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*Original Article*

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# Systematic conversion to generic tacrolimus in stable kidney transplant recipients

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**Abstract**

**Background.** Tacrolimus (Prograf®) is a key drug in the immunosuppressive treatment of renal transplant patients. Since the expiration of the patent for Prograf®, generic preparations have been approved in Europe as bioequivalence has been shown in healthy volunteers. However, few studies have investigated whether patients can be successfully converted from Prograf® to generic tacrolimus. Tacrolimus drug costs are by far the largest single item in the total drug expenditure for patients with renal disease in the Stockholm area. Considerable reductions in drug costs could be achieved if generic tacrolimus were to be used. The aim of this quality assurance study was to evaluate whether a switch from Prograf® to generic tacrolimus (Tacrolimus Sandoz®) could be safely performed in renal transplant patients. It further aimed to investigate changes of renal function (measured in estimated glomerular filtration rate, eGFR), need for dose changes and to calculate potential drug cost savings as a result of the conversion.

**Methods.** We planned to recruit at least 50 patients. Plasma creatinine levels and trough concentrations of tacrolimus were collected from patients with renal transplants at three occasions during treatment with Prograf® and three times after conversion to Tacrolimus Sandoz®. The eGFR was calculated before and after the conversion.

**Results.** Sixty-three of 67 enrolled patients (69% males, age 28–80 years) are included in this analysis. The ratio of mean trough concentrations of tacrolimus after comparison with before conversion was 1.02 (90% confidence interval 0.95–1.09). Fourteen patients experienced a change in tacrolimus levels >20% compared with baseline, no patients changed >20% in eGFR. The drug cost saving per daily dose was 33.40 SEK (∼€3.60, −23%).

**Conclusions.** Stable kidney transplant patients treated with Prograf® can be converted to Tacrolimus Sandoz® if trough concentrations of tacrolimus and plasma creatinine levels are closely monitored. The conversion brought savings, despite costs for extra monitoring.

**Keywords:** drugs; generic; kidney transplantation; tacrolimus; quality assurance project

## Introduction

Tacrolimus is a cornerstone of immunosuppressive treatment after solid organ transplantation. Since the European market exclusivity of Prograf® (Astellas Pharma) expired in June 2009, several generic preparations have been approved by the European Medicines Agency (EMA). However, the medical community has been reluctant to use generic tacrolimus, despite considerable potential cost savings [1, 2]. One of the reasons may be that bioequivalence studies are only performed in healthy volunteers, whereas tacrolimus has quite different pharmacokinetic properties in organ transplanted patients [3].

In order to be approved, a generic product must be shown to fit bioequivalence criteria. Bioequivalence is shown in single-dose cross-over studies in healthy volunteers. The pharmacokinetic parameters of peak concentration ($C_{max}$) and area under the concentration–time curve in one dosing interval ($AUC_{0-t}$) and $AUC_{0-72\,h}$ are determined in such studies. To be considered bioequivalent, the ratio of the geometric means of the generic to reference drug for each of these parameters must have a 90% confidence interval (90% CI) within 80.00–125.00%. The EMA applies tighter bioequivalence criteria for drugs that are considered to have a narrow therapeutic interval. For a drug with a narrow therapeutic interval, such as tacrolimus, the 90% CI of the generic to reference mean ratio of AUCs should be contained within 90.00–111.11% [4].

Only a few studies are published regarding the use of generic tacrolimus in clinical practice. The importance of

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using a bioequivalent generic formulation has been shown by Noceti *et al.* [5]. In 2011, Momper *et al.* published a retrospective study on the pharmacokinetic and clinical impact on switching from Prograf® to Tacrolimus Sandoz®. In this study, 48 liver and 55 kidney recipients were included and a reduction in mean tacrolimus trough concentration of 11% was noted after the conversion [6]. Recently, another retrospective study was published based on data from the Kaiser Permanente health-care system. In this paper, only one post-conversion measurement of creatinine and trough tacrolimus concentration was used. The authors could not confirm a systematic difference in tacrolimus exposure as reported by Momper *et al.* [7] but reported greater variability post-conversion than previous studies. McDevitt-Potter *et al.* reported a prospective study in 70 organ transplanted patients that underwent a brand-to-generic tacrolimus conversion. The median of the three tacrolimus trough levels before conversion was compared with a single trough level taken 4–7 days after the conversion. Changes in tacrolimus doses and trough levels were also compared at a control time point 6 months before the conversion. No significant change in mean tacrolimus trough levels were observed after the brand-to-generic conversion compared with the control period 6 months prior. However, the need for dose adjustments was significantly higher after conversion (21% of patients compared with 7% at the control time point) [8]. As there is a large inter individual variability in tacrolimus pharmacokinetics [9], it may take several days to reach a new steady state after a change in dose or formulation. Even if most patients reach steady state within 3 days [3], this may not be true for all patients. A single

