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Exploring the knowledge, Attitude, and Practice of Sudanese Medical Doctors Towards Tacrolimus, at Ahmed Gasim Hospital, Kidney Transplant Center Unit, Khartoum, Sudan (2022 – 2023)

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Abstract:
Tacrolimus is one of the most commonly prescribed immunosuppressive drugs that varies between individuals depending on different ethnic groups, the presence of different CYP3A5 genetic variants, and the duration of time since the transplantation, which makes targeting optimal tacrolimus concentration levels more challenging. This study aimed to explore the knowledge, attitude, and practice of Sudanese medical doctors towards Tacrolimus. An observational, cross-sectional study was conducted on the Sudanese medical doctors in the nephrology clinic at Ahmed Gasim Hospital, Kidney Transplant Center Unit, Khartoum, Sudan, who were in direct contact with kidney transplant patients under tacrolimus treatment. Data were collected using a questionnaire modified to record the pharmacogenomic impact. The data were analyzed using a statistical package for social sciences (SPSS). Total of 15 medical doctors, Female 8 (53.3%) and male 7 (46.7%) with mean ± SD age of 31.60 ± (3.906). All of them were currently practicing in governmental hospitals (n=15; 83.3%), private hospitals (n=2; 11.1%), and private clinics (n=1; 6.7%). There were 67% of the medical doctors had high knowledge about the genetic profile of the patient's impact on the tacrolimus trough concentrations, while 66.7% of the medical doctors had low attitude levels toward tacrolimus. The observations among the different Sudanese ethnic groups tacrolimus trough concentrations were found to be variable, as Arabs and Fulani were observed to have low trough concentrations (n=6; 40%), while Nuba and Beja were observed to have high trough concentrations (n=5; 33.3%), instead of fur observed to had fluctuations (n=2; 13.3%). A significant correlation between practice toward tacrolimus with the location of practice, doctor specialty, and years of experience was found ($P\ value \leq 0.05$). The medical doctors exerted a high level of knowledge about the impact of the genetic profile (metabolic alleles) in the dosing and dose adjustment of tacrolimus.

Keywords: Medical doctors, Kidney transplant patients, Tacrolimus, Sudanese ethnic groups, Metabolic alleles (CYP3A5)

Introduction:

Patients with end-stage renal illness can live longer and have a higher quality of life after receiving a kidney transplant, which can save their live(1). Transplantation is the preferred modality of replacement therapy for most patients with kidney failure. In the United States, more than 3,000 new patients are registered each month on the kidney transplant waiting list for this life-saving therapy(2,3). Transplant recipients require life-long immunosuppression to prevent allograft rejection(4,5). Tacrolimus is widely used as the cornerstone immunosuppressive agent after kidney transplantation for the prevention of acute rejection and deterioration of graft function. Tacrolimus has a narrow therapeutic index and displays variable pharmacokinetics between individuals, which makes it a good candidate for pharmacogenomic-guided dosing. The large intra- and inter-patient variability has been mostly associated with the genetic differences in *CYP3A5* genes(6–8), Tacrolimus exhibits inter- and intra-patient pharmacokinetic variability reflecting variation in cytochrome P-450 3A (CYP3A) isoenzymes and P-glycoprotein (P-gp)(9). In humans, four different CYP3A isoenzymes have been identified: CYP3A4, CYP3A5, CYP3A7, and CYP3A43. In adults, the dominant isoenzyme is CYP3A4, which is expressed in both the gut and the liver. CYP3A5 is likewise present in these tissues, but in addition, it is also present in the prostate and the kidney. CYP3A7 predominates in neonates, but becomes downregulated soon after birth and its role as a drug-metabolizing isoenzyme is considered negligible in adults. CYP3A43 is less well studied, and so little is known about its functions(10,11). besides P-glycoprotein, plasma protein concentrations, hematocrit, age, sex, ethnicity, time post-transplantation, type of transplanted organ, hepatic dysfunction, diurnal variations, food, and drug-drug interactions(10,12).

