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A Comparative Study on the Safety and Efficacy Parameters of Cyclosporine and Tacrolimus on Renal Transplanted Patients: A Malaysia Experience

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ABSTRACT

Calcineurin inhibitors, cyclosporine and tacrolimus are increasingly becoming part of the standard immunosuppresant therapies for renal-transplanted patients in Malaysia. In this study, the clinical safety and efficacy of cyclosporine and tacrolimus in a Malaysian renal-transplanted population is compared. A fourteen-year retrospective review on all renal-transplanted patients (from September 1991 to September 2015) or patients being followed up at University Malaya Medical Centre (UMMC) on cyclosporine or tacrolimus regime was conducted. We collected the clinical and laboratory parameters at 3-month, 6-month, 7-month, 8-month, 9-month, 10-month, 11-month, 12- months, 2-year and 3-year following from transplantation for each drug. The mean cyclosporine and tacrolimus trough levels were within the recommended therapeutic ranges (189.16 ± 69.10 ng/ml and 7.84 ± 2.18 mg/day respectively). The mean low-density lipoprotein (LDL) was significantly higher at eleven months for tacrolimus compared to cyclosporine. Similarly, the mean total bilirubin level was significantly higher with cyclosporine as compared to tacrolimus between 3 – 9 months post transplantation but did not show any significant difference (p = 0.49). The overall monthly means of serum uric acid levels in patients were also similar, 380 ± 87 mg/dL (cyclosporine) and 390.96 ± 95.97 mg/dL (tacrolimus) (p = 0.49). The Kaplan-Meier survival rate is significantly longer (p = 0.03) with cyclosporine-based treatment as compared to tacrolimus. Overall, cyclosporine and tacrolimus did not show any significant difference in terms of safety and efficacy parameters among Malaysian renal-transplanted patients indicating that they may be used interchangeably.

INTRODUCTION

The comprehensive safety and effectiveness of immunosuppressant medications such as calcineurin inhibitors like cyclosporine and tacrolimus are crucial to the overall success of organ transplantations. The discovery of cyclosporine led to tremendous improvements in the outcome following transplantation[1]. This benefit was further improved when tacrolimus began to be widely utilised in liver transplant patients, and subsequently in renal transplantation. At present, tacrolimus is prescribed to more than half of renal-transplanted patients as adjunct immunosuppressants regime[2].

Several studies comparing the use of cyclosporine and tacrolimus conducted in different populations have reported varying outcomes. The studies have indicated the benefits of tacrolimus which includes reduction in steroid use[3], [4], improvement in blood pressures5 and amelioration of lipid profiles in transplanted patients[6]. Furthermore, a study had demonstrated a reduction in the incidence of acute rejections (an average incidence of <20%) as well as improved graft survival (above 90%) in the first year post-transplantation with the use of the newer immunosuppressive regime[7]. Nevertheless, study showed that tacrolimus is associated with an higher risk of new-onset diabetes[8] and has poorer safety profiles in comparison with cyclosporine-based therapy[9]. In addition, the immunosuppressive protocol used may have been unbalanced, particularly with respect to corticosteroid dose tapering.

Besides the conflicting data, most studies are conducted in Caucasian population with paucity of data available for Malaysian renal-transplanted population which may have a different genetic make-up and may respond differently to the therapies. Over the years, there have been an increased number of Malaysian renal-transplanted patients being converted to tacrolimus-based regime. It has been reported that tacrolimus incurs an annual cost of USD23,254.46 as compared to only USD18,206.50 with cyclosporine[10]. Thus, an accurate assessment of the safety and efficacy profiles of the two drugs is timely to justify the increased use of tacrolimus among Malaysian patients. To our knowledge, this is the first report on the safety and efficacy profiles of cyclosporine and tacrolimus in a Malaysian clinical setting.

MATERIALS AND METHODS

This is a retrospective study of more than fifteen years on all renal-transplanted patients on follow up between June 1999 and October 2014 at the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. The patients received either cyclosporine (n = 155) or tacrolimus-based (n = 113) immunosuppressant regimes. The study was approved by the medical ethics committee of the UMMC (reference no 955.11) which complies with the World Medical Association Declaration of Helsinki. Demographic and clinical data were collected at 3, 6, 7, 8, 9, 10, 11 and 12 months as well as subsequently at 2 and 3 years post transplantation for both drugs.