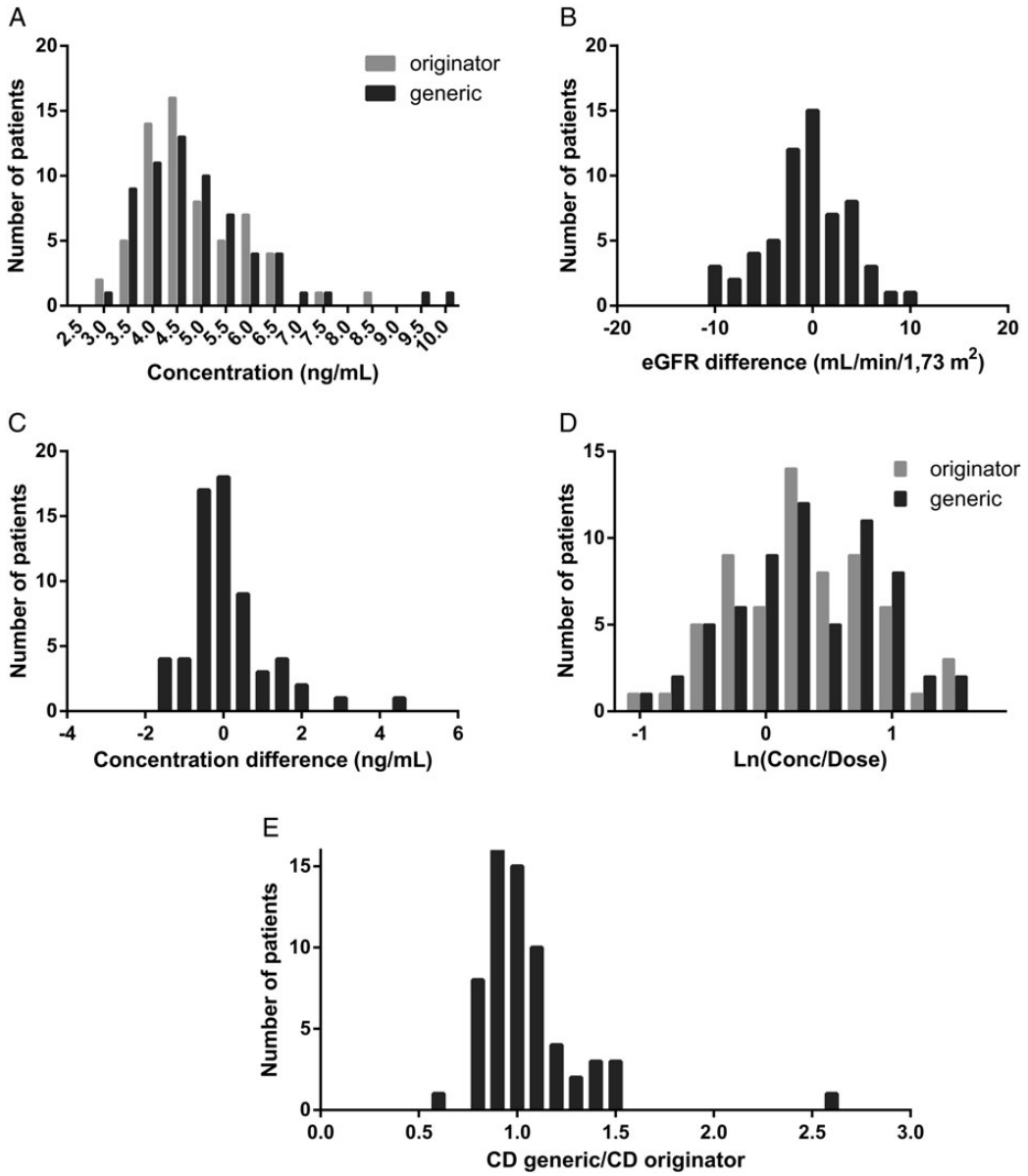


**Fig. 1.** Distributions of observed mean tacrolimus concentration before and after generic conversion (**A**). Panels (**B**) and (**C**) show the absolute changes in eGFR and mean tacrolimus concentration after generic conversion, respectively. Panel (**D**) shows the distributions of log-transformed generic and originator dose-normalized concentrations. Panel (**E**) shows the distribution of individual generic to originator ratios of dose-normalized concentrations.

sample 4–7 days after a switch to generic tacrolimus may therefore be too early for unveiling the full pharmacokinetic effect of a potentially slightly different formulation.

Alloway *et al.* conducted a randomized cross-over study of the repeated-dose pharmacokinetics of brand and generic tacrolimus in 71 stable kidney transplant recipients at least 6 months post-transplant. Patients were maintained on each preparation for 14 days and then switched to the comparator preparation. The 90% CIs of the generic-to-brand ratios was well within bioequivalence criteria for all pharmacokinetic parameters [10]. This was, however, not a true switch study, as the patients subsequently were switched back to their usual maintenance preparation once the pharmacokinetic study was completed.

The need for careful monitoring of drug levels and biochemical parameters in patients undergoing conversion to generic tacrolimus has been underscored by all authors mentioned above [6, 8, 10]. As tacrolimus is the single largest item in the drug expenses for patients with renal disease in Stockholm [11] and new expensive therapies are on their way, it may become necessary to materialize the potential cost savings of generic tacrolimus to allow such therapies to be introduced [12]. To facilitate safe conversion from brand-to-generic tacrolimus, we designed a standardized switch protocol for stable renal transplant patients. This protocol was then implemented in an outpatient setting at the renal outpatient clinics in Stockholm, and follow-up data were systematically collected and analysed.

