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Research Article

Assessment of Tacrolimus Adherence in Kidney Transplant Patients at Ahmed Gasim Hospital, Khartoum, Sudan (2022–2023)

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Abstract

Background: Adherence to the immunosuppressant agents is essential for reducing graft rejection. Several tools have been investigated to determine the adherence level of different medications, and the simplified medication adherence questionnaire (SMAQ) is considered one such tool, especially for tacrolimus. This study assesses adherence levels toward tacrolimus use in kidney transplant patients (KTPs).

Methods: This descriptive cross-sectional study was conducted at the Clinic of Nephrology, Ahmed-Gasim Hospital, Sudan, where a total of 166 KTPs responded to the questionnaire in the follow-up clinic, and those participants were treated with the immunosuppressant agent (tacrolimus). Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS, version 27.0).

Results: Out of the 166 responders, 157 (94.6%) exerted a high level of adherence, and 9 (5.4%) were nonadherent. Among different factors related to the low adherence level, forgetfulness (n = 22; 13.3%) was a significant factor. Patient's age (years), time since transplant (months), and the number of co-medications represented significant differences between the nonadherents and adherents (49.80 ± [10.592] vs 36.22 ± [11.434] $P < 0.05$), (9.80 ± [5.263] vs 4.27 ± [2.910] $P < 0.05$) (9(5.4%) vs 157 [94.6%] $P < 0.05$), respectively.

Conclusion: The adherence level of the studied participants was high. The nonadherence level was strongly associated with the patient's age, time since transplants, daily dose, and number of co-medications administered.

Keywords: kidney transplant patients, tacrolimus, adherence

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1. Introduction

Tacrolimus (Tac) is a calcineurin inhibitor extracted from *Streptomyces tsukubaensis* with a macrolide structure that binds to FK506-binding protein 12 and is used as an immunosuppressant agent post-transplant [1–3]. Exert pharmacokinetic variability is related to the variation among individuals' cytochrome P-450 3A (CYP3A) isoenzymes and P-glycoprotein (P-gp) [4]. Besides that, Tac variability in the trough concentrations considered for many factors may lead to variabilities in the drug response, socioeconomics, donor–recipient mismatches, racial variation, and other demographic factors, leading the patients to suffer from a range of toxic effects, which may lead to acute rejection [1]. Furthermore, one of the critical factors associated with graft loss is the adherence level to the immunosuppressant agent to ensure the patients are in the therapeutic range required for the clinically desired outcome [5]. Nonadherence is associated with graft loss, usually needing to enroll patients into dialysis sessions, and sometimes requiring retransplanting operations [6, 7]. The level of nonadherence accounts for 16.3–36.4% of kidney transplant patients (KTPs) related to graft losses, and 19.9% lead to late acute rejections [7]. Studies have shown many factors contributing to the poor adherence level toward immunosuppressant agents – a lack of trust in the medication prescribed, older patients, frequency of doses administrated, and mood changes such as depression and stress [5].

Poor adherence to immunosuppressant agents was high in recipients who had received kidney transplants compared to those with transplants of any other organ, with higher acute rejection rates [5]. Therefore, different measurements of adherence levels were evaluated through continuous monitoring, detection of drug levels in blood/serum, and an optimal questionnaire with precise questions for detecting adherence levels [8, 9]. The Simplified Medication Adherence Questionnaire (SMAQ) is one of the tools used to evaluate habits and behavior toward medication use and has been validated for measuring adherence in KTPs. The SMAQ questionnaire was developed as a modification to the Morisky-Green questionnaire, which is used to measure adherence to antiretroviral treatment in patients with acquired immunodeficiency syndrome (AIDS). This questionnaire consists of six questions that evaluate different aspects of patient compliance with treatment: forgetfulness, routine, adverse effects, and quantification of omissions, as being a tool for adherence measurement [10].

The lack of knowledge in this field in Sudan forces us to obtain more data on the degree of Tac adherence among KTPs. Therefore, this study aims to assess adherence levels to Tac use in KTPs using SMAQ, determine factors related to nonadherence habits, and shed light on the factors that could be related to inadequate Tac levels among Sudanese KTPs.

