10.5152/turkjnephrol.2021.20013

Original Article

Turkish Journal of Nephrology

Outcomes of De Novo Use of Generic Tacrolimus (Adoport®) in Living-Related Kidney Transplantation: A Single-Center, Real-Life Experience of 5 Years

Rezzan Eren Sadioğlu[1], Mert Karaoğlan[2], Merve Aktar[1], Şayeste Akkan Eren[1], Akın Fırat Kocaay[3], Acar Tüzüner[3], Şule Şengül[1], Kenan Keven[1]

[1]Department of Nephrology, Ankara University School of Medicine, Ankara, Turkey
[2]Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey
[3]Department of General Surgery, Ankara University School of Medicine, Ankara, Turkey

ABSTRACT

Objective: Tacrolimus (TAC), the mainstay immunosuppressive drug in kidney transplantation, is a narrow therapeutic index drug and has strict bioequivalence (BE) acceptance criteria adopted by regulatory agencies. Possible acute rejection resulting from the use of a generic drug is the main matter of concern for responsible physicians. We aimed to show the possible differences in drug dosages and serum concentrations and to share our experience on this subject.

Methods: We retrospectively screened all the patients who underwent living-related kidney transplantation between January 2016 and August 2020. There were 106 patients in the Prograf® group and 39 patients in the Adoport® group. We investigated the demographics, daily drug dosages of TAC (mg/day and mg/body weight (kg)/day), TAC trough levels (TTL), renal functions, biopsy-proven acute rejections, post-transplant complications (hypertension, diabetes, cytomegalovirus and BK replication), graft survival, and patient survival.

Results: The medical records of a total of 145 (47 females, 32%) patients whose mean age was 42.9 ± 12 were retrieved with a follow-up time of 31 (IQR, 19-44) months. Comparisons showed that there was no difference in drug dosages, TTLs, acute rejection, graft loss, and mortality, between the patients who received the generic TAC or the original one, at the end of the follow-up time. In total, 20 biopsy-proven acute rejections were seen (17, 16% in the Prograf® group and 3, 7% in the Adoport® group; $P = .213$). We found that although the drug levels and dosages were the same, creatinine and proteinuria were slightly higher in the Prograf® group in the first and second months. This difference was lost at subsequent time periods.

Conclusion: We concluded that the use of generic TAC in living-related kidney transplantation is a safe move, with efficacy and acceptable outcomes similar to the use of the original brand.

Keywords: Kidney transplantation, tacrolimus, generic drug, treatment costs

Corresponding author: Rezzan Eren Sadioğlu ✉ rezzanerensadioglu@gmail.com **Received:** December 29, 2020 **Accepted:** April 12, 2021

Cite this article as: Sadioğlu RE, Karaoğlan M, Aktar M, et al. Outcomes of de novo use of generic tacrolimus (Adoport®) in living-related kidney transplantation: A single-center, real-life experience of 5 years. *Turk J Nephrol*. 2021; 30(4): 255-261.

INTRODUCTION

Lifelong immunosuppression is one of the fundamental steps of solid organ transplantation. Because the economic burden of this treatment is huge, the use of generic drugs has been widely preferred. After the patent for tacrolimus (TAC) expired in 2008, The Food and Drug Administration (FDA) approved the first generic Tacrolimus-Sandoz® of the original brand (Prograf®, Astellas). TAC is a narrow therapeutic index drug, whose serum drug levels must be routinely monitored. It is known that low serum drug levels are associated with acute rejection and worse graft survival.[1] Besides, high drug levels can cause both toxicities, such as hyperkalemia and acute renal failure, and long-term complications, such as post-transplant diabetes mellitus (DM) and hypertension (HT).[2]

There are strict bioequivalence (BE) acceptance criteria adopted by regulatory agencies for narrow therapeutic index drugs. The limits of the peak concentration and

the area under the concentration–time curve must be within 90% confidence intervals of 90-111.2% when compared to the original drug, in accordance with the European Medicines Agency (EMA), and 80-125%, according to the FDA.[3–5] Several studies showed the similarity of the drug dose requirements and trough levels of tacrolimus (TTLs) of the generic TAC to those of the original one.[6–8] The potential cost savings coming from the generic substitution were calculated as $45/month per patient in a study.[7] Considering that 90% of the prescriptions given in the United States contain a generic drug, the cost savings are huge.[9] In Turkey, the average market price of Prograf® for a 1 mg capsule in 2020 was 6.18 TL, while it was 3.2 TL for Adoport®.[10] Because of these benefits, clinical practice guidelines also support the use of the generic drug.[11] Despite these findings, because the drug BE studies are done in healthy volunteers[12] who have a stable drug metabolism as opposed to the transplant patients,[13] and because there is a high interpatient variability in the bioavailability of TAC,[14] it can be intimidating for the responsible physicians, fearing an acute rejection, to decide to prescribe generic drugs in a transplant setting.

