Clinical and Safety Outcomes of Conversion Original Tacrolimus to Generic Tacrolimus in Turkish Kidney Transplant Recipients

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Research article

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Abstract

Background After the United States, The Food and Drug Administration approved the use of the first generic of the original tacrolimus in 2009, generic tacrolimus was preferred in many countries for cost-reducing reasons. This is the first study on the conversion of original tacrolimus to the generic tacrolimus, reported from Turkey. Methods The inclusion criteria of this single-center, retrospective study were 1) being ≥18 years old, 2) passing at least three months after kidney transplantation, 3) conversion from reference tacrolimus (Prograf®) to generic tacrolimus (Adoport®). The primary endpoints were acute rejection, an increase in serum creatinine, decreases in e-GFR, tacrolimus level, tacrolimus concentration/dose ratio. We applied the paired T-test to analyze the pre-conversion and final visit laboratory values. Results Thirty-six patients who agreed to use generic tacrolimus evaluated. The mean age was 39.8 years (± 11.6), % 52,7 were female, % 86,1 were living donor transplants. The patients followed up for 12 months (3-41). There was no increase in serum creatinine value, no decreases in e-GFR and tacrolimus concentration/dose ratio. We observed a decrease in tacrolimus level (p=0,037). Decreasing the target value may have caused this result, as there are 9 patients with positive BK-DNA. None of the patients needed a biopsy. Conclusion Based on the results of our study, renal outcomes are safe and the drugs could be changed safely. Whether Prograf® or Adoport®, whichever is used, it is important to continue taking the drug at the recommended dose and time. The physician should be careful in dose adjustment after conversion, especially for those who are in the first year of transplantation.

Background

Tacrolimus is one of the most important components of immunosuppressive therapy used after solid organ transplantation. In the follow-up period of organ transplant patients, it is correct not to change the immunosuppressive drugs if there is no reason for drug conversion. However, after the United States Food and Drug Administration (FDA) approved the use of the first generic (Tacrolimus-Sandoz®) of the original tacrolimus (Prograf®) in 2009, it has been preferred in many countries for cost-reducing reasons. In order to reduce the cost, New Zealand has made a mandatory conversion to generic tacrolimus (Tacrolimus-Sandoz®) in nationwide. From 1 May 2014, in New Zealand, the funded brand of tacrolimus has been changed from Prograf® to Tacrolimus-Sandoz®. Although generic preparations of the original tacrolimus have been on the market for over a decade (1,2), some of transplant physicians have hesitations about using them. One of the reasons for these hesitations was that generic products were tried in healthy volunteers rather than the actual patient population. However, a lot of studies have been published in recent years about the successful use of generic tacrolimus by switching from the original product or de novo use after transplantation (3-5). It has also been reported that conversion to generic tacrolimus is safe in the pediatric kidney transplant patients (6).

It has been shown in many studies that keeping tacrolimus at appropriate drug levels is crucial for reducing concentration-related rejection and toxicity risks (7-10). For a drug to be considered bioequivalent, the peak concentration (Cmax) and the area under the concentration-time curve (AUC0-t and AUC0-72h) must be within the % 80-125 limits and % 90 confidence interval (CI % 90). Tacrolimus drug concentrations, such as happens with other critical drugs, should be in a narrow therapeutic range. The European Medicines Agency (EMA) states that tacrolimus confidence interval and AUC values should be within % 90 and % 90-111, respectively (11,12).

In Turkey, patients have to pay an additional fee for all original drugs if they are expensive than a generic. This rule was not applied to the original tacrolimus®. In 2018, the national insurance institution removed this privilege

for Prograf®. Patients who preferred to use Prograf® had to pay an extra fee. This situation was corrected a few months later, but transplant physicians were hesitant about prescribing which generic tacrolimus to patients who stated they could not use Prograf® for economic reasons. There is no study about conversion original tacrolimus to generic tacrolimus in Turkey; this is the first study on this issue reported from Turkey. Generic tacrolimus (Adoport®, Sandoz, the arm of Novartis) was initiated in patients using the original tacrolimus (Prograf®, Astellas Pharma) to reduce drug costs. The effects of generic tacrolimus on drug level, serum creatinine value, and acute rejection were investigated.

