ORIGINAL RESEARCH PAPER

Nephrology

KEY WORDS:

COMPARATIVE STUDY COMPARING CYCLOSPORINE VS TACROLIMUS FIVE YEAR FOLLOW- UP IN AHMED GRTC AT KHARTOUM STATE (DECEMBER 2000-MARCH 2006)

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ABSTRACT

Background: Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). This study was undertaken to compare the efficacy of Tacrolimus with the micro- emulsion formulation of Cyclosporine in population under going renal transplantation. A five year, retrospective comparative study was conducted at AHMED GASIM RENAL TRANSPLANTATION CENTER (AGRTC).

Methods : 178 renal transplant recipients were studied retrospectively, using data recorded from (AGRTC) to evaluate efficacy of calcineurin inhibitors (Tacrolimus vs Cyclosporin A Microemulsion). Calcineurin inhibitors were used in combination with both Azathioprine and steroids. Follow-up data were collected at five year post-transplantation from 81 (45.5% of the study population) patients who received Tacrolimus and 97(54.5%of the study population) patients who received. Whereas whole blood level targets were 10–20 , 5–15 and 5-7 ng/ml for Tacrolimus and 100–400 ,100–200 and 125-150 ng/ml for CsA during months 0–3 ,4–6 and 7 -12 to 60 respectively.

Results: The study found no difference between cyclosporine and Tacrolimus in the composite primary efficacy endpoint, including biopsy-proven acute rejections, graft loss In the Tacrolimus treatment group, totaling 13 (16.1%). Cyclosporine totaling 20 (20.61%). and patient survival Calculated on whole populations, overall mortality (5.6% vs 10.6%; P.>0.05) was grater, but overall rate of graft loss (7.3% vs 10.7%; P = 0.938 in analysis) was not significantly different after 5 years with tacrolimus- vs cyclosporine-based immunosuppression. Thus, there was no significant loss or death difference. In the Tacrolimus arm, [10 (12.3% deaths]. In the cyclosporine group, [19 (19.5%) deaths].

Conclusions : The one five year follow-up results confirm that Tacrolimus is as efficacious as cyclosporine immunosuppressant in kidney transplantation.

INTRODUCTION:

Renal transplantation remains the treatment of choice for patients with end stage renal failure; as relatively normal life style usually re-established, also transplantation is associated with lower cost and a better quality of life than dialysis. [1, 2, 3, 4,]

The most important therapeutic aspect of transplantation is immunosuppressive agents. There is no consensus on the best immunosuppressive regimen, and the numerous dosing regimens in use primarily depend on the program and the specific organ to be transplanted. Athough a number of studies have attempt to evaluate the superiority of various regimens, comparisons are hampered by variables such as differences in donor selection and condition ,organ preservation and procurement ,organ ischemic (cold and warm) time ,recipient's pretransplant conditions comorbid and high or low risk factors, surgical procedures and individual surgical techniques, postoperative management and monitoring, and length of follow- up .Another important consideration is that many of the newer agents show significant effects during the first year ,but fail to show significant impact on long –term effects such as chronic rejection. [2, 3]

All transplant recipients must be followed up closely after transplantation to prevent rejection. Minimize drug toxicity (e.g., nephrotoxicity) and maintain good –quality organ function. Just as important is the prevention and management of a number of other long term complications that can occur after transplantation these include cardiovascular disease ,glucose intolerance bone and bone marrow conditions, nutrition and obesity, cancer, infections and compliance /non adherence .These contribute significantly to morbidity and mortality after transplantation this applies to all types of organ transplantations. [3]

Triple or quadruple therapy is used to take the advantages of different mechanisms of action and to reduce drug toxicity by using sequential therapy and small doses of multiple agent rather than larger doses of any agent used alone .How ever these multidrug combinations may lead to increased drug cost, compliance issues, a higher incidence of infection and malignancy, and difficulty in assessing adverse effects. [3]Calcineurin inhibitors are considered the mainstay of immunosuppression in renal transplantation [1, 2, 3, 4]. Cyclosporin A and Tacrolimus are currently the most widely used baseline immunosuppressant for prevention of acute rejection following kidney transplantation. Two large, randomized, multicentre studies conducted in Europe and the US demonstrated that the incidence of acute rejection was significantly less in 508 renal transplant recipients receiving Tacrolimus-based immunosuppressant compared with 355 receiving CsA-based immunosuppressant [10, 12]. Projected graft half-life was longer and chronic rejection less frequent with Tacrolimus-based immunosuppressant at 5 year follow-up [10]. Furthermore, renal function better after 5 years in patients

receiving Tacrolimus-based immunosuppressant compared with CsA-based immunosuppressant [11].