In Turkey, generic TAC (Adoport®, Sandoz) was approved in 2015, and most of the transplant centers adopted its use. In this study, we aimed to show our experience with the generic form of TAC (Adoport®, Sandoz) and compare it with the original drug (Prograf®, Astellas).

METHODS

The present retrospective observational study was approved by Ankara University School of Medicine Ethics Committee for Clinical Studies (I10-620-20). Because this was a retrospective study of the data from medical records, no patient consent form was obtained specifically for the present study. Written informed consent was obtained from all the patients before transplantation.

Main Points

- Lifelong immunosuppression, a fundamental step in solid organ transplantation, has a considerable economic burden, endorsing the wide use of generic drugs.
- There are strict bioequivalence (BE) acceptance criteria for narrow therapeutic index drugs, such as tacrolimus (TAC) . Despite these criteria, there are hesitations because of the fear of acute rejection as a result of prescribing generic drugs in the transplant setting.
- We demonstrated that generic TAC usage in living-related kidney transplantation is similar to the original TAC regarding drug dosages, drug levels, and relevant clinical long-term outcomes such as acute rejection, graft loss, or mortality, at the end of follow-up.
- The use of generic TAC in living-related kidney transplantation is a safe move, with efficacy and acceptable outcomes similar to those with use of the original brand.

In our center, a generic form of TAC (Adoport®) had been in use since January 2016. There were 199 kidney transplantations performed between January 2016 and August 2020. We excluded 44 deceased-donor kidney transplantations (DDKT), and 10 patients were excluded because of incomplete follow-up data or re-transplantation. The choice of drug, between the original branded TAC (Prograf®, Astellas Pharma Inc, Tokyo, Japan) or a generic TAC (Adoport®, Sandoz, Surrey, UK) was made randomly by the nephrologist. Patients received one of the chosen TAC preparations, and no drug switch was made during the follow-up. Eventually, there were 106 patients in the Prograf® group and 39 patients in the Adoport® group.

We investigated the demographics, donor–recipient match, antibody status, daily drug dosages of TAC (mg/day and mg/body weight(kg)/day), TTL, renal functions (estimated glomerular filtration rate (eGFR) and serum creatinine), proteinuria, biopsy-proven acute rejections, post-transplant complications (HT, DM, CMV and BK replication), graft survival, and patient survival.

Immunosuppression regimens were chosen on the basis of the patients' immunological risk profile. Desensitization, with plasmapheresis combined with 100 mg/kg IVIG, was performed if it was required in highly sensitized patients. IL-2 receptor blockers or anti-thymocyte globulin (ATG) were chosen for induction therapy. Basiliximab 20 mg was administered intra-operatively, and repeated on postoperative day 4. Daclizumab was given with a dose of 2 mg/kg within 24 hours of transplantation, followed by 4 doses of 1 mg/kg every 2 weeks. ATG was administered at the dose of 1.5 mg/kg, based on actual body weight. Additionally, all patients received 500 mg of methylprednisolone on the day of the operation and for the following 2 days. For maintenance therapy, oral methylprednisolone was initiated at a dose of 1 mg/kg and it was gradually reduced to 16 mg within a month. Peroral 0.05 mg/kg/d TAC was initiated the day before transplantation. Dose adjustments were made in accordance with the TTL. The TTLs were studied with a cloned enzyme donor immunoassay method from whole blood at our center (Qms Tacrolimus Immunoassay, Thermo Scientific, Fremont, CA, United States). As an institutional practice, TTLs were routinely drawn on a daily basis early after transplantation for the first 2 weeks, every 2 weeks for 3 months, and monthly for the first 12 months. As a part of a triple-drug regimen, either 1000 mg of mycophenolate mofetil (MMF) or 720 mg of mycophenolate sodium (MPA) twice a day was chosen. If an antiproliferative drug change was required because of an adverse drug effect, azathioprine at a dose of 1.5 mg/kg/day was administered instead of MMF or MPA.

