International Research Journal of Biological Sciences ISSN 2278-3202
Vol. **15(1),** 1-7, February **(2026)** *Int. Res. J. Biological Sci.*

Therapeutic monitoring and adverse effects of immunosuppressants in kidney transplant patients: a prospective immunoassay study at Batna University Hospital (Algeria)

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Available online at : www.isca.in, www.isca.me
Received 9th November 2025, revised 25th December 2025, accepted 16th January 2026

Abstract

The preferred course of treatment for end-stage renal failure is kidney transplantation, but its success depends on efficient and balanced immunosuppression. When taken with mycophenolate mofetil, calcineurin inhibitors (tacrolimus, ciclosporin) show significant pharmacokinetic variability and a high risk of toxicity, necessitating careful therapeutic monitoring. This study aims to assess plasma concentrations and side effects related to these compounds' use in kidney transplant recipients. A prospective, descriptive study was realised at the Benflis Touhami University Hospital in Batna (Algeria) between March 2014 and December 2019. It included 246 patients who had received renal transplantation from living donors ; 210 on tacrolimus and 36 on cyclosporine, all receiving mycopenolic acid (MMF) and corticosteroids, the residual (C_0) and post-dose (C_2) concentrations were mesured by electrochemiluminescence. Kidney function and side effects were assessed over a 12-month period. In patients treated with tacrolimus, mean concentrations decreased from 11.8 ng/mL at the beginning of the transplantto 8.5 ng/mL at the end of the first year after transplantation, with stable renal function. In patients treated with cyclosporine, a gradual increase in creatinine and a decrease in glomerular filtration rate were observed. Adverse skin effects (particularly acne) were significantly more frequent with cyclosporine (36.1%, $p < 0.001$), while neurological disorders (tremors 15.5%) predominated with tacrolimus. Strong correlations were found between plasma concentrations and renal function parameters, particularly for cyclosporine ($r = 0.859$ between C_0 and creatinine at 12 months). Therapeutic monitoring using immunological methods is a reliable and effective tool for the individualised monitoring of immunosuppressants in renal transplant patients. Tacrolimus has a better renal tolerance profile, while cyclosporine is more often associated with skin effects. These results highlight the importance of personalised pharmacological monitoring in order to optimise post-transplant care.

Keywords: Kidney transplantation, immunosuppressants, Tacrolimus, Cyclosporine, Electrochemiluminescence, Adverse effects.

Introduction

Renal transplantation is presently considered the preferred treatment for many pepoles with end-stage renal disease[1], a progressive and silent condition requiring dialysis or transplantation. The number of solid organ transplants performed worldwide continues to grow each year, with kidney transplants representing a substantial proportion of these procedures[2,3].

In the Arab world, transplant activity is characterised by the predominance of transplants from living donors. In Algeria, organ transplantation remains essentially limited to kidney transplants, mostly from living donors, with a stable rate of 6.5 to 7 transplants per million inhabitants for several years[4,5]. Post-transplant immunosuppressive treatment is based mainly on calcineurin inhibitors (cyclosporine and tacrolimus), often combined with mycophenolate mofetil (MMF). Although these agents have significantly improved graft survival, their use remains limited by their potential toxicity[6]. Nephrotoxicity, in particular, is a major obstacle to improving long-term outcomes. These molecules are characterised by high inter- and intra-individual variability, a narrow therapeutic margin and numerous drug interactions, making it essential to implement regular therapeutic drug monitoring (TDM) to adjust the dosage in order to maintain plasma concentrations within an effective and safe therapeutic range, thereby reducing the risk of rejection or toxicity[7,8].

Cyclosporine, which has been in use since the 1980s, is associated with dose-dependent nephrotoxicity and several undesirable metabolic effects (hypertension, hyperlipidaemia, diabetes), as well as neurological and cutaneous side effects[9-11]. Tacrolimus, a newer immunosuppressant, is often preferred because of its superior efficacy and more favourable metabolic profile, although it is more frequently associated with tremors and an increased risk of post-transplant diabetes[12-14]. Several studies have shown that patients with haematological disorders had significantly higher residual concentrations of MMF than those without adverse effects[15].