The objective of this study was to evaluate the superior efficacy of the corner stone immunosuppressive treatment for Sudanese renal transplant recipients as it has not been established before. In other words to estimate whether the superior efficacy of tacrolimus in preventing acute graft rejection was still valid when compared with the cyclosporine formulation. The 6- and 12-month data have been presented previously and demonstrated a halving of biopsy-proven and steroid-resistant acute rejection rates with tacrolimus vs Cyclosporine treatment [8,9]. In addition to rate and severity of acute rejection, graft survival, longer-term graft function and patient survival are focuses of medical therapy after renal transplantation .we performed a short –term unicenter retrospective study comparing the outcome of Tacrolimus versus Cyclosporine in Sudanese settings to focus on their efficacy estimation which is the backbone of choice of the initial immunosuppressive therapy following organ transplantation as it is remain a source of contraversary and challenge for both Sudanese clinicians and pharmacists .cyclosporine is included in most of the basis protocols for years but recently supplemented in many centers by the use of Tacrolimus –based protocols .

Renal allograft recipients in Khartoum may receive either Cyclosporine or Tacrolimus based initial immunosuppressant therapy along with Prednisolone and Azathioprine or (Moftil since 1999).The later is not commonly used in our Sudanese settings.

Most important aim of this study is to make the decision pardon criteria of selecting cyclosporine-based regimen or Tacrolimus one (depending: age, gender, diabetic status, and lipid status…etc) is individualized according to our local patient and environment by relaying on local Sudanese evidence based data.

As this study aiming to analyze the out come of patients from our local institutions treated with Tacrolimus or Cyclosporine which may give a clue on the determination of the efficacy of those based immunosuppressive regimens as they are widely used at our local setting. Such type of studies may give evidence sound for safety drug use and armamentarium against irrational use of them.

Methods

The present analysis focus on the result of graft and patient survival, acute rejection and renal function that is determined by serum creatinine during the period of (December 2000-March 2006).

This unicenter, comparative, retrospective study was conducted in AGRTC .Some of 200 patients aged 15-70 years old with end stage renal disease (definition: chronic renal failure that necessitates dialysis to sustain life) .were administered either Tacrolimus (N=81) or Cyclosporine (N=97) combined with Azathioprine and corticosteroids(Prednisolone). The study duration was two months to analyze one year follow up .The primary end point is graft function ,graft and patient survival and acute rejection. Secondarily renal fuction

Study population

178 of 200 Sudanese renal transplant recipients(RTR)with completed follow up admission sheet or (follow up record) were enrolled in this study. The study population was followed at AHMED GASIM RENAL TRANSPLANT CENTER (AGRTC) they include the whole population except those who were without complete follow up record, died during surgery or using Moftil instead of Azathioprine Between December 2001 to March 2006.And who have a complete comprehensive follow up record .The compared group consist of two groups allocated randomly; according to their received treatment either Tacrolimus or Cyclosporine ;Tacrolimus group consist of (81 RTR) 45.5%,(97 RTR) 54.5% for Cyclosporine group. Those individuals with renal transplantation identified from AG RTC and diagnosed there.

Treatment:

The Tacrolimus (Prograf)® dose (initial oral dose 0.3 mg/kg administered within 24 h of transplantation) was adjusted to maintain target whole blood trough levels of 10–20 ng/ml during the first 3 months , 5–15 ng/ml between months 4 - 6 and 5-7ng/ml between 7-12 month. Cyclosporine (Neoral) ® treatment started on day 0 with an oral dose of 4–5 mg/kg twice daily. Target whole blood trough levels of Cyclosporine were 100–400 ng/ml during the first 3 months, 100–200 ng/ml thereafter. In both groups, Azathioprine (1–2 mg/kg/day). Corticosteroid treatment comprised methylprednisolone boluses (day 0: 500 mg; day 1: 125 mg) followed by a rapid prednisolone taper from 20 mg (day 2) to 5 mg (day 43 and thereafter). During the investigator-driven follow-up after termination of the study (months 7–12) no specific calcineurin inhibitor target levels were required. Adverse events, laboratory parameters and renal function (serum creatinine) were recorded throughout the study.

