TACROLIMUS VERSUS CYCLOSPORINE IN LOW IMMUNOLOGICAL RISK PATIENTS AFTER KIDNEY TRANSPLANTATION INDUCTED BY ANTI-THYMOCYTE GLOBULIN

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ABSTRACT

Background

Global increase in the incidence of end-stage renal disease has necessitated the performance of kidney transplantation for many patients. To minimize the possibility of renal allograft failure and maintain graft function. Kidney transplant recipients are typically given immunosuppressive drugs such as tacrolimus and Cyclosporine in combination with other drugs.

Objectives

The present study was carried out to compare the effectiveness of tacrolimus versus Cyclosporine.

Patients and Methods

The present clinical non-randomized and non-controlled study was conducted on 201 kidney transplant patients in Shar teaching Hospital in Sulaimani, Kurdistan region-Iraq, from April 2020 to April 2021. The patients had received tacrolimus and Cyclosporine as immunosuppression drugs. Required data were collected from the patients through their hospital records and direct interviews with them. The collected data were analyzed through Statistical Package for Social Science (version 22.0).

Results

Most patients (60.7%) were aged 19-45 and males (70.6%). Most of them did not know the cause of chronic kidney failure (41.3%), focal segmental glomerulosclerosis in 14.4%, and diabetes mellitus in 12.4%. Most of the donors were non-related (90.5%). Induction treatment was anti-thymocyte globulin for most of them (76.6%), and treatment after transplant, mycophenolate mofetil, Cyclosporine and prednisolone in 75% of them. Acute cellular rejection was the most frequent complication after the transplant (23.4%). Tremor and new onset of diabetes were the most frequent side effects of tacrolimus; however, hirsutism, hyperkalemia, acne, hypertension, and hyperlipidemia are the most frequent side effects Cyclosporine. More patients on Tacrolimus than Cyclosporine developed new onset of diabetes (7.5%). However, serum uric acid ($p<0.001$), serum cholesterol ($p<0.001$), and serum triglyceride ($p=0.01$) levels elevate more with Cyclosporine group patients. Moreover, drug change has a significant association with haemoglobin level (HGB) ($p<0.001$) and serum triglyceride ($p<0.001$) in those group drug was changed to tacrolimus.

Conclusion

Similar rejection was obtained by using Tacrolimus and Cyclosporine within the first year after kidney transplant in low immunological risk patients; however, acute cellular rejection was less with the TAC group. It is less expensive than Cyclosporine in our region, but Cyclosporine is more available in the hospital.

Keywords: *Kidney transplantation, Chronic kidney disease, Anti-thymocyte globulin, Tacrolimus, Cyclosporine.*

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INTRODUCTION

Patients with end-stage renal disease (ESRD) usually undergo kidney transplantation, which improves the quality of life and increases life expectancy [1]. Nowadays, many patients select kidney transplants due to the increasing incidence of ESRD. Recently there has been significant improvement in the clinical outcomes of a kidney transplant, with a one-year patient survival rate and graft survival rate being more than 85% [2].

Failure of renal allograft and rejection episodes are prevented by administering immunosuppression (IS). However, no optimal regimen has yet been proposed for induction and maintenance therapy, although a triple IS following induction with anti-thymocyte globulin (ATG) is practiced by most centers [3]. At the time of kidney transplant, tacrolimus (TAC) and Cyclosporine (CSA), which are calcineurin inhibitors (CNI), are utilized to rapidly attain adequate immunosuppression in order to treat or prevent acute rejection episodes. Both have the exact mechanism for the desired and significant unwanted impacts; however, their pharmacokinetics, serum binding mechanisms, and minor side effects are different [4]. There has been an increase in using TAC, although CsA is the most widely used agent for primary immunosuppression in kidney transplants. However, very few studies have focused on comparing these two immunosuppressive agents [5]. Tacrolimus and Cyclosporine could have been proven to have different benefits and harms. Despite several recent randomized controlled trials comparing adverse effects and the efficacy of tacrolimus versus Cyclosporine, the results of such trials have not been conclusive [6].