Dosing recommendations are based on patient age, transplanted organ, time post-transplant, and concurrent immunosuppressive therapy, dosing suggestions are also provided based on race, with black patients requiring higher doses than white patients to achieve similar concentrations(10,13). Tacrolimus exhibits a narrow therapeutic index with troughs ranging from 3 to 15 ng/mL, which requires consistent monitoring in terms of dose adjustment, dose monitoring, routine follow-up, and toxicity management by health practitioners to ensure maintenance of a functional allograft and minimize adverse effects(14,15). Therefore, to maintain targeted drug exposure during patient management, evaluation of dosing regimen adjustments, and adherence assessment consider as important factors in the success of the treatment and the physician had huge impact of succussing that treatment regimen.

Due to the diversity of tacrolimus trough concentrations among different ethnic groups(14,16,17).Sudanese population structure from the male side of lineages, through the study of Y-chromosome variation of individuals representing some of the major ethnic groups in the country. Sudanese populations fall into haplogroups A, B, E, F, I, J, K, and R in frequencies of 16.9, 7.9, 34.4, 3.1, 1.3, 22.5, 0.9, and 13% respectively. Haplogroups A, B, and E occur mainly in Nilo-Saharan speaking groups including Nilotic, Fur, Borgu, and Masalit; whereas haplogroups F, I, J, K, and R are more frequent among Afro-Asiatic speaking groups including Arabs, Beja, Copts, and Hausa, and Niger-Congo speakers from the Fulani ethnic group(18). In this study the observation of the medical doctors to the different trough concentrations of tacrolimus among those different ethnic groups considered as the core of the research.

Method:

Study area:

In 1997, the Center for Heart Surgery and Kidney Transplantation was opened at Ahmed Gasim Hospital, in the city of Khartoum Bahri, and it is considered the first of its kind in the history of Sudan in this field. Since its establishment, the Center has played a clear national and reference role in providing diagnostic services, and treatment in the field of heart and kidney diseases in Sudan at an advanced level, keeping pace with the mutations that the medical field witnessed globally, regionally and locally.

Study design and population

Observational, cross-sectional study was conducted on 15 Sudanese medical doctors (nephrologists, registrars and medical officers) practicing in the nephrology clinic – transplant unit at Ahmed-Gasim hospital. The inclusion criteria for the sampling frame for medical doctors who were in direct contact with the kidney transplant patients under tacrolimus treatment from the starting day of use and worked at Ahmed-Gasim hospital- kidney transplant center. The exclusion criteria those medical doctors worked in other departments in the hospital and the medical doctors worked at the kidney transplant centers in other hospitals.

Data collection

Data collected by questionnaire to assess knowledge about the pharmacogenomic impact, attitudes, observations of the physicians for the diversity in the tacrolimus trough concentrations among the different Sudanese ethnic group (Arabs, Fur, Nuba, Fulani, Hausa, Beja, Nubian), where those are the ethnic groups of the patients admitted to the clinic in the period of the study, and practice toward toxicity management(7). Items were generated based on information collected from the literature, and a focus interview with two nephrologists. A draft of the questionnaire was then pilot-tested for content and format.

Ethical approval

The study was approved from Boards of the Faculty of Pharmacy and the post-graduate studies, University of Gezira. Ethical approval was obtained from Federal Ministry of Health – Department of Innovation, development, and scientific research and the National Medicines and Poisons Board – Secretariat General. Approval from the Department of Training and Research from kidney transplant center at Ahmed Gasim hospital was obtained.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 27.0) software was used to analyze the data obtained from the questionnaires. Descriptive statistics (mean, median, frequency, and percentages)were used to evaluate the data. ANOVA-test and Pearson Chi-Square were used to measure the significance. A p-value <0.05 was considered statistically significant. The results are presented as N(%) and mean value ± standard deviation. The scaling system for the knowledge and attitude were scored base on the correct answers, where those who obtained > 50% of the correct answers classified as known about the positive impact of pharmacogenomic in dosing regimen and highly attituded toward tacrolimus. Multivariate correlation explored the association between physician's knowledge, attitude, observation and practice toward tacrolimus and demographic characteristics.

Results:

The study conducted among the medical doctors in the transplant clinic, intensive care units (ICU) and rooms, total of 15 medical doctors, Female (n=8; 53.3%) and male (n=7; 46.7%) with mean ± SD age of 31.60 ± (3.906)

The governmental hospital considered as the most common health infrastructure the medical doctors currently practicing (n=15; 100%), beside private hospital (n=2; 13.3%) and private clinic (n=1; 6.7%). Most of the medical doctors in the study are registrars (n=13; 86.7%) beside one nephrologist and one medical officer also involved. The experiences ranged from (1 – 15) years, and location of their practices on urban, sub-urban and rural areas as (n=12;70.6%, n=3;17.6%, n=2; 11.8%) respectively as represented in Table (1).

