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Major Adverse Effects Associated with Tacrolimus (Fk506) Based Regimen among Saudi Kidney Transplant Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MAAS, ASA and MSAN designed the study, wrote the protocol, author MSAN collected the data, and supervise inclusion, exclusion of patients, authors EHA and MSAN did statistical analysis, authors HMAK, RA and MNAA, supported literature review, discussion, and editing of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Tacrolimus (Fk506)- based immunosuppressant regimen has become the cornerstone in managing kidney transplant patients (KTP) , where it has been used typically used on chronic basis. However, various adverse effects on multiple organ systems are expected and their incidence is depending on many variables including genetic and non-genetic factors. The present study aims to explore the adverse effects associated with the chronic use of Tacrolimus - based immunosuppressant regimen in Saudi kidney transplant patients (SKTP). It was performed retrospectively at Kidney

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Transplant Center AFHSR in Khamis Mushait (Saudi Arabia) and comprised 100 SKTP treated with Tacrolimus who were followed-up for 24 months (2012-2014).
The findings showed that the most common clinical complications associated with Tacrolimus - based regimen were as follows: nephrotoxicity (46%), hypertension (27%), new onset diabetes mellitus (18%), infections (22%) hyperlipidemia (28%) and hypomagnesaemia (85%). In addition nausea and insomnia were shown to be other common complaints .
Conclusion: The present study demonstrated a significant association between hypertension and chronic kidney rejection. as well as between nephrotoxicity and chronic rejection High trough levels of Tacrolimus were documented as a risk factor for the development of new onset diabetes mellitus (NODM) in SKTP.

Keywords: Tacrolimus; kidney transplant; side effects; therapeutic drug monitoring.

1. INTRODUCTION

Tacrolimus is a potent macrolide immunosuppressant drug. It is a calcineurin inhibitor (CNI) including inhibition of interleukin 2 (IL-2) , suppression of the development and proliferation of T cells (adaptive immunity). It is now extensively used in the management of many autoimmune disorders and solid organ transplantations as an essential component with other immunosuppressing agents (Corticosteroids, Mycophenolate Mofetil (MMF) or Sirolimus) [1]. Regarding kidney transplantation, the use of tacrolimus is associated with favorable clinical outcomes in terms of better graft survival compared to Cyclosporine A (CsA) -based regimens [2]. Tacrolimus has a narrow therapeutic range with great inter and intra-patient pharmacokinetic (PK) variability. Thus, the contribution of various variables on its PK has to be considered to optimize its use in clinical practice [3]. Drug transporters and metabolizing enzymes are among the most significant biological factors known to affect tacrolimus PK [4]. In this context, CYP3A5 is the predominant enzyme for metabolism of tacrolimus. However ,CYP3A4, has a minimal contribution. In addition to CYP3A4 and CYP3A5; the efflux transporter P-glycoprotein (P-Gp) also plays a major role in the pharmacokinetics of tacrolimus [5,6].

Chronic use of tacrolimus-based regimen is associated with a vast array of adverse effects of variable incidences and severity [2]. There are several randomized clinical trials and meta-analyses comparing the efficacy and clinical outcomes of CsA -based regimen with those on tacrolimus -based regimen in KTP. These studies proved that tacrolimus is superior to CsA in terms of preventing acute rejection and death-censored graft loss [7,8].

However, tacrolimus was associated with an increased incidence of development of new-onset diabetes mellitus (NODM) and neurotoxicity. Nevertheless, the incidence of hypertension, dyslipidemia and cosmetic side effects was decreased compared to CsA [8].

The correlation between tacrolimus level and incidence of rejection was discussed in our previously related publication. Thus the current investigation was carried out to study he incidence rates of complications commonly experienced with tacrolimus -based regimen in SKTP and to investigate the association between certain complications and kidney rejection. In addition to evaluate the relationship between the occurrence of major adverse effects and trough tacrolimus levels.

