Original Research Article

A Study on the Pharmacokinetic Profile and Clinical Outcome of Generic Tacrolimus (Cidimus®) versus Reference Tacrolimus (Prograf®) in De Novo Kidney Transplant Recipients

ABSTRACT

OBJECTIVES: Tacrolimus is the cornerstone immunosuppressive medication of kidney transplantation. This study sought to demonstrate bioequivalence and non-inferiority in the clinical outcomes of renal transplant recipients administered either reference tacrolimus (Prograf®) or generic tacrolimus (Cidimus®).

METHODOLOGY: A randomized controlled study on standard immunologic risk primary kidney transplant patients were given either reference or generic Tacrolimus and standard doses of mycophenolate mofetil and prednisone and followed up to 6 months post-transplant. An abbreviated area under the curve (AUC) profile on Day 3 post-transplant using C0, C2 and C4 and Cmax and Tmax were determined. Adverse events including new onset diabetes after transplant (NODAT) were noted. Graft biopsy was performed for suspected acute rejection (BPAR). Graft and patient survival were reported.

RESULTS: There were 44 patients randomized and 22 were assigned to each arm. Baseline characteristics were similar in both groups. There was 100% patient and graft survival between the two groups after 6 months ($p<0.05$). The most common adverse event was urinary tract infection (UTI) in 6.82% of the study population. Incidences of biopsy proven acute rejection (BPAR) (p 0.55) and new onset diabetes after transplant (NODAT) (p 0.32) were not statistically significant between the two groups. There were 1 (4.55%) and 2 (9.09%) patients who developed BPAR in the Prograf and Cidimus group respectively. One patient (4.55%) in the Cidimus group developed NODAT. Both CMAX and AUC of

Cidimus® and Prograf® had a 90% CI of differences of -0.1662 to 0.0695 and -0.1594 to 0.0356 respectively, which is within the bioequivalence confidence interval of -0.2231 to 0.223.

CONCLUSION: Generic Tacrolimus Cidimus® was bioequivalent to reference Tacrolimus (Prograf®) and was non- inferior based on pharmacokinetic parameters and clinical outcomes up to 6 months post-transplant.

Keywords: Tacrolimus, Pharmacokinetics, Kidney Transplant, Bioequivalence

1. INTRODUCTION

Kidney transplantation provides the best treatment for patients with end stage kidney disease. One of the cornerstone immunosuppressive medications of kidney transplantation is Tacrolimus (Prograf®, Astellas Pharma, USA) which came off patent in April 2008. Since the expiration of its market exclusivity, there were numerous generic formulations of tacrolimus which offered considerable cost savings. The use of generic drugs means important economic savings as the price of generic drugs on the market is around 40–60% less than the reference product (1).

There were bioequivalence studies on generic tacrolimus done abroad but none on generic tacrolimus among Filipino kidney transplant recipients. Tacrolimus has quite different pharmacokinetic properties in organ transplanted patients. (2) There are few studies published regarding the use of generic tacrolimus in clinical practice. Using a bioequivalent generic formulation of tacrolimus was shown to be important by Noceti et al. due to its narrow therapeutic drug index, huge intra and interindividual variability, and is most frequently prescribed. (3) A published retrospective study done by Momper et al in 2011, showed the pharmacokinetic and clinical impact on switching from Prograf® to Tacrolimus®. 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 (4). Perhaps, the

shortage of data is one of the reasons why the transplant medical community in the Philippines has been reluctant to use generic tacrolimus, despite considerable potential cost savings. Since 2015, a new formulation of generic tacrolimus, called Cidimus® has been available in the Philippines. This is an immediate-release, twice-daily, oral tacrolimus preparation licensed for the prevention and treatment of transplant rejection resistant to other immunosuppressants.

The tacrolimus pharmacokinetics are relatively complex with a high degree of inter- and intrapatient variability. The blood levels of tacrolimus can be affected by different factors, including patient demographics, liver function, diurnal variation, concomitant immunosuppressants, gastrointestinal disturbances, coexisting diabetes mellitus and genetic differences in CYP3A4 and P-glycoprotein expression (5). Among kidney transplant patients, the key contributors to intrapatient variability in immunosuppressant dosing are usually drug–drug, drug–disease and food–drug interactions.