Table (1): Areas of currently Practicing, Doctor specialty, years of Experience and location of practice:

		N	%		
Health infrastructure currently practicing:	Governmental hospital	15	83.3%		
	Private hospital	2	11.1%		
	Private clinic	1	5.6%		
Doctor Specialty	Medical	1	6.7%		
	Nephrologists	1	6.7%		
	Registrar	13	86.7%		
	N	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Year of Experiences	15	1	15	5.87	4.138
N			**%**		
Location of practice	Urban area	12	70.6%		
	Suburban area	3	17.6%		
	Rural area	2	11.8%		

In Table (2) 10 (67%) of the medical doctors considered the knowledge about genetic profile and the tacrolimus level were strongly correlated beside the impact of the ethnicity among the different Sudanese ethnic groups, the following items were used:

- Do you think that a patient's genetic profile can influence their response towards tacrolimus?
- Do you think the information provided by genetic testing may change the therapeutic management?
- Do you think genetic testing of alleles is essential for the metabolism of tacrolimus?
- In your expert opinion dose tacrolimus response differ across Sudanese ethnic groups?

The answers “Yes” got the higher percentage as follow; 10 (66.7%), 12 (80.0%), 10 (66.7%), 9 (60.0%) respectively.

Table (2): knowledge about genetic profile and the tacrolimus level:

Genetic Impact Level		
	N	%
High Impact	10	66.7%
No Impact	5	33.3%

There were 10 (66.7%) of the medical doctors represented low attitude level, in term of (monitoring of

tacrolimus level), as 15 (60%) depend only on the tacrolimus level, (adjustment of the dose) where 14 (58.3%) adjusted the dose according to the trough plasma concentration, and usually this was occurred by ± 1 of the daily doses and depend mainly on the duration of post-transplant. Weekly follow-up at the first year of the transplant considered as the most approach of follow-up by 13 (54.2%). The good tacrolimus level ranged based on the time post-transplant as (10 – 15 ng\ml) with 5 (38.5%) considered as the clinical target in the first month after transplant. Represented in Table (3).

Table (3): Attitude toward Tacrolimus:

		N	%
Q1: How do you monitor Tacrolimus?	Clinical symptoms	10	40.0%
	Tacrolimus level	15	60.0%
Q2: How do you adjust tacrolimus dose?	According to the tacrolimus level	14	58.3%
	Dose Adjustment	10	41.7%
Q3: How often should tacrolimus level be checked?	Weekly of the first months following transplantation	13	54.2%
	Monthly in the subsequent 3 months following transplantation (4-, 5- & 6-months post transplantation)	7	29.2%
	Quartile from month 7 to 12-month post-transplantation	2	8.3%
	Twice a year following post transplantation lasting for 12 months .	2	8.3%
Q4: What is the good tacrolimus level?	10 – 15 ng\ml	5	38.5%
	7 – 10 ng\ml	4	30.8%
	5 – 7 ng\ml	4	30.8%

The observations of the medical doctors on the high and low tacrolimus level among the different Sudanese ethnic groups, demonstrated on (Arabs, Fur, Nuba, Fulani, Beja) and no observations were recorded for Hausa & Nubian ethnic groups, as represented in Table (4).

Table (4): The observations of Tacrolimus trough concentrations among Sudanese ethnic groups:

	N	%
High tacrolimus Trough concentrations		
Arabs	2	9.5%
Fur	1	4.8%
Nuba	3	14.3%
Fulani	3	14.3%
Beja	2	9.5%

No observation	10	47.6%
Low tacrolimus Trough concentrations		
Arab	3	15.8%
Fur	1	5.3%
Nuba	1	5.3%
Fulani	3	15.8%
Beja	1	5.3%
No observation	10	52.6%

Significant correlation between years of experience and the observation obtained for Nuba and Fulani ,and also for the group who weren't record any observations *P value* 0.040, 0.000, 0.003 respectively. Change in the brand of tacrolimus observed to affect the plasma trough concentration, and affect the clinical target required by 10(66.7%). The body weight 10 (28.6%) considered as the main factor affect the dose and dose adjustment after transplantation. Correlation between the toxicity guiding symptoms and (health infrastructure currently practicing and doctor specialty) shown significant correlation, and the toxicity management tools shown significant correlation with year of experiences and the symptoms guiding toxicity ($P\ value \leq 0.05$).

