SAFETY AND EFFICACY OF TWO TACROLIMUS FORMULATIONS (PROGRAF® AND ADVAGRAF®) IN MALAYSIAN RENAL TRANSPLANT PATIENTS: A COMPARATIVE STUDY

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Abstract

Aim: A once-daily formulation of tacrolimus, Advagraf®, is increasingly being used in place of twice-daily tacrolimus, Prograf®, as a standard immunosuppressive agent for transplant patients. In this study, the clinical safety and efficacy of Advagraf® were compared with Prograf®, among multi-ethnic Malaysian renal transplanted population.

Method: This retrospective study identified renal transplant patients who were converted from Prograf® to Advagraf® at the University Malaya Medical Centre (UMMC) (n=69). Clinical notes and laboratory records, including tacrolimus daily dose and trough levels, were obtained for one-year, pre-and post-conversion. Causality assessment of suspected adverse events were based on the WHO-Uppsala Monitoring Center criteria. Renal biopsy records were re-evaluated based on the updated Banff 2007 classification for biopsy-confirmed acute rejection (BPAR).

Results: Following conversion to Advagraf®, the mean tacrolimus trough level and daily dose decreased significantly (p<0.01) from 6.11±2.15 to 4.91±1.25 ng/mL and 4.08±2.19 to 3.48±1.79 mg/day, respectively. There was no significant difference in serum creatinine and estimated glomerular function. HDL was significantly increased (p=0.005) while triglycerides was significantly decreased following conversion to Advagraf® (p=0.003). The incidence of BPAR was 16% (4 cases in Prograf® and 7 cases in Advagraf®). No patients died or lost their grafts during the study period. There were 34 cases of adverse events which were classified as certain (5%), probable (36%), possible (23%) and unlikely (36%) with no significant difference between groups.

Conclusion: Prograf® and Advagraf® tacrolimus formulations have comparable safety and efficacy profiles among Malaysian renal transplant patients. Advagraf® may have an advantage in terms of lipid profile.

Keywords: *Prograf®, Renal Transplant, Advagraf®, Acute Rejection, Safety*

Introduction

Tacrolimus, a commonly used immunosuppressive agent, has been shown to significantly reduce the incidence and severity of acute rejection episodes in post-renal transplant patients (1). Two formulations of tacrolimus are available for prescription, namely Prograf® (Prograf; Astellas Pharma Europe, Ltd., Staines, UK) and the more recently introduced, Advagraf® (Advagraf; Astellas Pharma Europe, Ltd.). The current trend indicates preference towards Advagraf® which requires only a once-daily dosing compared to that of twice-daily dosing with Prograf®. This dosing promotes adherence to drug therapy (2), reduces variability in bioavailability (3) and therefore delivers more consistent blood concentration (4) in addition to financial implication of reduction in the cost of drug therapy (5). These advantages are thought to favour Advagraf® in terms of overall clinical outcomes including risk of acute rejection

associated with non-adherence to medication (6) amongst these renal transplant patients.

Although some studies have shown that Advagraf® is therapeutically equivalent to Prograf® (7,8), there is still a paucity of data regarding its use among renal transplanted populations in the South-East Asian region. Although Advagraf® is relatively new in this country, increasing numbers of patients are being converted to Advagraf®. Therefore, an accurate assessment to determine if both formulations have similar safety and efficacy profiles in this population is timely. Thus this single-centre retrospective study was aimed at examining and comparing the safety and efficacy profiles of the two tacrolimus formulations in the multi-ethnic Malaysian renal transplanted population who were converted from Prograf® to Advagraf®.

Methods

Study design and patient selection

This is a retrospective study of all renal transplant patients who have undergone conversion from Prograf® to Advagraf® at the University Malaya Medical Centre (UMMC) (n=69). Other immunosuppressive drugs remained unchanged after conversion to Advagraf®. Monthly records of clinical data were obtained both pre-conversion (patients received Prograf®) and post-conversion (patients received Advagraf®) for one year duration each (Figure 1). The study was approved by the UMMC ethics committee (reference no 955.11) which complies with the Declaration of Helsinki. All patients signed written informed consents.