Regulatory approval of generic products requires only evidence of equivalent relative oral bioavailability versus the originator drug in healthy volunteers. But kidney transplant patients exhibit a higher rate of tacrolimus clearance than healthy volunteers (6), possibly due to low hematocrit and albumin levels, concomitant administration of corticosteroids (7) and high rates of disturbed gastrointestinal motility and diabetes.

With these known facts, a careful examination of generic tacrolimus preparations compared to the reference preparation (Prograf®) is essential to ensure that exposure is similar upon substitution in de novo kidney transplant patients. Hence, robust data in the kidney transplant population would be highly relevant to transplant physicians considering adoption of a generic formulation.

OBJECTIVES OF THE STUDY

Primary Objective

1. To demonstrate bioequivalence and non-inferiority in the clinical outcomes of renal transplant recipients administered either reference tacrolimus or generic tacrolimus (Cidimus®).

Secondary Objectives

1. To determine the efficacy of the generic tacrolimus (Cidimus®) at the end of the study by measuring patient and graft survival
2. To determine the safety profile of generic tacrolimus (Cidimus®) by measuring adverse events of the drug, incidence of BPAR and incidence of NODAT
3. To compare the pharmacokinetic profile of reference tacrolimus with the generic tacrolimus (Cidimus®) by measuring AUC, Tmax and Cmax.

2. MATERIAL AND METHODS

This is a prospective, randomized comparative study of standard low immunologic risk primary kidney transplant patients performed in the National Kidney and Transplant Institute (NKTI) with the following criteria:

Inclusion Criteria:

1. Patients must be 18 – 65 years old
2. Patients must be for primary kidney transplant with a living donor
3. Patients must be standard risk (negative PRA screen, or PRA specific <20%, at least 1 DR match)
4. Female patients with child bearing potential must have a negative pregnancy test
5. Female patients with male sexual partners and with child bearing potential must agree to use a medically acceptable method of contraception throughout the treatment period and for 12 weeks after discontinuation of study medication
6. Patients will be placed on a protocol composed of tacrolimus, mycophenolate mofetil and prednisone with induction.
7. Patients must provide written informed consent.

Exclusion Criteria:

1. Patients with known hypersensitivity or medical contraindications to the use of tacrolimus
2. Patients who are unable to take oral medications
3. Use of another experimental drug two months prior to inclusion into the study
4. Unable to follow-up for at least 3 months
5. Patients with known hepatitis B or hepatitis C.
6. Patients from CMV positive donors to CMV negative recipients.

Study Design

This is an open-labelled randomized control study. A total of 44 patients were randomized to Group A (Cidimus®) and Group B (Prograf®), with 22 patients in each arm, and followed up for 6 months. Simple randomization was performed and the patient could withdraw his informed consent at any time. Induction with either basiliximab or rATG was provided to all patients.

Patients were started on their assigned tacrolimus one day prior to transplantation at 0.1 mg/kg in 2 divided doses and placed on standard doses of mycophenolate mofetil and prednisone as per hospital practice. Routine prophylactic antibiotics were also given.

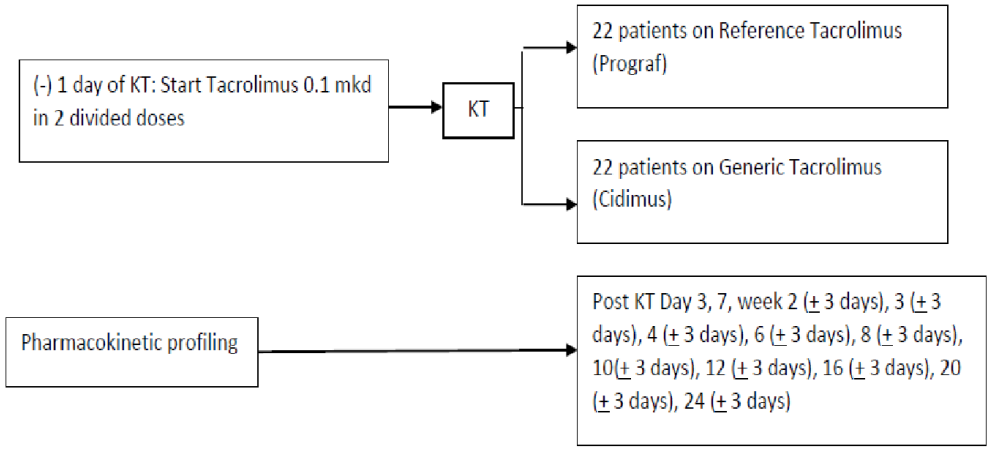
This is an investigator-initiated study which was partially sponsored by Multi Product Line (MPL) Pharma Inc. Cidimus® tablets and all the laboratory tests for both groups were provided by MPL.

