Research Article

ประสิทธิภาพและความปลอดภัยของยากดภูมิคุ้มกันในผู้ป่วยปลูกถ่ายไต โรงพยาบาลสรรพสิทธิประสงค์

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บทคัดย่อ

ประสิทธิภาพและความปลอดภัยของยากดภูมิคุ้มกันในผู้ป่วยปลูกถ่ายไต โรงพยาบาลสรรพสิทธิประสงค์

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รับบทความ : 27 มิถุนายน 2561 **แก้ไขบทความ:** 9 ตุลาคม 2561 **ตอบรับ:** 16 ตุลาคม 2561

ยากดภูมิคุ้มกันมีบทบาทในการป้องกันการปฏิเสธไตเฉียบพลันในผู้ป่วยปลูกถ่ายไต อย่างไรก็ตามการปฏิเสธไตยังสามารถเกิดขึ้นได้แม้จะได้รับการรักษาด้วยยากดภูมิคุ้มกันอย่างเหมาะสม **วัตถุประสงค์:** เพื่อศึกษาประสิทธิภาพและความปลอดภัยของยากดภูมิคุ้มกันในผู้ป่วยปลูกถ่ายไต ผลลัพธ์หลักคืออัตราการปฏิเสธไต ผลลัพธ์รองได้แก่ อัตราการเกิดเหตุการณ์ไม่พึงประสงค์จากยา อัตราการทำงานของไต อัตราการรอดชีวิตของผู้ป่วย และอัตราการรอดชีวิตของอวัยวะปลูกถ่าย **วิธีการ:** เป็นการศึกษาแบบย้อนหลังในผู้ป่วยปลูกถ่ายไตจำนวน 132 คนที่เข้ารับบริการที่แผนกไตเทียม โรงพยาบาลสรรพสิทธิประสงค์ ระหว่างวันที่ 1 มกราคม พ.ศ. 2541 ถึง 31 ตุลาคม พ.ศ. 2559 ผู้ป่วยที่เข้าการศึกษาจะถูกจัดกลุ่มตามสูตรยากดภูมิคุ้มกันที่ได้รับ **ผลการศึกษา:** จากผู้ป่วยที่เข้าการศึกษาจำนวน 103 คน ค่าเฉลี่ยอายุเท่ากับ 40 ปี เป็นเพศชายร้อยละ 68.9 เป็นไตจากผู้บริจาคสมองตายร้อยละ 83.5 มีผู้ป่วยจำนวน 9 คน, 89 คน และ 5 คนตามสูตรยาในระยะแรก และมีผู้ป่วยจำนวน 2 คน, 85 คน และ 16 คนตามสูตรยาในระยะยาว ถูกจัดอยู่ในกลุ่ม cyclosporine, tacrolimus และ everolimus ตามลำดับ ค่าเฉลี่ยของ serum creatinine เท่ากับ 1.99±1.01 mg/dL, 1.59±0.85 mg/dL และ 1.54±0.63 mg/dL และค่าเฉลี่ยของ eGFR เท่ากับ 45.04±16.75 mL/min, 57.48±22.98 mL/min และ 69.46±23.29 mL/min ในกลุ่มที่ได้รับ cyclosporine, tacrolimus และ everolimus ตามลำดับ เมื่อเปรียบเทียบยาในกลุ่ม calcineurin inhibitor (CNI) พบว่าในกลุ่มที่ได้รับ tacrolimus มีการทำงานของไตที่เหนือกว่า cyclosporine อย่างมีนัยสำคัญทางสถิติ (P<0.0001) พบการปฏิเสธไต จำนวน 6 คน คิดเป็นร้อยละ 5.9 ซึ่งไม่แตกต่างกันในกลุ่มที่ได้รับ cyclosporine และ tacrolimus (11.1% vs. 5.6%; P=0.448) ไม่พบการปฏิเสธไตในกลุ่มที่ได้รับ everolimus อัตราการรอดชีวิตของผู้ป่วยและของอวัยวะปลูกถ่าย ที่ 3 เดือน คิดเป็นร้อยละ 97.1 และ 95.1 ตามลำดับ ส่วนที่ 1 ปี, 3 ปี และ 5 ปี คิดเป็นอย่างละร้อยละ 83.5, 46.6 และ 12.6 ตามลำดับ อัตราการเกิดเหตุการณ์ไม่พึงประสงค์จากยาไม่แตกต่างกันระหว่างกลุ่มผู้ป่วย และส่วนใหญ่จัดเป็นระดับความรุนแรง 1 และ 2 **สรุปผล:** ยากดภูมิคุ้มกันมีประสิทธิภาพในการป้องกันการปฏิเสธไต การได้รับ tacrolimus ทำให้การทำงานของไตเหนือกว่าสูตรอื่น และมีอัตราการเกิดเหตุการณ์ไม่พึงประสงค์จากยาที่ยอมรับได้

คำสำคัญ: การปฏิเสธไต, ยากดภูมิคุ้มกัน, การปลูกถ่ายไต

Efficacy and Safety of Immunosuppressive Drugs in Kidney Transplant Recipients; A Case Study in Sunpasitthiprasong Hospital