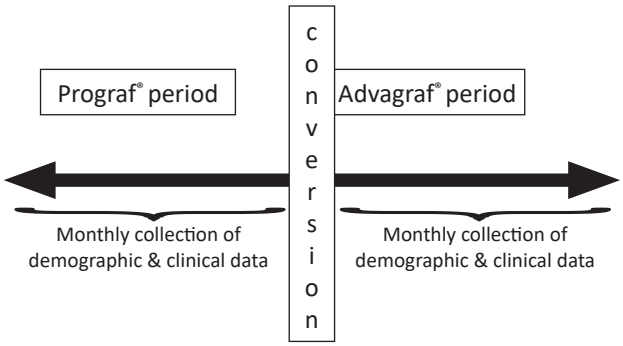

Figure 1: Monthly pre- & post conversion clinical data collection

Demographic and clinical information

Demographic information included were date of birth, gender and ethnicity from the patient information system (PIS). Clinical information such as age at transplant, donor types, primary kidney disease, types of immunosuppressants and other concomitant medications, body weight, systolic and diastolic blood pressure (BP) measurements and other clinical diagnoses were obtained from patient records, both available electronically and manually. Biochemical profiles, including serum creatinine, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, total bilirubin, albumin, lipid profiles (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and tryglycerides (TG)), haemoglobin and haematocrit, were obtained from the laboratory information system (LIS) during the specified study period. Tacrolimus dose and trough which were measured at routine clinical follow up were obtained from LIS and were cross-referenced with clinical notes one-year prior to conversion and one-year post-conversion.

Biopsy-confirmed acute rejection (BPAR)

Records of renal biopsies within the study period were obtained and were re-evaluated and scored by a local histopathologist based on the updated Banff 2007 classification (9) for BPAR. Graft loss was defined as death, retransplant, or return to dialysis following conversion.

Suspected adverse events and causality assesment

Suspected adverse events were extracted from clinical notes, both available electronically and manually. Biochemical profiles were screened for abnormalities. Suspected adverse events were reviewed by three independent reviewers, who included two nephrologists and a clinical pharmacologist with a combined clinical experience of more than 30 years using the World Health Organization-Uppsala Monitoring Center criteria (10). Each suspected adverse event was classified as certain, probable, possible, unlikely, conditional and unaccessable. Any discrepancy in scoring was re-reviewed together as a panel.

Statistical analyses

Categorical data were presented as percentages whilst continuous data were expressed as means ± SD, unless otherwise stated. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Comparison between the two tacrolimus formulations were performed using the chi-square test for categorical variables and paired *t*-test or Wilcoxon Signed Rank as appropriate for continuous variables. Pearson's correlation was used to examine the relationship between the trough concentration and the dose of the two tacrolimus formulations. A two-sided *p*-value of less than 0.05 was considered as statistically significant. All analyses were performed using SPSS software for Windows (Version 23.0; IBM Statistics Corp, NY).

Results

Baseline characteristics of study population

This study included 69 stable renal transplant patients who were predominantly men (74%) and of Chinese ethnicity (74%) with a mean age of 35.5 ± 10.59 years (Table 1). All patients received their first transplantation. More than 50% of the transplanted grafts were from living related donors and the majority (75%) of grafts were performed within the country. The leading cause of

primary end stage renal disease in the renal transplanted population was hypertension (25%). The most common immunosuppressive agents used as an adjunct were corticosteroids and mycophenolate mofetil. The mean duration from transplantation to conversion of Prograf® to Advagraf® was 6.5 ± 5.4 years.

Table 1: Demographic data and patients' baseline characteristics (n=69)

Patient characteristics	n (%) or mean ±SD
Sex	
Male	51 (74)
Female	18 (26)
Race	
Malay	13 (19)
Chinese	51 (74)
Indian	5 (7)
Age at transplant (years)	35.5 ± 10.59
Donor type	
Living-related transplant	36 (52)
Non-living related transplant	12 (17)
Cadaveric	21 (31)
Body mass index (BMI) (kg/m^2)	25.25 ± 6.15
Primary kidney disease	
Hypertension	17 (25)
Glomerulonephritis	8 (12)
Diabetes mellitus	4 (6)
Bilateral small kidneys	14 (20)
Idiopathic	14 (20)
IgA nephropathy	5 (7)
Others (polycystic kidney disease and reflux nephropathy)	7 (10)
Immunosuppressants	
Prednisolone, tacrolimus, azathioprine	14 (20)
Prednisolone, tacrolimus, mycophenolate mofetil	55 (80)
Transplant duration (years)	8.41 ± 5.46