2. Materials and Methods

2.1. Study area

In 1997, the Center for Heart Surgery and Kidney Transplantation was established at Ahmed Gasim Hospital in Khartoum, Bahri, Sudan. The center is considered the first of its kind in the history of Sudan. Since its establishment, the center has played a pivotal national and reference role in providing advanced-level diagnostic services and treatment in the fields of heart and kidney diseases in Sudan, keeping pace with the mutations that the

medical field witnessed globally, regionally, and locally. Based on the 2017 statistics, the kidney operation center consists of two fully equipped operation rooms and intensive care units supplied with all necessary devices. In 2018, a total of 132 kidney and 173 heart transplant operations were done.

2.2. Study design and population

This descriptive cross-sectional study was conducted at the Department of Nephrology, Ahmed-Gasim Hospital, Khartoum, Sudan. Out of the 167 patients included initially, 1 was later excluded as he was shifted to cyclosporine. The sample size of KTPs out of the total number of new transplant operations per year was approximately 288. It included those attending follow-up visits from November 2022 until February 2023 and aged at least 18 years. The patients were under continuous monitoring and follow-up at the kidney transplant unit, under the treatment of Tac as immunosuppressant therapy, and the trough concentration of Tac of at least one laboratory finding was obtained. The participants under the treatment regimen of immunosuppressant (Tac), mycophenolate mofetil, and prednisone as basic prescription post-transplant were included in the study. The patients agreed to participate in the study, giving their agreement by signing a consent form.

2.3. Data collection

Data were directly collected from patients to obtain sociodemographic profiles and clinical data. The adherence assessment was obtained using a validated questionnaire for KTPs [5, 6, 10].

The first part of the questionnaire about the demographic and clinical data was recorded through direct interviews with the patients and from their medical files. In the adherence part, patients were classified according to their responses to the questionnaire as adherent and nonadherent. The positive responses belong to the adherent group, corresponding to the first, second, and fifth questions. The third and sixth questions had the following response options: missed at all, double dose the next day, take it when you remember, stop using your medication, go back to counseling the doctor, and call the doctor for advice, respectively. The fourth question recorded the number of doses missed last week. Finally, the seventh question recorded the number of days the patient missed taking their medication since the last visit. Patients who missed fewer than two days were considered adherent to the medication.

2.4. Statistical Analysis

Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS, version 27.0) to obtain the required statistical values for the questionnaire. Frequency and percentages were determined for the categorical variables, the mean, median, range, and standard deviation, besides the minimum and maximum values for continuous variables. Pearson correlation was used to measure the correlation of the adherence level with gender, age, time since transplant, daily dose of Tac (mg), TAC level, and number of co-medications with *P*-value <0.05 considered significant.

3. Results

The total number of patients included in the study was 166, with 122 (73.5%) male patients and 44 (26.5%) female. The average age was 36.49

± 11.54 (range 18–66) years, and the average weight was 62.193 ± 6.0919 (range 32–118) kgs. Additionally, 95 (57.2%) participants lived outside of Khartoum. Approximately half of the participants were unemployed, while the rest had a range of 0–40 years of working experience. Furthermore, 92 (55.4%) patients were married, and the family size (father, mother, and children) ranged from 1 to 26 members, as presented in Table **1**.

The mean time since the transplantation was 4.40 ± 3.108 (range 0–19) months, and all of the participants used Tac with a mean daily dose of 5.931 ± 3.6775 (range 1–16) mg, adjusted according to the guidelines of the required plasma level of Tac based on the duration post-transplant and Tac trough concentrations measured in each visit. A total of 465 trough concentrations were obtained from the participants. The required Tac level is based upon the duration of the transplants to be in clinical targets. The causes of kidney failure were mostly found to be related to kidney atrophy in 40 (12.0%), hypertension in 46 (27.7%), and other causes in 48 (28.9%) participants. For the rest of the participants, causes ranged from uncertain etiology to recurrent urinary tract infections, diabetes nephropathy, obstruction neuropathy, polycystic kidney disease, and Pyelonephritis. Hypertension (38.0%) was considered the most common comorbidity presented among the transplant patients. Most of the KTPs were in the acute period of transplantation. Therefore, multi-pharmacy was prescribed, where 83 (49.4%) patients were given four to six medications. Observations of agents affecting the Tac trough concentrations can be seen in Table **2**.

The participants were adherent (n = 157) and nonadherent (n = 9). The rate of adherence was found to be 94.6%. No significant correlation was found between gender and adherence level, while old age showed significant differences between nonadherent 49.80 ± 10.592 and adherent 36.22 ± 11.434, P <0.05.