Kidney transplant recipients are given various immunosuppressive regimes to maintain long-term graft function and prevent rejection. A combination of induction therapy with an interleukin-2 receptor antagonist (IL2RA) and tacrolimus (TAC), mycophenolate mofetil (MMF), plus prednisolone (Pred) is used as the standard therapy in most kidney transplant centers [7]. The results of a large randomized clinical trial on comparing low-dose sirolimus, low-dose CsA, and low-dose TAC with standard-dose Cyclosporine (CsA) indicated that MMF and Pred were used as an additional treatment for all patients, and daclizumab and IL2RA were given to patients who were treated with a low-dose prescription during the first two months. Comparing these different regimes showed that a low-dose TAC regime outperformed all other regimes in terms of 1-year graft survival, acute rejection, and renal function [8]. The results of following up kidney transplant patients for three years indicated that CsA and TAC were not significantly different in terms of graft survival for both; however, TAC outperformed CsA regarding freedom from biopsy-proven rejection and renal function [9].

The most prevalent induction immunosuppression drug used to prevent allograft rejection is anti-thymocyte globulin (ATG) which causes dose-dependent lymphocyte depletion; however, its optimal dose is unknown. It should be noted that underdoes of ATG can cause elevated rejection risks, and its overdoses lead to infection. Nevertheless, early acute rejection episodes following kidney transplant have been proved to be prevented through induction therapy with ATG [10]. Because kidney transplants and related immunosuppression exert huge costs on ESRD patients, it is necessary to perform a robust economic assessment of appropriate technologies for this purpose. In this regard, it is essential to compare new and old products in terms of their costs and benefits [11]. The present study is aimed at comparing the effectiveness of TAC versus CsA in low immunological risk patients after kidney transplantation inducted by ATG antibody.

PATIENTS AND METHODS

Study design and setting: The present clinical non-randomized and non-controlled trial was carried out on 201 patients who had undergone a kidney transplant in Shar teaching hospital located in Sulaimani, Kurdistan region-Iraq from April 2020 to April 2021.

Study sample and sampling method: The study sample consisted of 201 patients who were chosen by the convenience sampling method. The sample size was calculated through an online sample size calculator and based on the population size of 420 and expected frequency of 50%, and confidence limit of 95%. The inclusion criteria were kidney transplant patients, patients who were inducted by ATG (2.5 mg/kg one day before kidney transplant and 1.5 mg/kg on day four), patients who used TAC (0.15mg/kg in two divided doses) or CsA (8 mg/kg in two divided doses) with adjusted dose after kidney transplant, and low immunological risk patients (i.e., those patients with no sensitization and have compatible HLA matching). The exclusion criteria were children under the age of 13 years, patients who were inducted by Basiliximab, and high-risk patients (second kidney transplant, multiple blood transfusion, HLA incompatible and high doner

specific antibody).

Data collection: Required data were collected through the patients' hospital records and direct interviews during their visit to the nephrology center in Shar teaching hospital for their regular follow-up.

Statistical analysis: The collected data were analyzed using Statistical Package for Social Science (SPSS version 22.0). Mean and standard deviation was used for continuous variables, frequency distribution table for categorical variables, Chi-square test and T-test for association and significant difference between variables.

Ethical considerations: To take ethical considerations into account, informed written consent was obtained from the patients who were also provided with enough information about the study aim and duration. The patients were also given the right to withdraw from the study whenever they wished to. Moreover, the research protocol was approved by the Scientific Research Protocol Committee on September 27, 2020.

RESULTS

The results revealed that most of the patients were aged 19 to 45 years (60.7%) and 46 to 65 years (29.4%) according to WHO classification (See Figure 1).

According to the results, most of the patients were males (70.6%) and did not smoke (90.5%) (Table 1).

Regarding the cause of chronic kidney disease (CKD), the results revealed that the cause was not known in 83 cases (41.3%), while focal segmental glomerulosclerosis (FSGS) in 30 cases, diabetes mellitus (DM) in 25 cases, and hypertension (HT) in 20 cases. It was also seen that before kidney transplant (KT), 129 patients (64.2%) experienced hemodialysis (HD), 124 (61.7%) had hypertension, and 24 (11.9%) had diabetes mellitus (Table 2).

The results obtained two weeks after the kidney transplant showed that the donor was unrelated in 182 cases (90.5%). Also, anti-thymocyte globulin (ATG) and thyroglobulin were used as induction therapy for 154 and 47 cases, respectively. Moreover, 75.6% of the patients received mycophenolate mofetil (MMF) with Cyclosporine and prednisolone and 24.4% mycophenolate mofetil (MMF) with tacrolimus and prednisolone as treatment (Table 3).