Statistical Analysis

Statistical analysis included descriptive statistics: means and standard deviations for quantitative variables and the frequency and percentage for qualitative variables. The

Wilcoxon Signed Rank Test was used to compare the graft function between the 2 groups. Intention to treat analysis principle was adopted. Differences between means was tested using Student's t-test or Mann–Whitney U test for non-normal data. Normality was assessed by visual inspection of probability plots. Differences between proportions were tested using Fisher's exact test. Kaplan–Meier analysis of graft and patient survival, and time to first rejection, was performed. The groups were compared using a log rank test. P-values <0.05 were considered statistically significant. All tests were two-tailed. For the estimation of bioequivalence, a comparative estimate was used by measuring the mean and the confidence interval.

Image 1: Pharmacokinetic profile



This is a pilot study on the generic tacrolimus on 44 patients, 22 for each group. An abbreviated AUC profile was done once on Day 3 post-transplant using C0, C2 and C4 determinations for all the patients. The tacrolimus dose for both groups was adjusted to maintain a C0 (trough) level of 5-7 ng/ml.

All patients were followed up weekly in the first month, then fortnightly thereafter till the sixth month. All participants had their follow- up with their respective AP for both service and private patients for the adjustment of tacrolimus dose based on the judgment of the AP. After being seen by the AP, the participants went to the Research Assistant (RA) for the

dispensing of meds and subsequently the participants were also seen by the PI for physical examination. The tacrolimus to be dispensed was based on the dose prescribed by the AP.

Therapeutic drug monitoring using C0 (trough) levels with appropriate dose adjustments were done weekly (± 2 days) for the 1st month, then every 2 weeks (± 3 days) for the 2nd and 3rd months, and monthly (± 3 days) from 4th to 6th month and as clinically indicated. Adverse reactions were noted and addressed and reported to the Research Ethics Committee. Graft biopsy was performed for suspected acute rejection, or as required by the physician.

Graft outcomes at 1, 3 and 6 months were monitored and documented for both groups.

Baseline Patient Information

The following data was collected from the patients: age, sex, weight, number of HLA mismatches, PRA, type of dialysis prior to kidney transplantation, living donor type (sibling, parent, child, first cousin or not related), primary renal disease, and other co-morbid conditions like history of pulmonary tuberculosis (PTB) or other significant infections, hypertension or diabetes.

Glossary

1. Cidimus® – brand name of the generic tacrolimus
2. Narrow therapeutic index – property of a drug wherein the desired therapeutic concentration is almost the toxic concentration
3. Pharmacokinetic profile – the measurement of the body's total exposure to the administered medication as measured by the area under the curve (AUC) which is a reflection of concentration of the drug over a specified time
4. Limited AUC or abbreviated sampling – obtaining blood level concentration of a drug during a specific time point; reflective of the total AUC

5. Bioequivalence – a characteristic used to describe products that are pharmaceutically equivalent in terms of absorption, metabolism, excretion, mode of action, efficacy, safety profile and route of administration
6. Cmax – maximum concentration of the drug over a specified period of time
7. Tmax – the time to reach the maximum concentration of a particular drug
8. Acute rejection (AR) - is defined by a >25% rise in serum creatinine from baseline, or other graft dysfunction that is confirmed by histological findings of rejection on allograft biopsy based on Banff criteria.
9. Adverse event (AE) - is any untoward medical occurrence regardless of causality assessment. It can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease whether or not considered related to it.
10. Serious AE (SAE) - is any untoward medical occurrence that is
    a. fatal
    b. life-threatening
    c. requires or prolongs inpatient hospitalization
    d. results in persistent or significant disability/incapacity
    e. a congenital anomaly/birth defect
    f. examples are microangiopathy, seizures, severe anemia (hemoglobin < 8g/l), leukopenia (< 3,500/ml), thrombocytopenia (<100,000/ml)
11. Non serious AE - is any untoward medical occurrence that does not meet any of the criteria for SAE.
12. Graft survival - is defined by the presence of renal function adequate to prevent the patient from resuming maintenance dialysis.
13. Graft loss - is defined by the patient's permanent return to dialysis defined as 1 month of hemodialysis dependence.