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Abstract

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Immunosuppressive drugs play a major role for prevention of acute graft rejection in kidney transplant patients. However, graft rejection can still occur despite a proper immunosuppressive therapy. **Objectives:** To investigate the efficacy and safety of immunosuppressive drugs among kidney transplant patients. The primary outcome was the graft rejection rate. The secondary outcomes were the rate of adverse drug events, renal function, patient survival, and graft survival. **Methods:** A retrospective study was conducted among 132 kidney transplant patients who were followed-up at dialysis unit, Sunpasitthiprasong hospital from January 1, 1998 to October 31, 2016. All eligible patients were grouped according to the immunosuppressive regimen. **Results:** Among overall 103 included patients, the mean age was 40 years old and 68.9% of them were male. Of these, 83.5% had received a cadaveric kidney transplants. Cyclosporine, tacrolimus, and everolimus were given as an initial immunosuppressive regimen in 9, 89, and 5 patients, respectively. Whereas 2, 85, and 16 patients had received maintenance immunosuppressive regimen with cyclosporine, tacrolimus, and everolimus, respectively. The mean serum creatinine was 1.99±1.01 mg/dL, 1.59±0.85 mg/dL, and 1.54±0.63 mg/dL, the mean estimated glomerular filtration rate (eGFR) was 45.04±16.75 mL/min, 57.48±22.98 mL/min, and 69.46±23.29 mL/min along the period of the study among cyclosporine, tacrolimus, and everolimus group, respectively. Among the calcineurin inhibitor based regimen, in tacrolimus treated patients had significantly better renal function maintenance than cyclosporine treated patients (P<0.0001). The graft rejection was found in 6 patients (5.9%) and the rate of graft rejection was not significantly different between the cyclosporine and tacrolimus group (11.1% vs. 5.6% P=0.448) and none of graft rejection in everolimus group. At three months, the patient and graft survival rate were 97.1% and 95.1%, respectively. The patients' survival rate at 1 year, 3 years, and 5 years, were 83.5%, 46.6%, and 12.6%, respectively. Adverse events had been similar between three groups and almost categorized into severity grade 1 to 2. **Conclusion:** Cyclosporine, tacrolimus, and everolimus have a satisfactory clinical efficacy and well tolerability for prevention of acute graft rejection among kidney transplant patients. Tacrolimus, however, there appears to be an attractive option due to a better preservation of kidney function maintenance with an acceptable adverse events.

Keywords: graft rejection, immunosuppressive drugs, kidney transplantation

Introduction

Kidney transplantation is an alternative treatment for patients with end-stage renal disease (ESRD) (Garcia-Garcia *et al.*, 2012; Suthanthiran and Strom, 1994; Collins *et al.*, 2015). The report from the kidney transplantation registry in the United States of America during 1998 to 2007 showed that the number of patients on the kidney transplant waiting list was increasing by 86% from 40,825 cases to 76,070 cases (McCullough *et al.*, 2009). This number was dramatically raising to 99,886 in 2016, whereas only 17,878 cases could be able to receive kidney transplantation at the end of year 2015. Of these, 12,250 and 5,628 cases received kidney transplantation from deceased and living donors, respectively (United Network for Organ Sharing [UNOS], 2015). In Thailand, the overall number of patients who received kidney transplantation was 8,132 cases. Of these, 4,311 and 3,821 cases were the kidney transplant recipients from deceased and living donor, respectively. Among the 4,748 patients on the Thailand kidney transplant waiting list, only 636 patients was carried out for a kidney transplant in 30 hospitals across the country. Of these, 219 and 417 cases were the kidney transplant recipients from deceased and living donor, respectively (Thai Transplantation Society, 2017).

Although the first year survival rate was more than 90% for either patient undergoing kidney transplantation or dialysis, patient undergoing kidney transplantation has a better survival rate at 5 and 10 years. Based on the data from Thai Transplantation Society, the survival rate at 1, 5 and 10 years for recipients of living donor kidney transplant were 98.9%, 95.9% and 91.3%, respectively. While, the survival rate at 1, 5 and 10 years for recipients of deceased donor kidney transplant were 95.9%, 91.5% and 82.8%, respectively, the graft survival rates at 1, 5 and 10 years were 98.5%, 94.3% and 82.6%, respectively for a living donor recipients, and 94.6%, 85.0% and 71.6%, respectively for a deceased donor recipient (Thai Transplantation Society, 2017). Graft rejection is the immune responding to transplanted organ which is related to T-cell and B-cell, and it can be called “alloimmune response”. As graft rejection can lead to graft loss (Halloran, 2004). All kidney transplant patients are required to take life-long immunosuppressive drugs after transplantation to prevent acute and chronic graft rejection from host immune response (Kaufman and Batuman, 2015). A result from previous study conducted during 1985 to 1999 showed that the incidence of acute graft rejection was 37% in kidney transplant recipients from deceased donors who were treated with cyclosporine-A based regimen.

Despite receiving a standard immunosuppressive treatment according to the practice guideline, graft rejection can still occur. The risk of graft rejection varies by the type of immunosuppressive regimen. Marcen R et al conducted a study to examine the incidence of graft rejection among various immunosuppressive regimes in Spanish kidney transplant patients during 1979-2007. The results of the study showed that the incidence of acute graft rejection among patients treated with azathioprine, cyclosporine, and tacrolimus were 68.7%, 38.2%, and 11.4%, respectively (Marcen *et al.*, 2009). Kidney transplant center at Sunpasitthiprasong Hospital, a 1,000 beds tertiary level hospital, is one of the 30 kidney transplant center across Thailand. This service has been provided since 1998. Currently, more than the 100 recipients have undergone kidney transplants from both deceased and living donors. In our center, the immunosuppressive regimen comprised the 3 drugs of the calcineurin inhibitor (CNI) (cyclosporine or tacrolimus) or mammalian target of rapamicin (mTOR) inhibitor (everolimus) as a mainstay treatment with corticosteroids (prednisolone) and purine antagonist (mycophenolate mofetil or mycophenolate sodium) as a concomitant therapy. In the early stages, cyclosporine was primarily used up until the year 2012, and then tacrolimus was used instead of cyclosporine. However, data on the graft rejection and toxicity from immunosuppressive drug on our site has never been systematically evaluated. This is the first major study of those kidney transplant patients in this center to compare the efficacy and toxicity of immunosuppressive drugs among kidney transplant recipients at kidney transplant center, Sunpasitthiprasong Hospital.

Methods

Study design and patient population

A retrospective cohort study was performed among the patients who received a surgery kidney transplantation and there had been followed-up at nephrology unit, Sunpasitthiprasong Hospital from January 1, 1998 to October 31, 2016 were included. A patient who received a surgery from the other hospitals, the patients who did not receive the immunosuppressive drugs regimen that provide used in Sunpasitthiprasong Hospital and patients with loss of follow up after transplantation were excluded from the study.

