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ORIGINAL ARTICLE

Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients

Chi Yuen Cheung, Kim Ming Wong, Hoi Wong Chan, Yan Lun Liu, Yiu Han Chan, Ho Sing Wong, Wai Leung Chak, Koon Shing Choi, Ka Foon Chau and Chun Sang Li

Department of Medicine, Queen Elizabeth Hospital, Hong Kong, China

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Correspondence
Dr Chi Yuen Cheung, Department of Medicine, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong, China. Tel.: 852 29588888; fax: 852 29585230; e-mail: simoncycheung@gmail.com

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Summary

Few studies used paired kidneys for comparison between tacrolimus and cyclosporine in renal transplantation. Most of the published data used whole blood trough levels for drug monitoring. However, the use of limited sampling strategy and abbreviated formula to estimate the 12-h area under concentration–time curve (AUC_{0-12}) allowed better prediction of drug exposure. Sixty-six first cadaveric renal transplant recipients receiving paired kidneys were randomized to receive either tacrolimus-based ($n = 33$) or cyclosporine microemulsion (Neoral)-based therapies ($n = 33$). Abbreviated AUC_{0-12} was used for drug monitoring and dose titration. Mean follow-up duration was 2.8 ± 2 years. The patient and graft survival were comparable. Fewer incidence of acute rejection was observed in tacrolimus group (15% vs. 27.3%) though the difference was not significant ($P = 0.23$). The absolute value and the rate of decline of creatinine clearance were both significantly better in tacrolimus-treated patients. Prevalence of hypertension, post-transplant diabetes mellitus, infection, and malignancy were similar in both groups. Prevalence of hypercholesterolemia (11/33 vs. 4/33) and gum hypertrophy (6/33 vs. 1/33) was more common in cyclosporine-treated patients ($P = 0.04$ in both parameters). This was the first prospective, randomized study with paired kidney analysis showing the renal function was significantly better in tacrolimus-treated patients than in cyclosporine-treated patients.

Introduction

One of the most important developments in renal transplantation in recent years was the introduction of new immunosuppressive agents for the prevention of acute rejection. Until 1980s, corticosteroids and azathioprine were the main immunosuppressive agents. Cyclosporine was introduced in renal transplantation in the 1984 [1]. The major advantages included reduction in the incidence of acute rejection and improvement in 1-year graft survival [2–4].

Since 1995, cyclosporine/Sandimmune (Sandoz, Switzerland) has been gradually replaced by cyclosporine/Neoral (Novartis, Switzerland), a microemulsion formula with a bile-independent and consistent absorption profile, which led to lower intra-patient variability than Sandimmune [5]. In controlled trials, Neoral had proven to be superior to Sandimmune in the prevention of acute rejection [6–8]. After 1995, tacrolimus (FK 506) (Prograf, Fujisawa, Japan), another calcineurin inhibitor, was employed by many centers as an alternative therapy to Neoral.

Acute allograft rejection was significantly reduced with tacrolimus-based therapy compared with cyclosporine-based therapy in different large-center randomized trials and meta-analysis [9–14]. It had been argued that this

superior effect of tacrolimus over cyclosporine might not be observed with the improved microemulsion formulation of cyclosporine. In this regard, randomized trials had been performed to compare tacrolimus and Neoral cyclosporine [15–22]. The superior results of tacrolimus-based therapy persisted even after changing to Neoral cyclosporine, which had a more consistent absorption. The better short-term results had translated into improved long-term outcome. Long-term follow-up results from the two multicenter trials revealed a more stable renal function and longer projected half-life in those patients receiving tacrolimus-based therapy compared with cyclosporine-based therapy [23,24]. Use of tacrolimus resulted in advantages in cardiovascular risk profile in terms of reduction in the prevalence of hypertension and hyperlipidemia [9,11,12,17,18,25]. Although tacrolimus-therapy was associated with an increased incidence of post-transplant diabetes mellitus [9,10,14], most of them were reversible and dose-dependent [14,23].

Despite of the available information, there were few published comparative data on paired kidney analysis. Moreover, majority of the published data used whole blood trough level for dose monitoring and titration of tacrolimus and cyclosporine therapies. It had been shown that the trough level had a poor correlation with AUC_{0-12} [26–31]. Our group favored the use of limited sampling strategy and abbreviated formula to estimate the AUC_{0-12}, which allowed better prediction of drug exposure [26].