## Materials and methods

### *Patients*

The main objective of this clinical project was to systematically convert and follow-up stable kidney transplant recipients to generic tacrolimus. The project was planned by the Drug Expert Panel for Renal Medicine in Stockholm as a quality assurance project within ordinary health care and was not primarily intended as a research study. Hence, according to Swedish law, ethical approval was not obliged. The project was funded by the Drug Therapeutic Committee of Stockholm County Council. All adult renal transplant patients followed at the renal clinics at the Danderyd University Hospital and the Karolinska University Hospital were eligible. According to local practice, patients are followed at the transplantation clinic for the first post-transplant year and then referred back to their respective renal clinic. Thus, no patients in the early post-transplant period were included. Inclusion criteria were stable renal function as defined by $\leq$20% change in plasma creatinine over the last 6 months, estimated glomerular filtration rate (eGFR) according to the MDRD 4-variable formula [13] of at least 25 mL/min/1.73 $m^2$ and stable drug treatment. Exclusion criteria were active neoplasm or pregnancy. Patients were included from January to December 2012.

All patients received oral and written information about the project by their treating physician. A date for the generic switch was decided, and the patients were asked to leave blood samples for plasma creatinine and whole blood tacrolimus concentrations at their usual laboratory. Generic conversion was made on a mg:mg basis. Drug and biochemical monitoring were done on the day of the switch, 1, 2 and 4 weeks after the switch. The same data were collected from the last two visits before conversion.

The primary outcome measurement was change in mean tacrolimus concentration after generic conversion. Secondary outcome measurements were change in renal function and need for dose adjustments.