Time since transplant when the patient exceeds 10 months post-transplantation showed significant differences in the adherence level (nonadherent: 6.67 ± 5.292 vs adherent: 4.27 ± 2.910), P < 0.05. Tac levels for nonadherent patients did not meet the clinical targets or show significant differences between the adherence levels in the groups. An increased number of drugs prescribed to the patients represents a significant difference, P <0.05. Forgetfulness was the most common reason (n = 22; 13.3%) for nonadherence to Tac. Factors with significant correlation are represented in Table **3**.

4. Discussion

Achieving the desired therapeutic outcomes by using immunosuppressive medication is essential in patients after organ transplantation to reduce the rejection rate. Therefore, adherence to the medication plays a vital role in positive clinical outcomes. Based on the literature, assessing immunosuppressive medication (Tac) adherence after kidney transplantation in Sudanese patients was not investigated [11]. Detecting factors related to the irregular trough Tac concentrations among Sudanese KTPs due to an insufficient dosing adjustment requires additional research into factors that lead to intra- and inter-individual variability [1].

Studies investigating the nonadherence rate in KTPs reported a variable range of 28.2%, 34.5%, and 55.1% [10]. One study conducted in three centers in Sudan recorded a range of 45%, 33%, and 22%, and the studied participants reported high, medium, and low adherence, respectively

Table 1: Demographic data of the participants.

	Number	Mean	Standard deviation	Minimum	Maximum
Age	166	36.49	11.54	18	66
Body weight (Kg)	166	62.193	16.0919	32	118
Gender					
Male	122	73.5			
Female	44	26.5			
Current residence					
Outside Khartoum	95	57.2			
Inside Khartoum	71	42.8			
Occupational situation					
Unemployed	88	53			
Employed	78	47			
Experience (in months)	78	55.55	88.636	6	480
Marital status					
Single	69	41.6			
Married	92	55.4			
Divorce	5	3			
Family size	166	6.97	3.548	1	26

[11]. In this study, the nonadherence rate toward Tac was lower than the reported rates, where only nine (5.4%) of the study population exerted nonadherence toward Tac use, which may be due to the awareness of those patients about the risk of nonadherence to Tac. Because the level of adherence is considered a key factor influencing the variability of the Tac plasma concentration [3, 12], many studies have measured adherence levels. In the United States, a high adherence of 81.6% was reported. Similarly, the present study found a high adherence rate of 94.6%. This aligns with a study in Serbia, where adherence was 71.7%, with 28.3% not following the prescribed therapy [10, 13]. Another study reported a high adherence of 67.4% (297 patients) [14]. The most common factor contributing to low adherence was forgetfulness, affecting 22 (13.3%) patients, even those with a generally good adherence profile. This finding is consistent with other studies [3, 10, 14].

Gender and trough Tac concentrations in non-adherent patients were insignificant (*P*-value = 0.633 and 0.982, respectively). This is consistent with other studies that found no association between medication adherence and gender [15–18]. However, other studies found a link between sex and trough Tac concentrations [12, 18, 19]. Sub-therapeutic and super-therapeutic Tac trough concentrations are associated with undesired effects. In this study, up to 50% of the participants showed inadequate Tac levels. Similarly, another study found low calcineurin inhibitor levels in 75% of patients [7, 18]. These findings highlight the need to explore other factors that could lead to treatment failure post-transplant.

Table 2: Clinical data of the participants.

	Number	Mean	Standard deviation	Minimum	Maximum
Post-transplant period (month)	166	4.4	3.108	0	19
Daily dose of tacrolimus (mg)	166	5.931	3.6775	1	16
Tacrolimus level	465	11.7571	6.8969	0.9	40.1
Retransplant					
Yes	1	0.6			
Causes of renal failure					
Uncertain etiology	20	12			
Hypertension	46	27.7			
Recurrent UTI	3	1.8			
Kidney atrophy	40	24.1			
Diabetes mellitus	5	3			
Obstruction neuropathy	1	0.6			
Polycystic kidney disease	2	1.2			
Polynephritis	1	0.6			
Other	48	28.9			
Comorbidities					
Null	74	44.6			
Hypertension (HTN)	63	38			
Diabetes mellitus (DM)	7	4.2			
HTN + DM	15	9			
Cardiovascular disease	2	1.2			
Respiratory disease	1	0.6			
Other	4	2.4			
No. of co-medications					
≤3	73	44.6			
4–6	83	49.4			
7–9	10	6			

This study found a significant correlation between adherence levels and factors such as patient age, post-transplant time, daily dose, and the number of co-medications. Older patients exhibited lower adherence (49.80 ± 10.592), which aligns with some studies. However, other studies have associated younger age with nonadherence, while some found no significant correlation [7, 20–22].

