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RESEARCH ARTICLE

SIDE EFFECTS OF CYCLOSPORINE COMPARED TO TACROLIMUS AMONG YEMENI KIDNEY TRANSPLANT PATIENTS WHO SHARE THE SAME ADJUVANT AGENTS: MYCOPHENOLATE MOFETIL AND PREDNISONE

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Abstract

Background: A renal allograft is the optimum therapeutic option for patients with end stage renal diseases. Nevertheless, rejection still represents a large challenge. So as to overcome this matter, treatment strategies comprise the combined use of anti-inflammatory and immunosuppressive agents, although they are not free from complications. Interestingly, the major cause of morbidity and mortality after the first transplanted year are due to disorders unrelated directly to immunologic etiology or disease related to immunosuppressive drugs.

Objectives: The purpose of this study is to determine the side effects in renal transplant Yemeni patients adherence to cyclosporine compared to tacrolimus sharing the same adjuvant agents which are mycophenolate mofetil "MMF" and prednisone.

Subject and methods: This prospective study was carried on 100 kidney transplanted Yemeni patients divided into two groups: cyclosporine group (n=50) and tacrolimus group (n=50), each member of these groups was visited three times, blood samples were collected for biochemical functions including fasting blood sugar, liver enzymes, kidney functions, lipid profiles and white blood cells counts and results were obtained from the tests performed. Body weight and blood pressure had been examined; clinical complications were also recorded.

Results: This study showed that serum total and direct bilirubine, gamma glutamyl transferase "GGT" and lipid profiles were elevated in cyclosporine group, whereas in tacrolimus group they were within normal range. The incidence of complicated events reported as follows: Hairtusim, gum hyperplasia, herpeszoster, CUSHING face and obesity were obviously present in cyclosporine group, while in tacrolimus group diabetes mellitus, hair loss and gastrointestinal tract infections were in existence.

Conclusion: This study found that a tacrolimus-based treatment was significantly better than an immunosuppressive regimen based on cyclosporine due to the generally less side effects associated with tacrolimus, despite its effect on increasing diabetes among kidney transplant patients.

Keywords: Cyclosporine, mycophenolate mofetil "MMF", prednisone, renal transplant, side effects, tacrolimus, Yemen.

INTRODUCTION

Kidney transplantation is the ideal action for most patients with end-stage kidney disease (ESRD)¹. Kidney transplantation for patients with ESRD can enhance survival and quality of life, and lower the cost of health care. Currently, the 1-year patient survival rates and graft survival rates are 94% and 82%,

respectively^{2,3}. The incidence of ESRD in Yemen is 120 cases per million annually, which is comparable to the incidents reported in other posts in the same region^{4,5,6}. In Yemen, the kidney transplant program began intermittently since 1998. However, there has been a well-established program that has been running regularly since the beginning of 2005 in the Urology and Nephrology Center at Al-Thawra Modern General

Hospital, Sana'a⁷. Despite significant advances in the field of kidney transplantation, long-term graft survival has not increased significantly due to the continuing effect of immunosuppressive and infectious disease on transplant recipients^{8,9}.

Several immunosuppressive agents are currently in use in protective immunity in kidney transplant recipients. Usually utilized oral immunosuppressive agents fall into three categories: calcineurin inhibitors (cyclosporine and tacrolimus), antiproliferative agents (azathioprine and mycophenolate mofetil) and steroids (prednisone). The combined use of one agent in each class is known as triple therapy, and it is the standard regimen for early to mid-term immunosuppression after transplantation. This provides broad immunosuppression based on the different mechanisms of action for each group¹⁰. Medicines are not without challenges and hazards. Patients need to maintain to take immunosuppressive drugs for the rest of their lives to obstruct allograft rejection, and this trend to morbidity and mortality from organ failure to risks of cancer and infection. Additionally, these drugs are on the verge of contribute to increased mortality from cardiovascular disease, which is the leading cause of premature death in kidney transplant recipients¹⁰. At the time of transplantation to achieve adequate immunosuppression and to prevent acute rejection attacks, Cyclosporine A (CyA) and tacrolimus (TAC), are used as calcineurin inhibitors³. CyA was revealed in 1971, and in 1983, this drug was permitted for the prevention of organ transplant rejection. TAC (Prograf) was discovered in the early 1980's and from 1989, and is used to prevent liver transplant rejection. After that, the use of this drug quickly developed for transplantation of other organs¹¹.