The study subjects were adult, stable renal-transplanted patients with observed high serum creatinine (i.e. not more than 10%) six months prior to the study. Patients with a raised serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) of more than three times the upper limit of normal serum level a month prior to the transplantation, received a solid organ transplantation other than a kidney or had an episode of rejection in the previous six months were excluded. The kidneys were transplanted from living-related donors, non-living related or cadaveric donors.

Laboratory parameters such as trough levels of drugs, serum creatinine, ALT, AST, lipid profiles including total cholesterol,

high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), haemoglobin, haematocrit, total bilirubin, total protein and albumin were retrieved from either the patient's case notes or the laboratory information system of the hospital. Additionally, other concomitant medications received by the patients (if any) were also recorded.

Primary Immunosuppressive Protocol

An interleukin-2 (IL-2) antagonist (Thymoglobulin) was administered as an induction therapy to all patients. For maintenance therapy, the patients received triple immunosuppressive agents which include either cyclosporine or tacrolimus, prednisolone and an antimetabolite or a mechanistic target of rapamycin (an mTOR inhibitor). Following transplantation, cyclosporine was administered at 5.0 mg/kg every 12 hours. Subsequently, the target trough concentration of cyclosporine in whole blood was adjusted to a therapeutic level (150 – 400 ng/ml) in the first 3 months after transplantation and subsequently 100 – 300 ng/ml for the study duration. In case of tacrolimus, it was administered at an initial oral dose of 0.10 mg/kg twice daily. The target trough level was 7 – 10 ng/ml (in the following one year after transplantation) and 3 – 7 ng/ml (thereafter).

Additionally, patients also received either mycophenolate mofetil (Cellcept®) (1 g bid) or mycophenolic acid (Myfortic®) (720 mg bid) in the first three months. The dose of the drugs was gradually tapered to 500 to 750 mg bid (Cellcept®) or to 360 to 540 mg bid (Myfortic®). Prednisone was administered at 10 mg/day and subsequently tapered based on the clinician's decision. As routine practice of the hospital, drug's trough blood levels were conducted a week later to ensure that the level remained within the recommended therapeutic ranges.

Safety Profiles

Other outcomes such as graft and patient survivals were also collected from the patients' case notes. Graft loss was defined as death of patient or graft failures. Specifically, the former includes (1) death of patient, (2) those who needed to undergo nephrectomy, (3) those who died with a functioning graft, or (4) graft failure which had to be retransplanted while the latter is defined as a permanent return to a dialysis (≥30 days). Additionally, renal biopsies were evaluated and scored by a local histopathologist dedicated to the study based on the updated Banff 2007 classification[11]CTA can undergo immune-mediated rejection; therefore standardized criteria are required for characterizing and reporting severity and types of rejection. This article documents the conclusions of a symposium on CTA rejection held at the Ninth Banff Conference on Allograft Pathology in La-Coruna, Spain, on 26 June 2007, and proposes a working classification, the Banff CTA-07, for the categorization of CTA rejection. This classification was derived from a consensus discussion session attended by the first authors of three published classification systems, pathologists and researchers from international centers where clinical CTA has been performed. It was open to all attendees to the Banff conference. To the extent possible, the format followed the established National Institutes of Health (NIH.

Statistical Analyses

Data analyses were performed using SPSS software for Windows (Version 23.0; SPSS, Chicago, IL, USA). Continuous data were expressed as means ± SD, whilst categorical data were presented as percentages (unless otherwise stated). Comparison between cyclosporine and tacrolimus was performed using a chi-square test for categorical variable while paired *t*-test or Wilcoxon Signed Rank were used for continuous variables. A two-sided *p*-value <0.05 was considered as statistically significant. Descriptive summaries

for the time-to-event data for patient and graft survivals were prepared by a using the Kaplan-Meier product limit estimator.

RESULTS

Baseline Characteristics of the Study Population

The study included stable renal transplant patients (*n* = 268) who were predominantly males (64%) and of Chinese ethnicity (74%) as determined by two generations, with a mean age of 40 years (Table 1).