Methods

Study design: This single-center, retrospective, non-randomized study was conducted in a tertiary training hospital after the approval of the hospital Ethics Committee. All the patients in our kidney transplant outpatient clinic were monitored by the same nephrologist. Study data were obtained from patient files.

Inclusion criteria: 1) being ≥18 years old, 2) passing at least three months after transplantation, 3) conversion from reference tacrolimus (Prograf®) to generic tacrolimus (Adoport®). All patients who met the inclusion criteria were included in the study. None of them were excluded. There was no limit for serum creatinine value. Patients in all serum creatinine were included in the study.

Monitoring: All patients monitored by the same physician. Patients informed in detail. It stated that the time of taking the new drug should be the same as the old one. The changes made in a 1:1 ratio. At subsequent controls, the dose of the generic tacrolimus adjusted according to the therapeutic dose targets. No changes made on the other immunosuppressive treatments. In only one patient, mycophenolate was replaced by azathioprine (AZA), as she wanted to conceive, 7 months after drug change. There was no selection criterion based on primary renal disease, number of mismatches, panel reactive antibody (PRA) positivity. In the outpatient follow-up, tacrolimus targets were 7-9 ng/ml between 4-5 months, 5-8 ng/ml between 6-12 months, and 3-7 ng/ml after the first year. Tacrolimus targets were reduced in patients with positive plasma BK-DNA or history of BK-DNA positivity. PRA follow-up was performed in every six months. If PRA is positive, donor-specific antibody (DSA) was examined. Surveillance biopsies were not performed, because it is not routinely performed in our transplantation unit.

The primary endpoints of the study were the presence of acute rejection, an increase in serum creatinine, decreases in estimated glomerular filtration rate (e-GFR), tacrolimus level and tacrolimus concentration/dose ratio. The secondary endpoints were increases in tacrolimus level and tacrolimus concentration/dose ratio to asses the risk of calcineurin toxicity.

Statistics: SPSS 16.0 version (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were used to identify demographic data. Qualitative variables were expressed as frequencies and percentages; quantitative variables were expressed as median (minimum-maximum) and mean (± standard deviation). As variables were normally distributed, we applied the paired T-test to analyze the pre-conversion and final visit laboratory values, such as serum creatinine, e-GFR, tacrolimus level, tacrolimus concentration/dose ratio. P values were two-sided, and P values of less than 0.05 were considered statistical significance.

Results

Forty-eight patients who were prescribed generic tacrolimus (Adoport®) while using original tacrolimus (Prograf®) between July 2016 and September 2019 were examined. Twelve patients refused to use the generic product. Thirty-six patients who agreed to use Adoport® were evaluated. Two of the 36 patients had drug conversion between July 2016 and October 2016, and the remaining 34 patients had after October 2018. Demographic data were summarized in table 1. The mean age was 39.8 years (± 11.6; 18-63), % 52,7 were female, % 86,1 were living donor transplants. There were no combine transplanted patients. There were 7 patients (% 19,4) with positive PRA, before conversion. The ratio of mismatches was 2,67(±SD 1,7). Immunosuppressive regimens were prednisolone, mycophenolate mofetil, tacrolimus in % 63,8, and prednisolone, mycophenolate sodium, tacrolimus in % 30,5 of the patients. The median time between transplantation and conversion was 27 months (3-76 months). The patients followed up for a median of 12 months (3-41). The first control time after conversion was 32 days (2-90 days).

The number of patients whose drug dose was changed at the first control was 10 (% 27,7). In 5 of them (% 13,8) the dose was increased, in 5 (% 13,8) the dose was reduced. In % 72,2 of patients, the dose was not changed at the first control. In 19 of the 24 patients (% 79,1) who completed the first year follow up after the transplantation, the dose was not changed at the first control; the dose was increased in 1 (% 4,1), and the dose was decreased in 4 (% 16,6). In 7 of 12 (% 58,3) patients who did not complete the first year follow up after the transplantation, the dose was not changed at the first control; the dose was decreased in 1 (% 8,3), and the dose was increased in 4 (% 33,3). In 7 patients, plasma BK-DNA positivity observed pre-conversion; BK-DNA became positive in two patients whose were negative before conversion. With appropriate decreases in immunosuppressive treatments, none of the patients with positive BK-DNA had graft dysfunction, and no biopsy was required.