This was the first open-label controlled randomized trial with paired kidney analysis to compare the efficacy and safety of tacrolimus with Neoral cyclosporine-based immunosuppressive therapy in first cadaveric renal transplant recipients using estimated AUC_{0-12} approach for dose titration.

Materials and methods

Trial design

This was a prospective, open-label, randomized, parallel group study. All Chinese patients receiving paired kidneys in their first cadaveric renal transplants consecutively between 1st June 1998 and 31st December 2004 in Queen Elizabeth Hospital, Hong Kong were included in the study. Follow-up outcome data were collected until 31st March 2005.

The study was performed in accordance with Declaration of Helsinki. Informed and written consent were obtained and the patients were randomized to receive triple immunosuppressive therapy with either tacrolimus or Neoral cyclosporine, concomitantly with prednisolone and azathioprine therapy. The randomization process occurred preoperatively and was on 1:1 basis.

Immunosuppressive regimens

Neoral cyclosporine was initially administered orally as a loading dose of 10 mg/kg within 12 h of surgery and then 5 mg/kg b.i.d. Abbreviated formula based on limited sampling strategy was used in this study to estimate the cyclosporine area under 12-h concentration–time curve (AUC_{0-12}). Calculation of cyclosporine AUC_{0-12} was based on the formula: $452.4 + C_0 \times 17.5 + C_{1.5} \times 1.89$ [C_0: cyclosporine trough level; $C_{1.5}$: 1.5-h postdose cyclosporine level] [31]. The dose of cyclosporine was gradually titrated to maintain the abbreviated AUC_{0-12} at around 6000–8000 ng × h/ml in the first 3-month post-transplant and 4000–6000 ng × h/ml from 3-month post-transplant onwards [33]. Whole blood levels of cyclosporine were monitored by Abbott TDX monoclonal specific assay (Abbott Laboratories, Abbott Park, IL, USA).

Tacrolimus was administered orally as capsules with loading dose of 0.3 mg/kg within 12 h of surgery and then 0.15 mg/kg b.i.d. Abbreviated tacrolimus AUC_{0-12} monitoring was used. Calculation of tacrolimus AUC_{0-12} was by the formula: $16.2 + C_2 \times 2.4 + C_4 \times 5.9$ [C_2: 2-h postdose tacrolimus level; C_4: 4-h postdose tacrolimus level]. Based on our previous pilot study in stable patients on tacrolimus, AUC_{0-12} value was kept at around 100–150 ng × h/ml in first 3 months and around 80–100 ng × h/ml after 3 months [26]. Whole blood levels of tacrolimus were monitored by means of IMx tacrolimus II assay (Abbott Laboratories).

Concomitant immunosuppressive therapy was identical in the two arms of the trial. A bolus dose of i.v. methylprednisolone 500 mg was given on day 1. This was followed by i.v. hydrocortisone 100 mg every 6 h for 3 days and followed by oral prednisolone 30 mg daily. The dose of prednisolone was gradually tapered after the first month at a rate of 2.5 mg every 2 weeks and then maintained at 5 mg daily. Azathioprine was given at a dose of 1.5 mg/kg daily since day 1.

Since 1999, some of our patients have also received interleukin-2 receptor antagonist during induction therapy on a voluntary basis. Patients on Neoral cyclosporine was given Basiliximab (Simulect, Novartis, Switzerland) while patients on tacrolimus was given Daclizumab (Zenapax, Roche, NJ, USA). Basiliximab was given at a dose of 20 mg around 2 h before transplantation and the second dose was given 4 days after transplantation. Daclizumab was given at 1 mg/kg infusion around 2 h before transplantation and then every 14 days for four more doses.

If a rejection episode occurred, our protocol prescribed pulse methylprednisolone therapy as first-line treatment with the dosage of 500 mg daily for 3 days. In case of steroid resistant rejection, appropriate antibody therapy was started.

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Clinical outcome parameters

Primary endpoints were patient survival, graft survival and the overall rate of acute rejection. Graft loss was defined as the need to resume long-term dialysis, re-transplantation, transplant nephrectomy or death. Rejection was defined as any episode with the relevant clinical and laboratory signs and symptoms and all clinically apparent episodes of rejection were confirmed by core biopsy. Rejection was classified according to Banff 97 classification [34] after assessment by local pathologists.