Data tool collection

All participants have a completed data collection form (RENAL TRANSPLANT OUTCOME QUESTIONNAIRE 2006), which is offered to all RTRs as a copy from their follow up rescored and is completed by our colleagues at **AGRTC** ;the 6 page instrument covers information on: **patient information**(demographics, cause of renal failure, family history of renal impairment ,smoking, patient medical condition). **Donor's information**, **operation information** (graft function post renal transplantation which is defined as,

Immediate: a good diuresis begins immediately and continues, and the serum creatinine rapidly declines to<2.5 mg/dl

Delayed: need for haemodialysis (HD) during first week post renal transplantation.

Primary none functioning: those experience anuria or oliguria require dialysis in the early period, and takes days to week to recover Immunosuppressant, patient follows up (1month, 6months, and 12months).

Statistical analysis:

Spss analysis software program was used .Descriptive analysis included student t-test of means for comparison groups for continuous variables ,and chi- square tests for categorical variables , null hypothesis testing was included a P –value of 0.05 value was set and a significant level at a 95% confidence interval (CI) was set.

Results

Descriptive characteristics of the study population are shown in Table 1. There were no differences between compared groups (cyclosporine and Tacrolimus) with respect to age and sex.

Table (1)

Characteristic of **178** renal transplant recipients using Tacrolimus based vs. cyclosporine based- **AGHCS&RTC (December 2000-march 2006)**

	Tacrolimus group(n=81)	Cyclosporine group (n=97)	Total (n=178)	P value
Sex*				
Male	73%(n=59)	78%(76)	100%(n=135)	ns
female	27%(n=22)	22%(21)	100%(n=43)	ns
Age**	30.5(**(8.76)**	29.5**(9.11)**	-	ns

** Mean (SD); differences in means detected using independent t-tests .2 n (%); differences in proportions detected using chi-square tests.

Figure (1) illustrates the number of renal transplant s (December 2000-March2006) it shows that 2005 is the year with the greatest renal transplantation recipients.

Figure 1: Number of Renal Transplants (December 2000-March 2006)

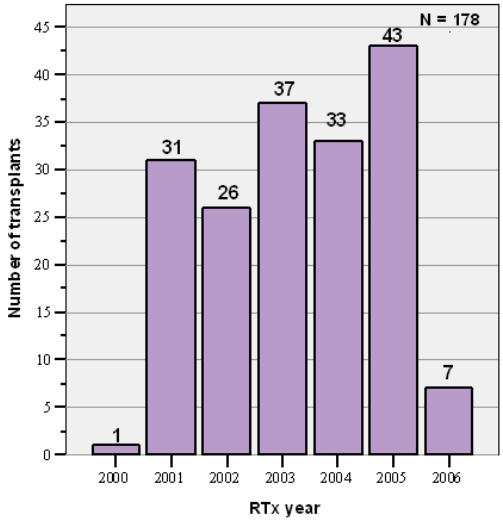


Figure 60: Patient's Survival Vs Year of Transplant

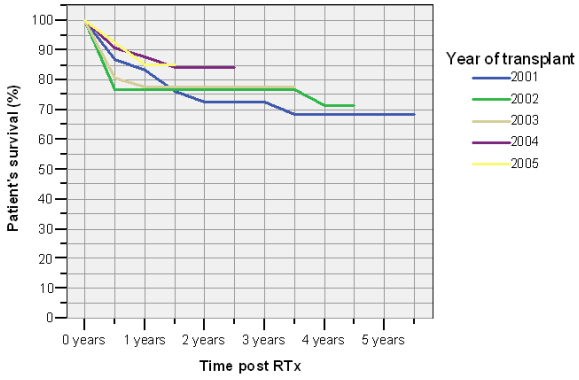
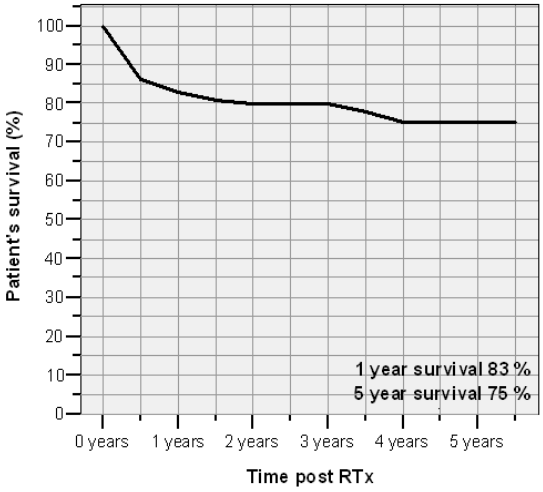