Because of the possibility of different effects in Yemeni patients compared to other nationalities, and also that there was no study on this topic in advance in Yemen, so this follow-up study was done with the aim of evaluating the differences in kidney transplant patients, who share the same immunosuppressive adjuvants, which are mycophenolate mofetil. MMF + prednisone but differs in the calcineurin inhibitor, one group used cyclosporine and another group used tacrolimus regarding its effect on kidney and liver function, lipid properties, and complete blood cell count. Also investigating the possible relationship between the group's cyclosporine and tacrolimus with respect to other clinical side effects such as hypertension, diabetes, obesity, and dysmorphic changes.

SUBJECTS AND METHODS

This study was conducted at Al-Thawra Hospital and the National Center for Public Health Laboratories in Sana'a on one hundred Yemeni patients with kidney transplants ranging in age (14 - 60 years): 59 men and 41 females between September 2016 to September 2017. They were divided into two groups: (Group A) 50 patients (39 males, 11 females) on a cyclosporine-based immunosuppressant regimen, (group B) 50 patients (20 males and 30 females) with a tacrolimus-

based immunosuppressive regimen. All patients were informed of the aim of the study and gave their consent. Both drugs were administered in two divided doses and the dose was adjusted according to clinical responses and blood trough levels for 12 hours. The whole blood trough level of tacrolimus was maintained between 5-15 ng/ml and cyclosporine between 100-200 ng/ml. Doses were tapered based on the concentration of the drug in whole blood and clinical examination.

Sample processing: Blood samples were drawn for all measurements in the morning from 8 am to 11 am. Two tubes with EDTA one for cyclosporine or tacrolimus and the second for CBC, another plain tube for chemical parameters. Analysis was performed on the same day of collection and results were recorded at three-month intervals. The samples were taken for analysis of cyclosporine and tacrolimus blood levels, fasting blood sugar, kidney function tests (KFT) including urea and creatinine tests, liver functions tests (LFT) included bilirubin total and direct, glutamate oxaloacetate transaminase GOT, glutamate pyruvate transaminase GPT, alkaline phosphatase ALK, and gamma glutamate transaminase GGT tests, lipid profiles (total cholesterol, high density lipoprotein, low density lipoprotein and triglyceride) also the complete blood count CBC were determined. Blood pressure and body weight were also recorded with an automatic scale. Data from the renal recipient records were investigated retrospectively to determine the immunosuppressant complications among the renal allograft recipients.

Ethical consideration: Ethical approval was obtained from the Ethical Committee of the medical research at Sana'a University. Approval was obtained from all participants before recruiting them to the study and after explaining for them the aim of the study.

Statistical analysis: Data of completed questionnaire obtained, and were manipulated using Statistical Package for the Social Science version 21.0 software (SPSS version 21.0).

RESULTS

The recipient's age, ranged from 14-60 years and their mean age was 32.4 years in both groups. A significant difference was only found in recipients aged at > 45 years as in cyclosporine group was 16% while in tacrolimus it was 8%. With regard to gender 78% male and 22% female have been found in cyclosporine group while in tacrolimus group were 40% male and 60% female (Table 1). Their causes of renal failure was clinically diagnosed as follows: Hypertension (37%), Kidney atrophy (14%), Chronic urinary tract infection (14%), Stones (10%), Antibiotic abuse (4%), Hereditary (4%), Diabetes mellitus (3%), and (14%) unknown cause (Table 2). All renal recipients received a single kidney from a living donors aged between 18-55 years, in cyclosporine group (46%) of the donors were relatives and (54%) were non-relatives, while in tacrolimus group (72%) of the donors were relatives and (28%) were non-relatives.

Table 1: The patient characteristics.

Character	Cyclosporine group		Tacrolimus group		Total	
	No	%	No	%	No	%
Sex						
Male	39	78	20	40	59	59
Female	11	22	30	60	41	41
Total	50	100	50	100	100	100
Age group						
< 15 years	0	0	1	2	1	1
15-25 years	15	30	18	36	33	33
26-35 years	16	32	17	34	33	33
36-45 years	11	22	10	20	21	21
>45 years	8	16	4	8	12	12
Total	50	100	50	100	100	100

Table 2: The original causes of renal failure among our study group.

Character	Cyclosporine group		Tacrolimus group		Total	
	No	%	No	%	No	%
Hypertension	21	42	16	32	37	37
Kidney atrophy	7	14	7	14	14	14
Recurrent UTI	6	12	8	16	14	14
Obstructive Nephropathy	4	8	6	12	10	10
Hereditary	2	4	2	4	4	4
Antibiotic abuse	1	2	3	6	4	4
Diabetes mellitus	2	4	1	2	3	3
Unknown	7	14	7	14	14	14
Total	50	100	50	100	100	100

Also the drugs levels were similar in both groups; 62% and 64% of the cyclosporine and tacrolimus respectively and were within normal ranges of the trough blood level which is 100-200 ng/ml for cyclosporine and 5-15 ng/ml for tacrolimus, and 38% in cyclosporine group and 36% in tacrolimus group were shifted from their trough blood level (Table 3).