14. Patient death with functioning graft - is defined by all causes resulting in death of a patient with graft function sufficient to obviate the need for dialysis.
15. Drop-out– those patients who died during the course of the study but whose death is not related to the drug under study (Cidimus®), and those patients who are on Cidimus® but opted to be shifted to Prograf during the period of investigation.
16. Treatment Failure - those who were shifted to Prograf due to acute rejection despite adequate tacrolimus levels or due to intolerable adverse reactions to Cidimus®

Compliance

The compliance of the patients in both groups was evaluated based on the therapeutic drug level of Tacrolimus (Tacrolimus Trough) which was done weekly, every two weeks and every 3 months. Patients were also interviewed and asked about their compliance.

Acute Rejection Episodes

Patients who were clinically considered to have acute rejection underwent graft biopsy. BPAR was treated with a 3-day course of methylprednisolone. Patients on Cidimus® were shifted to Prograf®. These patients were considered as treatment failure. For patients with steroid resistant acute rejection, rescue therapy with rATG was administered.

Criteria for Stopping the Study

Tacrolimus remained the standard anti-proliferative adjunct immunosuppression for kidney transplant. In this study, the acute rejection rates of patients on Cidimus® were reviewed each month. If there are three patients in the Cidimus® group (20%) who developed acute rejection, the results were reviewed immediately, and recommendation to terminate the study would ensue. These Cidimus® patients with acute rejection will then be

shifted to innovator brand Prograf®. Any mortality arising from the intervention will be reviewed and decisions will be made for stopping the study.

Reporting Procedures for all Adverse Events

Adverse events were recorded in the chart for all subjects from the time of administration of the first dose of study drug through the subject's completion of the study. The Investigators were responsible for ensuring that all AEs observed by the Investigator or reported by subjects were collected and recorded in the subjects' medical records and for SAEs on the serious adverse event report (SAER) form. It will be left to the Investigator's clinical judgment to determine whether an AE is related and of sufficient severity to require the subject's removal from treatment or from the study.

Ethical Review

The protocol was submitted to the Research Ethics Committee of the National Kidney and Transplant Institute for review and approval prior to the commencement of the study.

The patient's written informed consent to participate in the trial was obtained after a comprehensive explanation was given regarding the treatment regimen, its potential complications, the randomization procedure, blood determinations and serial follow-ups.

The right of the patient to refuse to participate without giving reasons was respected. After the patient has entered the study, the clinician remained free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the patient's best interest. However, the patient will need to remain within the trial for the purpose of follow up and data analysis. The patient remained free to withdraw at any time from protocol treatment without giving reasons and without prejudice to his/her further treatment.

3. RESULTS AND DISCUSSION

The study screened a total of 46 patients and randomly assigned 23 patients to the Cidimus arm and another 23 patients to the Prograf® arm. Forty-four patients completed follow up to 6 months and were included in the safety analyses, 22 patients on each arm. One patient from the Prograf® arm withdrew consent to be included in the study for personal reasons. Another patient was also excluded from the study in the Cidimus arm due the donor being rejected for hypertension.

There was no significant difference in age, weight, sex, number of HLA mismatches and etiology of end stage renal disease between the two groups. Mean age was 36 (Prograf® group) and 35 (Cidimus® group) years, and predominantly male in both groups. Most of the patients had chronic glomerulonephritis as their native kidney disease.

There was also no statistical difference noted in terms of induction therapy and donor source. Majority of the patients had living related donors. Majority of patients on Prograf® had rATG as induction whereas most of those on Cidimus® received Basiliximab. (Table 1).