Patient compliance throughout the follow-up period was excellent. Two patients had temporary tremors on their hands. One patient complained of increased hair growth in his arms and legs at the visit two weeks after the drug change. There was no increase in drug level. In the following months, the complaint improved spontaneously in that patient. One patient got pregnant two months after conversion. In one patient, mycophenolate was replaced by AZA due to a desire for pregnancy, 7 months after the drug change. Before the switch, BK-DNA was positive in 7 patients. It became negative in four patients, it decreased to < 1000 cp/ml in two patients and continued as > 10,000 cp/ml in one patient. In 2 patients, < 1000 cp/ml positivity was detected after the switch. Both were negative at follow-up (Table 1).

When the study completed, there was no increase in mean serum creatinine value, no decreases in mean e-GFR and mean tacrolimus level/dose ratio (Figure 1,2). But we observed a decrease in mean tacrolimus level. None of the patients needed a biopsy. Renal outcomes are summarized in table 2. At the end of the study, the number of patients with an increase in serum creatinine was 14, with a decrease was 22. However, since it is not correct to evaluate and interpret minimal serum creatinine changes such as 0.1-0,2 mg/dl, changes in the range of ± 0.2 mg/dl did not interpret as significant. The number of patients with serum creatinine value within the range of ± 0.2 mg/dl, with a greater decrease, with a greater increase in serum creatinine at the first visit compared to the switch time, were 32, 1 and 3, respectively. At the end of the study, these numbers were 30, 4 and 2, respectively (Table 2). At the final visit, there were two patients with an increase in serum creatinine value more than 0.2 mg/dl. The serum creatinine values of these patients were 0.7 mg/dl (0,47 mg/dl to 0,7 mg/dl) and 1,05 mg/dl (0,84 mg/dl to 1,05 mg/dl) at the last visit. These patients continued to be followed. No biopsy has been planned yet.

Discussion

Generic tacrolimus has been used in organ transplant practice all over the world for more than ten years. In the prospective study of Guleria (13), generic tacrolimus (PanGraf®) used successfully in 155 de novo kidney transplant recipients. In Kim's multicenter study (14), generic tacrolimus (TacroBell®) found to be effective and safe in de novo kidney transplant recipients. The first study reported on the conversion from the original tacrolimus to the generic one was Momper's single-center, retrospective study (10). In this study, concentration/dose ratio of tacrolimus decreased % 15,9 and % 11,9 in liver (n=48) and kidney (n=55) transplant patients, respectively. So it was reported that close follow-up required, but renal outcomes were safe and the drugs could be changed safely. In another multicenter study (15) in which Prograf® changed to Tacrolimus-Sandoz®, no difference observed in drug levels. But dose titration was required in 15/70 patients (increase in 7 and decrease in 8). In a randomized, prospective, multicenter study (16), the pharmacokinetic effects of generic and reference tacrolimus examined. Seventy-one kidney transplant patients using Prograf® or Tacrolimus-Sandoz® divided into two groups (Group 1: reference to generic, group 2: generic to reference) and evaluated for $AUC_{0-12\ hours}$ and C_{max}. It stated that Tacrolimus-Sandoz® is bioequivalent to Prograf® according to FDA and EMA criteria. In Spence's study (17), none of 234 patients using reference tacrolimus showed acute rejection after conversion to the generic product. In a study of 28 patients in the geriatric age group (18), generic tacrolimus (Tacni®) was not found to be bioequivalent with the reference product (Prograf®). In the study of Melilli (19), 60 patients using reference tacrolimus (Prograf®; Astellas) and 60 patients using the generic product (Adoport®; Sandoz) compared. At the six-month follow-up, there was no difference between the groups in drug concentration (post-transplant on the 7th day, 1st, 3rd and 6th months), concentration/dose ratio (6th month), e-GFR (6th month), proteinuria (6th month), de novo donor-specific antibody development (6th month) and protocol biopsy results (6th month).