The post transplant means values of sugar, LFT, KFT, and lipid profiles are summarized in (Table 4), the significant difference were found in the elevation of total and direct bilirubin, GGT, total cholesterol, LDL, HDL, and triglycerides in cyclosporine group while not in tacrolimus group ($p < 0.0001$). No differences in the other biochemical test parameters detected between the two groups as shown in table 4. There was a significant difference in Hb ($p < 0.0001$) and platelets ($p < 0.023$) while no difference had been found in WBCs between

the two groups (Table 5). The incidence of adverse events reported in Table 6 included: 64% hairtumor, 54% obesity, 16% gum hyperplasia, 22% Cushing face, 10% herpes zoster, 28% herpes simplex, and 2% Kaposi sarcoma were associated with cyclosporine group, and this was significant.

Table 3: The drug monitoring levels during study.

Character	Cyclosporine group		Tacrolimus group		Total		p
	No	%	No	%	No	%	
Decrease	0	0	1	2	1	1	
Normal	31	62	32	64	63	63	
Increase	19	38	17	34	36	36	0.16
Total	50	100	50	100	100	100	

Table 4: The main effects of Cyclosporine and Tacrolimus in biochemical functions in a hundred renal recipients (Mean± S.D).

Character (normal range)	Cyclosporine group=50	Tacrolimus group=50	p
Sugar (3.05-6.38 mmol/L)	5.39±1.67	5.6±2.1	0.581
Urea (1.5-8.3 mmol/L)	6.18±2.1	7.99±8.3	0.143
Creatinine (55-124 mmol/L)	113±32.5	116±74.4	0.761
T-bil (up to 18 mmol/L)	14.8±7.8	9.4±5.7	<0.0001*
D-bil (up to 5.1 mmol/L)	4.8±2.7	2.2±1.6	<0.0001*
Got (up to 35U/L)	25.3±25.1	23.2±24.5	0.686
Gpt (up to 40 U/L)	35.3±46.4	24.9±17.1	0.139
Alk (35-129U/L)	112.5±45.9	98.4±42	0.112
GGT (5-61U/L)	59.8±72.2	29.1±11.4	0.004*
CHOL (up to 200 mg/dl)	209.2±47.4	144.1±39.8	<0.0001*
HDL (>35 mg/dl)	42.3±12.0	34.7±5.2	<0.0001*
LDL (<150 mg/dl)	128.3±36.7	81.8±31.5	<0.0001*
TG (up to 200 mg/dl)	235.3±109.8	157.8±60.4	<0.0001*

*Significant

Table 5: The main effects of Cyclosporine and Tacrolimus in complete blood count "CBC" in a hundred renal recipients (Mean±S.D).

Character (normal range)	Cyclosporine group =50	Tacrolimus group =50	p
Hb (115-180 g/l)	145.8±17.6	144.1±39.8	<0.0001*
WBC (4-10×10 ⁹ cell/L)	8.3±2.6	8.3±2.6	0.998
Plts (150-400×10 ⁹ cell/L)	267.5±71.1	238.9±50.4	0.023*

*Significant

Table 6: The complications of Cyclosporine group and Tacrolimus group in a hundred renal allograft recipients.

Character	Cyclosporine group		Tacrolimus group		p
	No	%	No	%	
Gum hyperplasia	8	16	0	0	0.003*
Hairtumor	32	64	2	4	<.001*
Being diabetic	1	2	10	20	0.004*
Herpes zoster	5	10	0	0	0.001*
GITI	7	14	12	24	0.2
UTI	4	8	5	10	0.7
Coughing face	11	22	0	0	<.001*
Fatigue	9	18	11	22	0.6
Kaposi sarcoma	1	2	0	0	0.15
Hair loss	0	0	10	20	0.001*
Polycythemia	0	0	1	2	0.3
Gastritis	2	4	5	10	0.23
Obesity	27	54	14	28	<0.001*
Hypertension	12	24	5	10	0.09
Herpes simplex	14	28	3	6	0.003
No complication	6	12	4	8	0.5

*Significant

On the other hand gastrointestinal infection 24%, DM 20%, hair loss 20% ,10% gastritis and had been found in tacrolimus group while not in cyclosporine group. Total 12% of cyclosporine group and 8% of tacrolimus group had no complications during the follow up time (one year).