As it is shown in table 3, 152 patients were under maintenance by Cyclosporine, 36 (23.6%) of them was Acute cellular rejection, and 49 patients were under maintenance by tacrolimus, 11 (22.4%) of them were acute cellular rejection. However, tacrolimus leads to better results (1.2%). Figure 2.

As indicated in Figure 3, 153 patients did not change their treatment (76.1%), while 23.9% changed CsA to TAC.

Regarding the complications after kidney transplantation, the results showed that 75 cases (37.3%) had no complications. Acute cellular rejection (ACR) was seen in 47 cases (23.4%), recurrent renal failure or disease or graft loss as a result of recurrent disease in 16 (8%), and acute tubular necrosis in 13 (6.5%). Moreover, 119 cases (59.2%) had new hypertension, and 40 (19.9%) had new diabetes mellitus. Also, 43 (21.4%) required blood transfusion. Serum uric acid was normal in 124 cases (See Table 4).

The results revealed that TAC and CsA caused no side effects in most cases (75.6% in TAC and 70.1% in CsA). The most frequent side effects that TAC caused tremors in 20 cases (10%) new onset of diabetes mellitus in 15 cases (7.5%).

The most frequent side effects caused by CsA were hirsutism, hyperkalemia, acne, hypertension, and hyperlipidemia in 18 cases (9%), tremor in 9 cases (4.5%), and hirsutism in 8 cases (4%) (See Table 5).

Comparing the patients treated with TAC and CsA after kidney transplant, the study revealed that there was a significant difference regarding the new onset of diabetes mellitus after the kidney transplant (p-value<0.001) such that more patients who were treated with TAC developed new onset of diabetes than those who were treated with CsA (51% versus 9.9%) (Table 6).

A significant difference was also seen between the two groups of patients regarding their serum uric acid level (p-value<0.001), such that most patients treated with TAC had normal serum uric acid compared with those treated with CsA (81.6% versus 55.3%) respectively. Age different was not significant (p-value=0.6) (See Table 7)

The results indicated that the two groups of kidney transplant patients were significantly different in terms of their serum cholesterol (p-value<0.001), such that patients who were treated with CsA had higher levels

of serum cholesterol than those who were treated with TAC (173.25 versus 148.37) respectively. The two groups were also significantly different in terms of serum triglyceride (STG) (p-value=0.01), such that patients who were treated with CsA had higher levels of STG than those who were treated with TAC (159.30 versus 135.12) respectively. Regarding renal function, haemoglobin, serum potassium, there were no significant differences between the two groups (Table 8).

According to the results, significant relationships were seen between drug change with haemoglobin level (HGB) (p-value<0.001) and serum triglyceride (STG) (p-value<0.001) (Table 9).