Comparison of tacrolimus dose and trough levels concentrations post conversion

Following conversion from Prograf® to Advagraf®, both mean tacrolimus trough level and daily dose decreased significantly (6.11 ± 2.15 ng/mL to 4.91 ± 1.25 ng/mL and 4.08 ± 2.19 mg/day to 3.48 ± 1.79 mg/day, respectively) as shown in Table 2. Of the 69 patients, 74% had a lower post-conversion tacrolimus trough level while 48% showed more than 20% reduction of tacrolimus trough level following conversion. Although there was a strong positive correlation between the dose of the two different tacrolimus formulations (r=0.88, p<0.0001), the correlation was of moderate strength for the trough levels (r=0.46, p<0.0001). However, trough concentrations were maintained within the therapeutic range.

Table 2: Laboratory parameters when patients received Prograf® followed by conversion to Advagraf® (n=69)

Variables	Prograf®	Advagraf®	*p*-value
Mean trough concentration (ng/mL)	6.11 ± 2.15	4.91 ± 1.25	0.000
Mean tacrolimus dose (mg/day)	4.08 ± 2.19	3.48 ± 1.79	0.000
Mean systolic blood pressure (SBP) (mmHg)	138.42 ± 15.07	139.05 ± 14.49	0.780
Mean diastolic blood Pressure (DBP) (mmHg)	80.87 ± 9.23	81.57 ± 7.18	0.290
Mean total cholesterol (mmol/L)	4.96 ± 0.89	5.04 ± 0.97	0.400
Mean low density lipoprotein (LDL) (mmol/L)	2.83 ± 0.75	2.89 ± 0.81	0.440
Mean high density lipoprotein (HDL) (mmol/L)	1.37 ± 0.29	1.46 ± 0.33	0.005
Mean triglycerides (mmol/L)	1.67 ± 0.71	1.50 ± 0.69	0.003
Mean haemoglobin (g/L) Male Female	133.91 ± 17.83 119.75 ± 14.45	134.77 ± 21.83 122.16 ± 20.53	0.260
Mean haematocrit (SI) Male Female	0.39 ± 0.05 0.37 ± 0.04	0.41 ± 0.05 0.38 ± 0.06	0.080
Mean alanine aminotransferase (ALT) (U/L)	31.39 ± 16.66	26.69 ± 17.09	0.003
Mean aspartate aminotransferase (AST) (U/L)	22.92 ± 8.17	21.87 ± 8.17	0.580
Mean total bilirubin (µmol/L)	11.08 ± 5.84	11.32 ± 4.64	0.250
Mean total protein (g/L)	72.82 ± 5.02	72.24 ± 5.56	0.270
Mean albumin (g/L)	39.49 ± 3.64	42.10 ± 3.38	0.000
Mean aglomerular filtration rate (GFR) (mL/min/1.73 m^2)	50.32 ± 19.66	56.16 ± 21.21	0.520
Mean serum creatinine (µmol/L) Male Female	176.21 ± 105.45 153.14 ± 117.48	156.94 ± 73.22 148.89 ± 118.60	0.150

Changes in clinical parameters, including renal functions, post conversion

There were no significant difference found in mean systolic and diastolic BP when patients were converted to Advagraf. HDL was significantly increased (p=0.005) while triglyceride level was significantly decreased following conversion to Advagraf® (p=0.003). ALT was significantly decreased (p=0.003) while serum albumin level was significantly increased following conversion (p<0.0001). There was no significant difference found between haemoglobin and haematocrit levels for both formulations.

The mean serum creatinine level was above normal ranges (male: 70-120 µmol/L; female: 50-90 µmol/L) which was reflected in the below-normal range estimated glomerular function for both formulations . However, the differences between the two formulations were not statistically significant (Table 2).