Along with TTLs, the daily TAC dosage and drug dosage/body weight, proteinuria, and creatinine were recorded during the follow-up.

Statistical Analysis

Clinical and laboratory data are expressed as percentages, means (± SD) or medians [interquartile range (IQR)], as appropriate. The continuous variables in the characteristics of the 2 groups were compared by the *t*-test or Mann–Whitney *U*-test, and categorical variables with Pearson's chi-square or Fischer's exact tests. A threshold value of $P < .05$ was considered as statistically significant. The calculations were made with Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Baseline Characteristics

A total of 145 (47 females, 32%) living-donor kidney transplant recipients whose mean age was 42.9 ± 12, were reviewed. The median follow-up time was 31 (IQR, 19-44) months. The most common underlying renal disease was chronic glomerulonephritis ($n = 43$, 29.6%). The Median HLA mismatch number was 3 (IQR, 2-4). Desensitization was required for 17 (11.7%) patients. Induction therapy was administered to 64% of the patients. The triple-drug combination mainly consisted of steroids, MMF, and TAC (either Prograf® or Adoport®) ($n = 104$, 71.7%).

Drug Levels and Efficacy

During the first 2 weeks, there was no difference in serum creatinine, proteinuria, daily TAC dosages, and TTLs between the 2 groups (Table 1). Although the drug levels and dosages were the same, creatinine and proteinuria were slightly higher in the Prograf® group in the first and second months. As it is shown in Table 2, the parameters related to drug were very similar.

Post-Transplant Follow-Up, Graft, and Patient Survival

There were 74 patients who had been diagnosed with a new-onset HT and 25 with DM after transplantation. Developments of post-transplant HT or DM were not different between the 2 groups. The viral replication rates (CMV and/or BK-JC virus) were not different between the groups.

In total, 20 biopsy-proven acute rejections were seen (17, 16% in the Prograf® group and 3, 7% in the Adoport® group; $P = .213$). There were 2 graft losses and 1 death in the Prograf® group; however, it was not statistically different when compared to the Adoport® group (Table 3).

DISCUSSION

In our study, we demonstrated that usage of the generic TAC in living-related kidney transplantation is safe, and comparisons between the patients who received a generic TAC and the ones who received the original one showed that at the end of the follow-up period, there were no differences in drug dosages, TTLs, and the relevant clinical long-term outcomes such as acute rejection, graft loss, death, BK-JC, or CMV viremia, post-transplant DM, HT, or erythrocytosis.

Differences in CYP3A4 and P-glycoprotein expressions, drug–drug, drug–disease, and drug–food interactions are important issues in terms of toxicities and treatment efficiency in a transplantation setting.[15] The transplant population has a higher rate of clearance of TAC than healthy volunteers do, possibly due to low the hematocrit and albumin, and the concomitant steroids.[16] Additionally, as shown in Robertsen et al.[17] study, Tacni® did not meet the BE criteria, despite the similar TTLs, because systemic drug exposure was higher in the generic arm in elderly transplant patients.[17] These emphasize the importance of the differences in drug metabolism between individuals. All these aspects endorse the hesitation in going for generic drugs.

The majority of the clinical data related to generic drugs comes from short-term conversion studies. The heterogeneity of the study populations and brands of the generic drugs made interpreting the results difficult. Even so, conversion studies have led us to the conclusion that the use of a generic TAC is acceptable. Alloway et al.[18] in their prospective pharmacokinetic cross-over study with kidney transplant patients, showed the similarity of the generic (Tacrolimus-Sandoz®) to the original TAC (Prograf®). Gonzales et al.[19] on the other hand, found that although TTLs and daily dosages were similar, pre-conversion serum creatinine levels were lower than the post-conversion values. They included patients who had a transplantation at least 3 months prior, and they measured TTLs after 4 weeks of a stable drug dosage. They indicated uncertainty over whether this was a random laboratory variation. Momper et al.[20] observed lower TTLs/drug dose ratio and a drop in TTLs after switching to a generic (Tacrolimus-Sandoz®) TAC, without any deterioration in kidney function or an acute rejection rate. Similar to this, Gunay[8] stated a decrease in TTLs without any increase in drug dose or acute rejection rate after conversion to Adoport®. McDevitt-Potter et al.[21] noted that a further dose adjustment was required, in spite of similar drug doses and TTLs in both liver and kidney transplant populations.

