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ORIGINAL ARTICLE

De-novo use of generic tacrolimus (Adoport) in renal transplant recipients: A single center experience from Türkiye*

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ABSTRACT

Objective: Renal transplantation is the best treatment for end-stage kidney disease, and tacrolimus has become an important immunosuppressive treatment for kidney transplant patients since it was introduced. After the first generic tacrolimus has been approved by the FDA, studies have begun to compare the effectiveness and safety of generic tacrolimus with the original tacrolimus. When using generic immunosuppressive therapies, it is also necessary to ensure that it provides adequate immunosuppression and does not cause severe toxicity.

This study aims to compare clinical outcomes, including acute rejection, graft loss and adverse reactions, in patients receiving brand tacrolimus (Prograf, Astellas Pharma, U.S.) or generic tacrolimus (Adoport, Sandoz, UK) from the start of kidney transplant therapy.

Study Design: Renal transplant recipients between 1 January 2015-1 March 2020 were screened retrospectively. All patients receiving de novo generic tacrolimus (n:51) and randomly selected 102 control renal transplant recipients receiving original tacrolimus were included in this study.

Materials and Methods: We evaluated and recorded demographic, clinical and laboratory data including age, gender, primary kidney disease, donor type (live or dead), induction and death regimen, tacrolimus dose, tacrolimus through levels, serum creatinine, biopsy-confirmed acute rejection episodes, delayed transplant function, positive BK polyomavirus in the urine, BK polyomavirus-related nephropathy, cytomegalovirus infection in 1-year follow-up.

Results: Most of the patients were male (64.1%) with a mean age of 38.3 years. There was no significant difference in demographic characteristics between the original and generic tacrolimus groups. No differences were found in terms of creatinine levels, total daily dose of tacrolimus and tacrolimus trough levels at discharge and the first year. Additionally, biopsy-confirmed acute rejection in the following year after transplantation, BKPyV positivity in urine, BKPyVAN, CMV viremia and adverse reactions related to tacrolimus were similar between the two groups.

Conclusion: With this study, we aimed to contribute to the literature with our experience on the use of generic tacrolimus from our country. As a result of our study, we noted that generic tacrolimus can be safely preferred for de-novo use with close drug-level monitoring because it is an immunosuppressant agent with a narrow therapeutic index. There is a continuing need for randomized prospective-designed and multi-centric studies with a wide range of patients.

Keywords: Transplantation, generic drugs drugsimmunosuppressants

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INTRODUCTION

Renal transplantation is the best type of treatment modality for end stage kidney disease [1]. Since its discover in 1984 tacrolimus became an important immunosuppressive agent for renal transplant patients. Tacrolimus, also known as FK506, is a macrolide antibiotic that is derived from *streptomyces tsukubaensis*. It binds to "FK-506 binding protein" with the binding ring it contains. This structure prevents the enzyme activity of calcineurin and this inhibition stops T lymphocyte activation and proliferation [2]. Food and Drug Administration (FDA) approved usage of tacrolimus for renal transplantation in 1997 due to the superior results from randomized controlled trials [3-5].

Subsequently, FDA approved the first generic tacrolimus in August 2009 for cost-saving after the patent duration of the brand tacrolimus ended in April 2008. Generic medications require both pharmaceutical equivalence and bioequivalence with the reference formulation. Bioequivalence tests include comparing the mean maximal plasma concentration (Cmax) and the mean area under the maximal plasma concentration-time curve (AUC) of drugs in 18 to 36 healthy volunteers. If the products mean Cmax and mean AUC ratio are between 80-125% of the reference product, it is considered bioequivalent [6]. However regulatory approval do not require generic medications to undergo bioequivalence tests in renal transplant recipients. This is an important issue as data related to bioequivalence cannot be extrapolated from healthy volunteers to renal transplant recipients who have faster clearance of tacrolimus as a result of several factors including low hematocrit and albumin levels, co-administration of corticosteroids, and high rates of disturbed gastrointestinal motility and diabetes [7,8]. A generic tacrolimus is available at less cost in our country since 2015. There are only a few studies that compare the effectiveness and safety of generic tacrolimus and brand tacrolimus in the literature. Although other bioequivalent medications such as antihypertensives or antidiabetics can be monitored with blood pressure measurements or blood glucose levels, no test measures the effect of immunosuppression provided by generic immunosuppressive agents. Keeping the balance between serious toxicity and adequate immunosuppression is essential. Though the generic tacrolimus has been found safe and effective in studies, the skepticism about generic immunosuppressive drugs seems consistent [9-14].

The aim of this study was to compare clinical outcomes that include acute rejection, graft loss and adverse reactions of the patients administered either brand tacrolimus (Prograf, Astellas Pharma, USA) or generic tacrolimus (Adoport, Sandoz, UK) from the outset of renal transplantation day (de-novo use) in our transplant center.