The secondary endpoints were the course of renal function, the cardiovascular risk profile, the incidence of infection, and malignancy. Renal function parameters were serum creatinine and estimated creatinine clearance (CrCl) by means of Cockcroft–Gault formula and expressed in milliliter per minute [35]. The annualized change of CrCl (ml/min/year) was used to monitor the progression of renal function decline. Positive value means improvement or stabilization of renal function while negative value means decline in CrCl.

The cardiovascular risk profile was assessed by the incidence of hypertension, hypercholesterolemia, and diabetes mellitus. Hypercholesterolemia was defined as total cholesterol >5.8 mM (224 mg/dl) or requiring lipid-lowering agent. The use of drugs for hypertension or hypercholesterolemia was established from the medical record. Post-transplant diabetes mellitus was defined as fasting blood glucose more than 7 mM (126 mg/dl) on two occasions at any time after transplantation in those patients with no previous history of diabetes mellitus.

Statistical analysis

The intention-to-treat population was used for analyses of both efficacy and safety and included all randomized patients who underwent transplantation and received at least one dose of study medication. Values were expressed as mean (SD) or median (range). Baseline and demographic data were compared by Student's *t*-test, Pearson's chi-squared test or Fisher's exact test where appropriate. Pearson's chi-squared test or Fisher's exact test was used to compare the rates of adverse events between treatment groups. Kaplan–Meier model and log-rank test were used to compare the patient survival, graft survival and rejection-free survival. The annualized change of CrCl for each patient was determined using simple linear regression. At least three estimates over two consecutive years of follow-up were required to calculate the annualized change of CrCl. A *P*-value of <0.05 was considered to be statistically significant.

Results

One hundred consecutive Chinese cadaveric renal transplant recipients were performed during the study period. Among them, 66 patients received paired cadaveric kidneys (for each pair of graft kidneys from the same donor, one was transplanted in tacrolimus group and the other transplanted in cyclosporine group). The remaining 34 patients received unpaired cadaveric kidneys (when only one kidney was available for transplantation because of single kidney donation or sharing with other transplant centers). In this study, only those paired kidney recipients were analyzed.

There were 33 patients randomized to each group and the mean follow-up duration was 2.8 ± 2 years. The baseline characteristics were depicted in Table 1. No statistically significant differences were observed in baseline parameters in both groups of patients. There were also no differences between those with or without interleukin-2 receptor antagonists (Table 2).

Patient survival

Two patients in the tacrolimus group (6.1 %) died with a functioning graft during the study. One patient died 1 year after renal transplantation because of acute myocardial infarction while the other died of carcinoma of stomach 3.5 years after kidney transplant. On the other hand, the patient survival in the cyclosporine group was 100% during the study. There was no significant difference in patient survival ($P = 0.16$).

Graft survival

A total of five patients had graft failure in the first year. Three of them belonged to the tacrolimus group while two belonged to cyclosporine group. Early graft nephrectomy was done in two patients because of graft vascular thrombosis (one in either group), in two patients (one in either group) because of graft artery anastomotic leakage and in one patient (tacrolimus group) because of rupture of graft kidney. The ruptured graft was shown to have Banff type III acute rejection on histology. The first year graft survival rate, not censored for death, in the tacrolimus group during the study was 91% while in the cyclosporine group, it was 94%. There was also no difference between both groups ($P = 0.25$).

Acute rejection

A total of 14 patients (five patients in tacrolimus group and nine patients in cyclosporine group) were treated

Table 1. Baseline characteristics of the paired kidneys.

	Tacrolimus ($n = 33$)	Cyclosporine ($n = 33$)	*P*-value
Age (years)	42.4 ± 7.5	41.2 ± 12.6	0.65*
Male (*n* %)	17 (51.5)	20 (60.6)	0.46†
HLA-A & -B (≥2 mismatch) (*n* %)	27 (81.8)	28 (84.8)	0.74†
HLA-DR (≥1 mismatch) (*n* %)	27 (81.8)	31 (93.9)	0.13†
PRA (%)	22.3 ± 33.2	19.3 ± 26.7	0.69*
Donor age (years)	47.4 ± 13.6	47.4 ± 13.6	1.00*
Donor kidney weight (grams)	182.5 ± 42.7	182.1 ± 47.6	0.97*
Cold ischemic time (hours)	10.0 ± 6.8	7.9 ± 4.8	0.15*
Anastomotic time (minutes)	47.2 ± 9.8	50.9 ± 16.8	0.28*
Use of interleukin-2 (IL-2) receptor antagonist (*n* %)	20 (60.6)	19 (57.6)	0.80†
Primary cause of renal failure (*n* %)			
Chronic glomerulonephritis	20 (60.6)	20 (60.6)	1.00†
Diabetes mellitus	3 (9.1)	2 (6.1)	1.00†
Polycystic kidney disease	2 (6.1)	0 (0)	0.47†
Others/unknown	8 (24.2)	11 (33.3)	0.41†