Data collection and analysis

The participated patients were classified into 3 groups, cyclosporine, tacrolimus and everolimus based on their initial and maintenance immunosuppressive therapy. The demographic data on each visit were collected including, sex, age, body weight, underlying disease, date of transplantation, type of kidney donor, and immunosuppressive regimen (initial and maintenance). The laboratory data on each visit were blood pressure, serum creatinine, eGFR-CKD-EPI, fasting blood sugar, hemoglobin, white blood cells, platelet counts, cholesterol, triglycerides and albuminuria and any other suspected complications were evaluated on each visit according to the report in medical record. The graft rejection, death and graft rejection on each visit were also evaluated. Because of its narrow therapeutic index property, the drug level were detected in Sunpasitthiprasong Hospital with whole blood sample (EDTA) include cyclosporine (Neoral®) and tacrolimus (Prograf®) by the chemiluminescence immunoassay (CLIA) method with the Cobas® 6000 from Roche pharmaceutical company. The drug level of everolimus (Certican®) had been measured at Siriraj Hospital by fluorescence polarization immunoassay (FPIA) method. The patient survival was meaning the time of living of patients after transplantation until to death status and the graft survival was defined as the time of living of the new kidney organ after transplantation until to graft loss diagnosed.

The parameters monitoring included laboratory of each patient on each visit were determined at the first day of kidney transplant until the index date. The graft rejection was confirmed by the graft biopsy and the Banff classification was used to classify the type of graft rejection (Solez *et al*., 1993). Serum drug levels were interpreted according to the therapeutic range of immunosuppressive drugs for maintenance therapy from Thai Transplantation Society (Thai Transplantation Society, 2017). Adverse drug event after kidney transplantation were assessed by the Naranjo's algorithm (Naranjo *et al*., 1981). Acute kidney injury, hypertension, hyperglycemia, hypertriglyceridemia, and hypercholesterolemia were considered if those laboratory were above the normal range, then anemia, leukopenia, and thrombocytopenia were considered if those laboratory were less than the normal range, of these were based on the Common Terminology Criteria for Adverse Events; CTCAE version 4.0 (National Cancer Institute, 2009). The patient and graft survival rates were analyzed at first three months, 1 year, 3 years, and 5 years of follow-up.

Statistical analysis

All demographic data were presented by descriptive statistics. Categorical data (sex, underlying disease, date of transplantation, type of donor, drugs regimens in induction therapy, initial and long-term maintenance regimen, graft rejection rate, adverse drug event) were described as frequency and percentage. The event per person time was used to analyze the adverse drug event for both initial and maintenance therapy. For the continuous variables (age, body weight, blood pressure, cyclosporine level, tacrolimus level, everolimus level, fasting blood sugar, serum creatinine, eGFR, hemoglobin, white blood cells, platelet counts, cholesterol, triglycerides) following the normal distribution, data were presented in mean with standard deviation (SD), otherwise, the median with interquartile range (IQR) was used.

Chi-Square tests were used to compare the percentage of graft rejection and adverse drug reaction between the immunosuppressive groups. Independent *t*-tests or Nonparametric tests were used to compare the means or median of continuous variables between immunosuppressive groups. In addition, the Kaplan-Meier method was used to measure the survival rate among the group of immunosuppressive regimens.

Results

Patients and treatments

One hundred and thirty-two patients with kidney transplantation were followed up at nephrology unit, Sunpasitthiprasong Hospital, from January 1, 1998 to October 31, 2016. Of these, 103 patients met the inclusion/exclusion criteria and were evaluated for the study. The mean age was 40 years old and 68.9% of them were male. Most patients (83.5%) had received a cadaveric kidney transplant. Patients were found to have hypertension, dyslipidemia, and diabetes as co-morbidities in 64.1%, 15.5%, and 7.8%, respectively. There were 87.4% of patients received interleukin-2-receptor antagonist (IL2-RA) and 1.0% received antithymocyte globulin for induction therapy. Cyclosporine, tacrolimus, and everolimus were given as an initial maintenance regimen in 2.0%, 82.5% and 15.5% of patients, respectively (Table 1). Whereas, 2.0%, 82.5% and 15.5% of patients received cyclosporine, tacrolimus, and everolimus for a long-term maintenance regimen, respectively. During the long-term maintenance regimen, 7 patients (77.8%) in the cyclosporine group were switched to another group (1 and 6 patients had switched to everolimus and tacrolimus, respectively). While 10 patients (11.2%) in tacrolimus group were switched to everolimus group. All of them had a reason for switching the treatment due to adverse drug events. The patients who remained in their initial treatment were 22.2% for cyclosporine, 88.8% for tacrolimus, and 100.0% for everolimus. Most of patients had remained in their original azathioprine, mycophenolate mofetil or mycophenolate sodium and prednisolone (Table 2).

Table 1 Demographic data of kidney transplantation patients in the study

Characteristics	Total (N=103)
Gender, n (%)	
Male	71 (68.9%)
Female	32 (31.1%)
Age, median (IQR) (years old)	40 (30,49)
Co-morbidity, n (%)	
Hypertension	66 (64.1%)
Dyslipidemia	16 (15.5%)
Diabetes melitus	8 (7.8%)
Type of donor, n (%)	
Cadaveric donor	86 (83.5%)
Living donor	17 (16.5%)
Induction therapy, n (%)	
Interleukin-2-recepter antagonist	90 (87.4%)
Antithymocyte globulin	1 (1.0%)
Initial immunosuppressive based therapy, n (%)	
CSA based regimen	9 (8.7%)
TAC based regimen	89 (86.4%)
EVR based regimen	5 (4.9%)

Table 1 Demographic data of kidney transplantation patients in the study (*Continue*)

Characteristics	Total (N=103)
Initial maintenance therapy, n (%)	
CSA plus AZA	1 (1.0%)
CSA plus MMF	4 (3.9%)
CSA plus MSD	4 (3.9%)
TAC plus MMF	25 (24.3%)
TAC plus MSD	64 (62.1%)
EVR plus MMF	3 (2.9%)
EVR plus MSD	2 (1.9%)
Baseline laboratory	
Creatinine, mean (SD) (mg/dL)	1.98±1.14
eGFR, median (IQR) (mL/min)	37 (26,52)
Fasting blood sugar, mean (SD) (mg/dL)	120.79±67.34
Hemoglobin, median (IQR) (g/dL)	9.7 (8.8,11)
White blood cells count, median (IQR) (cells/mm^3)	9915 (7320,13380)
Platelet count, mean (SD) (*10^3 cells/mm^3)	280.97±95.36
Cholesterol, mean (SD) (mg/dL)	247.31±61.75
Triglyceride, median (IQR) (mg/dL)	169 (128,219)
Albuminuria, n (%)	11 (13.1%)