Comparison of BPAR

During the study duration, the incidence of BPAR (excluding borderline cases) was 16% in all cases whereby 4 cases were observed with Prograf® and 7 cases were observed during Advagraf® treatment. On the other hand, borderline changes were observed in 25% of patients while on Prograf® and 33% of patients while on Advagraf®. No patient experienced any loss of graft during the study period (Table 3).

Table 3: Pathologic findings of BPAR based on BANFF classification during Advagraf® (n=69) and Prograf® (n=69) treatments

BANFF classification	**Advagraf®**	**Prograf®**
All acute rejection	7	4
T-cell mediated rejection: Grade IA	7	0
T-cell mediated rejection: Grade IB	0	3
T-cell mediated rejection: Grade 2A	0	0
T-cell mediated rejection: Grade 2B	0	0
Antibody-mediated rejection (AMR): Immediate	0	1
Antibody-mediated rejection (AMR): Delayed	0	0
New-onset of chronic allograft nephropathy (CAN): Mild	1	2
New-onset of chronic allograft nephropathy (CAN): Moderate	3	1
New-onset of chronic allograft nephropathy (CAN): Severe	0	0
#Other changes	2	6
^Borderline changes	23	12

Other changes = Observed changes which might not be considered as direct effects of rejection, but, however, may coincide with acute rejection categories (e.g mild tubulitis, hypertensive changes, focal segmental glomerulosclerosis)
^ Borderline changes are also known as 'suspicious' of acute rejection; the presence of a mild tubulitis with no intimal arteritis (24).
BANFF = Banff Working Classification of Renal Allograft Pathology

Comparison of suspected adverse events

In this current study, there were 34 cases of suspected adverse events that occurred throughout the observation period (Figure 2). Based on the World Health Organization-Uppsala Monitoring Centre criteria, the overall suspected adverse events were classified as certain (5%), probable (36%), possible (23%) and unlikely (36%). The most common was respiratory disorders such as cough and shortness of breath while the most common infections were urinary tract infection and cytomegalovirus infection. There were no significant differences in the suspected adverse events between the two formulations. No mortality was observed from any cause during the study period.

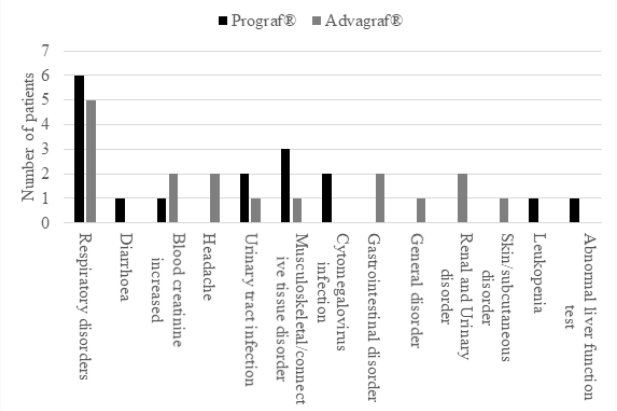

Figure 2: Suspected adverse effects during pre-conversion (Prograf®) and post-conversion (Advagraf®)

Discussion

The present study demonstrated a significant decrease in both trough level and dosage of tacrolimus within one year following conversion from Prograf® to Advagraf®. A significant increase in HDL levels with a decrease in triglycerides was observed with Advagraf®. In addition, there were also a decrease in ALT levels and an increase in albumin levels post- conversion while renal functions and haematocrit levels remained stable. There was no difference in the incidence of BPAR between the two formulations within the one-year study period. The rates of graft and patient survival were high in all patients throughout the period they received both formulations. In terms of suspected adverse events, both tacrolimus formulations showed similar profiles of adverse events.

The decrease in both trough level and dosage during the Advagraf® period following conversion from the Prograf® period was similar to findings in our earlier study as well as those found in Caucasian populations (11). The manufacturer of Advagraf® had also suggested that conversion to the once-daily prolonged-release formulation on a 1:1 (mg:mg) total daily- dose basis among stable kidney transplant patients may result in a lower systemic exposure (12). Nevertheless, the observed lower exposure of tacrolimus had no significant clinical consequence in this study, as indicated by the patient, graft

survival rates and renal functions of patients. A properly conducted bioequivalence study of the two tacrolimus formulations should ideally be undertaken to determine the best conversion dosage in our multi-ethnic population.