2. SUBJECTS AND METHODS

The present study was implemented in the AFHSR in Khamis Mushait, Saudi Arabia. It included 100 SKTP who were treated and followed up for 24 months (2012-2014). The inclusion criteria included: age (between 18-60 years), both males and females, Saudi patients with first kidney transplantation, who used tacrolimus after renal transplantation in combination with MMF and prednisolone, recipients of kidney (from living or deceased donors), follow-up in Kidney Transplant Center in AFHSR, as well as those who either succeeded in renal transplant or suffered from acute or chronic rejection. The exclusion criteria included: patients treated with CsA-based regimen either after renal transplant or for any other diseases and non-compliant patients. Demographic characteristics are presented in Table 1. Out of 100 SKTP enrolled in the present study, 59 were males and 41 were females. Their ages ranged between 18 and 60 years, with mean age ± SD of 37.4±14.2 years. The BMI was ranging

Table 1. Demographic data for the SKTP (41 male, 59 female, total 100) enrolled in the study

Statistics	Age (years)	Height (m)	Weight (Kg)	BMI (Kg/m^2)
Mean ± SD	37.4±14.2	1.58±0.08	68.8±18.4	27.3±6.6
Median	34.5	1.58	68.4	26.9
Range	18-60	1.4-1.78	36.8-125	16.4-47.4

between 16.4 and 47.4 Kg/m^2 with mean BMI ±SD of 27.3±6.6 Kg/m^2.

The parameters used for outcome measurements included: acute and chronic kidney rejection as indicated by clinical manifestations (i.e. graft enlargement, fever, malaise, hypertension, oliguria and decreased renal clearance) and histopathological examination of biopsied specimens. Furthermore, findings such as: post-transplant NODM, hypertension, nephrotoxicity, and neurotoxicity such as headache and tremor were observed.

Criteria for labeling adverse effects were defined as follows: hypertension mean of three successive blood pressure readings above 135/ 90 mmHg. NODM was defined as the fasting glucose level above 130 mg/dl among patients who had previous normal blood glucose levels. Nephrotoxicity was defined when serum creatinine levels reached above 1.45 mg/dl. Gastrointestinal disturbances were documented through questioning the patients by the physician and recording complaints of nausea, vomiting or diarrhea. Neurotoxicity was similarly documented by recording patients' complaints of insomnia, tremor or headache.

Acute rejection was successfully managed by pulse dose of methylprednisolone (500 to 1000 mg for 3 to 5 days).

Statistical Package for Social Sciences (SPSS) software, version 22 was used for data analysis. Descriptive statistics (frequency, percentage, mean, standard deviation and range) were calculated. Chi-square test and t-test were applied for data analysis and p value < 0.05 was considered significant.

3. RESULTS

In the present study, all 100 patients survived through the follow-up period of 24 months. Most patients (90%) did not have kidney rejection, while 8% of patients suffered from acute rejection and 2% of patients showed chronic rejection. (end by graft loss).

The following is a brief description of medications that were administered chronically: most of the hypertensive patients were receiving β - Adrenergic blockers (ranked as Labetalol >Bisoprolol > Metoprolol). β blockers were usually prescribed in combination with a calcium channel blocker (ranked as amlodipine > nifedipine),. Few patients were receiving Angiotensin-converting enzyme inhibitor (Eosinophil).

Most diabetic patients were controlled on insulin regimen and few patients were receiving oral hypoglycemic drugs (Gliclazide, Metformin). In addition some patients received low dose aspirin.

Frequently, omeprazole and other proton pump inhibitors or ranitidine were administered. Most patients received erythropoietin, alfaclacidol, folic acid, multivitamin, iron or calcium supplements. ; few patients were taking statins. Other medications which had been prescribed for certain conditions as short courses were: antifungal drugs, antibiotics, analgesics, thyroxin, warfarin and clopidogrel.