Values expressed as mean ± SD or number (percentage).
*Student's *t*-test, †Pearson's chi-squared test.
PRA (panel-reactive antibody).

Table 2. Baseline characteristics of the patients with or without IL-2 receptor antagonists.

	Patients with IL-2R antagonists ($n = 39$)	Patients without IL-2R antagonists ($n = 27$)	*P*-value
Age (years)	40.9 ± 10.0	43.1 ± 10.9	0.39*
HLA-A & -B (≥2 mismatch) (*n* %)	33 (84.6)	22 (81.5)	0.73†
HLA-DR (≥1 mismatch) (*n* %)	34 (87.1)	24 (88.9)	0.84†
PRA (%)	17.5 ± 28.0	25.5 ± 32.5	0.29*
Donor age (years)	48.6 ± 18.2	44.6 ± 10.8	0.39*
Donor kidney weight (grams)	189.6 ± 36.1	171.5 ± 54.2	0.12*
Cold ischemic time (hours)	9.5 ± 6.4	8.5 ± 5.0	0.51*
Anastomotic time (minutes)	48.2 ± 8.8	50.0 ± 18.6	0.62*

Values expressed as mean ± SD or number (percentage).
*Student's *t*-test, †Pearson's chi-squared test.
PRA (panel-reactive antibody).

Table 3. Types of acute rejection (Banff 97 classification).

Episodes of acute rejection	Tacrolimus ($n = 5$)	Cyclosporine ($n = 9$)
Borderline	0	1
Type IA	0	3
Type IB	3	1
Type II A	1	2
Type II B	0	1
Type III	1	1

for acute rejection. All were confirmed by renal biopsy. The histological type of the rejection was depicted in Table 3. All patients responded to pulse steroid therapy except the patient in the tacrolimus group with type III rejection requiring graft nephrectomy for ruptured graft kidney while the one in the cyclosporine group with type IIB required plasmapheresis. The patient with type III rejection in the cyclosporine group responded well with pulse steroid. Fewer acute rejections were observed in the tacrolimus group: 15% (5/33) vs. 27.3% (9/33) but the difference was not statistically significant ($P = 0.23$). The rejection-free survival was similar ($P = 0.25$; Fig. 1).

Renal function

The CrCl was calculated using Cockcroft–Gault formula and was shown in Table 4 and Fig. 2. In the first 3 months, there was no significant difference between both groups. However, the CrCl was significantly better with tacrolimus therapy than cyclosporine therapy from 6 months onwards. There was no difference in the use of angiotensin-converting enzyme inhibitors or angiotension

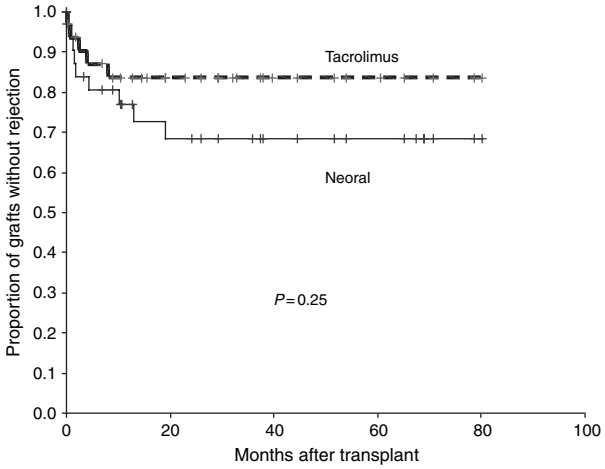

Figure 1 Kaplan–Meier estimates of rejection-free survival.

II receptor blockers between them (2/33 in tacrolimus group vs. 3/33 in cyclosporine group, $P = 0.64$).

If we excluded those with acute clinical rejection and compared the paired kidneys again, the CrCl was still significantly better with tacrolimus therapy than cyclosporine therapy from 1 year onwards (Table 5).

