$ ), while the between visits  $p$  values for V0-V1, V1-V6 and V6-V12 were  $< 0.001$ , 0.07 and 0.0046, respectively. Significant dose decrease was recorded between V0 and V6 as well as V0 and V12 (both  $p < 0.001$ ) while other pairwise comparisons did not show significant differences (Figure 3).

Upon switching to Tac-QD, tacrolimus dose was decreased in 45 patients, remained unchanged in 59 patients and was increased in 17 patients.

For further analysis, tacrolimus levels were categorized as  $> 5$  ng/mL or  $\leq 5$  ng/mL; no statistically significant differences were found in GFR at any visit between the patients with lower and patients with higher tacrolimus blood levels (Figure 4).



**Fig. 4.** GFR means grouped by tacrolimus levels ( $> 5$  ng/mL,  $\leq 5$  ng/mL) through the follow-up period

No statistically significant differences were found for any parameter at any visit between patient groups receiving different mycophenolate mofetil doses.

No statistically significant differences were found between values of individual variables (AST, ALT, GGT, AP) at different visits. Changes in GFR, proteinuria, P/C ratio and enzyme levels (AST, ALT, GGT, AIP) were analyzed with respect to the previously received immunosuppressive therapy (Prograf,  $n=110$ ; Tacrocel,  $n=11$ , Cyclosporine,  $n=8$ ), with no statistically significant differences found for any variable at any visit.

With the mean follow-up of 2 years (range 12 months to 37 months), among complications recorded after switch to Tac-QD urinary tract infections were recorded in 10 patients, viral infections in 16 patients (1 BKV, 3 CMV, 2 VZV, 10 respiratory viral infections), neurotoxicity in 3 patients (vertigo, dizziness, cognitive impairment), biopsy proven acute rejection in 5 patients, leukopenia in 5 patients, diarrhea in 4 patients, malignancy in 2 patients (planocellular skin cancer, lung cancer) and fungal pneumonia, acute myocardial infarction and stroke in one patient each. New-onset diabetes after transplantation was already present in 13 patients treated with Tac-BID, with stable glycemic control after conversion to Tac-QD.

## Discussion

The potential advantages of Tac-QD are better adherence and a safety profile. However, data on outcomes of conversion from Tac-BID to Tac-QD is scarce.

Our study demonstrated the safety and efficacy of conversion from Tac-BID or cyclosporine to Tac-QD at different stages after renal transplantation. We observed a significant reduction in tacrolimus dose in the long term and trough levels accompanied with improvement of renal allograft function. Patients were switched from their previous calcineurin inhibitor (either cyclosporine or tac-BID, Prograf®, Astellas or Tacrocel®, Sandoz) based on individual decision of seven different nephrologists, which is the main value of our observational, non-controlled study, while our data clarify efficacy and safety of Tac-QD in everyday clinical practice.

Hougardy *et al.* retrospectively reviewed data from 55 patients switched from Tac-BID to Tac-QD. They observed a significant increase in tacrolimus daily doses at 6 months ( $P < 0.0001$ ). After conversion, they observed a quick and sustained decrease in trough tacrolimus levels, decreasing from 8.05 ng/mL at day 0 to 6.30 ng/mL at day 180 ( $P=0.0009$ ). Allograft functions were stable, without episodes of acute rejection [7]. An Italian group

switched 41 patients at 36.6±16.1 months after kidney transplantation from Tac-BID to Tac-QD. All patients maintained stable renal function after the conversion. Adverse events included dizziness and tinnitus in 1 patient, and one acute rejection episode [8]. Nakamura *et al.* switched 33 stable Japanese patients who had undergone kidney transplantation ≥1 years before from Tac-BID to Tac-QD, with the dose conversion ratio 1:1. Patients were followed for 2 months. Graft function remained stable without side effects [9]. Sixty-seven kidney transplant recipients were converted from Tac-BID to Tac-QD. Authors reported that at 2-years postconversion patient survival was 100% and graft survival 98.5%, with low incidence of biopsy-proven acute rejection (6.0%), and favorable safety profile [10]. Additionally, studies have shown that prolonged release tacrolimus enables steroid withdrawal [11,12].

Our transplant centre prefers low tacrolimus (trough levels around 5 mg/mL) and full recommended dose of mycophenolate. Results of the current study further support this approach with possible additional benefit of Tac-QD instead of Tac-BID. Further follow-up is needed to see possible difference between groups with trough level higher than 5 and lower than 5 ng/mL, while one year after the switch patients with lower tacrolimus trough level had higher GFR (although statistically not significant).

### Conclusion

Switch from Tac-BID or cyclosporine to Tac-QD is safe and may improve renal allograft function.

*Conflict of interest statement.* None declared.

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