IQR; interquartile range, SD; standard deviation, eGFR; estimated glomerular filtration rate, CSA; cyclosporine, TAC; tacrolimus, EVR; everolimus, AZA; azathioprine, MMF; mycophenolate mofetil, MSD; mycophenolate sodium

Table 2 Long-term maintenance regimen at index date

Immunosuppressive regimens	Initial regimen N=103	Long-term regimen N=103	Switch N (%)	Remain N (%)
Immunosuppressive based group				
CSA based group	9 (8.7%)	2 (2.0%)	7 (77.8%)	2 (22.2%)
TAC based group	89 (86.4%)	85 (82.5%)	10 (11.2%)	79 (88.8%)
EVR based group	5 (4.9%)	16 (15.5%)	0	5 (100.0%)
Immunosuppressive regimens				
CSA plus AZA	1 (1.0%)	1 (1.0%)	0	1 (100.0%)
CSA plus MMF	4 (3.9%)	1 (1.0%)	3 (75.0%)	1 (25.0%)
CSA plus MSD	4 (3.9%)	0	4 (100.0%)	0
TAC plus MMF	25 (24.3%)	25 (24.3%)	3 (12.0%)	22 (88.0%)
TAC plus MSD	64 (62.1%)	60 (58.3%)	8 (12.5%)	56 (87.5%)
EVR plus AZA	0	3 (2.9%)	0	0
EVR plus MMF	3 (2.9%)	5 (4.9%)	0	3 (100.0%)
EVR plus MSD	2 (1.9%)	8 (7.8%)	1 (50.0%)	1 (50.0%)

CSA; cyclosporine, TAC; tacrolimus, EVR; everolimus, AZA; azathioprine, MMF; mycophenolate mofetil, MSD; mycophenolate sodium

Efficacy

Maintenance of renal function

The mean of serum creatinine in cyclosporine, tacrolimus and everolimus based regimen group were 1.99±1.01 mg/dL, 1.59±0.85 mg/dL and 1.54±0.63 mg/dL, respectively. The mean of eGFR in cyclosporine, tacrolimus and everolimus based regimen group were 45.04±16.75 mL/min, 57.48±22.98 mL/min and 69.46±23.29 mL/min, respectively. For the calcineurin inhibitor (CNI) based regimen group, both serum creatinine and eGFR of patients in tacrolimus group were significantly better than patients in cyclosporine group with statistical significantly difference (P<0.0001). The mean of serum creatinine was 1.64±0.87 mg/dL and the eGFR was 56.77±22.91 mL/min among the patients, the maintenance of serum creatinine and eGFR in each of immunosuppressive agents (Figure 2-3). The data showed that, the mean of serum creatinine was 1.67±0.85 mg/dL for the first three months after transplantation, 1.76±1.08 mg/dL, 1.49±0.57 mg/dL and 1.73±0.90 mg/dL for 1 year, 3 years and 5 years after transplantation follow-up, respectively. There were 21.32% and 19.33% of serum creatinine levels had tend to increase in cyclosporine group at 3 years and 5 years after transplantation, respectively. There were 16.13% and 9.52% of serum creatinine levels had tended to decrease in tacrolimus group at 1 year and 3 years after transplantation, respectively. In addition, there were 7.20% and 13.85% of serum creatinine levels had tend to decrease in everolimus group at 3 years and 5 years after transplantation, respectively. The mean of eGFR was 49.74.86±21.83 mL/min for the first three months after transplantation, 51.39±23.48 mL/min, 63.71±21.38 mL/min and 61.35±22.65 mL/min for 1 year, 3 years and 5 years after transplantation follow-up, respectively. There were 11.26% of eGFR levels had tend to increase at 1 year after transplantation and 13.65% of eGFR levels had tend to decrease at 3 years in cyclosporine group. There were 15.41%, 4.32% and 1.76% of eGFR levels had tend to increase in tacrolimus group at 1 year, 3 years and 5 years after transplantation, respectively. There were 2.67% and 4.38% of eGFR levels had tend to decrease in everolimus group at 1 year and 3 years after transplantation, respectively and 3.31% of eGFR levels had tend to increase in everolimus group at 5 years after transplantation.

Graft rejection

The result of biopsy-proven acute rejection was confirmed by diagnosis with the examination of kidney biopsy (Table 3). The data showed that, graft rejection rate was found in 6 patients (5.9%) among the kidney transplantation patients, there was 1 patient (11.1%) with living kidney transplant in cyclosporine based regimen and 5 patients (5.6%) with cadaveric kidney transplant in tacrolimus based regimen, which these are not difference (P=0.448) and none of graft rejection in everolimus based regimen. There was 1 patient had rejected which found in cyclosporine plus mycophenolate mofetil group, 1 patient in tacrolimus plus mycophenolate mofetil group and 4 patients in tacrolimus plus mycophenolate sodium group. There were 2 patients (33.3%) had classified to acute cellular rejection and 4 patients (66.7%) had classified into chronic allograft rejection according to the Banff classification for allograft rejection diagnosed. The results of immunosuppressive blood concentration were determined in Table 4. In 103 patients, there were 99 (96.1%), 100 (97.1%) and 86 (83.5%) of patients had occurred at least one of subtherapeutic range, on therapeutic range and over therapeutic range, respectively. There were 555 (21.3%), 1,604 (61.5%) and 450 (17.2%) of monitoring tests were classified into subtherapeutic range, on therapeutic range and over therapeutic range, respectively. In all 6 rejected patients, 42 (23.6%), 117 (65.7%) and 19 (10.7%) of monitoring tests were classified into subtherapeutic range, on therapeutic range and over therapeutic range, respectively. In all 6 rejected events, 2 (33.3%) and 4 (66.7%) of events were classified into subtherapeutic range events and on therapeutic range events, respectively which were not difference (P=0.414). The mean of drugs level were 171.2±108.8 ng/mL, 6.0±1.0 ng/mL and 7.7±1.8 ng/mL for cyclosporine, tacrolimus and everolimus concentration levels, respectively.