After excluding a pair of primary nonfunctioning kidneys, we compared the remaining 32 pairs of kidneys separately. Twenty-four patients belonging to tacrolimus group had a better CrCl than their counterparts. On the other hand, only eight patients belonging to cyclosporine group had a better CrCl.

Stability of renal function over time

The annualized change in CrCl in the tacrolimus group was 2.73 ± 5.14 ml/min/year while in the cyclosporine group, the annualized change in CrCl was −1.13 ± 4.08 ml/min/year. The difference was statistically significant ($P < 0.01$). A total of 80% of tacrolimus-treated patients had improvement in CrCl while 20% had a decline. This was significantly better than cyclosporine-treated patients (42.1% had improvement while 57.9% showed a decline) ($P = 0.02$).

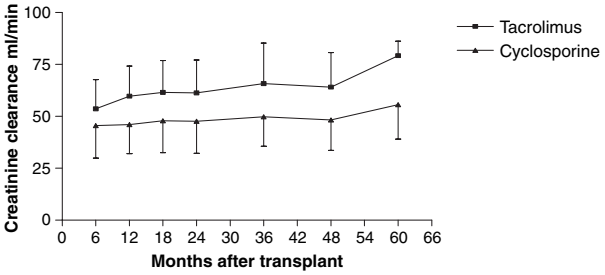

Figure 2 Changes of creatinine clearance over time.

Dose of immunosuppressive agents

In the tacrolimus group, the starting dose was 0.3 mg/kg/day and gradually decreased to 0.07 ± 0.01 mg/kg/day as the maintenance dose. In the cyclosporine group, the starting dose was 10 mg/kg/day and gradually decreased to the maintenance dose at 2.86 ± 0.71 mg/kg/day (Table 6).

Level of immunosuppressive agents

For monitoring and dosage adjustment, AUC_{0-12} levels of tacrolimus and cyclosporine were estimated by using abbreviated equations [26, 32]. These were shown in Table 7.

Hypercholesterolemia

Significantly more patients in the cyclosporine group (11/33, 33.3%) suffered from hypercholesterolemia when compared with tacrolimus group (4/33, 12.1%) ($P = 0.04$; Table 8).

Hypertension

There was no significant difference between the cyclosporine group (25/33, 75.8%) and tacrolimus group (27/33, 81.8%) ($P = 0.52$; Table 8). Patients in the cyclosporine group tended to use more antihypertensive medications

Table 4. Changes of creatinine clearance (CrCl) over time (intention to treat).

Mean ± SD CrCl (ml/min)	Tacrolimus group	Number of patients	Cyclosporine group	Number of patients	*P*-value
1 month	49 ± 15	30	42 ± 18	31	0.143
3 months	60 ± 18	30	51 ± 18	31	0.072
6 months	54 ± 14	30	46 ± 16	31	0.043
12 months	60 ± 15	30	46 ± 14	31	0.002
24 months	61 ± 16	24	48 ± 15	26	0.012
36 months	66 ± 20	22	50 ± 14	24	0.033
48 months	64 ± 16	15	48 ± 15	18	0.050
60 months	79 ± 7	10	56 ± 17	13	0.012

Table 5. Changes of creatinine clearance over time after excluding those with acute rejection.

Mean ± SD CrCl (ml/min)	Tacrolimus group	Number of patients	Cyclosporine group	Number of patients	*P*-value
6 months	55 ± 14	27	45 ± 18	26	0.176
12 months	61 ± 14	26	50 ± 14	24	0.025
24 months	61 ± 16	24	51 ± 15	24	0.050
36 months	66 ± 20	22	50 ± 14	24	0.033
48 months	64 ± 17	15	48 ± 15	18	0.050
60 months	79 ± 7	10	56 ± 17	13	0.012

Table 6. Change of dose of immunosuppressive agents over time.

Mean ± SD dose of drug	Tacrolimus (mg/kg/day)	Neoral (mg/kg/day)
0 day	0.30	10
2 weeks	0.21 ± 0.06	7.20 ± 1.16
1 month	0.18 ± 0.07	5.84 ± 1.71
3 months	0.12 ± 0.06	4.08 ± 1.20
6 months	0.09 ± 0.05	3.61 ± 0.99
12 months	0.07 ± 0.03	3.61 ± 1.06
24 months	0.06 ± 0.02	3.28 ± 0.78
36 months	0.06 ± 0.02	3.18 ± 0.80
48 months	0.07 ± 0.01	3.06 ± 0.81
60 months	0.07 ± 0.01	2.86 ± 0.71

Table 7. Change of concentration–time curve of immunosuppressive agents over time.