Due to their pharmacokinetic variability, these molecules require rigorous and precise therapeutic monitoring. Measuring residual concentrations (C_0) remains the gold standard method for tacrolimus and mycophenolate mofetil, whereas for cyclosporine, an additional measurement taken two hours after administration (C_2) is preferable, as it better reflects the efficacy and toxicity of the treatment[16]. Electrochemiluminescence (ECLIA) has established itself as the reference analytical method, combining sensitivity, specificity and speed, while offering perfect compatibility with hospital laboratory automation[17,18].

At the Benflis Touhami University Hospital in Batna, therapeutic monitoring of calcineurin inhibitors by electrochemiluminescence is an essential tool for optimising post-transplant care. This approach allows for rapid and individualised adjustment of immunosuppressive treatments, thereby helping to prevent complications related to drug toxicity.

Objective of the study: This study aims to analyse residual plasma concentrations of immunosuppressants (ciclosporin, tacrolimus and mycophenolate mofetil) in kidney transplant patients monitored at the Batna University Hospital using the electrochemiluminescence method, in order to evaluate the contribution of therapeutic drug monitoring to the optimisation of post-transplant care.

Materials and Methods

This is a descriptive, prospective and single-centre study, conducted at the toxicology laboratory of the Benflis Touhami university hospital centre (CHU) in Batna (Algeria), in collaboration with the nephrology department, between March 2014 and December 2019.

Population of study: Our study included 246 patients who had received kidney transplants from living donors. All received an immunosuppressive induction protocol. The patients were divided into two groups:

Group A (n = 210) on tacrolimus, mycophenolate mofetil (MMF) and corticosteroids, and Group B (n = 36) on cyclosporine, MMF and corticosteroids.

Inclusion and exclusion criteria: All kidney transplant patients, regardless of age or gender, followed at the Batna University Hospital and receiving immunosuppressant dosing at the toxicology laboratory were included in this study. Patients transplanted at other centres, those receiving immunosuppressive treatment for a condition unrelated to kidney transplantation, and patients whose pharmacological follow-up could not be ensured locally were excluded.

Monitoring biological in post-transplant: Pharmacological monitoring: Dosages were measured for tacrolimus (C_0) 12 hours after the last dose, MMF (C_0) and cyclosporine (C_0 and C_2), the latter measured two hours after dosing. Blood samples were taken on days 7, 1, 2, 3, 6 and 12 months post-transplant, in éthylènediamine tétraacétiqueacide (EDTA) tubes for calcineurin inhibitors and in heparinised tubes for MMF and biochemical parameters.

Renal function: Renal function was assessed by measuring urea, creatinine, renal clearance and glomerular filtration rate (GFR), estimated using the MDRD and CKD-EPI equations.

Analytical methods: Calcineurin inhibitors (tacrolimus, ciclosporin) were measured by competitive electrochemiluminescence immunoassay, using streptavidin-coated microparticles and specific biotinylated antibodies. Urea was measured by a kinetic enzymatic method using urease and glutamate dehydrogenase at 340 nm, while creatinine was measured by a colorimetric method based on the reaction with picric acid.

Mycophenolic acid (MPA) was quantified by an enzymatic test based on IMPDH II in the presence of nicotinamide adenine dinucleotide (NAD). Samples were stored in accordance with the manufacturer's recommendations, and all analytical steps were performed according to standard operating procedures. The assays were performed on Cobas Integra analysers (Roche Diagnostics).

Data collection: Biological, clinical and demographic data were collected from consultation registers and sample collection forms. The variables analysed included the characteristics of the donor and recipient couples, immunosuppression protocols, comorbidities, biological parameters and adverse effects.

Statistical analysis: The quantitative variables were expressed as mean ± standard deviation, median, minimum and maximum intervals, compared using Student's t-test. However the qualitative variables were expressed as frequencies and percentages, compared using the chi-square test. Correlations were assessed using Pearson's test. The significance threshold was set at $p < 0.05$.

Ethical considerations: The data were processed anonymously and confidentially, in accordance with medical confidentiality requirements. No conflicts of interest were declared.