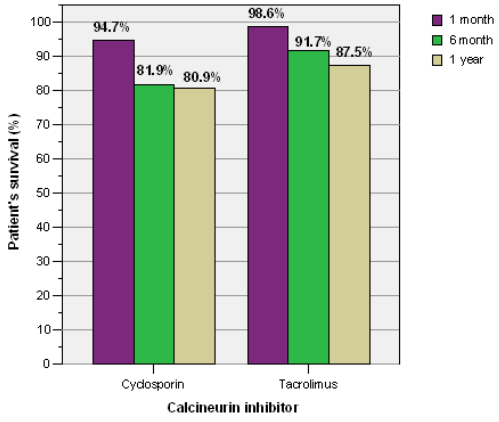
Figure 59: Patient's Survival Post RTx



Of the original 178 patients randomized to treatment, 81 (45.5% of 178) patients in the tacrolimus treatment group and 97 (54.49 of 178) patients in the cyclosporine group were assessed at 1year follow-up .In the Tacrolimus arm, tow patients died at 0–1 months five at 2–6 months, and three at 7-12 months [10 (12.3%) deaths]. In the cyclosporine group, five patients died at 0–1 months, thirteen at 2-6 months and one at 7–6 months [19 (19.5%) deaths] overall mortality (5.6% vs 10.6%; P>0.05).figure (44) and table (2)

Month	Calcinurin inhibitors		Total of deaths
	Cyclosporine	Tacrolimus	
1month	94.7%(92)	98% (79)	5 vs. 2
6 months	81.9%(79)	91%(74)	18 vs. 7
12months	80.9%(75)	87%(71)	19 vs10

Figure 44: Patient's survival Vs Calcineurin Inhibitor

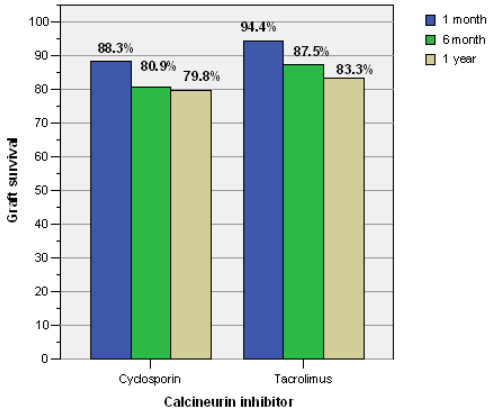


In the Tacrolimus treatment group, five grafts were lost between months 0 and 1 and five between 2- 6 months and three at 7-12 months, totaling 13 (16.1%). Eleven grafts were lost in the cyclosporine treatment group between months 0 and 1 and eight between months 2 and 6 and one between 7-12months, totaling 20 (20.61%). Calculated on whole populations, overall rate of graft loss (7.3% vs 10.7%; P = 0.938 in analysis) was not significantly different after 1 years with Tacrolimus- vs cyclosp orine-based immunosuppression (Figures 45 and table3).

Table (3) graft survival/ Calcinurin inhibitors cross tabulation

Month	Calcinurin inhibitors		Total of graft loss
	Cyclosporine	Tacrolimus	
1month	88.3%(86)	94.4% (76)	11 vs. 5
6 months	80.9%(78)	987.5%(71)	19 vs. 10
12months	79.8%(77)	83.3%(68)	20 vs13

Figure 45: Graft Survival Vs Calcineurin Inhibitor



Biopsy-proven acute rejection was significantly lower (22.1%) with tacrolimus than with cyclosporine (26%) during months 0–6 (P<0.0001), but was not significantly different during months 7–12 of follow-up (1.7% with tacrolimus and 4.7% with cyclosporine) (Table 3). During months 1–6, biopsy-proven acute rejection was diagnosed in 15 tacrolimus and 25 cyclosporine graft recipients. Figure (41)

Table (3) Incidence **of Acute rejection VS calcinurine inhibitors (minimal 6 month of follow up**