The total daily dose showed significant differences among the nonadherent patients. Additionally, post-transplant duration was observed to affect adherence negatively. This study confirmed that adherence declines over time, aligning with

Table 3: Demographic and clinical characteristics according to tacrolimus adherence level.

	Nonadherent	Adherent	P-value
Gender			
Male	6 (4.9%)	116 (95.1%)	0.633
Female	3 (6.8%)	41 (93.2%)	
Age (yrs)	49.80 ± (10.592)	36.22 ± (11.434)	0.019
Time since transplant (yrs)	6.67± (5.292)	4.27 ± (2.910)	0.024
A daily dose of tacrolimus (mg)	7.33 ± (3.288)	5.85 ± (3.692)	0.05
TAC level, ng/ml	11.1600 ± (3.160)	10.9141± (5.414)	0.982
No. of co-medications			
≤ 3	3 (1.8%)	71(42.8%)	0.0001
4–6	5 (3%)	77 (46.4%)	
7–9	1 (0.6%)	9 (5.4%)	

previous research. One study found that at 5 months post-transplant, 95% of KTPs remained adherent; however, by 12 months, only 48% of the same cohort maintained adherence. Other studies also reported low adherence in the early post-transplant period [23, 24].

The number of co-medications had a significant role in adherence among the KTPs, as an increasing number of medications negatively affected the patient's adherence to Tac [25]. A study in China also detected medication regimen complexity as a primary factor for nonadherence among KTPs [12].

The weight-based dosing protocol was the most commonly used regimen for Tac administration among the patients. However, many patients experienced adverse effects from the medication. Consequently, numerous studies have investigated the impact of BMI and drug levels on adherence, and a positive correlation was found. Similarly, the present study showed a significant correlation between BMI and adherence (*P*-value = 0.021) [7, 18, 26, 27]. However, this study found no significant relationship between BMI and adherence, which is consistent with a Turkish study's findings [18].

5. Limitations

The study area should be broadened to cover a broader range of kidney transplant centers in Sudan, allowing for a larger sample size to generalize the results. Moreover, the study design should follow patients from their first day of immunosuppressant use over a long period to obtain more precise measurements and investigate additional factors influencing adherence to transplant medication.

6. Conclusion

The KTPs demonstrated high adherence to Tac, which was significantly correlated with younger age, shorter time since transplant, lower daily doses, and fewer co-medications. Sudanese KTPs showed strong awareness of the importance of proper medication use and sought medical advice in case of side effects. However, irregular trough plasma concentrations of Tac were found. Further studies are needed to investigate additional factors that may influence Tac levels.

Declarations

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Ethical Considerations

Ethical approval was obtained from the Federal Ministry of Health – Department of Innovation, Development, and Scientific Research and the National Medicines and Poisons Board. The patients agreed to participate in the study and signed a consent form.

Competing Interests

None.

Availability of Data and Material

Data is available upon request.

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Abbreviations and Symbols

KTPs: Kidney transplant patients

SPSS: Statistical Package of Social Sciences

Tac: Tacrolimus

CYP3A: Cytochrome P-450 3A

P-gp: P-glycoprotein

SMAQ: Simplified Medication Adherence Questionnaire

AIDS: Acquired immunodeficiency syndrome

SD: Standard Deviation

No.: Number

Min: Minimum

Max: Maximum

References

[1] Campagne, O., Mager, D. E., & Tornatore, K. M. (2019). Population pharmacokinetics of tacrolimus in transplant recipients: What did we learn about sources of interindividual variabilities? *Journal of Clinical Pharmacology, 59*(3), 309–325. https://doi.org/10.1002/jcph.1325

[2] Jing, Y., Kong, Y., Hou, X., Liu, H., Fu, Q., Jiao, Z., Peng, H., & Wei, X. (2021). Population pharmacokinetic analysis and dosing guidelines for tacrolimus co-administration with Wuzhi capsule in Chinese renal transplant recipients. *Journal of Clinical Pharmacy and Therapeutics, 46*(4), 1117–1128. https://doi.org/10.1111/jcpt.13407