Table (5): Practice toward tacrolimus

Correlation (*P value*)							
		N	**%**	Health infrastructure currently practicing	Doctor Specialty	Year of Experiences	Toxicity Guiding
Change in tacrolimus brands cause a greater variability in tacrolimus trough concentration	No	5	33.3 %				
	Yes	10	66.7 %				
Factors affect dose and dose adjustment after transplantation	Gender	5	14.3 %				
	Body Weight	10	28.6 %	0.000	0.009		
	Doses of corticosteroids & mycophenolate mofetil	7	20.0 %				
	CYP3A5 Genotypes	6	17.1 %				

	Other	7	20.0 %				
Toxicity Guiding	Tremor	14	32.6 %				
	Electrolytes disturbance	4	9.3%				
	Headache	3	7.0%				
	Increase Scr.	11	25.6 %				
	Acute Renal Failure	8	18.6 %				
	Diarrhea	3	7.0%				
Management of tacrolimus toxicity	Hemodialysis	3	15.0 %			0.050	0.035
	Plasma exchange	2	10.0 %				
	Gastric lavage	1	5.0%				
	Activated. Charcoal	2	10.0 %				
	Dose Adjustment	12	60.0 %				

Discussion:

This is the first study explore the tacrolimus trough concentrations variability among the Sudanese ethnic groups. The male represents old age when compared with females in this study. All of the medical doctors worked in the governmental hospital as it's area of diversity in population of patients. Years of experiences being in low level because most of the medical doctors were registrars. Some of them practicing in suburban and rural areas which gave a chance for looking upon different geographical areas so more ethnic groups. It is likely that medical doctors (nephrologist, registrar and medical officers) in practice for several years have received limited information about the tacrolimus. Continuing medical education programs might help these medical doctors appreciate the benefits of proper tacrolimus management.

In the monitoring the tacrolimus level the guideline and tacrolimus level detected by trough concentrations; both should be considered. Doses were adjusted based on tacrolimus trough concentrations with the therapeutic target concentrations of (15 - 20 ng/ml) 0 – 2 weeks, (10 – 15 ng/ml) 2 – 4 weeks, (7 – 10 ng/ml) 1 – 6 months, (5 – 7 ng/ml) three after(20,21). The dose adjustment not occur by just calculated the dose base on the BMI only, but the plasma level plays an important role. Machine-learning based approaches, statistic modelling, and genetic analyses, which have been proven to be effective in dose calculation recently in clinical practice(6,12,22). In the present study the medical doctors kept attention for the tacrolimus trough concentration level more than other parameters. Monitoring duration should be on base of the time post-transplants. The good tacrolimus level also should be based on duration post-transplants. However in clinical settings tacrolimus is still dosed using a trial and error method with frequent trough concentration monitoring(6). The knowledge of the medical doctors at the impact genetic

profile on the tacrolimus level contributed to the metabolic alleles shown diversity among different ethnic groups, shown similarity in many studies mentioned in the racial diversity and the dose adjustment of tacrolimus(23).

The reason of low attitude as most the medical doctors in this study were in the pre-specialization period on other meaning had low years of experiences and they were in contact with new transplants patients most of the time therefore, their attitude toward those categories of patients being as the represented in their answers (dose adjusted according to the tacrolimus level, monitored very closely at the beginning the proper tacrolimus level should be in range of (10 -15 ng/ml) as its early post-transplant clinical target level of tacrolimus(9,24).

No significant correlation was found with level of attitude and (Age & years of experiences) as *P value* = (.219 & 0.068) respectively, and also non-significant with location of practicing were found in this study and may that for the same reasons mentioned lately.