Table 1 Demographic data and patients' baseline characteristics

Patients' characteristics, *n* (%) or mean ±SD	**Cyclosporine (*n* = 155)**	**Tacrolimus (*n* = 112)**
Sex Male Female	 98 (37) 58 (22)	 71 (27) 41 (15)
Race Malay Chinese Indian Others	 20 (8) 116 (45) 19 (7) 1 (0)	 38 (14) 84 (31) 10 (4)
Place of transplantation Overseas Local	 75 (28) 81 (30)	 46 (17) 66 (25)
Number of transplantation Once Twice	 156 (58) –	 – 2 (1)
Donor type Living-related transplant Non-living related transplant Cadaveric	 55 18 82	 39 25 49
Weight (kg)	66.26 ± 15.53	67.65 ± 18.06
Age at transplant (years)	39.67 ± 11.79	40.50 ± 11.56
Dialysis duration (months)	22.2 ± 29.42	31.02 ± 30.58
Primary kidney disease Hypertension Glomerulonephritis Diabetes mellitus Bilateral small kidneys IgA nephropathy Others (polycystic kidney disease, lupus nephritis, reflux nephropathy, etc.)	 40 (15) 22 (8) 23 (9) 30 (11) 16 (6)	 27 (10) 18 (7) 14 (5) 19 (7) 16 (6)
Immunosuppressants (Maintenance period) Prednisolone, azathioprine, cyclosporine Prednisolone, azathioprine, tacrolimus Prednisolone, mycophenolate mofetil (Cellcept®), cyclosporine Prednisolone, mycophenolate mofetil (Cellcept®), tacrolimus Prednisolone, mycophenolic acid (Myfortic®), cyclosporine Prednisolone, mycophenolic acid (Myfortic®), tacrolimus	 27 (10) – 74 (28) – 55 (21) –	 – 7 (3) – 61 (23) – 44 (16)

From the total number, only two patients had to undergo transplantation for the second time. More than half of the grafts originated from deceased donors and the majority (approximately 55%) of transplantation were performed locally. There were no significant difference in terms of age at transplantation ($p = 0.73$), weight at transplantation ($p = 0.20$) and dialysis duration prior to transplantation ($p = 0.25$). The main causative agent for primary end stage renal disease in this study is as similarly seen in other reports i.e. hypertension (25%), bilateral small kidneys (18%), glomerulonephritis (15%), immunoglobulin-A (IgA) nephropathy (12%) and diabetes mellitus (14%). Prednisolone and mycophenolate mofetil are the preferred immunosuppressive agents used as adjuncts.

Cyclosporine and Tacrolimus Trough Level Concentrations

The clinical characteristics are presented on Table 2. The overall means for cyclosporine and tacrolimus trough levels were 189.16 ± 69.10 ng/ml and 7.84 ± 2.18 mg/day respectively which were within the therapeutic range throughout the study period.

Lipid Profiles and Other Important Parameters

Although the mean total cholesterol was higher at three months up to nine months post transplantation for cyclosporine as compared to tacrolimus although this difference was not significant. Nevertheless, starting from 10 months post-transplantation, monthly mean total cholesterol for tacrolimus began to increase and became persistently higher than that for cyclosporine until the end of the three years post transplantation period although again there was no significant difference ($p = 0.31$) seen. Similarly, there was no significant different in the mean HDL and triglyceride levels between the two-treatment groups. However, mean LDL was significantly higher at eleven months for tacrolimus group compared to cyclosporine.

Both drug regimens showed no significant difference in the mean haemoglobin and haematocrit levels for both drugs. There was also no difference in the ALT and AST levels. Interestingly however, the mean total bilirubin level was significantly higher with cyclosporine as compared to tacrolimus between 3 – 9 months post transplantation ($p < 0.05$) although there was no significant difference in the levels after this duration.

In addition, there was no significant difference in terms of overall monthly mean total protein and albumin levels between the two drugs during the 3 years study period which was also similarly seen for serum uric acid levels which progressively increased in both groups, although the difference was not statistically significant ($p = 0.49$).

Renal Allograft Function

At baseline, all patients had stable serum creatinine concentration, but slowly increased during the study period (male: 70 – 120 µmol/L; female: 50 – 90 µmol/L) for both drugs. At 3 months, the levels increased to 134.63 ± 68.87 µmol/L (cyclosporine) and 130.39 ± 50.21 µmol/L (tacrolimus). Finally, at 3 years, the levels were 138.71 ± 75.15 µmol/L (cyclosporin) and 134.35 ± 64.42 µmol/L (tacrolimus). Nevertheless, there was no significant difference in the levels for the two drugs for the study duration.