The increase in HDL levels and decrease in triglycerides was observed with Advagraf®. An interesting finding was observed in a Caucasian study which demonstrated an improvement in lipid profile following conversion to once-daily tacrolimus (13). Low HDL and hypertriglyceridaemia are among risk factors associated with increased cardiovascular risk. In renal transplant patients, these may also be associated with chronic allograft nephropathy (14). This finding may further support the beneficial effect of Advagraf® formulation, possibly in decreasing cardiovascular risks in this specific population. Although a significant change in the mean level of albumin and ALT after conversion was observed, these values were still within the normal range. Other liver functions remained stable in both periods of tacrolimus formulations.

With regards to renal function, we did not establish any significant difference in terms of serum creatinine level and glomerular filtration rates following conversion from Prograf® to Advagraf®. Our study was in agreement with a similar multi-centre study involving over a thousand renal transplant patients whereby it was found that renal functions remained stable upon conversion . Even though a study by Abedini et al have reported a stable renal function following conversion (15), it could well be attributed to the reduced tacrolimus exposure following conversion. Although there may be some protective effect on renal function with the use of Advagraf®, due to the lower single peak exposure observed in this current study, a prospective multicentre study should be conducted in the future to demonstrate if this benefit is of clinical significance.

We found no significant difference in the incidence of BPAR for the two formulations as opposed to another study by Mecule A et al, which reported a higher risk of BPAR following conversion (16). Additionally, the similarity of the occurrence of borderline rejections at pre- and post-conversion biopsies may suggest that the true difference in BPAR burden between the two formulations may even be smaller than that reported. It is plausible that polymorphisms in the CYP3A locus (17), dietary factors (18) and gastrointestinal motility (19) may affect the absorption and exposure of tacrolimus thus leading to the difference in the outcomes in different populations. The low trough levels of tacrolimus maintained in our renal transplant population as well as the stable liver, haematocrit and renal functions may contribute to our similar risk of BPAR between formulations.

The overall proportion of adverse effects in the present analysis was lower than the incidence of adverse events previously described in clinical trials (20). Previous studies have reported an inconsistent outcome on the association of type of treatment and adverse effects. For example, a study by Iara et al has reported fewer adverse events with Advagraf® (21) as compared to Prograf®. In another study, it has been shown that a higher tacrolimus trough concentration is associated with adverse effects (22). It was noted that the mean trough levels for our renal transplant patients were below 10 ng/mL during treatment with both Prograf® and Advagraf®. In addition, it has also been reported that mycophenolate mofetil and azathioprine, a commonly use combination of immunosuppressants in our population, produce synergistic effects (23) and therefore have the potential to cause fewer adverse effects. It was reassuring to note that no patient showed marked haematological or laboratory abnormalities or adverse effects that necessitated discontinuation of tacrolimus. The strength of our study includes a period of one-year follow-up which enables a better comparison between Prograf® and Advagraf®, thus allowing both laboratory and clinical findings to be more likely to occur in stable conditions, lending to a higher degree of validity of the findings. All patients who were converted from Prograf® and Advagraf® were included, to reduce selective bias. The changes in dose were determined by only one nephrologist-in-charge who has a special interest in renal transplants and thus reduced the inter-physicians variability. Nevertheless, there were some limitations in our study. Those who were converted to Advagraf® may have had different clinical profile than those who were maintained with their previous tacrolimus formulation and may constitute selection bias in the study. The number of patients were rather small due to a single centre selection. However, this centre is one of the main tertiary centres for post-renal transplants in the country, Hence, the practice would reflect the practice in other hospitals. Patients might have continued to use their personal supply of tacrolimus at home despite having been supplied with the new generic product which may lead to some variations in the laboratory results. The possibility of food and drug interactions which may have affected the clinical findings were not examined since these were not controlled in a retrospective study setting. Therefore, future prospective studies with a larger number of patients will strengthen the data further.

Conclusion

To the best of our knowledge, this is the first local data to demonstrate that Prograf® and Advagraf® tacrolimus formulations have comparable safety and efficacy profiles among Malaysian renal transplant patients. The findings from this study indicated that that both drugs are useful in our population while Advagraf® may have an advantage in terms of lipid profile.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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