### *Tacrolimus assay*

All tacrolimus samples were measured by the routine method used at the Therapeutic Drug Monitoring laboratory at the Karolinska University Hospital. This quality-assured method was taken into the routine in June 2010. It is a liquid chromatography–tandem mass spectrometry (LC-MS/MS) method with a range of measurement from 0.5 to 50 ng/mL and a coefficient of variation (CV) of 6.9% at a measurement level of 6 ng/mL. Briefly, whole blood samples are lysed by the addition of water and aqueous 0.4 M zink sulphate in methanol. After centrifugation (5 min at 2100 *g*), samples are injected on a Thermo Fischer TSQ Quantum Ultra system with an Accela pump (Thermo Fischer Scientific, Inc., Waltham, MA, USA). Ascomycin is used as an internal standard. Mass transitions monitored are *m/z* 809–757 and 821–768 for ascomycin and tacrolimus, respectively.

### *Sample size calculation*

We considered a mean difference in tacrolimus concentrations of >20% to invalidate the use of the generic tacrolimus preparation. Mean and intra individual standard deviation of whole blood tacrolimus was calculated based on the 12 687 tacrolimus measurements in 1302 patients made between June 2010 and September 2011. Given a mean of 6.34 ng/mL and a standard deviation of 1.51 ng/mL, a sample size of at least 50 patients would give 80% power to detect a 20% mean change in tacrolimus concentration.

### *Statistics*

Data from the case report forms were manually entered into an Excel spreadsheet. Source data were checked against the electronic medical records of each patient.

Patients were excluded if they took a mixture of brand and generic tacrolimus or failed to leave at least a sample for plasma creatinine within 4 weeks of the conversion. All patients with at least two tacrolimus trough levels after the conversion were included in the pharmacokinetic analysis. All patients with post-conversion creatinine measurements were included in the safety analysis.

To adjust for the effect of dose adjustments, dose-normalized tacrolimus concentrations (concentration/dose, C/D ratios) were calculated for each time point. The project database was then analysed with Statistica 12 (Statsoft, Inc., Tulsa, OK, USA.).

Mean values of the three samples taken before the switch and the three samples taken after generic conversion were compared by dependent *t*-tests in accordance with Momper *et al.* [6]. In addition, one-way ANOVA was performed to check whether the variation in tacrolimus levels changed after the conversion. ANOVA was also used for the bioequivalence estimation. Graphs were drawn with GraphPad Prism 6.03 (GraphPad Software, Inc., La Jolla, CA, USA).

## Results

A total of 67 case report forms were collected until the end of February 2013. Forty-six men and 21 women were enrolled. On average, they were 57.6 (SD 11.0) years old and had a transplantation vintage of 7.4 (SD 4.1) years. Sixty-three patients completed the follow-up as intended. Four patients failed to follow the protocol; one patient switched gradually, two patients failed to give at least two post-conversion tacrolimus levels and one patient switched back to brand tacrolimus due to gastrointestinal discomforts. One patient was included despite having an eGFR below 25 mL/min/1.73 $m^2$ (19.2 mL/min/1.73 $m^2$), yet was included in the analyses.

There were no statistically significant changes of the mean absolute or dose-normalized tacrolimus concentrations or eGFR after the generic conversion (Table 1). Neither was there any indication of a change in variability of tacrolimus levels on a group level.

However, on an individual level, dose-normalized tacrolimus concentrations ranged from a 40% decrease to a 2.5-fold increase after conversion to generic tacrolimus (Figure 1). It can be noted that the patient subject to the 2.5-fold increase had shown increasing tacrolimus concentrations despite unchanged dose already before the switch and continued to increase after switching to generic tacrolimus. Generic tacrolimus could not be held responsible for this outlier value. Excluding this outlier, the most extreme increase in dose-adjusted tacrolimus concentration was 49%.

Fourteen patients experienced a change in tacrolimus trough levels of more than 20% after generic conversion. No patients increased or decreased more than 20% in eGFR.

Tacrolimus dose was changed in 12 patients before switching to generic tacrolimus and 8 patients had a dose adjustment after the switch. No patient experienced any clinically significant adverse events or acute rejections.

Since trough levels of tacrolimus are strongly correlated to tacrolimus exposure ($AUC_{0-\tau}$) [10, 14], dose-adjusted trough concentrations (C/D ratios) can be used as a proxy for $AUC_{0-\tau}$. Using this, the ratio of the geometric mean C/D ratios on generic versus originator tacrolimus can be calculated to be 1.02 with a 90% CI of 0.95–1.09, which is well within the EMA bioequivalence criteria for drugs with a narrow therapeutic interval (0.90–1.11). Excluding the outlier mentioned above, the mean would be marginally different (1.00, 90% CI 0.97–1.05).