Table 2. Prevalence of clinical complications associated with use of tacrolimus by SKTP

Clinical complication	Frequency or %
Hypomagnesaemia	85
Nephrotoxicity	46
Hyperlipidemia	28
Hypertension	27
Infections	22
New onset Diabetes mellitus	18
Gastrointestinal disturbances	15
Neurotoxicity	12
Weakness and Arthralgia	6
Hyperkaliemia	5
Anemia	3
Hypophosphatemia	2

The most common clinical complications associated with tacrolimus-based regimen among SKTP were presented in Table 2. They involved nephrotoxicity (46%), hypertension (27%), NODM (18%), infections (22%), hyperlipidemia (28%) and

Table 3. The impact of tacrolimus mean trough level (ng/ml) on incidence of NODM (N=18)

Kidney rejection	Post kidney transplant period	NODM	N	Tacrolimus trough level Mean ± SE	Range of Tacrolimus trough level	P-value*
Nil	1 - 14 days	No	69	11.5 ± 0.3	4.0 - 17.8	0.000
		Yes	13	15.2 ± 0.6	11.0 - 19.1	
		Total	82	12.1 ± 0.3	4.0 - 19.1	
	15 - 28 days	No	74	9.9 ± 0.2	5.5 - 16.1	0.000
		Yes	16	12 ± 0.5	8.4 - 15.4	
		Total	90	10.2 ± 0.2	5.5 - 16.1	
	29 - 180 days	No	74	8.5 ± 0.2	5.3 - 15.7	0.006
		Yes	16	10.2 ± 0.7	6.2 - 14.6	
		Total	90	8.8 ± 0.2	5.3 - 15.7	
	More than 180 days	No	74	7 ± 0.2	4.5 - 11.9	0.000
		Yes	16	9.2 ± 0.5	5.1 - 12.7	
		Total	90	7.4 ± 0.2	4.5 - 12.7	
Acute	1 - 14 days	No	4	9.3 ± 1.3	6.9 - 12.9	0.026
		Yes	1	21.3	21.3	
		Total	5	11.7 ± 2.6	6.9 - 21.3	

** Independent sample t test*

hypomagnesaemia (85%). Yet hypophosphatemia had the lowest prevalence (2%).

Nausea was the most frequently encountered gastrointestinal disturbance, insomnia was the most common neurotoxic complication and urinary tract infection was the most recorded infection (Fig. 1).

Table 3 demonstrates that the incidence of NODM, which was significant among patients, characterized by high tacrolimus mean trough level.

Table 4 provides the proposed target tacrolimus trough level (ng/ml).

Table 4. The proposed target tacrolimus trough level (ng/ml) through post kidney transplant periods

Post kidney transplant periods	Proposed range of tacrolimus trough level (ng/ml) (95 % CI)	
1 – 14 days	11.5	12.7
15 – 28 days	9.7	10.6
29 – 180 days	8.2	9.2
More than 180 days	6.9	7.8

A significant relationship between nephrotoxicity and acute kidney rejection was observed (p=0.013). Nephrotoxicity was developed in all SKTP with chronic rejection, in 87.5% of acute rejection patients and in 41% of those with no rejection. Furthermore, a significant relationship between hypertension and kidney rejection was observed (p=0.046), where 62.5% of acute rejection patients were found to be suffering from hypertension. Moreover another remarkable correlation between weakness, arthralgia and kidney rejection (p<0.001) was noted as 50% of acute rejection cases complained from weakness and arthralgia compared to 24.4% of those with no kidney rejection. (Table 5).

4. DISCUSSION

We describe the adverse effects due to chronic immunosuppressant regimen, (tacrolimus – MMF – prednisolone) in SKTP. Prednisolone has a significant contribution in major adverse effects: diabetes, hypertension, and hypercholesterolemia. MMF likely be responsible for most GIT adverse effects.

Nephrotoxicity was documented in 46% of SKTP. Variable incidences of calcineurin inhibitor - induced nephrotoxicity in KTP were reported [9,10].