Table 3 Rate of graft rejection in each of immunosuppressive drug

	Initial maintenance regimen N=103	Graft rejection N (%)	p-value[a]
Immunosuppressive based group			
CSA based group	9 (8.7%)	1 (11.1%)	0.448
TAC based group	89 (86.4%)	5 (5.6%)	
EVR based group	5 (4.9%)	0	
Immunosuppressive regimens			
CSA plus MMF	4 (3.9%)	1 (25.0%)	
TAC plus MMF	25 (24.3%)	1 (4.0%)	0.282
TAC plus MSD	64 (62.1%)	4 (6.3%)	

CSA; cyclosporine, TAC; tacrolimus, EVR; everolimus, AZA; azathioprine, MMF; mycophenolate mofetil, MSD; mycophenolate sodium

a. Chi-Square test

Table 4 The results of immunosuppressive blood concentrations

Status	Sub-therapeutic range group	On therapeutic range group	Over therapeutic range group	p-value[b]
Total monitoring test[a] (N=103 patients)	99 (96.1%)	100 (97.1%)	86 (83.5%)	-
Total monitoring test (N=2,609 tests)	555 (21.3%)	1,604 (61.5%)	450 (17.2%)	
Cyclosporine (N=179 tests)	72 (40.2%)	77 (43.0%)	30 (16.8%)	-
Tacrolimus (N=2,187 tests)	474 (21.7%)	1,392 (63.6%)	321 (14.7%)	
Everolimus (N=243 tests)	9 (3.7%)	135 (55.6%)	99 (40.7%)	
Monitoring test in 6 graft rejection patients (N=178 tests)	42 (23.6%)	117 (65.7%)	19 (10.7%)	-
Graft rejection event in 6 patients (N=6 patients)	2 (33.3%)	4 (66.7%)	0	0.414

a. Total monitoring test at least one test

b. Chi-Square test

Survival rate

In the cyclosporine group, 1 of 9 patients (11.1%) had died at 5.3 years, 6 patients from 89 patients (6.7%) had died at 1 month, 4 months, 7 months, 9 months, 1 year and 2.6 years in tacrolimus group. Totally, 7 patients from 103 patients (6.8%) had died in this study. At 1 year follow-up, mean survival time of patients was 11.7 months [95% Confidence interval; 95%CI (11.4-12.1)]. After 1 year, survival times were 33.2 months [95%CI (31.0-35.5)] at 3 year of follow-up and 46.6 months [95%CI (37.2-55.9)] at 5 year follow-up (Figure 1). In the cyclosporine group, 1 from 9 grafts (11.1%) had rejected at 5.1 years, 5 from 89 grafts (5.6%) had rejected at 0 month, 1 month, 4 months, 1.9 years and 2.6 years in tacrolimus group. Totally, 6 grafts from 103 grafts (5.8%) had rejected in this study. At 1 year

follow-up, mean graft survival time was 11.9 months. After 1 year, survival times were 2.9 years at 3 years and 4.4 years at 5 years follow-up which the graft survival rates could not plotted the Kaplan-Meier method because there was only one of graft loss and the follow-up time could not be reached to the evaluated index date and there was 1 patient who had a graft loss due to graft rejection after transplantation finished and turn to ESRD with continue hemodialysis. The overall mortality rate among the patients was 6.8% and mortality rate was 0.1%, 4.9%, 5.8% and 5.8% at 3 months, 1 year, 3 years and 5 years, respectively. At 3 months, the patients and graft survival rate were 97.1% and 95.1%, respectively. At 1 year, 3 years and 5 year, both the patient and graft survival rate were 83.5%, 46.6% and 12.6%, respectively.

Adverse drug event

The incidence of adverse drug events per person year between each of immunosuppressive based group was according to initial and long-term maintenance regimen (Table 5-6). For the original based group, 103 patients were analyzed and after switched based group could be calculate based on the numbers of switching based group included before and after in initial and long-term maintenance regimen in 17 patients that had switched. There were found 15.07, 16.64 14.55 and 10.65 events per person year for hypertension, anemia, hypertriglyceridemia and hypercholesterolemia, respectively in initial maintenance regimen with almost categorized into severity grade 1 to 2. For another adverse drug events in initial maintenance regimen had been similar between groups (P>0.05). For the long-term maintenance regimen, there were 21.83, 20.03, and 21.19 events per person year for hypertension, hypertriglyceridemia and anemia, respectively with almost categorized into severity grade 1 to 2. There were 19.40 events per person year of hypercholesterolemia with difference between groups. For another adverse drug events in long-term maintenance regimen had been similar between groups (P>0.05). There were 23 patients with history of acute kidney injury (AKI), AKI in between groups were comparable in cyclosporine and tacrolimus regimen with severity grade 3 to 4. Others complications included malignancy as skin cancer, non-Hodgkin lymphoma and kidney cancer diagnosed were not found in this study. Cosmetic adverse event included gingival hyperplasia was diagnosed 1 patient in cyclosporine regimen. There were 17 patients (16.5%) developed diabetic mellitus post kidney transplantation.

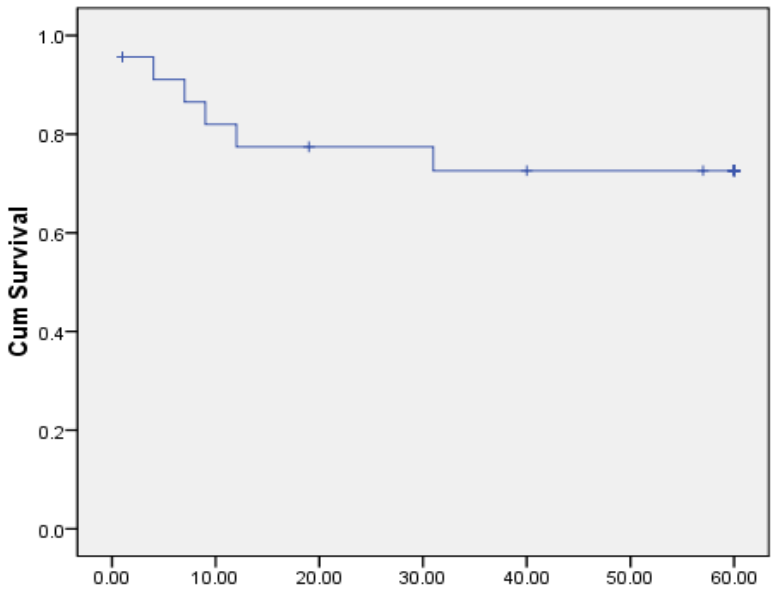

Figure 1 Kaplan-Meier plots for patient survival among the kidney transplantation patients