On the other hand, studies on the de novo use of TAC are fewer. Min et al.[22] showed an early and high-peak concentration with a generic form (TacroBell®), with similar clinical outcomes at the end of 9 months. In other studies investigating the use of de novo generic TAC, mortality, graft loss, and rejection rates were found to be similar between the generic and the original TAC.[23,24] Melili et al.[25] observed no difference in TTLs, acute rejection rates, renal functions, and histopathological findings obtained from protocol biopsies between the patients who received Prograf® and Adoport® for kidney transplantation. Interestingly, Kahn et al.[26] suggested, in their meta-analysis, that the pooled analysis for the risk of a biopsy-proven acute rejection showed that a generic TAC was favored in de novo use, whereas the original TAC was favored in conversion studies.

Table 1. Renal Functions and Pharmacokinetic Characteristics

	All Patients	Prograf® (*N* = 106)	Adoport® (*N* = 39)	*P*
Serum creatinine, week 1, mg/dL	1.40 ± 1.25	1.51 ± 1.44	1.12 ± 0.27	.011
Proteinuria, week 1, mg/day	513 ± 322	451 ± 329	648 ± 286	.226
Tacrolimus trough level, week 1, ng/mL	8.86 ± 3.18	8.62 ± 3	9.49 ± 3.40	.146
Tacrolimus dosage, week 1, mg/day	6.54 ± 2.28	6.46 ± 2.24	6.75 ± 2.41	.5
Tacrolimus dosage/BW, week 1, mg/kg	0.095 ± 0.036	0.092 ± 0.036	0.098 ± 0.037	.117
Serum creatinine, week 2, mg/dL	1.49 ± 1.29	1.60 ± 1.47	1.19 ± 0.28	.008
Proteinuria, week 2, mg/day	590 ± 1754	691 ± 2115	371 ± 191	.405
Tacrolimus level, week 2, ng/mL	11.8 ± 4.42	12.1 ± 4.46	11 ± 4.25	.190
Tacrolimus dosage, week 2, mg/day	6.66 ± 3.78	6.61 ± 3.75	6.82 ± 3.89	.781
Tacrolimus dosage/BW, week 2, mg/kg	0.098 ± 0.062	0.095± 0.058	0.107 ± 0.071	.323
Serum creatinine, month 1, mg/dL	1.22 ± 0.41	**1.27 ± 0.44**	1.09 ± 1.13	**.01**
Proteinuria, month 1, mg/day	421 ± 381	**455 ± 419**	311 ± 181	**.012**
Tacrolimus level, month 1, ng/mL	9 ± 3.16	9.67 ± 3.21	8.59 ± 2.9	.084
Tacrolimus dosage, month 1, mg/day	4.46 ± 2.72	4.51 ± 2.78	4.32 ± 2.59	.726
Tacrolimus dosage/BW, month 1 (mg/kg)	0.066 ± 0.043	0.067 ± 0.045	0.066 ± 0.036	.930
Serum creatinine, month 2, mg/dL	1.21 ± 1.14	**1.25 ± 0.427**	1.09 ± 0.257	**.013**
Proteinuria, month 2, mg/day	394 ± 632	**441 ± 722**	253 ± 108	**.017**
Tacrolimus level, month 2, ng/mL	9.47 ± 2.77	9.55 ± 2.87	9.21 ± 2.46	.539
Tacrolimus dosage, month 2, mg/day	3.59 ± 2.14	3.49 ± 1.9	3.89 ± 2.75	.371
Tacrolimus dosage/BW, month 2, mg/kg	0.053 ± 0.035	0.05 ± 0.031	0.061 ± 0.043	.128
Serum creatinine, month 3, mg/dL	1.26 ± 0.57	1.29 ± 1.16	1.14 ± 0,36	.199
Proteinuria, month 3, mg/day	258 ± 256	262 ± 284	247 ± 137	.777
Tacrolimus level, month 3, ng/mL	7.69 ± 2.66	7.95 ± 2.71	6.86 ± 2.31	.047
Tacrolimus dosage, month 3, mg/day	3.12 ± 2.11	3 ± 1.98	3.48 ± 2.45	.282
Tacrolimus dosage/BW, month 3, mg/kg	0.048 ± 0.035	0.046 ± 0.034	0,054 ± 0,039	.240
Serum creatinine, month 6, mg/dL	1.21 ± 1.14	1.23 ± 0.40	1.11 ± 0.34	.128
Proteinuria, month 6, mg/day	296 ± 504	311 ± 560	242 ± 203	.523
Tacrolimus level, month 6, ng/mL	6.72 ± 1.77	6.69 ± 1.72	6.86 ± 1.95	.650
Tacrolimus dosage, month 6, mg/day	3.57 ± 2	3.43 ± 1.80	4.05 ± 2.51	.225
Tacrolimus dosage/BW, month 6, mg/kg	0.053 ± 0.036	0.05 ± 0.032	0.065 ± 0.048	.122
Serum creatinine, month 12, mg/dL	1.25 ± 0.45	1.29 ± 0.47	1.14 ± 0.35	.133
Proteinuria, month 12, mg/day	324 ± 544	350 ± 613	241 ± 184	.356
Tacrolimus level, month 12, ng/mL	6.53 ± 1,63	6.5 ± 1,7	6.63 ± 1.42	.712
Tacrolimus dosage, month 12, mg/day	3.40 ± 1.93	3.34 ± 1.97	3.57 ± 1.82	.602
Tacrolimus dosage/BW, month 12, mg/kg	0.051 ± 0.036	0.050 ± 0.038	0.054 ± 0.033	.639