Table 1. Comparison of baseline demographic characteristics of Cidimus and Prograf

Variables	Intervention		
	Prograf (n=22)	Cidimus (n=22)	p-value
Age[a]	36.00 (11.88)	34.73 (10.84)	0.73
Weight[a]	56.07 (13.24)	57.60 (52.52)	0.68
HLA BDR MM[a]	3.91 (1.44)	3.91 (1.72)	1.00
HLA DR Match[a]	3.27 (0.63)	3.14 (0.71)	0.50
Sex[b]			
Males	15 (68.18%)	14 (63.64%)	0.67
Females	7 (31.82%)	8 (36.36%)	
Native Kidney Disease [b]			
CGN	16 (72.73%)	17 (77.27%)	
DMN	3 (13.64%)	1 (4.55%)	0.87
HPNS	2 (9.09%)	3 (13.64%)	
Not specified	1 (4.55%)	1 (4.55%)	

Donor Source[b]			
LNRD	5 (22.73%)	5 (22.73%)	1.00
LRD	17 (72.27%)	17 (72.27%)	
Tissue Crossmatch			
Positive	0 (0.00%)	0 (0.00%)	NA
Negative	22 (100.00%)	22 (100.00%)	
PRA Screen Class I[b]			
Positive	1 (4.55%)	0 (0.00%)	1.00
Negative	21 (95.45%)	22 (100.00%)	

[a] summary measures are mean (sd). p-value column refers to p-value from a t-test for two independent samples

[b] summary measures are counts (percentage). p-value column refers to p-value from a Fisher's Exact Test

The tacrolimus doses for both groups were adjusted to maintain a trough level of 5-7 ng/ml and were similar in the 2 groups until week 24 at a median daily dose of 3 mg per day (Figure 2). Median tacrolimus trough level was 6.75 ng/mL for both groups. (Figure 1)

Figure 1. Comparison of Mean Tacrolimus Dose

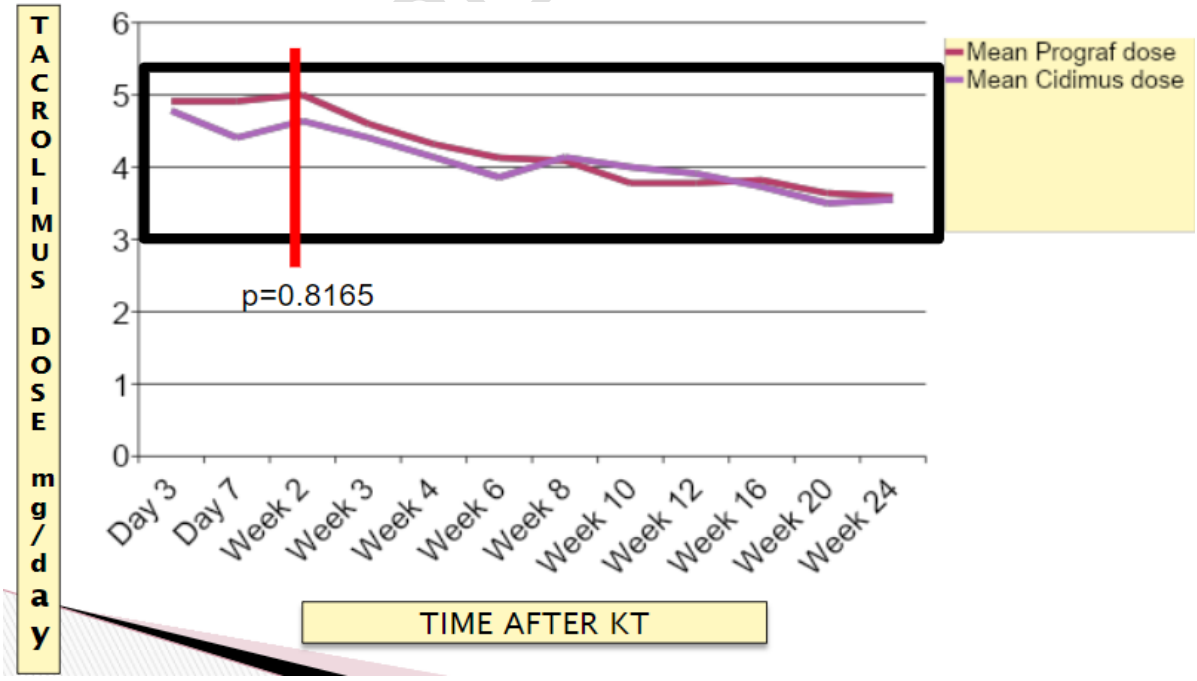
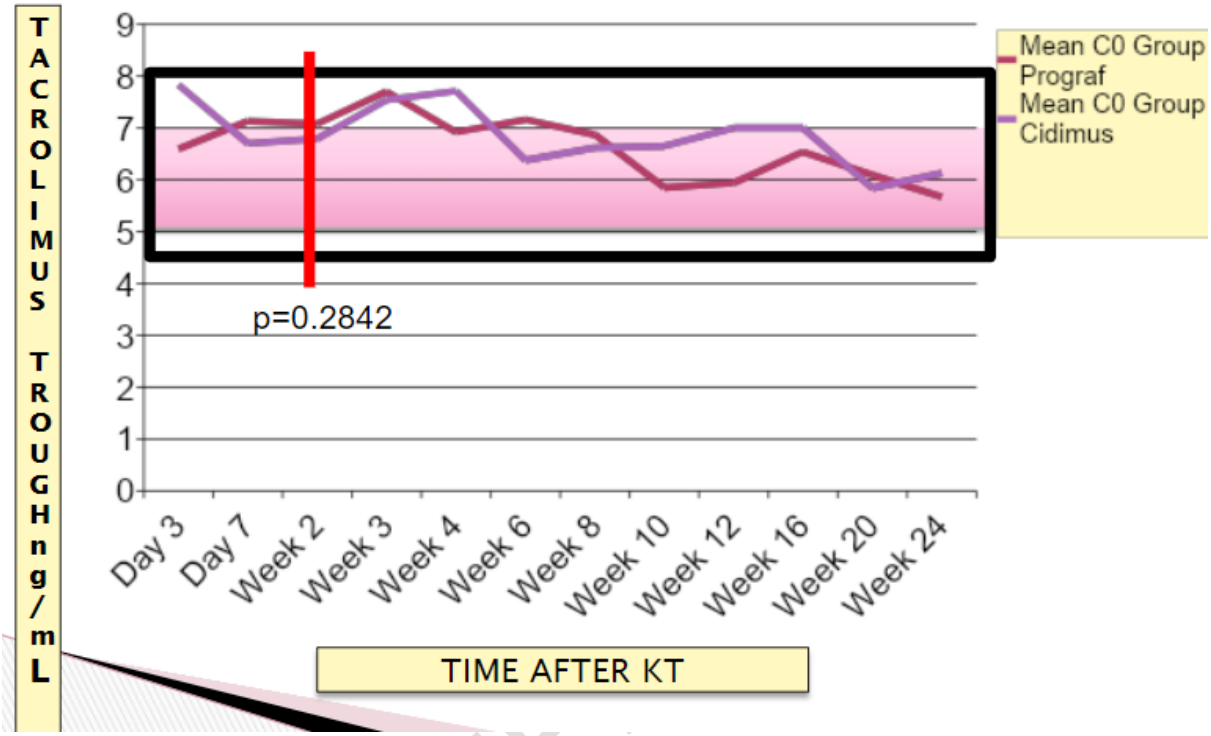