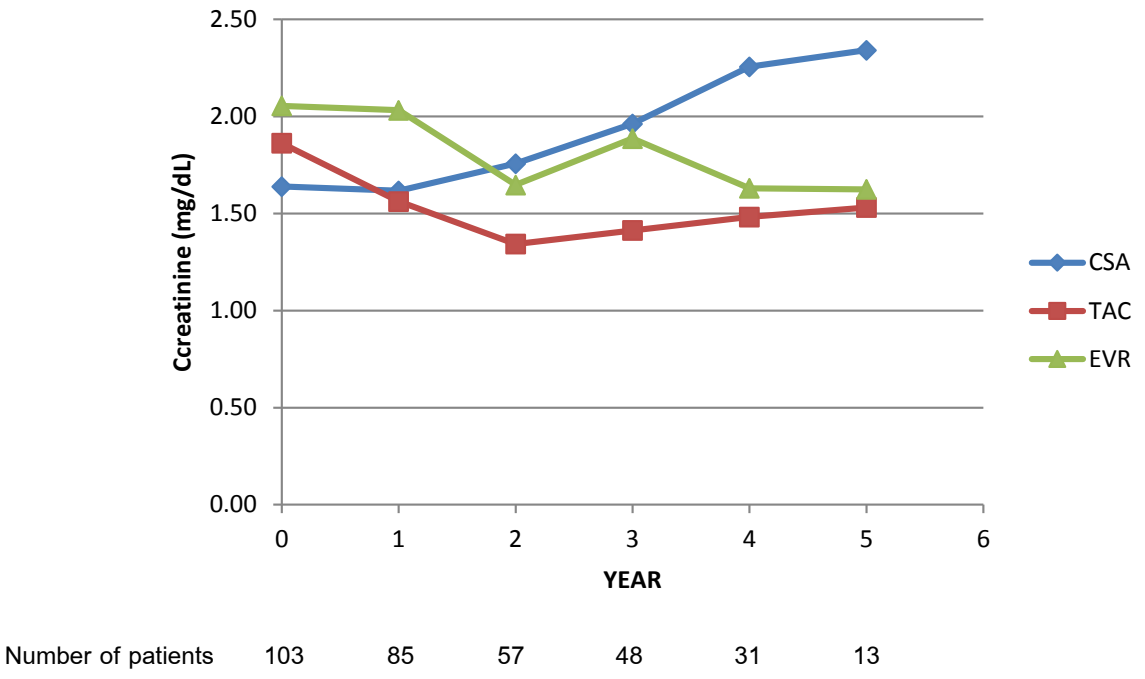

Figure 2 Maintenance of the serum creatinine in each of immunosuppressive agents

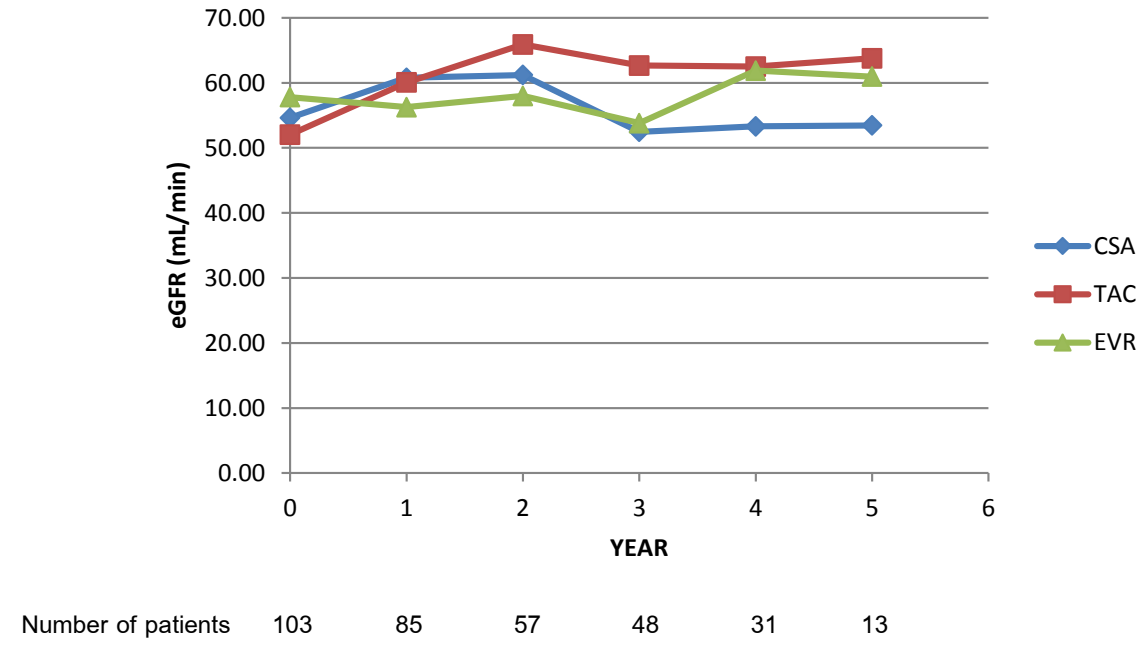

Figure 3 Maintenance of the eGFR in each of immunosuppressive agents

Table 5 Incidence of adverse drug events per person year between each of immunosuppressive based group in initial maintenance regimen

Adverse drug events	Initial maintenance regimen				p-value[a]
	Total N=103	Cyclosporine N=9	Tacrolimus N=89	Everolimus N=5	
Acute kidney injury	3.49	0.43 (12.3%)	2.87 (82.2%)	0.19 (5.5%)	0.474
Hypertension	15.07	8.25 (54.7%)	6.82 (45.3%)	0.00	0.414
Hyperglycemia	5.82	3.45 (59.3%)	2.18 (37.4%)	0.19 (3.3%)	0.096
Hypercholesterolemia	10.65	2.55 (24.0%)	3.80 (35.6%)	4.30 (40.4%)	0.522
Hypertriglyceridemia	14.55	3.90 (26.8%)	5.51 (37.8%)	5.14 (35.4%)	0.409
Anemia	16.64	5.63 (33.8%)	6.32 (38.0%)	4.70 (28.2%)	0.802
Leukopenia	4.34	1.60 (36.9%)	1.53 (35.3%)	1.21 (27.8%)	0.617
Thrombocytopenia	1.20	0.11 (9.5%)	1.09 (90.5%)	0.00	0.259
Albuminuria	8.56	3.34 (39.1%)	2.77 (32.4%)	2.44 (28.5%)	0.974

a. Kruskal Wallis test

Table 6 Incidence of adverse drug events per person year between each of immunosuppressive based group in long-term maintenance regimen