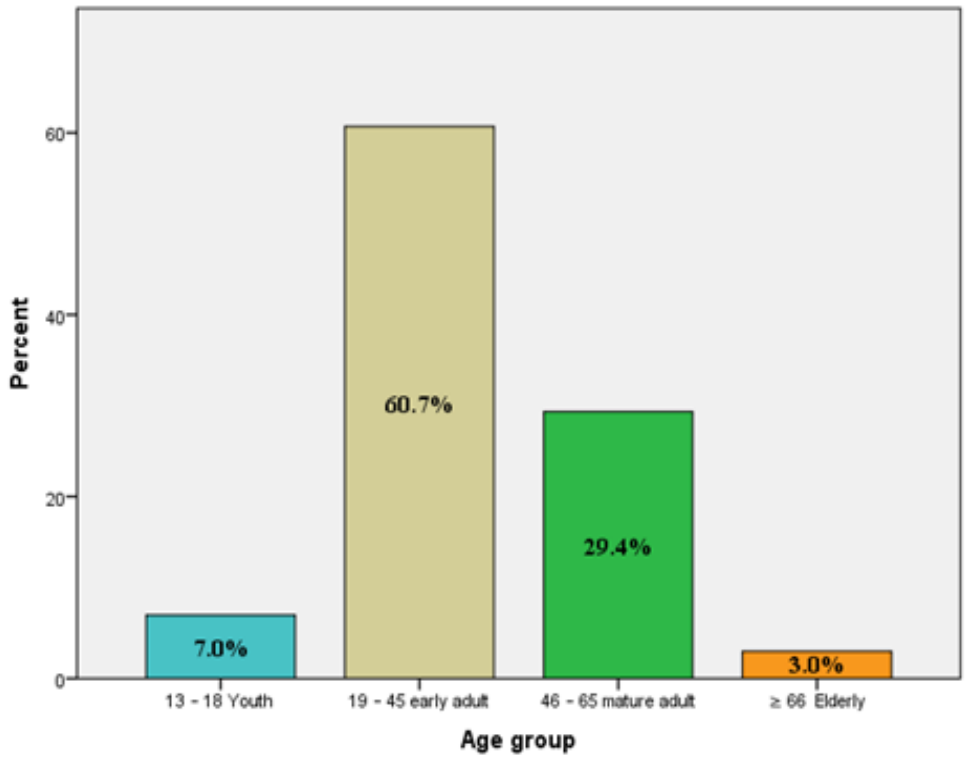

Figure 1. The patients' age groups.

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	Frequency (N)	Percentage (%)
Gender		
Female	59	29.4
Male	142	70.6
Total	201	100.0
Smoking		
Yes	19	9.5
No	182	90.5
Total	201	100.0

Table 2. Causes of chronic renal failure before kidney transplant.

	Frequency (N)	Percentage (%)
Cause of CKD		
Unknown	83	41.3
DM	25	12.4
HT	20	10.0
FSGS	30	14.9
NSAID (TIN)	10	5.0
Obstructive uropathy	9	4.5
Adult polycystic kidney disease	7	3.5
Congenital uropathy (neurogenic bladder)	8	4.0
Anti GBM disease	1	0.5
MPGN	3	1.5
Reflux nephropathy	1	0.5
Renal tuberculosis (TB)	1	0.5
IgA nephropathy	3	1.5
Total	201	100.0
HD		
Yes	129	64.2
No	72	35.8
Total	201	100.0
HT		
Yes	124	61.7
No	77	38.3
Total	201	100.0
DM		
Yes	24	11.9
No	177	88.1
Total	**201**	**100.0**

Table 3. Induction therapy and treatment after kidney transplant.

	Frequency (N)	Percentage (%)
Donor		
Related	19	9.5
Unrelated	182	90.5
Total	201	100.0
Induction		
AUG	154	76.6
Thymoglobulin	47	23.4
Total	201	100.0
Treatment after Transplant		
MMF with Cyclosporine and prednisolone	152	75.6
MMF with tacrolimus and prednisolone	49	24.4
Total	201	100.0

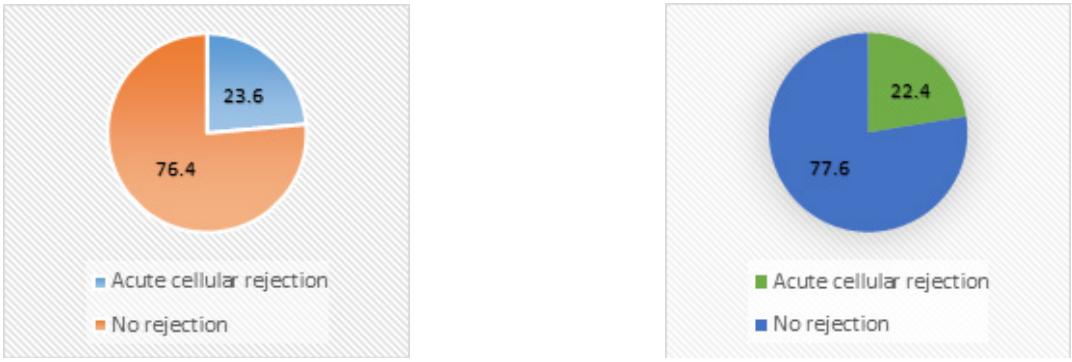

Figure 2. Acute cellular rejection according to CsA and TAC group.