There is one study reporting the generic tacrolimus (Sandoz) has higher acute rejection rates in de novo transplant recipients compared to the reference tacrolimus (20). In this single-center, retrospective study, there were 39 patients in the generic group. Average tacrolimus levels in the first week, third and sixth months after transplantation and rejection rates in the sixth month were similar. In the first year, the rejection rate was higher in the generic group. The authors of this article were the members of the speaker bureau of Astellas, Novartis, and Genzyme. They pointed out that there are 8 generic tacrolimus in the USA and local pharmacies make changes from generic to generic. Therefore, drug homogeneity in the generic group may be suspicious. In Lichvar's study (21), there were no differences in renal functions, acute rejection and hospitalization episodes between the groups of original tacrolimus (Prograf®, group 1), generic tacrolimus (Tacrolimus-Sandoz®, group 2), change from original to generic (group 3), change from generic to generic (group 4). In Liu's study (22), it was reported that generic tacrolimus was widely accepted in the USA, with a % 90 market share in some states. The most impressive example of using generic tacrolimus has been in New Zealand. In order to reduce the cost Tacrolimus-Sandoz® has been funded instead of Prograf® in nationwide, since 2014.

Kidney transplantation units are usually very dedicated work units. Hundreds of patients can contact their physicians day and night in many problems. Patients generally do not use drugs such as antibiotics and analgesics prescribed by other physicians without consulting their transplant physician. In Turkey, a significant number of transplant physicians do not prefer generic tacrolimus even if the patient is unable to take the original product for cost-related reasons. When generic tacrolimus is preferred, a broad spectrum population such as the patient, patient relatives, other physicians, pharmacy employees gives the opposite idea and makes the

conversion hard. When the generic tacrolimus is prescribed, generally stress occurs in both patient and the physician, the first control time is considered to be as early as possible. The main fears after conversion are the possibilities of a decrease in drug level and the occurrence of acute rejection. In our study, the first control dates were taken earlier in the first 8 patients. It was observed that there were no decreases in drug levels in these patients, the first control times of the other 28 patients determined according to their routine schedules. There was no indication for a biopsy during the study. Although it is difficult to comment on subclinical rejections without biopsy, no laboratory findings were suggesting acute rejection. The endpoints, as an increase in serum creatinine, decreases in e-GFR and tacrolimus concentration/dose rate were not observed. We observed a significant decrease in the mean value of tacrolimus from 6.7 ng/ml to 5.7 ng/ml (p=0,037). Decreasing the target value may have caused this result, as there were 9 patients with BK-DNA positivity, and 12 patients (%33,3) were in the first year after transplantation. It should also be noted that the target value decreases over time in patients who are in the first year of transplantation even if BK-DNA is negative.

We should emphasize that 10/36 patients (%27,7) needed dose titration at the first control (increase in 5, decrease in 5). The physician should be careful in dose adjustment after conversion, especially for those who are in the first year of transplantation. Nonetheless, we observed that conversion to Adoport® can be made safely in the early period with a careful follow-up. An increase in the tacrolimus concentration/dose ratio from 2.27 to 2.37 suggested that the tacrolimus content of the Adoport® may be slightly higher than the same dose of the Prograf®. However, it should not be forgotten that this increase is not statistically significant (p=0,45) and our study population is small to insist on this claim.

Our study has many limitations. Retrospective design, single centered and limited number of patients are some of them.

Conclusions

Based on the results of our study, renal outcomes are safe and the drugs could be changed safely. Whether Adoport® or Prograf®, whichever is used, it is important to continue taking the drug at the recommended dose and time.

Declarations

Ethics approval and consent to participate: Prior to the beginning of the study, approval was obtained from the Ethics Committee of Gazi Yasargil Training and Research Hospital. If requested, a confirmation document will be sent. Our study was designed retrospectively. It did not contain personal information. For these reasons, individual consent was not obtained from the patients.

Consent for publication: Our study contained no personal information. There was no specific information, photographs or any other personal material. Individual consent was not obtained from patients for these reasons.