[3] Tornatore, K. M., Meaney, C. J., Attwood, K., Brazeau, D. A., Wilding, G. E., Consiglio, J. D., Gundroo, A., Chang, S. S., Gray, V., Cooper, L. M., & Venuto, R. C. (2022). Race and sex associations with tacrolimus pharmacokinetics in stable kidney transplant recipients. *Pharmacotherapy, 42*(2), 94–105. https://doi.org/10.1002/phar.2656

[4] Chen, L., & Prasad, G. R. (2018). CYP3A5 polymorphisms in renal transplant recipients: Influence on tacrolimus treatment. *Pharmacogenomics and Personalized Medicine*, *11*, 23–33. https://doi.org/10.2147/PGPM.S107710

[5] Ortega Suárez, F. J., Sánchez Plumed, J., Pérez Valentín, M. A., Pereira Palomo, P., Mu noz Cepeda, M. A., Lorenzo Aguiar, D., & Grupo de Estudio VATREN. (2011). Validación del cuestionario simplificado de adherencia a la medicación (SMAQ) en pacientes con trasplante renal en terapia con tacrolimus [Validation on the simplified medication adherence questionnaire (SMAQ) in renal transplant

patients on tacrolimus]. *Nefrología, 31*(6). https://doi.org/10.3265/Nefrologia.pre2011.Aug.10973

[6] Lehner, L. J., Reinke, P., Hörstrup, J. H., Rath, T., Suwelack, B., Krämer, B. K., Budde, K., & Banas, B. (2018). Evaluation of adherence and tolerability of prolonged-release tacrolimus (Advagraf^{TM}) in kidney transplant patients in Germany: A multicenter, noninterventional study. *Clinical Transplantation, 32*(1), e13142. https://doi.org/10.1111/ctr.13142

[7] Chisholm-Burns, M., Pinsky, B., Parker, G., Johnson, P., Arcona, S., Buzinec, P., Chakravarti, P., Good, M., & Cooper, M. (2012). Factors related to immunosuppressant medication adherence in renal transplant recipients. *Clinical Transplantation, 26*(5), 706–713. https://doi.org/10.1111/j.1399-0012.2011.01589.x

[8] Cossart, A. R., Cottrell, W. N., Campbell, S. B., Isbel, N. M., & Staatz, C. E. (2019). Characterizing the pharmacokinetics and pharmacodynamics of immunosuppressant medicines and patient outcomes in elderly renal transplant patients. *Translational Andrology and Urology, 8*(Suppl 2), S198–S213. https://doi.org/10.21037/tau.2018.10.16

[9] Tanriover, B., Stone, P. W., Mohan, S., Cohen, D. J., & Gaston, R. S. (2013, July). Future of Medicare immunosuppressive drug coverage for kidney transplant recipients in the United States. *Clinical Journal of the American Society of Nephrology; CJASN, 8*(7), 1258–1266. https://doi.org/10.2215/CJN.09440912

[10] Lalić, J., Veličković-Radovanović, R., Mitić, B., Paunović, G., & Cvetković, T. (2014). Immunosuppressive medication adherence in kidney transplant patients. *Medical Principles and Practice, 23*(4), 351–356. https://doi.org/10.1159/000362792

[11] Abbas, A. A., Ahmed, M. E., Mohammed, S. M. E., Gar-Alnabi, S. S., Mohammed, W. A., Ahmed, M. H., & Badi, S. (2022). Adherence to immunosuppressive medications in kidney transplant patients at three centers in Khartoum state, Sudan: A cross-sectional hospital study. *Sudan Journal of Medical Science*, *17*(3), 313–329. https://doi.org/10.18502/sjms.v17i3.12085

[12] Chen, T., Wang, Y., Tian, D., Zhang, J., Xu, Q., Lv, Q., Li, X., & Wang, J. (2022). Follow-up factors contribute to immunosuppressant adherence in kidney transplant recipients. *Patient Preference and Adherence, 16*, 2811–2819. https://doi.org/10.2147/PPA.S383243

[13] Terebelo, S., & Markell, M. (2010). Preferential adherence to immunosuppressive over nonimmunosuppressive medications in kidney transplant recipients. *Transplantation Proceedings, 42*(9), 3578–3585. https://doi.org/10.1016/j.transproceed.2010.08.027