BW, body weight. Statistically significant data were marked in bold.

Table 2. Demographic Characteristics

	All Patients	Prograf® (*N* = 106)	Adoport® (*N* = 39)	*P*
Age (mean ± SD)	42.9 ± 12	43.5 ± 12	41 ± 11.9	.268
Gender (F/M; *n*, %)	47, 32/98, 67	26, 24.5/80, 75.5	21, 53.5/18, 46.2	**.001**
Follow-up time, months (median, IQR)	31, 19-44	31, 17.75-42.25	36, 23-45	.782
Underlying renal disease (*n*, %)				-
Chronic GN	43, 29.6	34	9	
AA amyloidosis	4, 2.75	3	1	
AL amyloidosis	1, 0.68	1	-	
VUR/TIN/pyelonephritis	13, 8.96	8	5	
HT	19, 13.1	18	1	
DM	20, 13.7	14	6	
Congenital malformations	7, 4.8	3	4	
Other IC-related renal disease	7, 4.8	6	1	
Unknown	31, 21.3	19	12	
Mismatch (median, IQR)	3, 2-4	3, 2-4	3, 2-4	.299
PRA (*n*, %)				.971
Negative	93, 64	68, 64.2	25, 64.1	
Class 1	11, 7.6	8, 7.5	3, 7.7	
Class 2	17, 11.7	13, 12.3	4, 10.3	
Class 1 + 2	23, 16	16, 15.1	7, 18	
DSA (*n*, %)	18, 12.4	14, 13.2	4, 10.3	.880
Desensitization (*n*, %)	17, 11.7	14, 13.5	3, 7.7	.351
Induction therapy				
ATG induction (*n*, %)	45, 31	34, 32.1	11, 28.2	.655
IL-2 receptor blocker (*n*, %)	48, 33	35, 33	13, 33.3	.972
Immunosuppressive treatment (*n*, %)				.402
CS+MMF+TAC	104, 71.7	78, 73.6	25, 64.1	
CS+MPA+TAC	41, 28.2	27, 25.5	14, 35.9	

SD, standard deviation; F, female; M, male; GN, glomerulonephritis; VUR, vesicoureteral reflux; TIN, tubulointerstitial nephritis; HT, hypertension; DM, diabetes mellitus; IC, immunocomplex; IQR, interquartile range; PRA, panel-reactive antibody; DSA, donor-specific antibody; ATG, anti-thymocyte globulin; IL, interleukin; CS, corticosteroid; MMF, mycophenolate mofetil; MPA, mycophenolic acid; TAC, tacrolimus. Statistically significant data were marked in bold.

Table 3. Post-transplant Complications

	All Patients	Prograf® (*N* = 106)	Adoport® (*N* = 39)	*P*
Post-transplant HT (*n*, %)	74, 51	55, 52	19, 48.7	.735
Post-transplant DM (*n*, %)	25, 17.2	17, 16	8, 10.5	.484
Post-transplant erythrocytosis (*n*, %)	27, 18.6	22, 20.8	5, 12.8	.303
CMV replication (*n*, %)	7, 4.8	7, 6.6	-	.104
BK-JC replication (*n*, %)	13, 9	11, 10.4	2, 5.1	.345
Acute rejection (*n*, %)	20, 14	17, 16	3, 7	.213
Graft loss (*n*, %)	2, 1.4	2, 1.9	-	.388
Mortality (*n*, %)	1, 0.7	1, 0.9	-	.541

HT, hypertension; DM, diabetes mellitus; CMV, cytomegalovirus.