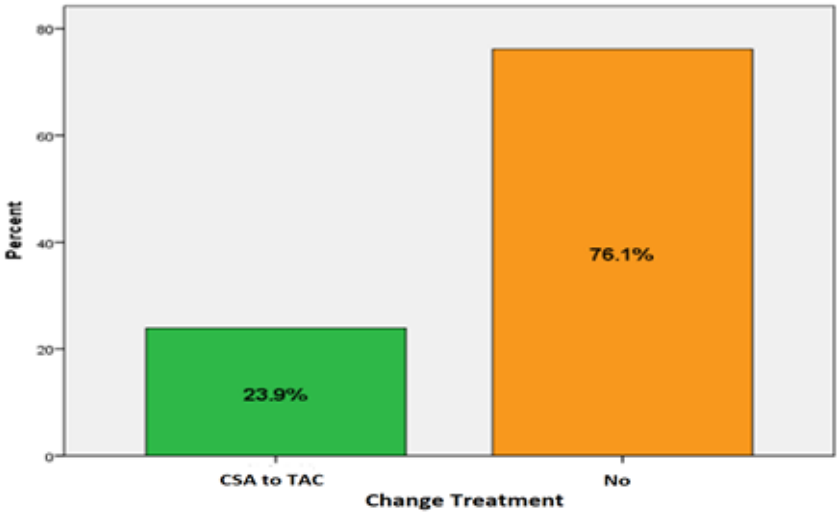

Figure 3. Treatment change after kidney transplant.

Table 4. Complications after kidney transplant.

	Frequency (N)	Percentage (%)
Complication		
No complication	75	37.3
COVID-19	4	2.0
Pyelonephritis	7	3.5
Cytomegalovirus	1	0.5
Recurrent disease	16	8.0
Interstitial nephritis /tubular atrophy	9	4.5
Acute cellular rejection	47	23.4
Thrombotic thrombocytopenic purpura	5	2.5
Chronic T cell rejection	5	2.5
Acute intestinal nephritis	3	1.5
Borderline rejection	2	1.0
Antibody-mediated rejection	6	3.0
Acute tubular necrosis	13	6.5
Diarrhoea	1	0.5
Cerebrovascular accident	1	0.5
Cancer	2	1.0
BK virus	4	2.0
Total	201	100.0
HT		
Yes	119	59.2
No	82	40.8
Total	201	100.0
DM		
Yes	40	19.9
No	161	80.1
Total	201	100.0
Blood transfusion		
Yes	43	21.4
No	158	78.6
Total	201	100.0
Serum uric acid		
Normal	124	61.7
Abnormal	77	38.3
Total	201	100.0

Table 5. Side effects of TAC and CsA.

	Frequency (N)	Percentage (%)
The side effect of TAC		
No side effects	152	75.6
Alopecia	3	1.5
New-onset DM	15	7.5
Tremor	20	10.0
Alopecia & Tremor	4	2.0
Tremor & HT	7	3.5
Total	201	100.0
The side effect of CsA		
No side effects	141	70.1
Tremor, hirsutism, & hyperkalemia	7	3.5
Tremor, acne, & hyperlipidemia	3	1.5
Tremor & HT	3	1.5
Hirsutism, hyperkalemia, acne, HT, & hyperlipidemia	18	9.0
Hyperkalemia, acne, HT & hand numbness	3	1.5
HT, DM & Hyperlipidemia	2	1.0
Tremor	9	4.5
Hirsutism	8	4.0
Acne	5	2.5
Hyperlipidemia	2	1.0
Total	201	100.0

Table 6. Comparing patients treated with TAC and CsA regarding complication, HT, and DM.

		Treatment after transplant			
		MMF with Cyclosporine and prednisolone	**MMF with tacrolimus and prednisolone**	**Total**	**P-value**
Donor	Related	11(7.2)	8(16.3)	19(9.5)	
	Unrelated	141(92.8)	41(83.7)	182(90.5)	0.09
Total		152(100.0)	49(100.0)	201(100.0)	
Induction	AUG	116(76.3)	38(77.6)	154(76.6)	
	Thymoglobulin	36(23.7)	11(22.4)	47(23.4)	0.86
Total		152(100.0)	49(100.0)	201(100.0)	
Complication	Yes	90(59.2)	34(69.4)	124(61.7)	
	No	62(40.8)	15(30.6)	77(38.3)	0.20
Total		152(100.0)	49(100.0)	201(100.0)	
HT	Yes	86(56.6)	33(67.3)	119(59.2)	
	No	66(43.4)	16(32.7)	82(40.8)	0.18
Total		152(100.0)	49(100.0)	201(100.0)	
DM	Yes	15(9.9)	25(51.0)	40(19.9)	
	No	137(90.1)	24(49.0)	161(80.1)	<0.001
Total		152(100.0)	49(100.0)	201(100.0)	

Table 7. Comparing patients treated with TAC and CsA regarding serum uric acid and age.