Availability of data and materials: Whole information is in excel file. This file is available to share.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: This manuscript is one-authored work. The idea of the study, the collection, evaluation, and writing of the data were all done by the corresponding author.

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Authors' information (optional)

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Tables

Table 1. Patient demographics

	Mean (±SD)	Range	%
Age (year)	39,8 (±11,6)	18-63	
Allograft age, at the conversion time (year)	46,7 (±14,1)	25-84	
Female (n=19)			52,7
Living donor (n=31)			86,1
Missmatch number	2,67 (±1,7)	0-6	
Number of PRA positive patient (n=7)			19,4
Transplantation to conversion time (month)	Median: 27 months	3-76	
First control time (day)	Median: 32 days	2-90	
Follow-up period (month)	Median: 12 months	4-43	
Number of patients whose drug dose İncreased[1] at the first control (n=5)			13,8
Number of patients whose drug dose Decreased[1] at the first control (n=5)			13,8
The number of patients whose drug dose did not change[1] at the first control (n=26)			72,2
BK-DNA			
Negative during follow-up (n=26)			72,2
< 1000 cp/ml positive (n=5)			13,8
1000-10000 cp/ml positive (n=1)			2,7
>10000 cp/ml positive (n=3)			8,3
Not measured (n=1)			2,7

Table legend: Patient demographics. [1]Tacrolimus dose targets were 7-9 ng/ml between 4-5 months, 5-8 ng/ml between 6-12 months, and 3-7 ng/ml after first year.

Table 2. Renal outcomes after conversion

	Switch day (n=36)	First control (n=36)	1. mo[1] (n=25)	3. mo (n=36)	6. mo (n=32)	12. mo (n=21)	Last (n=36)	ue
. (ng/ml, n=36)	6,7(±2,4)	6,7(±2,7)	7,0(±3,1)	6,3(±1,8)	5,8(±1,9)	5,9(±1,4)		
) 0,037*								
ıp A (n=12)	8,0(±3,6)							
0,1*								
ıp B (n=24)	6,1(±2,2)							
) 0,21*								
	2,2(±1,2)	2,3(±1,2)	2,4(±1,3)	2,2(±1,0)	2,3(±1,0)	2,5(±1,0)		
) 0,45*								
e (mg/dl)	1,08(±0,35)	1,1(±0,35)	1,11(±0,32)	1,1(±0,31)	1,04(±0,29)	1,04(±0,27)		
9) 0,24*								
l/mn)	74(±16,7)	74,2(±16,2)	73,1(±17,2)	73,9(±15,9)	75,8(±15,9)	77(±16,4)		
.7) 0,18*								
biopsy (n)		0	0	0	0	0	0	
of patients with atinine change 0.2 mg/dl		32 (%88,9)	23 (%92)	29 (%80,6)	25 (%78,1)	16 (%76,2)	30 (%83,3)	
of patients with l[4] serum creatinine .2 mg/dl		1 (%2,8)	2 (%8)	3 (%8,3)	3 (%9,4)	3 (%14,3)	4 (%11,1)	
of patients with [4] serum creatinine .2 mg/dl		3 (%8,3)	0	4 (%11,1)	4 (%12,5)	2 (%9,5)	2 (%5,6)	

Table legend: Renal outcomes after conversion. [1]mo: month, [2] Tac: Tacrolimus, [3]C/D: concentration/dose, [4]compared to switch day * paired t-tests were used to analyze the values of switch day and last visit. Group A: Transplantation to switch time is less than 12 months. Group B: Transplantation to switch time is more than 12 months.