[14] Prihodova, L., Nagyova, I., Rosenberger, J., Majernikova, M., Roland, R., Groothoff, J. W., & van Dijk, J. P. (2014). Adherence in patients in the first year after kidney transplantation and its impact on graft loss and mortality: A cross-sectional and prospective study. *Journal of Advanced Nursing, 70*(12), 2871–2883. https://doi.org/10.1111/jan.12447

[15] Denhaerynck, K., Dobbels, F., Cleemput, I., Desmyttere, A., Schäfer-Keller, P., Schaub, S., & De Geest, S. (2005). Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: A literature review. *Transplant International, 18*(10), 1121–1133. https://doi.org/10.1111/j.1432-2277.2005.00176.x

[16] Massey, E. K., Tielen, M., Laging, M., Beck, D. K., Khemai, R., van Gelder, T., & Weimar, W. (2013). The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: A cohort study. *Journal of Psychosomatic Research, 75*(3), 229–234. https://doi.org/10.1016/j.jpsychores.2013.07.006

[17] Gheith, O. A., El-Saadany, S. A., Abuo Donia, S. A., & Salem, Y. M. (2008). Compliance of kidney transplant patients to the recommended lifestyle behaviours: Single centre experience. *International Journal of Nursing Practice, 14*(5), 398–407. https://doi.org/10.1111/j.1440-172X.2008.00710.x

[18] Tecen-Yucel, K., Bayraktar-Ekincioglu, A., Yildirim, T., Demirkan, K., & Erdem, Y. (2023). Assessment of adherence to immunosuppressive treatment in kidney transplant patients: A descriptive study.

Turkish Journal of Nephrology, 32(3), 241–248. https://doi.org/10.5152/turkjnephrol.2023.21157239

[19] Griva, K., Davenport, A., Harrison, M., & Newman, S. P. (2012). Non-adherence to immunosuppressive medications in kidney transplantation: Intent vs. forgetfulness and clinical markers of medication intake. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, *44*(1), 85–93. https://doi.org/10.1007/s12160-012-9359-4

[20] Kuptsov, V. V. (1978). [Aspects of the public health management of a rural district]. *Sovetskoe Zdravookhranenie,* 7, 49–54.

[21] Russell, C. L., Cetingok, M., Hamburger, K. Q., Owens, S., Thompson, D., Hathaway, D., Winsett, R. P., Conn, V. S., Madsen, R., Sitler, L., & Wakefield, M. R. (2010). Medication adherence in older renal transplant recipients. *Clinical Nursing Research, 19*(2), 95–112. https://doi.org/10.1177/1054773810362039

[22] Tielen, M., van Exel, J., Laging, M., Beck, D. K., Khemai, R., van Gelder, T., Betjes, M. G., Weimar, W., & Massey, E. K. (2014). Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: A 2-year follow-up study. *Journal of Transplantation, 2014*, 675301. https://doi.org/10.1155/2014/675301

[23] Chisholm, M. A., Vollenweider, L. J., Mulloy, L. L., Jagadeesan, M., Wynn, J. J., Rogers, H. E., Wade, W. E., & DiPiro, J. T. (2000). Renal transplant patient compliance with free immunosuppressive medications. *Transplantation, 70*(8), 1240–1244. https://doi.org/10.1097/00007890-200010270-00020

[24] Nevins, T. E., Robiner, W. N., & Thomas, W. (2014). Predictive patterns of early medication adherence in renal transplantation. *Transplantation, 98*(8), 878–884. https://doi.org/10.1097/TP.0000000000000148

[25] Henkel, L., Jehn, U., Thölking, G., & Reuter, S. (2023). Tacrolimus-why pharmacokinetics matter in the clinic. *Frontiers in Transplantation, 2*, 1160752. https://doi.org/10.3389/frtra.2023.1160752

[26] Chauhan, P. M., Hemani, R. J., Solanki, N. D., Shete, N. B., Gang, S. D., Konnur, A. M., Srivastava, R., & Pandey, S. N. (2023). A systematic review and meta-analysis recite the efficacy of tacrolimus treatment in renal transplant patients in association with genetic variants of *CYP3A5* gene. *American Journal of Clinical and Experimental Urology, 11*(4), 275–292.

[27] Kuypers, D. R. J. (2020). Intrapatient variability of tacrolimus exposure in solid organ transplantation: A novel marker for clinical outcome. *Clinical Pharmacology and Therapeutics, 107*(2), 347–358. https://doi.org/10.1002/cpt.1618