Table 2 Clinical characteristics

Laboratory results	At 3-month PT			At 6-month PT			At 7-month PT			At 8-month PT			At 9-month PT		
	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*
Trough level (ng/mL or mg/mL))	272.88 ± 103.29	9.03 ± 2.74	NA	215.56 ± 78.27	8.54 ± 3.08	NA	191.09 ± 71.17	7.73 ± 2.86	NA	194.45 ± 83.02	7.78 ± 2.79	NA	179.29 ± 73.51	8.34 ± 3.48	NA
Mean serum creatinine(μmol/L)	134.63 ± 68.87	130.39 ± 50.21	0.61	141.26 ± 85.50	139.34 ± 63.29	0.86	149.07 ± 128.26	139.91 ± 77.11	0.57	140.55 ± 89.7	147.81 ± 74.96	0.58	134.02 ± 82.45	144.90 ± 90.58	0.42
Mean total cholesterol (mmol/L)	6.22 ± 8.20	5.41 ± 1.08	0.43	6.04 ± 8.75	5.06 ± 1.08	0.42	5.23 ± 1.11	5.10 ± 1.32	0.52	5.20 ± 0.99	4.96 ± 0.97	0.22	5.11 ± 0.97	5.05 ± 0.88	0.71
Mean low density lipoprotein (LDL) (mmol/L)	3.15 ± 1.06	2.97 ± 0.91	0.28	2.95 ± 1.14	2.84 ± 0.95	0.57	2.89 ± 0.91	3.15 ± 1.27	0.25	2.96 ± 0.99	2.91 ± 0.83	0.78	2.83 ± 0.90	2.95 ± 0.86	0.54
Mean high density lipoprotein (HDL) (mmol/L)	1.54 ± 0.54	1.55 ± 0.45	0.98	1.46 ± 0.47	1.42 ± 0.44	0.61	1.46 ± 0.46	1.41 ± 0.52	0.63	1.44 ± 0.58	1.37 ± 0.32	0.49	1.46 ± 0.59	1.51 ± 0.66	0.69
Mean triglycerides (TG) (mmol/L)	2.06 ± 0.91	5.95 ± 31.78	0.34	1.84 ± 0.90	1.69 ± 0.98	0.39	1.84 ± 0.99	1.73 ± 0.82	0.55	1.86 ± 0.98	1.73 ± 0.83	0.52	1.79 ± 0.92	1.68 ± 0.83	0.56
Mean haemoglobin (HB) (g/L)	121.30 ± 19.86	121.31 ± 20.33	0.99	122.43 ± 19.88	124.77 ± 19.70	0.40	123.45 ± 19.40	124.53 ± 22.34	0.73	127.26 ± 21.42	123.67 ± 121.24	0.28	128.48 ± 19.15	127.51 ± 21.92	0.76
Mean haematocrit (Hct) (SI)	1.52 ± 13.38	0.37 ± 0.06	0.40	1.62 ± 13.66	0.38 ± 0.06	0.39	0.38 ± 0.06	0.38 ± 0.07	0.52	0.39 ± 0.07	0.38 ± 0.07	0.20	0.39 ± 0.06	0.39 ± 0.07	0.89
Uric acid (mg/dL)	374.51 ± 98.55	369.54 ± 99.09	0.79	392.44 ± 104.30	380.73 ± 82.33	0.54	381.78 ± 72.50	393.06 ± 113.27	0.63	409.12 ± 116.02	419.79 ± 104.51	0.70	378.62 ± 99.05	412.00 ± 107.56	0.18
Mean alanine transferase (ALT) (U/L)	47.49 ± 28.33	45.07 ± 38.87	0.59	45.01 ± 30.94	40.73 ± 22.14	0.27	44.00 ± 43.22	41.83 ± 46.04	0.76	44.07 ± 39.66	33.81 ± 18.05	0.06	45.00 ± 43.12	36.81 ± 22.38	0.16
Mean aspartate transferase (AST) (U/L)	23.82 ± 17.48	23.75 ± 18.21	0.98	24.25 ± 19.85	24.27 ± 13.01	0.99	24.67 *±22.17*	25.15 ± 19.95	0.89	22.95 ± 17.51	20.80 *±9.17*	0.39	26.67 ± 35.73	22.82 ± 11.83	0.41
Total bilirubin (μmol/L)	12.78 ± 6.88	9.02 ± 4.06	**0.000**	12.73 ± 8.42	10.48 ± 5.80	**0.03**	12.35 ± 6.31	10.42 ± 4.39	**0.02**	13.18 ± 6.56	9.84 ± 4.25	**0.00**	13.36 ± 6.06	10.84 ± 4.93	0.01
Total protein (g/L)	67.52 ± 9.48	68.75 ± 6.84	0.29	70.56 ± 8.59	70.55 ± 6.84	0.99	71.97 ± 5.38	71.31 ± 7.07	0.50	72.26 ± 5.29	71.19 ± 5.88	0.25	72.88 ± 5.56	71.99 ± 6.34	0.36
Albumin (g/L)	37.04 ± 6.80	38.14 ± 5.51	0.20	40.05 ± 5.64	40.24 ± 4.67	0.80	38.80 ± 4.47	40.12 ± 5.25	0.08	39.80 ± 4.62	40.03 ± 5.51	0.78	39.79 ± 4.53	39.88 ± 5.91	0.91