The observations among the different Sudanese ethnic groups tacrolimus trough concentrations were found to be variable, as Arabs and Fulani were observed to have low trough concentrations (n=6; 40%), while Nuba and Beja were observed to have high trough concentrations (n=5; 33.3%), instead of fur observed to had fluctuations (n=2; 13.3%). In many studies in literature the tacrolimus trough concentrations were found to had significant correlation with the CYP3A5 genotypes and tacrolimus level, CYP3A5(*1/1)/(*1/3) known as expressor, indicated high dose required to obtained the target level, and CYP3A5 (*3/3) non-expressor therefore, low dose required for those category of patients to prevent toxicity (20,25,26). No study was done yet to detect the genotypes of the Sudanese population of kidney transplants, these results could be confirmed when the genotype alleles investigate.

The correlation between years of experience and the observations among the different Sudanese ethnic groups being with Nuba and Fulani and that may be due to high number of cases from those categories of ethnic groups and also could be related to the percentage of those groups in the whole population as recorded in literature by study investigated by H.Y. Hassan et al.(3,6). And for no observation as most of this study population had experience less than five years therefore, low level of interaction with transplant patients suggested to their poor knowledge about the different ethnic groups and trough concentrations diversity among them.

One brand of tacrolimus available in Sudan (Prograf® by Astellas), instead of that the patients who did the transplant operation out of Sudan came with different brands and therefore some of the physicians record abnormal trough plasma concentrations when they were shifted to the local available brand, which was a reasonable response among the pharmaceutical products as that differences on the impact of different pharmaceutical products observed also among the extended-release (ER-Tac) and immediate release (IR-Tac)(9,27). Bioequivalence between the generic or branded drugs and the original Prograf® has been shown in at least 10 publications, recently reviewed by Kocur et al. with the exception of the granular formulation (Modigraf®), which showed a 23% and 18% higher mean for Cmax and AUC, respectively(12,28–30). In the present study use of one brand exclude the impact of the drug formulation in the tacrolimus trough concentration among the population under study.

The body weight considered as the first factor used for dose calculation of tacrolimus, but the tract nowadays moves to the genotype guiding the dosing of tacrolimus which was shown huge impact on the desired outcome in the management of allograft rejection and decrease the frequency of retransplant (4,9,31), 6(17.1%) of the physicians aware about this point in this study. Other factors could affect the dosing were mentioned in the study such as; decrease the dose according to the duration post-transplant,

monitor patients by clinical symptoms, lab results, Infections, dehydration, diet, diarrhea, gastric ulceration, and availability of the drug.

Toxicity guiding of tacrolimus mainly the tremor as it the most type of symptoms appears when the patient came to the clinic beside the laboratory investigates and this result was compatible with literature, in study recorded 116 adverse drug reactions (ADRs) were reported in 82 patients, urinary tract infections due to tacrolimus were the most common ADR reported by patients and constitute 17.3% of all ADRs follow by termer by 12% approximately(23). In this study the most important management protocol was found to be the dose adjustment as the protocol, followed weight-based dose calculation and as the literature suggested the proper management of the trough plasma concentrations is through the dose adjustment to maintain the clinical target required(9,20,32).

Conclusion:

High level of knowledge about the impact of the genetic profile (metabolic alleles) in the dosing and dose adjustment of tacrolimus was seen in the Sudanese medical doctors. The attitude of the medical doctors toward tacrolimus affected by their experiences level. Observations in the variability in tacrolimus trough concentrations were found to be high in the fur and Fulani Sudanese's ethnic group. They demonstrated high level of practicing toward tacrolimus toxicity management. The pharmacogenetics of tacrolimus is complex, and a great number of factors likely contribute to its variability. However, improving the understanding in this area will have a significant impact on the health and well-being of patients treated with these drugs.

Limitation of the study:

This study is not without limitation. First, the study was conducted in one public center in Khartoum state, therefore the results of this study cannot be generalized in other geographical area in Sudan. Also, the sample size is small due to the limited number of medical doctors in the center. Moreover, the variability in the doctor's specialty required to broad the scope of the study.

Author,s Contribuation:

Marvit Osman Widdatallah Omer - Conceptualization, Literature Search, Study Design, Methodology, Data Collection, Data analysis, Data interpretation and original draft &Writing.
Yousif Omer Algili Yousif - Writing and Data collection.
Abdalla Omer Elkhawad - Supervision- Review and Editing.
Imad Tag Eldin - Supervision - Review and Editing.

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