MATERIALS and METHODS

Renal transplant patients that were transplanted in our renal transplantation unit between January 1, 2015 and March 1, 2020 were screened. All patients that were administered *de novo* generic tacrolimus (n:51) and 102 randomly selected control renal transplant recipients that were administered original tacrolimus included in this study.

All of the patients in this study had been received basiliximab (20 mg each intraoperatively and on day 4) or anti-thymocyte globulin ATG (1,5-3 mg/kg) depending on the immunological risk profile. 500 mg of intravenous methylprednisolone had also been given intraoperatively as a component of induction therapy.

Tacrolimus had been started from the 3rd day before the operation with a total dose of 0,1 mg/kg twice daily. In addition to tacrolimus, mycophenolate mofetil/mycophenolate sodium or steroids had been used for the maintenance immunosuppression regimen.

We evaluated and recorded Demographic, clinical and laboratory data including age, sex, primary renal disease, type of donor (living or deceased), induction and maintenance regimen, the dose of tacrolimus, tacrolimus trough levels, serum creatinine, biopsy-confirmed acute rejection (BCAR) episodes during the first year after transplantation, delayed graft function (DGF), BK polyomavirus

(BKPyV) positivity in urine, BKPyV associated nephropathy (BKPyVAN), cytomegalovirus (CMV) infection, adverse reactions that require switching medications in a 1-year follow-up.

BKPyV positivity in urine was defined as urinary BK virus copy number in any urine sample that was >107 copies/L. CMV infection was considered present if the patient was recommended to start antiviral treatment by infectious disease department along with any level of viremia. DGF was defined as the requirement of dialysis during the first 7 days post-transplant.

Statistical analysis

Data were collected and analyzed using IBM SPSS Statistics Version 26.0. Numerical variables are summarized with mean ± standard deviation or median (minimum-maximum) values and categorical variables are presented as numbers and percentages. The chi-square test was used to determine the relationships between categorical variables. Variables with normal distribution were compared by the t-test. $P < 0.05$ was considered statistically significant.

Ethical approval

The study was approved by the local ethics committee of Hacettepe University Medical Faculty and was conducted in accordance with the Declaration of Helsinki. Ethics committee approval date is 15.06.2021, approval number is GO21/535.

RESULTS

A total of 153 patients, 102 in the original tacrolimus group and 51 in the generic tacrolimus group, were included in this study. The demographic characteristics of the patients are presented in Table 1. The mean age of the study population was 38.3±13.0. Majority of the patients were male (98, 64.1%). Renal transplantation had been performed from living donors in 139 (90.8%) of the patients. Preemptive transplantation had been performed in 83 patients. There were no significant differences with regard to the demographic characteristics between the original and generic tacrolimus groups.

2 patients had delayed graft function. One of these patients was transplanted from a cadaveric donor with 9-hour cold ischemia time and one from a living donor. Both of them had biopsy-proven acute cellular rejection within 1 month of post transplantation. Post-transplant rejection and viral complications are presented in Table 2.

Nineteen of patients who used original tacrolimus and 9 of patients who used generic tacrolimus had BCAR in the first year after the transplant. There were no statistically significant differences in acute rejection within post-transplant 1 year between the two groups (p:1). There were no tacrolimus-related side effects that required drug changes in either group in one year follow up period.

Table 1. Demographic characteristics

	Original tacrolimus (n:102)	Generic tacrolimus (n:51)	Total (n:153)	P value
Age (mean)	38.0	38.9	38.3 (± 13.0)	0.7
Sex (F/M)	34/68	21/30	55/98	0.3
Etiology of renal disease				
Hypertensive nephrosclerosis	9	5	14	
Diabetic kidney disease	2	2	4	
Chronic glomerulonephritis	18	15	33	
Congenital urogenital anomalies	12	6	18	
Amyloidosis	5	3	8	
Other renal diseases	17	4	21	
Unknown	39	16	55	
Donor				
Cadaveric	11 (10.8%)	3	14	0.04*
Living	91 (89.2%)	48	139	

Table 2. Post-transplant rejection and viral complications

	Original tacrolimus (n:102)	Generic tacrolimus (n:51)	Total (n:153)	P value
BCAR				1.0
T-cell mediated	14	7	7	
Antibody-mediated	1	1	1	
Mixed	4	1	1	
CMV viremia	15 (14.7%)	11(21.6%)	11(21.6%)	0.36
BK viruria	11 (10.8%)	9 (17.6%)	9 (17.6%)	0.30

*BCAR: biopsy-confirmed acute rejection, CMV: cytomegalovirus

In the first post-transplant year, the BK virus positivity in urine was observed in 11 patients (10.8%) and 9 patients (17.6%) who were using original and generic tacrolimus, respectively.

CMV viral load positivity in blood was observed in 15 patients (14.7%) of the original tacrolimus group and 11 patients (21.6%) of the generic tacrolimus group within 1 year after transplantation.