Table 2 Clinical characteristics cont.

Laboratory results	At 10-month PT			At 11-month PT			At 12-month PT			At 2-year PT			At 3-year PT			Overall mean		
	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*
Trough level (ng/ml)	173.04 ± 89.31	7.65 ± 3.04	NA	159.04 ± 79.39	7.23 ± 2.70	NA	139.24 ± 56.56	7.21 ± 2.69	NA	92.07 ± 71.56	6.87 ± 2.15	NA	81.53 ± 42.90	6.35 ± 2.41	NA	189.16 ± 69.10	7.84 ± 2.18	NA
Mean serum creatinine (µmol/L)	139.25 ± 94.63	142.86 ± 82.22	0.80	135.16 ± 73.72	137.80 ± 79.97	0.84	136.47 ± 85.98	143.97 ± 79.21	0.56	142.85 ± 137.43	134.69 ± 73.94	0.66	148.26 ± 146.13	131.68 ± 77.77	0.45	138.71 ± 75.15	134.35 ± 64.42	0.48
Mean total Cholesterol (mmol/L)	5.06 ± 0.89	5.09 ± 0.94	0.84	4.96 ± 0.99	5.23 ± 1.14	0.18	5.11 ± 0.92	5.17 ± 1.15	0.79	5.05 ± 0.88	5.16 ± 0.88	0.48	4.91 ± 0.97	5.07 ± 1.16	0.48	5.47 ± 3.78	5.21 ± 0.87	0.31
Mean low density lipoprotein (LDL) (mmol/L)	2.80 ± 0.90	3.02 ± 0.83	0.24	2.70 ± 0.95	3.14 ± 0.96	0.03	2.83 ± 0.89	3.12 ± 0.93	0.16	2.79 ± 0.82	3.01 ± 0.87	0.18	2.71 ± 0.80	2.97 ± 1.00	0.17	2.91 ± 0.92	3.00 ± 0.77	0.47
Mean high density lipoprotein (HDL) (mmol/L)	1.45 ± 0.42	1.53 ± 0.53	0.41	1.43 ± 0.47	1.42 ± 0.33	0.87	1.46 ± 0.50	1.41 ± 0.41	0.63	1.39 ± 0.46	1.46 ± 0.56	0.49	1.37 ± 0.48	1.40 ± 0.39	0.74	1.45 ± 0.43	1.48 ± 0.41	0.46
Mean triglycerides (TG) (mmol/L)	1.83 ± 0.82	2.08 ± 2.55	0.51	1.73 ± 0.81	1.72 ± 0.82	0.97	1.70 ± 1.07	1.57 ± 0.64	0.53	1.92 ± 0.94	1.83 ± 1.06	0.65	1.80 ± 0.93	1.67 ± 0.77	0.47	1.89 ± 0.76	4.15 ± 24.32	0.66
Mean haemoglobin (HB) (g/L)	130.00 ± 21.17	132.41 ± 20.16	0.48	128.44 ± 22.76	130.19 ± 20.32	0.64	128.61 ± 23.49	129.57 ± 21.18	0.80	127.44 ± 21.03	131.15 ± 21.11	0.28	125.91 ± 17.95	130.59 ± 20.50	0.19	125.95 ± 18.11	127.41 ± 18.69	0.64
Mean haematocrit (Hct) (SI)	0.40 ± 0.07	0.41 ± 0.06	0.45	2.28 ± 17.07	0.40 ± 0.06	0.39	0.40 ± 0.07	0.40 ± 0.07	0.98	0.39 ± 0.06	0.40 ± 0.06	0.21	0.38 ± 0.05	0.40 ± 0.06	0.15	1.13 ± 6.91	0.39 ± 0.05	0.24
Uric acid (mg/dL)	367.46 ± 100.75	390.09 ± 134.86	0.45	366.02 ± 105.64	418.5 ± 115.78	0.08	383.83 ± 97.46	409.48 ± 132.6	0.41	370.71 ± 115.92	433.08 ± 137.05	0.14	378.42 ± 87.24	394.00 ± 101.31	0.65	380.87 ± 92.23	390.96 ± 95.97	0.49