Mean ± SD AUC_{0-12} (ng*h/ml)	Tacrolimus	Cyclosporine
2 weeks	149 ± 42	9828 ± 4839
1 month	143 ± 53	7573 ± 1389
3 months	126 ± 33	5482 ± 1661
6 months	109 ± 24	4813 ± 1351
12 months	98 ± 25	4007 ± 948
24 months	96 ± 26	3706 ± 652
36 months	90 ± 22	4438 ± 1028
48 months	97 ± 26	4843 ± 2280
60 months	98 ± 10	4951 ± 308

Table 8. Complications in tacrolimus and Neoral cyclosporine group.

Complications, *n* (%)	Tacrolimus ($n = 33$)	Cyclosporine ($n = 33$)	*P*-value
Hypertension	27 (81.8%)	25 (75.8%)	0.52
Hypercholesterolemia	4 (12.1%)	11 (33.3%)	0.04
Diabetes mellitus	3 (9.1%)	2 (6.1%)	0.64
Urinary tract infection	10 (30.3%)	8 (24.2%)	0.58
Opportunistic infection	13 (39.4%)	16 (48.4%)	0.25
Malignancy	2 (6.1%)	2 (6.1%)	1

(2.1 ± 1.6 in cyclosporine group versus 1.9 ± 1.3 in tacrolimus group); however, it did not reach statistically significant level ($P = 0.61$).

Post-transplant diabetes mellitus

The incidence of post-transplant diabetes mellitus was higher in tacrolimus group, but the difference was not statistically significant [9.1% (3/33) in tacrolimus group versus 6.1% (2/33) in cyclosporine group, $P = 0.64$; Table 8]. Of the three patients suffering from post-transplant diabetes mellitus in the tacrolimus group, one was able to withdraw all diabetic medications within the first year. On the other hand, the two patients in the cyclosporine group required diabetic medications during the study period.

Infection

The episodes of bacterial urinary tract infection were slightly more common in tacrolimus group (10/33 in tacrolimus group versus 8/33 in cyclosporine group). However, the difference was not significant ($P = 0.58$; Table 8). For opportunistic infection, the incidence in both groups was also comparable (13/33 in tacrolimus group versus 16/33 in cyclosporine group, $P = 0.25$; Table 8).

Malignancy

There were two patients in each group (6.1%) who developed malignancy after transplant. In the tacrolimus group, one had carcinoma of stomach while the other had carcinoma of thyroid. In the cyclosporine group, one had Kaposi sarcoma and the other had hepatocellular carcinoma. No statistical significant differences were observed between them ($P = 1$; Table 8).

Neurotoxicity

There were more tremor and numbness in tacrolimus group (21/33 in tacrolimus group versus 16/33 in cyclo-

sporine group), but the difference was not statistically significant ($P = 0.21$).

Cosmetic side effects

Acne and hirsutism were comparable in both groups, but the gum hypertrophy was more common in cyclosporine group (1/33 in tacrolimus group versus 6/33 in cyclosporine group, $P = 0.04$).

Discussion

Although there were many studies comparing tacrolimus and cyclosporine Sandimmune or Neoral in renal transplant recipients in recent years, most of the patients involved were Caucasian. There were very few similar comparative studies in Chinese patients. All of the patients in our study were from a homogeneous population. They were Chinese patients undergoing first cadaveric renal transplantation. To eliminate the confounding factors attributed to differences in the donor kidney status, patients recruited in this study received paired cadaveric kidneys (one to each group), which allowed better comparison between the two groups under similar donor factors. To the best of our knowledge, this was the first published single center and randomized trial with paired kidney analysis for direct comparison of tacrolimus and cyclosporine therapies. Furthermore, all the published data were based on the drug trough level for dose titration of both tacrolimus and cyclosporine. To improve the accuracy of therapeutic drug monitoring, we employed area under the curve (AUC_{0-12}) estimated by limited sampling equations to compare the efficacy and safety of tacrolimus and cyclosporine therapies.