		Treatment after Transplant			
		MMF with Cyclosporine and prednisolone	**MMF with tacrolimus and prednisolone**	**Total**	**P-value**
Serum uric acid	Normal	84(55.3)	40(81.6)	124(61.7)	<0.001
	Abnormal	68(44.7)	9(18.4)	77(38.3)	
Total		152(100.0)	49(100.0)	201(100.0)	
Age group	13 – 18 Youth	9(5.9)	5(10.2)	11(7.0)	0.6
	19 – 45 early adults	91(59.9)	31(63.3)	122(60.7)	
	46 – 65 mature adults	47(30.9)	12(24.5)	59(29.4)	
	≥ 66 Elderly	5(3.3)	1(2.0)	6(3.0)	
Total		152(100.0)	49(100.0)	201(100.0)	

Table 8. Association between the two groups after kidney transplant.

	Treatment after Transplant	**Mean±SD**	**P-value**
Haemoglobin	MMF with Cyclosporine and prednisolone	11.57±1.54	**0.19**
	MMF with tacrolimus and prednisolone	11.23±1.69	
Blood urea	MMF with Cyclosporine and prednisolone	74.53±35.98	**0.05**
	MMF with tacrolimus and prednisolone	86.69±42.50	
Serum creatinine	MMF with Cyclosporine and prednisolone	1.79±1.038	**0.07**
	MMF with tacrolimus and prednisolone	2.11±1.20	
Serum cholesterol	MMF with Cyclosporine and prednisolone	173.25±52.35	**<0.001**
	MMF with tacrolimus and prednisolone	148.37±24.61	
S. Triglyceride	MMF with Cyclosporine and prednisolone	159.30±73.77	**0.01**
	MMF with tacrolimus and prednisolone	135.12±53.28	
S. K	MMF with Cyclosporine and prednisolone	4.33±0.62	**0.11**
	MMF with tacrolimus and prednisolone	4.49±0.64	

Table 9. Association between drug change and other variables.

Change drug		Mean±SD	95% CI	P-value
Haemoglobin	Yes	10.91±1.45	-1.26 – -0.25	**<0.001**
	No	11.67±1.58	-1.24 – -0.27	
Blood urea	Yes	84.25±30.13	-3.46 – 21.22	**0.10**
	No	75.37±39.91	-1.86 – 19.62	
Serum creatinine	Yes	2.07±0.89	-0.09 – 0.62	**0.14**
	No	1.80±1.14	-0.05 – 0.58	
Serum cholesterol	Yes	158.29±37.05	-27.38 – 4.02	**0.09**
	No	169.97±51.06	-25.07 – 1.71	
S. Na.	Yes	132.02±51.74	-50.65 – -5.55	**<0.001**
	No	160.12±73.67	-47.03 – -9.17	
SK	Yes	4.48±0.67	-0.06 – 0.35	**0.15**
	No	4.33±0.61	-0.07 – 0.37	

DISCUSSION

With the increasing incidence and prevalence of end-stage renal disease all over the world, kidney transplant has recently become a viable therapy. To prevent renal allograft failure and maintain renal function, Cyclosporine and Tacrolimus are used normally in combination with other immunosuppressive drugs. Diabetes mellitus has been proven to be one of the main causes of renal failure [12]. In line with this, the results of the present study revealed that the cause of chronic renal failure is not known in more than 41% of participants, while Diabetes mellitus was responsible for Chronic renal failure in 12.4% of them. In the same regard, the results of the study conducted by Gheith et al. (2016) showed that about 20%-30% of diabetic patients develop renal disease [13]. Moreover, Dana A Sharif et al. (2017) observed that the most common cause of end-stage renal disease in Sulaimani was diabetes [14].