In our study, we analyzed the de novo use of the generic form. Due to its retrospective design, we could not match the patients; therefore, we did not include DDKT, in order to prevent any further statistical errors caused by the differences in drug dosage and TTLs between living and deceased donors. We recognized that although TTLs and dosages were the same, serum creatinine and proteinuria were higher in the Prograf® group than in the Adoport® group at months 1 and 2. This difference was lost at the late period of the transplantation. Although it is hard to compare the data, this finding probably represents the usual fluctuations of TTLs and renal functions in the early period of kidney transplantation, or at least, it was found to be relevant within the extent of our study.

There were several limitations to our study. First, this was a single-center, retrospective study with a relatively small number of patients. Second, pharmacokinetic measurements and genetic polymorphisms of CYP3A were not assessed. Third, the cost and benefit that come with the use of generic drugs were not evaluated. Nevertheless, having a relatively long follow-up time and comparisons of the major late-onset complications of transplantation are the strengths of our study.

In conclusion, the use of generic TAC in living-related kidney transplantation is a safe move, with the efficacy and acceptability of outcomes similar to those achieved with the original.

Ethics Committee Approval: Ethics committee approval was received from the Ankara University School of Medicine Ethics Committee for Clinical Studies (I10-620-20).

Informed Consent: Because this was a retrospective study of the data from medical records, no patient consent form was obtained specifically for the present study. Written informed consent was obtained from all the patients before transplantation.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – R.E.S., K.K.; Design – R.E.S., M.K., M.A., Ş.A.E., K.K.; Supervision – A.F.K., A.T., Ş.Ş., K.K.; Resource - R.E.S., M.K., M.A., Ş.A.E.; Materials - R.E.S, M.K., M.A., Ş.A.E.; Data Collection and/or Processing - R.E.S, M.K., M.A., Ş.A.E.; Analysis and/or Interpretation - R.E.S., M.K., M.A., Ş.A.E., A.F.K., A.T., Ş.Ş., K.K.; Literature Search – R.E.S, M.K., M.A., Ş.A.E; Writing – R.E.S.; Critical Reviews - A.F.K., A.T., Ş.Ş., K.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Aktürk S, Erdoğmuş Ş, Kumru G, et al. Average tacrolimus trough level in the first month after transplantation may predict acute rejection. *Transplant Proc*. 2017;49(3):430–435. [CrossRef]
2. Jindal RM, Sidner RA, Milgrom ML. Post-transplant diabetes mellitus. The role of immunosuppression. *Drug Saf*. 1997;16(4):242–257. [CrossRef]
3. Welage LS, Kirking DM, Ascione FJ, Gaither CA. Understanding the scientific issues embedded in the generic drug approval process. *J Am Pharm Assoc (Wash)*. 2001;41(6):856–867. [CrossRef]
4. European Medicines Agency. Guideline on the investigation of bioequivalence. 2010. Available at: https://www.ema.europa.eu/en/investigation-bioequivalence. Accessed December 28, 2020.
5. The Food and Drug Administration. Bioavailability and bioequivalence studies submitted in NDAs or INDs—general considerations. 2014. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-and-bioequivalence-studies-submitted-ndas-or-inds-general-considerations. Accessed December 28, 2020.
6. Rosenborg S, Nordström A, Almquist T, Wennberg L, Bárány P. Systematic conversion to generic tacrolimus in stable kidney transplant recipients. *Clin Kidney J*. 2014;7(2):151–155. [CrossRef]
7. Spence MM, Nguyen LM, Hui RL, Chan J. Evaluation of clinical and safety outcomes associated with conversion from brand-name to generic tacrolimus in transplant recipients enrolled in an integrated health care system. *Pharmacotherapy*. 2012;32(11):981–987. [CrossRef]
8. Günay E. Clinical and safety outcomes of conversion original tacrolimus to generic tacrolimus in Turkish kidney transplant recipients. *Transplant Rep*. 2020;5(3). [CrossRef].
9. The Food and Drug Administration. Information for Consumers and Patients — Buying and Using Medicine Safely — Generic Drugs. Available at: https://www.fda.gov/drugs/buying-using-medicine-safely/generic-drugs. Accessed December 28, 2020.
10. Türk İlaç Rehberi. Sandoz İlaçları— Adoport 1 mg 50 Kapsül 2020 Fiyatları. Astellas İlaçları— Prograf 1 mg 50 Kapsül 2020 Fiyatları. Available at: https://www.ilacrehberi.com/v/adoport-1-mg-50-kapsul-cf 0b/ilac-fiyati-2020/ and https://www.ilacrehberi.com/v/prograf-1-mg-kapsul-c68f/ilacfiyati-2020/. Accessed December 28, 2020.
11. van Gelder T, ESOT Advisory Committee on Generic Substitution. European society for organ transplantation advisory committee recommendations on generic substitution of immunosuppressive drugs. *Transpl Int Off J Eur Soc Organ Transplant*. 2011;24(12):1135–1141. [CrossRef]
12. Davit BM, Nwakama PE, Buehler GJ, et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States food and drug administration. *Ann Pharmacother*. 2009;43(10):1583–1597. [CrossRef]
13. Dreisbach AW. The influence of chronic renal failure on drug metabolism and transport. *Clin Pharmacol Ther*. 2009;86(5):553–556. [CrossRef]
14. Lemahieu WP, Maes BD, Verbeke K, Vanrenterghem YF. Alterations of CYP3A4 and P-glycoprotein activity in vivo with time in renal graft recipients. *Kidney Int*. 2004;66(1):433–440. [CrossRef]
15. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet*. 2004;43(10):623–653. [CrossRef]
16. Anglicheau D, Flamant M, Schlageter MH, et al. Pharmacokinetic interaction between corticosteroids and tacrolimus after renal transplantation. *Nephrol Dial Transplant*. 2003;18(11):2409–2414. [CrossRef]