In fact, it is not easy to attribute all cases of nephrotoxicity to tacrolimus since transplant patients often also receive other nephrotoxic medications and may have pre-existing or ongoing kidney diseases as well. CNI-

Table 5. Factors associated with kidney rejection in SKTP

	Kidney rejection			p-value*
	Nil N =90	Acute N=8	Chronic N=2	
Nephrotoxicity				
No (n=54)	53 (58.9)	1 (12.5)	0 (0.0)	
Yes (n=46)	37 (41.1)	7 (87.5)	2 (100)	0.013
Hypertension				
No (n=73)	68 (75.6)	3 (37.5)	2 (100)	
Yes (n=27)	22 (24.4)	5 (62.5)	0 (0.0)	0.046
Weakness and arthralgia				
No (n=94)	88 (97.8)	4 (50.0)	2 (100)	
Yes (n=6)	2 (2.2)	4 (50.0)	0 (0.0)	<0.001

** Chi-square test*

induced nephrotoxicity has been associated with poor long-term kidney allograft survival [11]. It has been postulated that CNI is considered as a major cause of chronic renal allograft damage [12].

Acute and chronic nephrotoxicity are generally similar with both CsA and tacrolimus. However, at lower doses, tacrolimus was shown to be less nephrotoxic without compromising clinical outcomes [13]. Several factors are postulated as risk factors to develop nephrotoxicity in KTP maintained on CIN, including advanced age, preexistent renal disease, intravascular volume depletion, pre-transplant diabetes and hypertension, hepatitis C virus infection, females and postoperative renal impairment etc [14]. Studies showed that CIN are associated with the increased production of vasoconstrictors (endothelin, thromboxane and angiotensin II), increased expression of osteopontin chemokines and transforming growth factor-beta and increased apoptosis. On the other hand, they were reported to be associated with lower release of vasodilators (prostaglandins and nitric oxide) and lower expression of trans-membrane P-Gp. Briefly, nephroprotective mechanisms were inhibited and nephrotoxic mechanisms were enhanced by CNI [15-18].

In the present study, new cases of hypertension were observed in 27% of SKTP, an incidence close to that by Bagnis et al. [19]. A complex interplay between several factors contributes to the development of hypertension after transplantation. Some factors are related to the kidney recipient, donor, surgical procedure and postsurgical complications as well as immunotherapy regimen [20].

In the current study, the overall incidence of NODM was 18%. It was found that the incidence of NODM was higher among patients characterized by high tacrolimus mean trough level. Webster et al. (2005)[8] reported that tacrolimus doubles the risk of NODM requiring insulin compared to CsA. The graft survival is maximized and the risk of NODM is minimized when tacrolimus targeted concentrations are maintained less than 10 ng/ml during the first year after transplantation. Several other studies confirmed the correlation between CNI and NODM in KTP [21-23].

Impaired glucose tolerance, prior transplantation and hyperglycemia in the immediate perioperative period may identify patients at higher risk for the development of NODM [24].

CsA and tacrolimus predispose the patients to diabetes through mechanisms such as β-cell toxicity, diminished insulin synthesis or release and decreased peripheral insulin sensitivity [25]. It was suggested that tacrolimus and CsA may act on different pathways and insulin resistance induced by these two drugs may also be different. A clinical study showed that tacrolimus-based therapy led to higher peripheral insulin resistance than CsA-based immunosuppression in kidney allograft recipients [26].

Other side effects due to tacrolimus -based regimen in the present study, gastrointestinal disturbances were (nausea, vomiting and diarrhea), neurological symptoms (insomnia, tremor and headache). In addition, UTI was the most recorded infection.

Tacrolimus therapy is also shown to cause high odds of neurotoxicity symptoms ranging from headache, tremor, neuralgia and agitation to motor weakness and seizures.