Focal segmental glomerulus sclerosis can be treated through medical treatment, kidney transplantation or dialysis [15]. In line with this, the result of this study showed that Focal segmental glomerulus sclerosis was responsible for chronic kidney disease in more than (14.9%) of the patients. In addition to Focal segmental glomerulus sclerosis, hypertension has been referred to as one of the leading causes of chronic kidney disease because of the adverse impacts of elevated blood pressure on kidney vasculature.

In the present study, donors were not related in more than 90% of cases. Additionally, 76.6% of the patients used Anti-thymocyte globulin (ATG) as induction therapy. In line with this finding, using Anti thymocyte globulin is especially significant for patients with contemplated steroid avoidance and sensitized patients. Despite its benefits, Anti thymocyte globulin does not improve long term kidney allograft survival [16]. The study of Mary Vacha et al. (2015) used high dose Anti thymocyte globulin 7.5 mg/kg as induction in high immunological risk patients, resulting in low rates of acute rejection [17]. In the different with the present study used ATG dose (2.5 mg/kg one day before kidney transplant and 1.5 mg/kg on day four) and low immunological risk patients.

According to the results of this study, more than (75%) of the patients received Mycophenolate mofetil (MMF) with Cyclosporine and prednisolone, in the study of Pishtewan H. Al-Bazzaz (2010) showed that the patients were under maintenance Cyclosporine, Mycophenolate mofetil and prednisolone have acute cellular rejection in (5.3%) of cases [18].

The most frequent complication after kidney transplantation in the present study was acute cellular rejection (ACR) which was seen in more than 23% of the patients. For this reason, CsA changed to TAC in 23.9% of patients at the time of ACR. However, the study of Garcia et al. (2016) showed a high risk of acute cellular rejection in one year's 14.3%, of which 46% were observed within six months after kidney transplant. In

this regard, they suggested that acute cellular rejection can be managed if kidney transplant patients strongly follow an established course of therapy and keep immunosuppressant drug concentrations stable. These measures should be considered particularly one year after a kidney transplant because nearly 50% of acute cellular rejection episodes happen after one year from a kidney transplant, which can have a negative impact on graft survival [19].

The results of the present study also showed that normal serum uric acid was more frequent in patients treated with TAC than those treated with CsA. Similarly, the results of a study by Kim et al. (2018) demonstrated that both TAC and CsA might lead to the development of hyperuricemia in kidney transplant patients but more with CsA. They also observed that hyperuricemia was not a sign to convert from CsA to TAC in kidney transplant recipients [20]. The study of M. Kanbay et al. (2005), they studied the effect of Cyclosporine and Tacrolimus on serum uric acid levels in a kidney transplant recipient with normal allograft function, both treatment regimens gradually increasing serum uric acid levels, when Cyclosporine changed to tacrolimus there was no revision in serum uric acid levels [21].

The results of the present study demonstrated that there was a significant difference between the two studied groups in terms of serum triglyceride (STG) and serum cholesterol, such that treatment with Cyclosporine led to higher levels of STG and serum cholesterol than treatment with Tacrolimus, Moreover, In a similar study conducted by Mahmood et al. (2020), it was concluded that kidney transplant patients treated with CsA and TAC were significantly different regarding their hyperlipidemia, hypertriglyceridemia, elevated LDL, post kidney transplant more with Cyclosporine group patients [22].

In the present study, there is no significant difference observed between the two groups in terms of their hypertension, serum creatinine, serum potassium, blood urea, haemoglobin. However, there was a significant difference regarding the new onset of diabetes mellitus after the kidney transplant such that more patients who were treated with TAC developed new onset of diabetes than those who were treated with Cyclosporine (51% versus 9.9%). The results of a similar study carried out by Azarfar et al. (2018) in Saudi Arabia indicated that tacrolimus was significantly superior to Cyclosporine, such that patients who were treated with tacrolimus had a lower level of post-transplant diabetes mellitus (DM) incidence ($p<0.001$) [23].

CONCLUSION

Tacrolimus and Cyclosporine, in combination with MMF and steroids, are used to prevent acute cellular rejection, especially in the first years after kidney transplant. Additionally, tacrolimus is more cost-effective than Cyclosporine for the primary prevention of graft rejection in kidney transplantation, but Cyclosporine is more available in the hospital. For this reason, our patients more use Cyclosporine. HGB and STG could be affected significantly by changing drugs from CsA to TAC.

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