Figure 2. Comparison of Mean Tacrolimus Trough Levels



There was no statistically significant difference in all clinical outcomes, such as patient survival, graft function, BPAR, incidence of adverse reactions and NODAT between the 2 treatment groups after 6 months. (Table 2) The mean estimated glomerular filtration rates (eGFR) at 6 months was 83.27 mL/min and 89.45 mL/min for Prograf® and Cidimus® respectively. One patient in the Prograf® arm had acute T cell mediated rejection Banff Grade 1A. This patient underwent methylprednisolone pulsing for 3 days. In the Cidimus® arm, 2 patients had BPAR. One had acute antibody mediated rejection. No donor specific antigens were noted. The other patient had acute T-cell mediated rejection Banff Gr1B. Both patients had methylprednisolone pulsing. All these patients responded to treatment with a mean serum creatinine of 2.8 mg/dL at 6 months post KT. A total of 8 cases of adverse reactions were documented, 4 on each arm, all of which were resolved. In the Prograf® group, there were 2 complicated urinary tract infections (UTI) and 2 patients developed infectious diarrhea. None required hospitalization. In the Cidimus group, 1 patient had

pneumonia on the 2nd day post-transplant that resolved with antibiotics, 1 had infectious diarrhea, 1 had a UTI and 1 developed severe anemia and thrombocytopenia and was switched from mycophenolate mofetil to mycophenolate sodium. There was 100% patient and graft survival in both groups up to 6 months after transplantation.