17. Robertsen I, Åsberg A, Ingerø AO, et al. Use of generic tacrolimus in elderly renal transplant recipients: precaution is needed. *Transplantation*. 2015;99(3):528–532. [CrossRef]
18. Alloway RR, Sadaka B, Trofe-Clark J, Wiland A, Bloom RD. A randomized pharmacokinetic study of generic tacrolimus versus reference tacrolimus in kidney transplant recipients. *Am J Transplant*. 2012;12(10):2825–2831. [CrossRef]
19. González F, López R, Arriagada E, et al. Switching stable kidney transplant recipients to a generic tacrolimus is feasible and safe, but it must be monitored. *J Transplant*. 2017;2017:5646858. [CrossRef]
20. Momper JD, Ridenour TA, Schonder KS, et al. The impact of conversion from Prograf to generic tacrolimus in liver and kidney transplant recipients with stable graft function. *Am J Transplant*. 2011;11(9):1861–1867. [CrossRef]
21. McDevitt-Potter LM, Sadaka B, Tichy EM, Rogers CC, Gabardi S. A multicenter experience with generic tacrolimus conversion. *Transplantation*. 2011;92(6):653–657. [CrossRef]
22. Min SI, Ha J, Kim YS, et al. Therapeutic equivalence and pharmacokinetics of generic tacrolimus formulation in de novo kidney transplant patients. *Nephrol Dial Transplant*. 2013;28(12):3110–3119. [CrossRef]
23. Lindner C, Lindnér P. A 1-year Comparison of Generic Tacrolimus (Tacni®) and Prograf® in Renal Transplant Patients: A Retrospective Matched Group Analysis. *J Clin Exp Transplant.* 2017;2(1):113.
24. Arns W, Huppertz A, Rath T, et al. Pharmacokinetics and clinical outcomes of generic tacrolimus (Hexal) versus branded tacrolimus in de novo kidney transplant patients: a multicenter, randomized trial. *Transplantation*. 2017;101(11):2780–2788. [CrossRef]
25. Melilli E, Crespo E, Sandoval D, et al. De novo use of a generic formulation of tacrolimus versus reference tacrolimus in kidney transplantation: evaluation of the clinical results, histology in protocol biopsies, and immunological monitoring. *Transpl Int*. 2015;28(11):1283–1290. [CrossRef]
26. Kahn J, Pregartner G, Schemmer P. Immunosuppression with generic tacrolimus in liver and kidney transplantation-systematic review and meta-analysis on biopsy-proven acute rejection and bioequivalence. *Transpl Int*. 2020;33(4):356–372. [CrossRef]