Acute rejection	Calcineurin inhibitors		Total
	Cyclosporine	Tactolimus	
Yes	25(26%)	18(22.1%)	43(24.4%)
No	72(74%)	63(77.9%)	135(75.8%)
Total	97(100%)	81(100%)	178(100%)

Figure 41: Incidence of Acute Rejection Vs Calcineurin Inhibitor (minimal follow-up of six months)

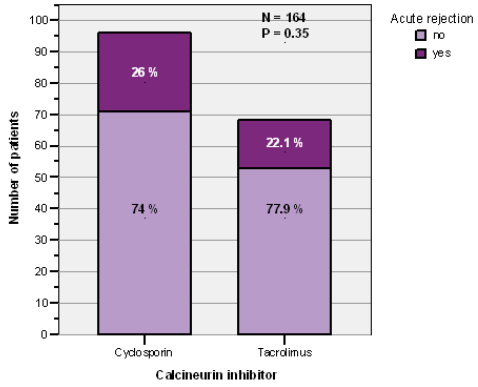


Table (4) and figure (39) illustrate the graft function post renal Transplan6tation.

Graft Function Post RTx * Calcineurin inhibitor Crosstabulation

		Calcineurin inhibitor		Total
		Cyclosporin	Tacrolimus	
Graft Function Post RTx	Immediate	85	77	162
		87.8%	95.0%	91.0%
	Delayed	4	2	6
		4.1%	2.5%	3.4%
	Primary non-function	8	2	10
		8.2%	2.5%	5.6%
Total		97	81	178
		100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	P_value
Pearson Chi-Square	3.250	2	.200

Figure 39: Graft Function Post RTx Vs Calcineurin Inhibitor

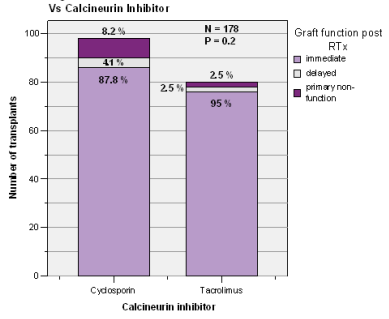
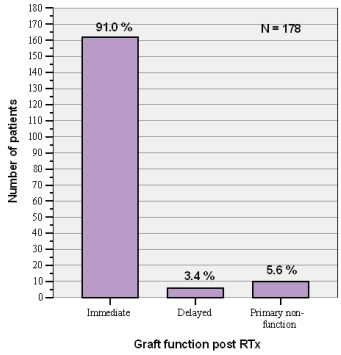


Figure 26: Graft Funtion Post RTx



Mean serum creatinine concentrations were 1.6,1. 3, 1.3mg/dl tacrolimus group for one, six and 12 months respectively.

and 1.7 ,1.6,1.4 mg/dl in the CsA group by month 1,6 and12. Mean serum creatinine concentrations were 1.3±0 .8 mg/dl (*n* =81) in the tacrolimus group and 1.3±0.8 mg/dl (n = 97) in the cyclosporine group at 12 months (*P*>0.01).

S. creatinine					
			1 month (P = 0.83)	6 months (p = 0.05)	1 year (P = 0.69)
Calcineurin inhibitor	Cyclosporin	Mean	1.6	1.3	1.3
		SD	1.3	0.4	0.4
		N	79	59	63
	Tacrolimus	Mean	1.7	1.6	1.4
		SD	1.3	1.2	0.4
		N	61	45	27
	Total	Mean	1.6	1.4	1.3
		SD	1.3	0.9	0.4
		N	140	104	90

Serum creatinine tend to be of equal range in Tacrolimus group (1.26+- 0.42) vs. (1.6 +- 1.16),P ns in Cyclosporine group at one year.

Figure 29: Drug Prescription Rate Among Renal Transplant Recipients

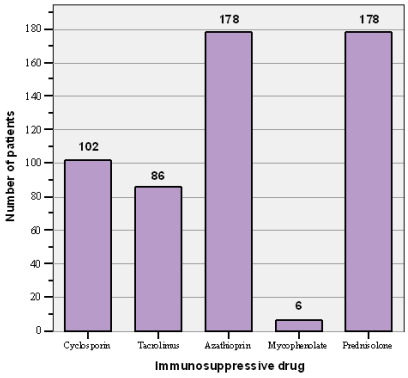


table Current immunosuppression at the center

cyclosporine	**51%**	**102**
Tacrolimus	**43%**	**86**
Steroids	**89%**	**178**
Azathioprine	**89%**	**178**
MMF	**3%**	**6**

Discussion

As an evaluation summary of findings; results from this retrospective trial which compare the efficacy of Tacrolimus based regimen with cyclosporine based regimen at one year follow-up. The demographic and baseline characteristics were similar between the two treatment groups.