Mean alanine transferase (ALT) (U/L)	40.72 ± 23.59	44.22 ± 40.33	0.53	39.36 ± 18.78	41.20 ± 33.75	0.18	40.65 ± 32.79	47.25 ± 55.54	0.66	37.42 ± 18.91	37.65 ± 35.91	0.29	40.10 ± 21.44	41.63 ± 36.63	0.31	42.44 ± 21.95	43.23 ± 33.65	0.59
Mean aspartate transferase (AST) (U/L)	22.72 ± 13.77	26.79 ± 19.92	0.16	23.47 ± 14.24	26.30 ± 21.34	0.53	23.24 ± 18.45	28.43 ± 29.14	0.08	22.72 ± 14.98	23.51 ± 19.10	0.92	24.18 ± 14.14	26.73 ± 17.76	0.72	23.36 ± 12.61	25.22 ± 16.31	0.49
Total bilirubin (µmol/L)	12.13 ± 5.91	12.26 ± 6.46	0.90	13.26 ± 6.51	11.51 ± 6.45	0.13	14.13 ± 8.78	12.43 ± 9.34	0.27	13.42 ± 8.30	12.12 ± 5.55	0.29	12.55 ± 6.63	11.50 ± 5.44	0.38	13.39 ± 6.30	10.96 ± 4.60	0.41
Total protein (g/L)	73.00 ± 5.26	74.63 ± 5.41	0.08	72.85 ± 6.81	73.37 ± 4.17	0.62	73.51 ± 5.85	73.59 ± 4.32	0.93	74.25 ± 5.16	72.85 ± 5.56	0.14	72.33 ± 5.48	72.39 ± 6.15	0.11	71.62 ± 6.02	71.57 ± 5.23	0.20
Albumin (g/L)	39.65 ± 4.55	40.75 ± 4.56	0.16	39.63 ± 4.74	40.52 ± 4.09	0.26	39.76 ± 5.15	40.39 ± 4.41	0.44	40.60 ± 5.66	40.44 ± 5.06	0.87	40.34 ± 3.43	41.04 ± 8.91	0.60	39.30 ± 4.52	39.78 ± 4.47	0.57

Acute Rejection

The findings from biopsy-confirmed acute rejection (BPAR) are shown in Table 3. There were 27 cases of BPAR (excluding borderline cases) which was higher with cyclosporine (17 cases) as compared to tacrolimus (10 cases). On the other hand, borderline changes were observed in 11 cases (cyclosporine) and 17 cases (tacrolimus), whilst an acute antibody-mediated rejection was seen only a single case during tacrolimus treatment which resolved after given plasmapheresis and intravenous immunoglobulin (IVIG).

Table 3 Pathologic findings of BPAR based on BANFF classification

BANFF classification	Cyclosporine	Tacrolimus
All acute rejection	17	10
T-cell mediated rejection: Grade IA	9	6
T-cell mediated rejection: Grade IB	7	3
T-cell mediated rejection: Grade 2A	1	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	0	0
New-onset of chronic allograft nephropathy (CAN): Moderate	0	0
New-onset of chronic allograft nephropathy (CAN): Severe	0	0
#Other changes	0	0
^Borderline changes	11	17

#Other changes are observed changes which might not be considered as a direct effect on rejection, however, may coincide with acute rejection categories (e.g. mild tubulitis, hypertensive changes, focal segmental glomerulosclerosis).