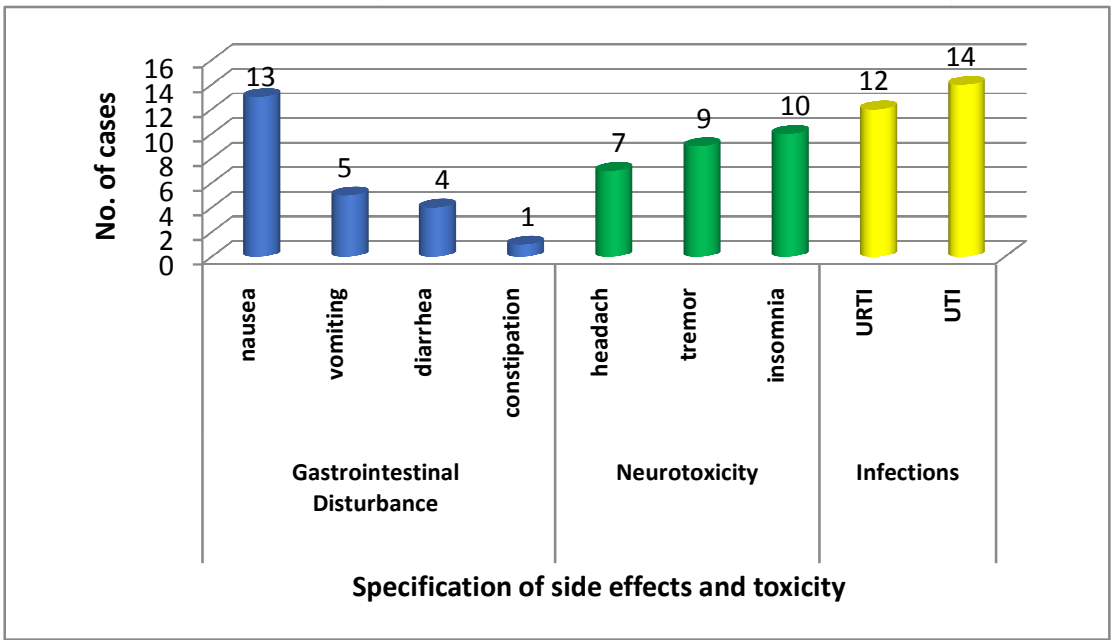

Fig. 1. Specification of side effects and toxicity associated with use of tacrolimus-based regimen by Saudi kidney transplant patients (UTI: urinary tract infection, URTI: upper respiratory tract infection)

The underlying mechanism of such symptoms is due to the inhibition of calcineurin by tacrolimus [27,28]. Tacrolimus-induced neurotoxicity was suggested to occur among patients with hepatic impairment associated with higher concentration of tacrolimus [29].

In the present study, 85% of patients had hypomagnesaemia, lower values (43 %) was reported by another investigator [30]. Hypomagnesaemia appears to be related to impairment of magnesium conserving mechanisms [3].

In this study, the correlation between nephrotoxicity, hypertension and weakness/arthralgia and the incidence of kidney rejection among SKTP was observed. The immunologic and non-immunologic risk factors for chronic renal allograft rejection were assessed retrospectively by Massy et al. [31]. Proteinuria, triglycerides, hypertension and serum albumin were found to be the non-immunologic risk factors for chronic rejection.

5. CONCLUSION

In fact we couldn't attribute the incidence of major complications to tacrolimus alone or tacrolimus- based triple regimen due to complex nature the adverse effects in SKTP which can be summarized in the following points 1) All transplant patients in our study received. corticosteroids, which is known to produce hypertension, hyperglycemia, electrolyte disturbance among other complications. [32] 2) SKTP, possibly have different genetic or non-genetic predisposing factors which contribute to the development of hypertension diabetes mellitus (DM) and nephrotoxicity. [33] 3) The interaction between hypertension and DM predispose the patients to nephrotoxicity. [34] Despite the above-dilemma, the current study demonstrated the existing association between hypertension and kidney rejection. It documented that high trough levels of tacrolimus as a risk factor for the development of NODM among SKTP.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee

has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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