Table 2. Comparison of Clinical Outcomes of Cidimus and Prograf at 6 months post KT

Efficacy Measures	Intervention Prograf (n=22)	Cidimus (n=22)	p-value
%Patient Survival	100.00%	100.00%	1.00
Graft function (CKD-EPI Formula)	83.27	89.45	0.44
BPAR	4.55%	9.09%	0.55
Incidence of Severe Adverse reaction	13.6 per 100	13.6 per 100	1.00

Both CMAX and AUC underwent logarithmic transformation and the 90% CI in the differences between the two groups was computed (Table 3). The 90% CI of differences in CMAX of Cidimus® and Prograf® was -0.1662 to 0.0695 and is within the bioequivalence confidence interval of -0.2231 to 0.223. In addition, the mean difference of -0.0484 in CMAX (p = 0.4878) was not significant.

Table 3. Comparison of the Pharmacokinetic Profiles of Cidimus and Prograf

	CIDIMUS (n=22)	PROGRAF (n=22)
CMAX		
Back-transformed after logarithmic transformation		
Mean	17.33	15.51
Variance of Logs	0.06	0.02
Mean Difference on log-transformed scale	-0.0484	
SD of differences	0.3212	
90% CI of differences	-0.1662 to 0.0695	
Bioequivalence Confidence Interval	-0.2231 to 0.223	
p value	0.4878	
Conclusion	Bioequivalence	
AUC		
Back-transformed after logarithmic transformation		
Mean	115.72	100.35

Variance of Logs	0.0442	0.0184
Mean Difference on log-transformed scale	-0.06189	
SD of differences	0.05667	
90% CI of differences	-0.1594 to 0.0356	
Bioequivalence Confidence Interval	-0.2231 to 0.223	
p value	0.2872	
Conclusion	Bioequivalence	

Similarly, the 90% CI of differences in AUC of Cidimus® and Prograf® was -0.1594 to 0.0356 and is within the bioequivalence confidence interval of -0.2231 to 0.223. The mean difference of -0.06189 (p=0.2872) was likewise not significant. Thus, Cidimus® and Prograf® were bioequivalent in terms of Cmax and AUC.

DISCUSSION

This study compared the pharmacokinetic parameters and clinical outcomes of generic Tacrolimus (Cidimus®) with the reference Tacrolimus (Prograf®) until 6 months post-transplant among standard risk primary kidney transplants. There was no statistically significant differences in effectiveness and safety between the 2 groups, and they were shown to be bioequivalent.

This study showed 100% graft and renal survival up to 6 months post-transplant. No statistically significant adverse effects nor incidence of NODAT were also seen between generic tacrolimus and the innovator. Three incidences of BPAR were noted, 1 in the Prograf® arm and 2 on the Cidimus® arm but these were not statistically significant. This echoed the findings in the study by Marfo et al in 2013 on clinical outcomes after conversion from branded tacrolimus to a generic formulation. They found that generic tacrolimus did not confer negative clinical outcomes and was safe and effective (10).

With the assumption that abbreviated Tacrolimus AUC values were representative of true actual 12-hour AUC's, generic tacrolimus (Cidimus®) showed a similar pharmacokinetic profile to reference tacrolimus, as assessed by a comparison of AUC, CM ax and Tmax.

Thus, the generic tacrolimus Cidimus was bioequivalent to reference tacrolimus (Prograf®).

Many studies have shown that generic Tacrolimus has a similar pharmacokinetic profile to the reference drug and is bioequivalent in kidney transplant recipients. In the study by Alloway et al in 2012, ratios of geometric means were 1.02 (90% CI 97–108%, p = 0.486) for AUC0–12h and 1.09 (90% CI 101–118%, p = 0.057) for Cmax. Mean (SD) C0 was 7.3(1.8) ng/mL for generic tacrolimus versus 7.0(2.1) ng/mL for reference tacrolimus based on data from days 14 and 28. Correlations between 12 h trough levels and AUC were r = 0.917 for generic tacrolimus and r = 0.887 for reference drug at day 28. (9) In another study by Arns et al in 2017 comparing the pharmacokinetic and clinical characteristics of generic tacrolimus formulation (TacHexal) versus the reference drug (Prograf®) in stable renal transplant patients in de novo kidney transplant patients, the dose-normalized AUC0-12h ratio at month 1 post-transplant, was similar with Hexal or Prograf: back-transformed geometric means of adjusted log transformed values (ANOVA) were 18.99 ng*h/L (TacHexal) and 20.48 ng*h/L (Prograf®) (ratio 1.08 [90% CI 0.84; 1.38]; p=0.605). The dose-normalized peak concentration (Cmax) geometric means at month 1 was also comparable between treatments (ratio 1.16 [90% CI 0.88; 1.54], p=0.377). (11)