The study found no difference between cyclosporine and Tacrolimus in the composite primary efficacy endpoint, including biopsy-proven acute rejections, graft loss In the Tacrolimus treatment group and Cyclosporine and patient survival Calculated on whole populations, overall mortality was grater for cyclosporine than Tacrolimus without significant meaning, but overall rate of graft loss was not significantly differ after 1 years with Tacrolimus- vs. cyclosporine-based immunosuppression .Thus, there was no significant loss or death difference for Tacrolimus and cyclosporine group.

All previous studies reported some evidence of equivalent efficacy between cyclosporine based regimen and Tacrolimus based regimen (5, 7, 8, and 9).

However the direct trial state that there is a significant lower loss incidence in cyclosporine group (5).and (Bernhard et al); shows that there is significant lower in acute rejection in Tacrolimus based group than in cyclosporine one. (9)

To determine whether the superior efficacy of tacrolimus in preventing acute graft rejection was still valid when compared with Cyclosporine. The 6- and 12-month data have been presented previously and demonstrated that biopsy-proven and acute rejection rates with tacrolimus vs cyclosporine treatment is lower in Tacrolimus [12]. Studies have demonstrated that severe and recurrent acute rejections as well as late and vascular-type acute rejections have a significant adverse impact on graft survival and chronic allograft nephropathy [14../AppData/ Local/Packages/ Microsoft.MicrosoftEdge_8wekyb3d8bbwe/TempState/Downloads/nada/968.htm - BIB7#BIB7../AppData/ Local/ Packages/ Microsoft.MicrosoftEdge_8wekyb3d8bbwe/TempState/Downloads/nada/968.htm - BIB8#BIB8]. Tacrolimus-based immunos uppression positively influences long-term graft function and survival. In support of this assumption, two recent randomized, controlled trials demonstrated less upregulation of profibrotic growth factors and less interstitial fibrosis with tacrolimus treatment [15]. In healthy subjects, Cyclosporine is known to decrease glomerular filtration rate (GFR) and renal blood flow and increase renal vascular resistance, whereas tacrolimus does not [11]. Recently, long-term data from the Cardiff Tacrolimus vs Cyclosporin Kidney Transplant Study (randomization of 232 patients to tacrolimus or Cyclosporine microemulsion cornerstone immunotherapy) demonstrated higher 6 year graft survival, longer estimated graft half-life and significantly better renal function (GFR) with tacrolimus[13].

These discrepancies in result may be partly explained by differences in study designs (prospective vs. retrospective, multicenter vs. unicenter, ethnicity, and duration of the study...etc.)

The limitations of this study are that our analysis of the renal transplanted follow-up records at AGRTC was limited to only 178 out of 200 of the original renal transplanted recipients due to the either incomplete follow –up or record since some records were not completed.

Never the less we thing that our analysis is valid since patient were randomly allocated to Tacrolimus or Cyclosporine treatment within the center and 178 recipients with a complete follow –up record .

The information bias is expected in such type of study due to lack of blinding.

In conclusion these data are consistent with some previously published literature. It confirms that Tacrolimus have equivalent efficacy to cyclosporine in graft and patient survival; but not in acute rejection rate for patient under going kidney transplantation.

Recommendation:

The ideal immunosuppressive treatment for Sudanese kidney transplanted recipient was not been established so performance of long term prospective randomized trial comparing the result of cyclosporine and Tacrolimus in Sudanese population is needed.

The choice of the initial immunosuppressive therapy following solid organ Trans plantation remains a source of controversy.

There is a few data directly comparing cyclosporine blood level vs. Tacrolimus blood level in renal function, and cardiovascular risk factor.

Inclusion of all studies randomized trial centers in a multicenter study will provide good representation of Sudanese population because the use of these immunosuppression based on improve under standing of their mechanism of action and their mechanism of rejection in different population, different setting different time.

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