In the US and European trials, whole blood tacrolimus and cyclosporine trough levels were used for drug monitoring and dosage adjustment [9–12]. On the other hand, abbreviated AUC method was used for dose optimization in our center. Many centers relied on measurements of tacrolimus trough level (C_0), because it was generally thought that they could reflect AUC_{0-12} [36]. However, different studies yielded different results recently [26,27,37,38]. Our group had reported a pharmacokinetic study in 18 stable Chinese renal transplant recipients [26]. We found that C_0 had a poor correlation with AUC_{0-12} ($R^2 = 0.12$). On the other hand, abbreviated AUC_{0-12} obtained by two-time point regression equation using 2- (C_2) and 4-h (C_4) tacrolimus concentrations obtained an R^2-value of 0.93. In present study, the target abbreviated AUC_{0-12} for tacrolimus was 100 ng × h/ml after 3 months. By extrapolation of the relationship between C_0 and AUC_{0-12}, this corresponded to a C_0 of around 6 ng/ml. This explained the lower tacrolimus dose and lower incidence of post-transplant diabetes in our center. Moreover, cyclosporine trough level was not a reliable indicator of total drug exposure and subsequent clinical events [39]. As a result, investigators had advocated using time point sampling to estimate AUC_{0-12} [29–32]. In our study, we used the two-time point regression equation obtained from the Chinese population to estimate the AUC_{0-12} [32].

The use of interleukin-2 receptor antagonists in some of our patients might introduce bias to this study. However, we showed that there were no differences in the baseline characteristics between those receiving interleukin-2 receptor antagonists and those did not. Moreover, there was also no difference in the percentage of patients on interleukin-2 receptor antagonists in both treatment groups. Although two different preparations of interleukin-2 receptor antagonists were used, there were no controlled studies showing any differences between basiliximab and daclizumab in terms of prevention of acute rejection, incidence of infections, and malignancies [40]. We could say that the use of interleukin-2 receptor antagonists were identical in both arms.

Both tacrolimus and cyclosporine were nephrotoxic drugs [41]. Many studies showed that the renal function was comparable between tacrolimus and cyclosporine after transplantation. [9–11,15,16,18,21]. In a study using paired kidney analysis [42], serum creatinine was significant lower in tacrolimus group. However, the slope of 1/Cr did not appear to be different between the two agents. In present study, we calculated the CrCl using Cockcroft–Gault formula. Equation derived from the Modification of Diet in Renal Disease (MDRD) study was not used in our study, because it had not been validated in Chinese population [43–45]. We found that patients treated with tacrolimus had a significant better CrCl starting from 6-month after transplantation. The difference sustained throughout the 5-year period. The maintenance of renal function in the tacrolimus group was further evident by slower decline of CrCl during the follow-up period. We also found that more patients in Neoral cyclosporine group suffered from deterioration in renal function. As this was a paired kidney analysis, the difference was unlikely because of the differences in any donor variables. One of the main reasons for this deterioration could be due to the development of chronic allograft nephropathy in the cyclosporine group. In a study of healthy volunteers by Klein *et al.*, tacrolimus had no effect on renal hemodynamics and systemic blood pressure. In contrast, cyclosporine led to a decrease in glomerular filtration rate (GFR) and renal plasma flow and an increase in blood pressure. This difference in functional nephrotoxicity might contribute to structural lesions found in chronic calcineurin-inhibitor nephrotoxicity [46]. This would affect the long-term renal graft

survival. Another possible explanation for the better renal function in tacrolimus-based patients might be related to the lower incidence of subclinical rejection. Subclinical rejection was shown to correlate closely with subsequent allograft dysfunction [47,48]. However, it could not be shown in this study because protocol biopsies were not performed in our center.

In conclusion, we found that both the absolute value and the rate of decline in CrCl over time were significantly better in tacrolimus group compared with cyclosporine group in this paired kidney analysis. A lower incidence of acute rejection was also observed in our Chinese patients when compared with the Caucasian. The use of abbreviated AUC_{0-12} might provide an alternate tool for drug monitoring, especially with the many limitations of using trough level as discussed above. Although there was a lower incidence of acute rejection in tacrolimus group, the difference was not statistically significant. The patient and graft survival were comparable in both groups of patients. No significant differences were noted between tacrolimus and cyclosporine-based therapies in terms of prevalence of hypertension, post-transplant diabetes mellitus, infection, malignancy, and neurotoxicity. However, hyperlipidemia and gum hypertrophy were more common in cyclosporine group.

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