Limitations of the study include its small sample size. Since this is only a pilot study, only 44 patients were randomized. Further prospective randomized cross-over studies using a larger cohort of patients are warranted.

4. CONCLUSION

There was no significant difference in patient survival and graft survival with generic Tacrolimus (Cidimus®) compared to reference Tacrolimus at 6 months post-transplant. There was also no significant difference in the safety profile of the 2 groups. BPAR in the Prograf and Cidimus® arms were 4.55% and 9.09% respectively. NODAT occurred in only 1 patient in the Cidimus® arm. Results of the AUC, Cmax, and Tmax of the 2 tacrolimus

formulations demonstrated that there were no significant pharmacokinetic differences between Cidimus® and Prograf and were thus shown to be bioequivalent. In conclusion, Generic Tacrolimus (Cidimus®) was non inferior to reference Tacrolimus (Prograf®) based on pharmacokinetic parameters and clinical outcomes at 6 months post-transplant.

CONSENT (WHERE EVER APPLICABLE)

Please see attached documents for the informed consent form.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

The protocol was submitted to the Research Ethics Committee of the National Kidney and Transplant Institute for review and approval prior to the commencement of the study.

The patient's written informed consent to participate in the trial was obtained after a comprehensive explanation was given regarding the treatment regimen, its potential complications, the randomization procedure, blood determinations and serial follow-ups.

The right of the patient to refuse to participate without giving reasons was respected. After the patient has entered the study, the clinician remained free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the patient's best interest. However, the patient will need to remain within the trial for the purpose of follow up and data analysis. The patient remained free to withdraw at any time from protocol treatment without giving reasons and without prejudice to his/her further treatment.

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

1. Cidimus® – brand name of the generic tacrolimus

2. Narrow therapeutic index – property of a drug wherein the desired therapeutic concentration is almost the toxic concentration

3. Pharmacokinetic profile – the measurement of the body's total exposure to the administered medication as measured by the area under the curve (AUC) which is a reflection of concentration of the drug over a specified time

4. Limited AUC or abbreviated sampling – obtaining blood level concentration of a drug during a specific time point; reflective of the total AUC

5. Bioequivalence – a characteristic used to describe products that are pharmaceutically equivalent in terms of absorption, metabolism, excretion, mode of action, efficacy, safety profile and route of administration

6. Cmax – maximum concentration of the drug over a specified period of time

7. Tmax – the time to reach the maximum concentration of a particular drug

8. Acute rejection (AR) - is defined by a >25% rise in serum creatinine from baseline, or other graft dysfunction that is confirmed by histological findings of rejection on allograft biopsy based on Banff criteria.

9. Adverse event (AE) - is any untoward medical occurrence regardless of causality assessment. It can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease whether or not considered related to it.

10. Serious AE (SAE) - is any untoward medical occurrence that is

a. fatal

b. life-threatening

c. requires or prolongs inpatient hospitalization

d. results in persistent or significant disability/incapacity

e. a congenital anomaly/birth defect

f. examples are microangiopathy, seizures, severe anemia (hemoglobin < 8g/l), leukopenia (< 3,500/ml), thrombocytopenia (<100,000/ml)

11. Non serious AE - is any untoward medical occurrence that does not meet any of the criteria for SAE.

12. Graft survival - is defined by the presence of renal function adequate to prevent the patient from resuming maintenance dialysis.

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14. Patient death with functioning graft - is defined by all causes resulting in death of a patient with graft function sufficient to obviate the need for dialysis.

15. Drop-out– those patients who died during the course of the study but whose death is not related to the drug under study (Cidimus®), and those patients who are on Cidimus® but opted to be shifted to Prograf during the period of investigation.

16. Treatment Failure - those who were shifted to Prograf due to acute rejection despite adequate tacrolimus levels or due to intolerable adverse reactions to Cidimus®