The potential cost savings for switching to generic tacrolimus could be estimated by calculations based on sales statistics. In 2012, 206 540 defined daily doses (DDDs) of originator tacrolimus (Prograf®) were sold at an average price of SEK 146/DDD, whereas 7780 DDDs of the generic (Tacrolimus Sandoz®) were sold at an average price of SEK 112.60 [11]. Thus, the average saving per DDD during the studied period was SEK 33.40 (€3.60), i.e. a reduction by 23%. Using the present protocol, the cost for switching to generic tacrolimus was the cost for four extra tacrolimus analyses, which in 2012 was SEK 420 per analysis, i.e. SEK 1680 (€182) per patient. This means that the cost for extra sampling was saved after 49 days of generic tacrolimus. Consequently, conversion to generic tacrolimus in all renal transplant recipients in the Stockholm County would save more than SEK 3.3 million (€360 000) annually.

**Table 1.** Mean and 95% CIs for tacrolimus concentration, plasma creatinine and eGFR on originator and generic tacrolimus

| | Originator | | Generic | |
|---|---|---|---|---|
| Variable | Mean | 95% CI | Mean | 95% CI |
| Tacrolimus concentration (ng/mL) | 4.8 | (4.5–5.0) | 4.9 | (4.6–5.2) |
| Creatinine (μmol/L) | 129 | (118–140) | 131 | (119–143) |
| eGFR (mL/min/1.73 $m^2$) | 51 | (47–55) | 51 | (47–55) |

## Discussion

As far as we know, this clinical quality assessment/assurance project is the first prospective evaluation of systematically switching renal transplant recipients to generic tacrolimus. We conclude that stable renal transplant recipients can be safely and cost-effectively converted to generic tacrolimus. We confirm that the generic tacrolimus that we used (Tacrolimus Sandoz®) is statistically bioequivalent to the reference drug (Prograf®) in the clinical setting. However, since individual patients may experience significant changes in tacrolimus concentrations after switching to generic tacrolimus, we strongly recommend that tacrolimus concentrations are carefully monitored.

There are many reasons for changes in tacrolimus trough levels. First, timing of the sampling in relation to last dose intake will influence the measured concentration. Second, tacrolimus is subject to a wealth of drug–drug and food–drug interactions [3]. We have tried to standardize for such factors and most samples were taken 10–14 h after the last dose. There was no systematic difference in the timing of samples before and after the switch. Treating physicians were asked to report any change in medication.

We do not confirm the increased need for tacrolimus dose adjustments observed in the retrospective study by Momper *et al.* [6]. However, our data do not allow a straightforward interpretation of the need for dose adjustments. We collected data for several months before the generic conversion, but only for 4 weeks afterwards. Thus, the number of dose adjustments per unit time was lower before the generic conversion. Still, the decision to adjust the dose is probably influenced more by the result of a recent therapeutic drug monitoring than by time in itself. In our material, most patients that were subject to dose adjustments after the switch to generic tacrolimus showed a trend of change in tacrolimus trough concentrations even before the generic conversion. Since the project ended a year ago, no significant adverse events have been reported in the participants during routine follow-up.

The results of this project are probably applicable to other solid organ recipients. However, careful monitoring is recommended. We would not recommend unmonitored switching between different generic preparations. Bioequivalence is shown for a generic drug in comparison to the originator drug, not to another generic. It should be remembered that bioequivalence is based on the mean and the CI of the mean. Individual variability is much greater than the CI of the mean. Indeed, only 16 of our 63 patients had C/D ratios that fell within the 90% CI of the mean.

One could always argue about the meaning of careful monitoring. A reasonable minimum follow-up would be tacrolimus and creatinine levels within a week after generic conversion and then again when steady state is certainly established even in slow metabolizers, i.e. around 4 weeks after the switch.

Lately, the price difference in Sweden between the originator and generic tacrolimus has further increased, meaning that the potential savings are even greater today than a year ago. Such savings may prove to be necessary to allow for the introduction of novel and costly therapies within the field of kidney transplantation.

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