DISCUSSION

The results of this study showed that the fasting blood sugar levels in both groups were similar and at the top of their normal range. Although, diabetes mellitus as a clinical complication appeared in 20% of tacrolimus group whereas in cyclosporine group was only 2%. This is in agreement with the fact that after renal transplantation some 45% of patients may show abnormal glucose tolerance and 20–25% may develop diabetes¹². Another study showed that tacrolimus is associated with diabetes mellitus, due to the increased concentration of FKBP (FK binding protein) in pancreatic islets relative to cyclophilin during drugs metabolism. Morphologic changes in the islets comprise vacuolization, cytoplasmic swelling and apoptosis, plus normal immune-staining for insulin, this outcome is dose related and may be amplified by concomitant corticosteroid use especially prednisone¹³. Some previous studies suggested that tacrolimus affects glucose metabolism by reducing insulin secretion in the pancreas in a dose-dependent manner¹⁴. Initially, an increased insulin resistance was also reported¹⁵, but this seems to be the result of the co-

administration of steroids¹⁴. Both prednisone and calcineurin – inhibitors provide additional risk factors, with tacrolimus conveying an increased risk, as compared to cyclosporine. Corticosteroids have been shown to produce peripheral insulin resistance and to cause alteration in pancreatic beta-cell insulin secretion. Cyclosporine and tacrolimus also appear to alter peripheral insulin sensitivity and to diminish islet function¹⁶. In the current study, the mean serum values of urea and creatinine were at the upper limit of their normal range. This is supported by another study, which reported that both cyclosporine and tacrolimus produce a chronic arteriopathy and chronic toxicity with irreversible kidney damage¹⁷ and this elevation indicate a significant, potentially graft-endangering event¹⁸. Calcineurin inhibitors CsA and FK506 generate dose-related reversible renal vasoconstriction that specifically affects the afferent arteries; the glomerular capillary ultrafiltration coefficient also decreases. Most of the studies on the mechanism of this effect have used cyclosporine rather than tacrolimus¹⁹. This have explained why cyclosporine affect on kidney function is obvious, as the main adverse effect of cyclosporine is nephrotoxicity, long-term use of CsA can lead to chronic toxicity associated with an irreversible and progressive decrease in renal function and this is characterized by interstitial fibrosis and degenerative hyaline changes in the walls of the connecting arteries²⁰, this lead to vasoconstriction that causes acute reversible decrease in GFR “glomerular filtration rate”²¹. Although this study have shown that

the blood concentration of urea and creatinine were higher in tacrolimus group (urea: 7.99 ± 8.3 , creatinine: 116 ± 74.7) than in cyclosporine group (urea: 6.18 ± 2.1 , creatinine: 113 ± 32.5), this is not agreement with some studies that indicated tacrolimus and MMF²² mycophenolate mofetil significantly improved kidney function²², and the serum creatinine concentrations were better in tacrolimus group, due to MMF²³. But agreement with a study reported that, the majority of renal transplant patients tolerate long-term cyclosporine therapy without evidence of progressive toxic nephropathy²⁴. There was a significant increase in total, direct bilirubin blood levels and gamma glutamyl transpeptidase "GGT" in cyclosporine group rather than tacrolimus group. This is in agreement with the study that reported episode of hepatic dysfunction typically manifesting as sub clinical, mild, self limiting, and dose-dependent increase of serum aminotransferase levels with slight hyperbilirubinemia occur in nearly half of all kidney transplant recipients taking cyclosporine and occur less frequently in those taking tacrolimus. No specific hepatic tissue lesion has been described in humans, hyperbilirubinemia is a reflection of disturbed bile secretion rather than hepatocyte damage, and cyclosporine itself does not result in progressive hepatic disease; another reason, most often one of the causes of viral hepatitis, even some studies have found that both cyclosporine and tacrolimus cause liver toxicity and impair liver function^{26,27}.

Lipid profiles including total cholesterol, HDL, LDL, TG were significantly altered with cyclosporine and elevated in comparison to tacrolimus group in the current study. This results were similar to those obtained by another studies which assessed hyperlipidemia is one of the metabolic adverse effects of cyclosporine and tacrolimus but its greater in cyclosporine A than in tacrolimus the mechanism related to cyclosporine alteration of lipids is through its direct effect on cell membrane cholesterol concentration and regulatory pools, resulting in both increased synthesis of cholesterol and decreased clearance of LDL, HDL levels are typically normal or elevated in obesity; however cardio protective HDL fraction may remain low^{28,30}.