^Borderline changes is also known as 'suspicious' of acute rejection, the presence of a mild tubulitis with no intimal arteritis[12]Banff 97, developed by investigators using the Banff Schema and the Collaborative Clinical Trials in Transplantation (CCTT.

Patient and Graft Survivals

Six months post transplantation, two patients (all during cyclosporine-based treatment) died while four patients experienced loss of graft [a single case during cyclosporine treatment and three during tacrolimus treatment]. Kaplan-Meier curve indicated that the mean survival time is significantly longer (p = 0.03) with cyclosporine-based treatment (105.48 ± 4.71 months) as compared to tacrolimus-based treatment (81.70 ± 5.71 months) as indicated by Figure 1.

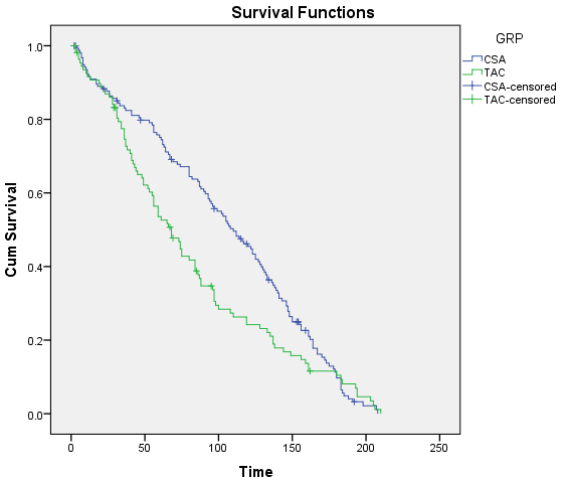

Figure 1 Comparison of mean survival time between cyclosporine-based treatment and tacrolimus-based treatment

DISCUSSION

According to our knowledge, our current study is the first local report to demonstrate that

cyclosporine and tacrolimus have a comparable safety and efficacy profiles among Malaysian renal-transplanted patients. Most importantly, the study shows that the rates of graft and patient survival as well as freedom from BPAR were high in all patients throughout the period of both drugs indicating that that these drugs can be used interchangeably. Additionally, these findings in our unique population are useful, since many factors may affect the pharmacokinetics properties of cyclosporine and tacrolimus, leading to differences in the outcomes of different populations.

Overall, there are no inferior clinical consequence as exemplified by excellent high patient, graft survival rates and a minimal incidence of acute rejection, although the drug's trough level were on the lower side of the targeted range. There are cases of BPAR reported in both drugs (a higher incidence with cyclosporine-based treatment), however, no patients experienced a Banff grade of ≥2A rejection or needed an anti-rejection therapy. This study showed similar results with another study[9] which reported a higher risk of BPAR with cyclosporine. We speculated that the higher occurrence of borderline rejections may indicate that the true difference in BPAR burden between the two drugs may even be smaller than those reported. There are other important factors that could affect the absorption and exposure of drugs that may lead to acute rejection such as CYP3A polymorphisms, dietary intake[13] and rate of gastrointestinal peristalsis[14]. Still others have documented the efficacy of combining tacrolimus with MMF with a lower incidence of acute rejection episodes as compared with combination of cyclosporine and MMF (4% vs 11%)[9]. Interestingly, more than half of the studied populations were on combination with MMF during the maintenance period.

In our current study, two patients died at 6 months post transplantation (during cyclosporine treatment and unrelated to the treatment regime) and four patients experience loss of graft (one during cyclosporine treatment and three during tacrolimus treatment) at 6 months post transplantation. Interestingly, an analysis by Kaplan-Meier showed significantly higher survival time with cyclosporine-based treatment compared with tacrolimus-based treatment. Our results are similar to the data that were recently reported for a large, phase III U.S. multicentre trial, comparing tacrolimus and cyclosporine in adult renal-transplanted patient[15]. The differences in the incidence and severity of acute rejection in renal-transplanted patients amongst cyclosporine and tacrolimus raise an important issue with regards to long-term patient and graft survival. It has been shown in several studies that acute rejection is a major risk factor for graft loss, due to a subsequent development of chronic rejection.