Adverse drug events	Long-term maintenance regimen				p-value[b]
	Total N=120[a]	Cyclosporine N=9	Tacrolimus N=95	Everolimus N=16	
Acute kidney injury	3.96	1.00 (25.2%)	2.77 (69.9%)	0.19 (4.9%)	0.351
Hypertension	21.83	8.44 (38.7%)	7.33 (33.6%)	6.06 (27.7%)	0.644
Hyperglycemia	16.81	10.50 (62.5%)	2.21 (13.1%)	4.10 (24.4%)	0.083
Hypercholesterolemia	19.40	9.20 (47.4%)	3.65 (18.8%)	6.55 (33.7%)	0.002
Hypertriglyceridemia	20.03	8.09 (40.4%)	5.69 (28.4%)	6.26 (31.2%)	0.722
Anemia	21.19	8.38 (39.6%)	6.92 (32.7%)	5.88 (27.7%)	0.468
Leukopenia	4.81	2.00 (41.6%)	1.60 (33.3%)	1.21 (25.1%)	0.452
Thrombocytopenia	1.34	0.25 (18.7%)	1.09 (81.3%)	0.00	1.000
Albuminuria	11.87	3.95 (33.3%)	3.00 (25.3%)	4.92 (41.4%)	0140

a. The numbers of switching based group included before and after in initial maintenance regimen and long-term maintenance regimen

b. Kruskal Wallis test

Discussion and conclusion

Most of patients had received tacrolimus after kidney transplantation with 89 cases (86.4%) and 85 cases (82.5%) for the initial and long-term maintenance regimen respectively during the year 2012 onwards and there was mostly used instead of tacrolimus instead of cyclosporine. The results were based on the guideline recommendations for maintenance regimen (Kidney Disease: Improving Global Outcomes [KDIGO], 2009).

For the renal function maintenance among the CNI based regimen group, the mean serum creatinine and eGFR in tacrolimus group were better than cyclosporine group which the same reported with the previous study (Mayer

et al., 1997; Vincenti *et al.*, 2002; Kramer *et al.*, 2005). All patients were considered into chronic kidney disease (CKD) after kidney transplantation, measuring changes in serum creatinine and eGFR had the recommended method for monitoring kidney allograft function (Kidney Disease: Improving Global Outcomes [KDIGO], 2009). There is one patient with the low of serum creatinine baseline and had received in early kidney transplantation until at index date, so the overall of serum creatinine was likely to decrease, and in fact the serum creatinine should be tend of increased after transplantation. The report from one study showed, during the one-year serum creatinine values had steadily improved, from 1.82±0.82 mg/dL to 1.67±0.82 mg/dL (Hariharan *et al.*, 2002). But the overall of eGFR was likely to decrease among the patients after transplantation with the same report from previous study, that demonstrated a significantly slower decline in GFR in treated patients (Gill *et al.*, 2004; Kramer *et al.*, 2005). One study showed that, the $\geq$30% decline in eGFR with detected in 10% between years 1 and 3 after kidney transplant was common and strongly associated with risks of graft failure (Clayton *et al.*, 2016). In the present study, there are a few of follow-up time until the index date in each patient and there were increasing of kidney transplantation during after the year 2012.

There were 5.6% of graft with biopsy-proven acute rejection (BPAR) in tacrolimus based treated patients at 0 month, 1 month, 4 months, 1.9 years and 2.6 years which that less than BPAR in the cyclosporine (11.1%) at 5.1 years with no differences between groups. There was 19.6% and 37.3% of BPAR in tacrolimus and cyclosporine based group at 0-6 months in the Kramer's study (Kramer *et al.*, 2005), and 11.4% vs. 38.2% in the Marcen's study (Marcen *et al.*, 2009). In our study, the graft rejection rates were lower than in other countries, this may cause by the risk factors that affect different the graft rejection such as race, recipient and donor age, delayed graft function or the cold ischemic time. And in this study, it may be not adequately power to detect the effects of different the rejection rate endpoint between groups because BPAR diagnosis had confirmed by graft biopsy but in general practice, there is not adequately biopsy on our site, so may be more common of rejection rate if there is a routine biopsy in patients who are suspected or there is abnormal rising of serum creatinine. Rejection rate is most likely to occur in cases with a history of subtherapeutic range at least one test but not significant difference among groups. The differences in pharmacokinetics and pharmacodynamics properties in each patient can result in inter-individual variability of serum drug concentration. Although there is no difference between the rejection rates and drug level at subtherapeutic range, the drug level should be kept within therapeutic range to avoid the rejection occurrence when the serum drug level is low and the toxicity when serum level is above the therapeutic range (Mohammadpour *et al.*, 2010).

The kidney transplant report from the Thai Transplantation Society has been updated, the current data is the 2017 report. But in this study, the 2016 report in comparison due to the end of index date and not long all the year, so could not comparable to the 2017 report. Moreover, the survival rates in this study compares with the survival rates of deceased donor data due to more than 80% of recipients has been received from the cadaveric donors. In our study, the overall patient survival rate was 83.5% and 12.6% at 1 year and 5 years, respectively. There was likely to found the patient survival less than the previous data both in abroad and in Thailand which is reported the survival rate of more than 90% at 1 year and more than 70% at 5 years in kidney transplant patients (McCullough *et al.*, 2009; Mazzuchi *et al.*, 1999; Ojo *et al.*, 2001). The survival rates at 1 year and 5 year in kidney donated by deceased donors were 96.3% and 91.4% in Thailand (Thai Transplantation Society, 2016). Several studies had found that the graft survival after kidney transplantation at 1 year and 5 years in the range of 85-96% and 53-81% (McCullough *et al.*, 2009; Ojo *et al.*, 2001). In Thailand, the data showed that the graft survival rate at 1 year and 5 years was to 94.1% and 86.3%, respectively in the case from deceased donor (Thai Transplantation Society, 2016). For the overall graft survival rate at 1 and 5 years, they were less than the above data,

83.5% and 12.6% at 1 year and 5 years, respectively in our study. This caused the patients and graft survival rates to be lower than other studies because there were 5 deaths from 103 patients after transplanted due to infection and the remaining patients had complete follow-up in each of year.