The total blood cell counts were similar in the two study groups, and this is in agreement with another studies that assessed cyclosporine A and corticosteroids which have no suppressor effects on bone marrow cells, also mycophenolate mofetil usually do not cause bone marrow suppression³¹, even if another study found that prednisone inhibited the expression of polymorphonutriphils to the tissue. This lead in turn to their accumulation in the peripheral blood³². Even severe anemia appeared due to selective depression of erythropoiesis by immunosuppressive drugs³³, anemia resolved when tacrolimus was replaced with cyclosporine, more generalized bone marrow suppression has also been reported³⁴. This result was shown as significant difference between the two groups, although hemoglobin was within normal range, as the excellent graft function is achieved, a burst of erythropoietin secretion is normally followed by

effective production of erythrocytes³⁵. There was a significant difference in platelets between the two groups, it seems to be thrombocytosis in cyclosporine group, but not in agreement with a study that reported thrombocytopenia is associated with cyclosporine therapy³⁶. There was a significant presence of gingival hyperplasia or gum hyperplasia in cyclosporine group while not in tacrolimus group. These findings are consistent with the results obtained from other studies which reported that cyclosporine is well known to be associated with the development of gingival overgrowth³⁷, the reason for this localization of this effect in the gums is not known, although it is possible that the periodontal tissues are exposed to higher concentrations of drugs compared to other tissues, and this is strong evidence that the drug works on the growth and function of both gingival fibroblasts and gingival epithelial cells via cytokines and growth factors³⁸. CsA may also cause gingival hyperplasia by increasing the number of fibroblasts and the production of collagen by them³⁹. It was shown that Hirstism is significantly incidence in cyclosporine group while hair loss is significantly found in tacrolimus group, and these were supported by another study that reported Hirstism found in cyclosporine⁴⁰ and hair loss in tacrolimus⁴¹. CsA may cause hypertrichosis on the face, arms, shoulders, and back, and is particularly troublesome in young women and children, particularly if dark-haired. This disorder is dose-dependent, and, at least in experimental animals, seems to be related to the inhibition of NFAT in follicular keratinocytes⁴².

A significant difference in herpes zoster and Kaposi sarcoma and dysmorphic changes that were found more in cyclosporine in the current study. This is in concordance with the results obtained in another study which found that the herpes zoster develops in approximately 10% of adult renal transplant recipients and may involve two to three adjoining dermatomes; infection is usually caused by reactivation of latent diseases. Post transplant infection can be primary or transmitted from the donor kidney and is associated with Kaposi sarcoma occurring at median of 30 months post transplant. Diagnosis is supported by pathology and by the presence of human herpes viruses⁴³.

There was no significant difference in hypertension as a complicated disease' between cyclosporine and tacrolimus groups and this is supported by other studies that reported hypertension as common after transplantation and may be caused by the effect of cyclosporine or tacrolimus⁴⁴, Cyclosporine may cause renal vasoconstriction through several mechanisms⁴⁵. As a consequence, there is a reduction of glomerular filtration rate and of renal blood flow⁴⁶. In turn, these functional abnormalities lead to retention of salt and water, to an increase in extracellular fluids, and to an increased cardiac output⁴⁷.

The apparently normal production of renin by the allograft and by the native kidney is inappropriately elevated in a setting characterized by extracellular fluid expansion, collaborating with hypertension⁴⁸. Tacrolimus also produces clinical post-transplant hypertension via mechanisms similar to those of cyclosporine⁴⁹ although hypertension is less common

in patients given tacrolimus than in those receiving cyclosporine⁵⁰. There is a significant difference in obesity in the two study groups, it was clearly obvious in cyclosporine group due to high appetite in these patients and this is associated with steroid therapy that potentate in combination with cyclosporine⁵¹.

CONCLUSIONS

This study found that a tacrolimus-based treatment was significantly better than an immunosuppressive regimen based on cyclosporine due to the generally less side effects associated with tacrolimus, despite its effect on increasing diabetes among kidney transplant patients. We also hope to conduct more studies to prevent widespread renal failure by knowing the factors predisposing to kidney failure and researching factors that can affect medical compliance after kidney transplantation in Yemen.

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AUTHOR'S CONTRIBUTION

Al-Akwa'a IA: laboratory work, thesis writing. **Abu-Asba NWA:** supervised the clinical works. **Al-Moyed KAK:** investigation, conceptualization. **Al-Shamahy HA:** formal analysis, critical review. **Al-Haddad AM:** editing, methodology. All authors revised the article and approved the final version.

DATA AVAILABILITY

The datasets generated during this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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