Figures

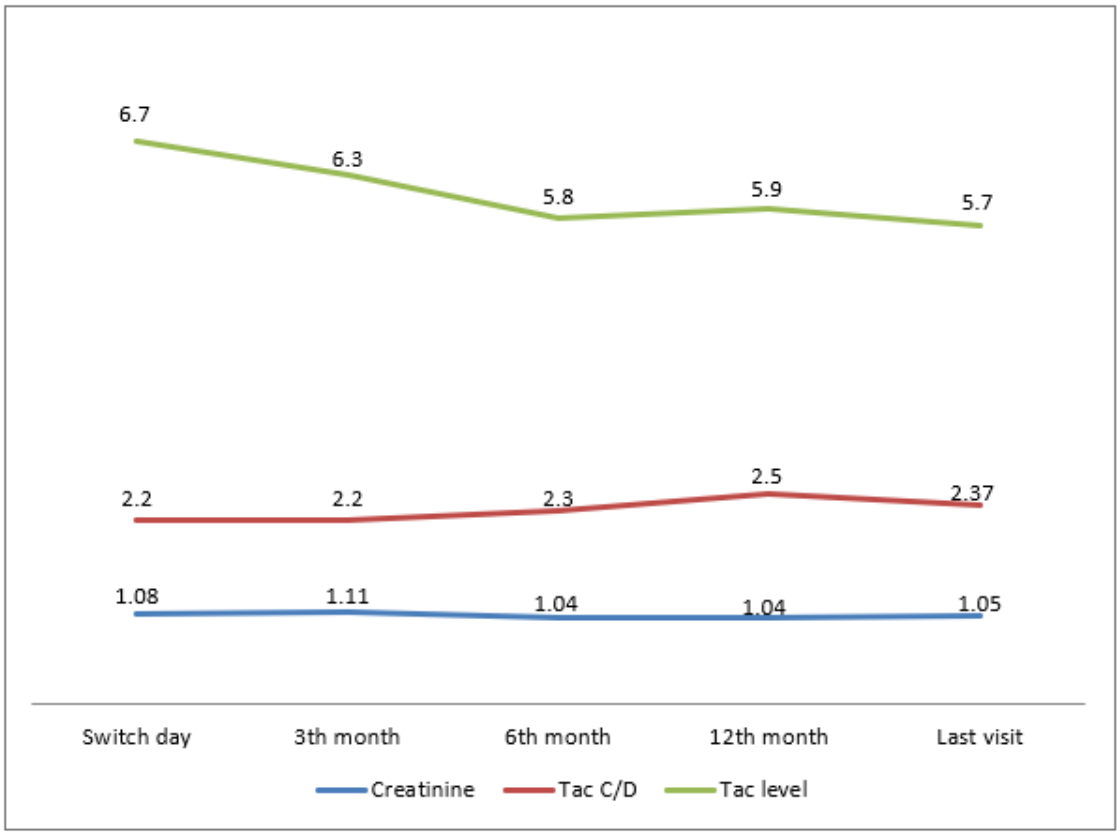

Figure 1

Serum creatinine, tacrolimus level, tacrolimus concentration/dose ratio of the patients.legend: Creatinine: Serum creatinine, mg/dl. Tac C/D: Tacrolimus concentration/dose. Tac level: Tacrolimus level, ng/ml.

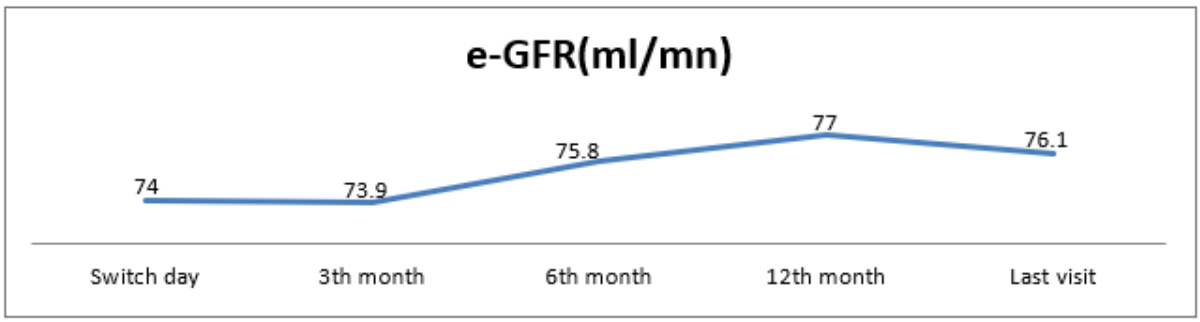

Figure 2

e-GFR values of the patients

Supplementary Files

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