Although we did not observe any significant difference in mean monthly level in terms of lipid profiles between cyclosporine and tacrolimus group of treatment, an interesting trend was seen. Both treatment group shows a decrease in the serum total cholesterol and serum LDL (22% vs 6.3%, 14% vs 0% at 3-month and 3-year post transplantation). It is proposed that cyclosporine blocks the 25-hydroxylase step in bile acid synthesis. This enzyme inhibition results in increased levels of LDL cholesterol[16]. It is plausible that the mean LDL and total cholesterol are higher on overall with tacrolimus-based treatment in this study. A study by Joung et al.[17] had also demonstrated no significant changes of lipid profiles after conversion from cyclosporine to tacrolimus. This is in contrast with the reported positive effect on hyperlipidaemia with tacrolimus caused by removing the adverse effect cyclosporine on lipid metabolism[6]. Moreover, serum HDL levels rose higher in cyclosporine-based treatment by 11% (only 9.7% increase in tacrolimus group). Interestingly, a higher decrease in the mean monthly triglyceride level with tacrolimus-based treatment by 72% as compared with cyclosporine group of only 13% at 3-month and at the end of 3-year post transplantation was observed in this study. This

is in agreement with a similar clinical studies which reported a beneficial effect of tacrolimus in decreasing cardiovascular complication in renal-transplanted patient[18]. This finding is crucial as update guidance to clinicians on the increasingly crucial role of triglycerides in the evaluation and management of cardiovascular disease (CVD) risk. Cyclosporine has also been associated with elevated triglyceride levels through inhibition of lipoprotein lipase. However, the difference in response may be a result of the lack of diabetic patients in the previous study[18], and in this study we were not able to collect data on diabetic profiles due to incomplete collection of data.

In addition, our study indicates that liver function test remained stable in both periods of cyclosporine and tacrolimus. Studies have shown that renal-transplanted patients exhibit a higher rate of tacrolimus clearance[7], partly due to low haematocrit and albumin levels. Although a decrease in the mean level of albumin and ALT was observed, these values were still within the normal range. This explains the incidence of BPAR with a trough level within a therapeutic range and excellent patient and graft survival as observed in both periods of drug treatment. However, to confirm these findings, a bioequivalence study of cyclosporine and tacrolimus should ideally be undertaken in the future among the Malaysian populations.

In this study, we found that both cyclosporine and tacrolimus administration increases the serum uric acid level in renal-transplanted patients, in contrast to previous study[19]. There are several factors[20] which may contribute to the development of hyperuricaemia, including poor graft function (decreased glomerular filtration rate), hypertension, immunosuppression (especially cyclosporine), and diuretic therapy. The drug's effects are important because hyperuricaemia and gout may adversely affect renal function, and also may complicate the rehabilitation of renal-transplanted patients. Moreover, a more recent finding suggests that uric acid levels are independently associated with cardiovascular events and related to mortality and long-term transplant survival. The result of this study showed that hyperuricaemia is not an indication to convert from cyclosporine to tacrolimus in our renal-transplanted patients since both drugs produced a comparable outcome.

With regards to renal function, we did not find any significant difference in terms of serum creatinine level between cyclosporine and tacrolimus. This is despite the facts shown by other investigators the effects of calcineurin inhibitors on renal haemodynamics, especially with cyclosporine[21]. In contrast, tacrolimus has been reported to have protective effect on the renal function[22]. However, a more sensitive test for renal function formula such as Modification of Diet in Renal Disease (MDRD)[23] may be useful to demonstrate if this benefit really exists.

The strength of our study includes a long period of three years follow-up which enables a better comparison between cyclosporine and tacrolimus, thus allowing both laboratory and clinical findings to be more likely to occur in stable conditions, lending a higher degree of validity of the findings. Nevertheless, there were some drawbacks. There is the possibility of food and drug interactions which may affect the laboratory findings since patient's diet could not be controlled especially in a retrospective study. Therefore, future prospective studies with a larger number of patients will strengthen the data further.

CONCLUSION

In conclusion, tacrolimus is a convenient and safe drug to be used among renal-transplanted patients in Malaysia as well as another useful alternative to the standard cyclosporine.

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