BK virus positivity in urine and CMV viremia were not significantly different between the two groups (p: 0.30, p: 0.36, respectively). BKPyVAN was not detected in any of the patients.

There was no difference between the two groups in terms of creatinine levels, tacrolimus dose and tacrolimus trough levels at discharge and at first year (Table 3).

DISCUSSION

Since tacrolimus is an immunosuppressive drug with a narrow therapeutic index, it is important that bioequivalent should be stringent similar to the original tacrolimus to provide adequate immunosuppression without developing toxicity. There are many studies from all over the world that showed the safety and effectiveness of several generic tacrolimus in both *de novo* use and also after conversion from original tacrolimus in kidney transplant patients since 2008 [9,11,12,15,16]. We believe that these studies may have different results in different races due to pharmacogenetic diversity and increasing these studies will provide useful data for clinicians dealing with patients using immunosuppressive drugs.

A prospective, multicenter, parallel-group, open-label study in *de novo* kidney transplant patients was published in 2017. The patients in this study were randomly assigned to receive generic tacrolimus (TacHexal) and the original tacrolimus (Prograf). The study was conducted with a total of 73 patients, 35 in generic and 38 in original tacrolimus groups. At the end of the 6-month follow-up, it was shown that drugs were similar in pharmacokinetic terms and there was no difference in terms of BCAR, safety, adverse reactions. However, the authors stated that it may not be valid for other generic drugs [9].

In a study by Robertson et al. in elderly patients, it was stated that the generic tacrolimus they used (Tacni; Teva Pharmaceutical Industries Ltd., Petah Tikva, Israel) was not bioequivalent to the original tacrolimus, and a higher dose should be given to obtain a similar tacrolimus trough level, which may increase the incidence of side effects in the long term [17]. As a result of these studies, it was thought that there may be differences between generic drugs and individual variability may

Table 3. Laboratory results and tacrolimus dose at discharge and at first year

	Original tacrolimus	Generic tacrolimus	P value
Cre (mg/dL) at discharge	1.17±0.39	1.03±0.27	0.09
Cre (mg/dL) at first year after transplant	1.26±0.40	1.20±0.35	0.18
Tacrolimus level at discharge	7.5±3.7	7.6±2.5	0.68
Total dose at discharge (mg)	6.9±2.1	7.5±2.1	0.09
Tacrolimus level at first year	6.7±2.4	6.3±2.2	0.52
Total dose at first year (mg)	3.6±1.6	4.2±1.9	0.07

Cre: creatinine

contribute to these differences. Therefore, studies were continued with different generic tacrolimus preparations.

To our best knowledge, the study from the South West Transplant Center is the first study to compare the clinical outcomes of patients receiving generic tacrolimus with the original tacrolimus. Conner et al. reported in this study that there was no difference in clinical outcomes between the two groups in *de novo* use during the 6-month follow-up period [14].

In a *de novo* study with the same generic tacrolimus as in our study, the 6-month results of a total of 120 kidney transplant patients were evaluated. Renal function, tacrolimus trough concentrations and tacrolimus dose, acute rejection incident, delayed graft function were similar between the two groups as in our study. Additionally, in this study, the patients were evaluated histopathologically with the protocol biopsy performed at the 6th month, and *de novo* DSA evaluation was performed with the single antigen bead assay, and no difference was found in either of them [15].

In a study from our country, evaluating the data about conversion from original tacrolimus to generic tacrolimus in 36 patients, it was stated that generic tacrolimus was safe and effective [18]. Similar to our study, in another study from our country, the data of 145 patients using *de novo* generic tacrolimus were presented, the authors stated that there was no difference in renal function, adverse reaction, BKPyV and CMV viremia, acute rejection at the end of a median of the 31-month follow-up period [19].

We have compared the clinical outcomes within 1-year after transplantation of 102 patients *de novo* receiving original tacrolimus and 51 patients *de novo* receiving generic tacrolimus at a single center. No differences were found in terms of creatinine levels, total daily dose of tacrolimus and tacrolimus trough levels at discharge and at the first year. Additionally, biopsy-confirmed acute rejection in the following year after transplantation, BKPyV positivity in urine, BKPyVAN, CMV viremia and adverse reactions related to tacrolimus were similar between the two groups.

With this study, we aimed to give our experience in the use of generic tacrolimus from our country to the literature. As a result of our study, we stated that generic tacrolimus can be safely preferred in *de novo* use with close drug level monitoring since it is an immunosuppressive agent with a narrow therapeutic index.

The requirement for a multicentric study with a randomized prospective design and large patient number continues.

Author contribution

Study conception and design: NSC, TY; data collection: NSC; analysis and interpretation of results: NSC, TY; draft manuscript preparation: NSC, TY, ŞRY, YE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee of Hacettepe University (Protocol no. GO 21/535 /15.06.2021).

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Conflict of interest

The authors declare that there is no conflict of interest.

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