Among the both calcineurin inhibitor based regimen, the incidence of acute kidney injury was higher in tacrolimus than cyclosporine. This differs from the previous report that nephrotoxicity was found to be higher in cyclosporine than tacrolimus (Halloran, 2004), it may be caused by the higher of tacrolimus using. According to the most common adverse drug events of cyclosporine and tacrolimus, many adverse effects are related to the drug concentration included nephrotoxicity and commonly occur in cyclosporine than tacrolimus. Furthermore, most of patient with kidney disease are prone to have hypertension as an underlying disease. Our study found that hypertension was the most common adverse effects in tacrolimus group. Hyperglycemia, hypercholesterolemia, and hypertriglyceridemia also frequently occurred with a similar number between immunosuppressive groups. Anemia was the most common hematotoxicity from an immunosuppressive drugs, while leukopenia and thrombocytopenia were the second and third. As the kidney patients are more likely to have an anemia due to insufficiency of erythropoietin production, risk of anemia will be increase while receiving immunosuppressive drugs. The each of adverse effects in everolimus treated group had less than tacrolimus and cyclosporine treated groups. Our results, however, revealed that the incidence of adverse effects while receiving immunosuppressive drugs seemed to be similar between three groups. Naranjo's algorithm was used in the assessment between the adverse drug events and the drugs relationship to confirm the occurrence of immunosuppressive drugs after kidney transplantation. It has to be noted that due to an inadequate number of patient and short duration of follow-up, the malignancy side effects, such as skin cancer, non-Hodgkin lymphoma and kidney cancer, were less to be found in our study. All of the patients died from the infection cause but a specific detail of infection or death were not fully reported in the document. However, infection is still an important cause of death in the real practice in patients receiving tacrolimus and cyclosporine (Kramer *et al.*, 2005). Based on our results, all of the immunosuppressive regimens among kidney transplant patients at Sunpasitthiprasong Hospital are effective in preventing graft rejection. Tacrolimus provides a better maintenance of renal function with acceptable adverse drug events.

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References

Collins BH, Shapiro R, Johnston TD, Kim ED, Talavera F. Renal transplantation [Internet]. 2015 [cited 2016 Jun 9]. Available from: http://www.emedicine.medscape.com/article/430128-overview

Garcia-Garcia G. Harden P, Chapman J. The global role of kidney transplantation. *Indian J Nephrol* 2012;22(2):77-82.

Gill JS, Tonelli M, Mix CH, Johnson N, Pereira BJ. The effect of maintenance immunosuppression medication on the change in kidney allograft function. *Kidney Int* 2004;65(2):692-9.

Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Eng J Med* 2004;351(26): 2715-29.

Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-Transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002; 62(1):311-8.

Kaufman DB, Batuman V. Assessment and management of the renal transplant patient [Internet]. New York; 2015 [cited 2016 Jun 10]. Available from: http://emedicine.medscape.com/article/429314-overview

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009;9(Suppl 3): S1-155.

Kramer BK, Montagnino G, Castillo D, Margreiter R, Sperschneider H, Olbricht CJ. *et al.* Efficacy and safety of tacrolimus compared with cyclosporine A microemulsion in renal transplantation: 2 year follow-up results. *Nephrol Dial Transplant* 2005;20(5):968-73.

Marcen R, Fernandez-Rodriguez A, Rodriguez-Mendiola N, Ponte B, Galeano C, Villafruela JJ, *et al.* Evolution of rejection rates and kidney graft survival: A historical analysis. Transplantation Proceedings 2009;41(6):2357-9.

Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, *et al.* Multicenter randomized trial comparing tracrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. Transplantation 1997;64(3):436-43.

Mazzuchi N, Gonzalez-Martinez F, Carbonell E, Curi L, Fernandez-Cean J, Orihuela S. Comparison of survival for haemodialysis patients vs renal transplant recipients treated in Uruguay. *Nephrol Dial Transplant* 1999;14(12):2849-54.

McCullough KP, Keith DS, Meyer KH, Stock PG, Brayman KL, Leichtman AB. Kidney and pancreas transplantation in the United States, 1998-2007: Access for patients with diabetes and end-stage renal disease. *Am J Transplant* 2009;9(4 Pt 2): 894-906.

Mohammadpour N, Elyasi S, Vahdati N, Mohammadpour AH, Shamsara J. A review on therapeutic drug monitoring of immunosuppressant drugs. *Iran J Basic Med Sci* 2010;14(6):485-98.

Mota A. Acute rejection in cadaveric renal transplantation under cyclosporine based therapy. *Acta Med Port* 2004;17(1):8-14.

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE version 4). Published: May 28, 2009 (v4.03: June 14, 2010).

Ojo AO, Hanson JA, Meier-Kriesche H, Okechukwu CN, Wolfe RA, Leichtman AB, *et al.* Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 2001;12(3):589-97.

Clayton PA, Lim WH, Wong G, Chadban SJ. Relationship between eGFR decline and hard outcomes after kidney transplants. *J Am Soc Nephrol* 2016;27(11): 3440-46.

Solez K, Axelsen RA, Benediktsson H, Burdick JF, Cohen AH, Colvin RB, *et al.* International standardization of criteria for the histologic diagnosis of renal allograft rejection: The Banff working classification of kidney transplant pathology. *Kidney Int.* 1993; 44(2):411-22.

Suthanthiran M, Strom TB. Renal transplantation. *N Eng J Med* 1994;331(6):365-76.

Thai Transplantation Society. (2016). Report of organ transplantation of 2015. Bangkok: Wetchasan Printing House.

Thai Transplantation Society. (2017). Report of organ transplantation of 2016. Bangkok: Wetchasan Printing House.

United Network for Organ Sharing (UNOS). Data [Internet]. c2015 [cited 2016 Jun 9]. Available from: https://www.unos.org/data/transplant-trends/

Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. Transplantation 2002;73(5):775-82.