Results and Discussion

General characteristics: The study population consisted of 246 patients, divided between donors and recipients. The sociodemographic characteristics are shown in Table-1:

Proportions of adverse effects by treatment: The incidence of adverse effects related to the use of tacrolimus and cyclosporine in kidney recipients in our study are shown in Table-2:

Primary nephropathy: Table-3 presents the distribution of the different causes of primary kidney disease by immunosuppressive treatment.

Dialysis period and type: Pre-transplant dialysis characteristics, including presence and dialysis modality, are presented in Table-4.

Evolution of biological and pharmacokinetic parameters post-transplant: The longitudinal trajectories from day 7 to month 12 for each parameter are shown in Table-5.

Comparison of study parameters by sex and age: The comparison of sociodemographic factors under the two calcineurin inhibitors is presented in Table-6.

Main correlations among biological, pharmacokinetic, and clinical parameters by post-transplant period: The correlation between biological, pharmacokinetic and clinical parameters according to the post-transplant period is shown in Table-7.

Table-1: Sociodemographic characteristics of the study population (n=246).

Variables		Patients	Results (%)
Donors	Age (years)	Mean ± SD	43,36 ± 10,26
	Most common age group 41–50 years old	31	
	Sex	Female/male	59 / 41
Receveurs	Age (years)	Mean ± SD	35,54 ± 9,82
	Most commonage group	31–40 years old	34
	Sex	Female/male	68,3 / 31,7
	Body mass index	Normal (18,5–24,9 kg/m²)	64
	Marital status	Married	66
	Place of residence	Wilaya of Batna / Outside Batna	40 / 60
	Socio-economicstatus	Civil servants	73,6
	Occupation	Freelance work / Students & homemakers	29 / 20
	Donor-recipient relationship	Mother / Brother	27 / 22
	Blood group	O Rh+	42

Table-2: Incidence of adverse effects according to immunosuppressive treatment.

Variables	Category	Tacrolimus (n=206)	Cyclosporine (n=36)	p-value (Chi2)
Neurological disorders	Tremors	15.5%	8.3%	0.38
Cutaneous disorders	Acne	5.8%	36.1%	<0.001
	Chute de Cheveux	10%	0%	0.05

Gastrointestinal disorders	Diarrhea and Vomiting	4.8%	2.8%	0.1
Infectious disorders (unspecified)	------	5.3%	8.3%	0.34

Table-3: Origin of nephropathy among recipient patients.

Variable	Origin of nephropathy	Tacrolimus	Cyclosporine	p-value (Chi2)
Primary nephropathy	Hypertension	47.6% (98)	41.7% (15)	0.35
	Diabetes	19.4% (40)	19.4% (7)	
	Autosomal dominant polycystic kidney disease	8.7% (18)	13.9% (5)	
	Malformative uropathy	7.3% (15)	5.6% (2)	
	Undetermined	17.0% (35)	19.4% (7)	

Table-4: Dialysis type and modalitys.

Variable	Observation	Tacrolimus	Ciclosporine	P-valeur
Dialyse	Presence	90.3%	94.4%	0.65
Type de dialyse	Hemodialysis	82.5%	77.8%	0.72
	Peritonealdialysis	9.7%	11.1%	

Table-5: Evolution of biological and pharmacokinetic parameters post-transplant.

Paramètres	Treatment administered	J7	1M	2M	3M	6M	12M
Creatinine (µmol/L)	Tacrolimus	124,5	111,6	107,1	106,1	102,6	102,0
	Cyclosporine	108,0	116,6	119,0	119,4	128,8	133,2
Urea (mmol/L)	Tacrolimus	8,30	7,51	7,14	6,88	6,76	6,78
	Cyclosporine	8,63	8,46	8,35	8,14	8,06	7,92
GFR MDRD (mL/ min/1.73m^2)	Tacrolimus	71,6	73,2	74,5	75,1	75,8	75,9
	Cyclosporine	70,7	69,1	67,8	66,7	65,2	64,0
GFR CKD-EPI (mL/min/1.73 m^2)	Tacrolimus	74,4	77,9	79,9	81,1	82,3	82,9
	Cyclosporine	76,3	73,4	71,2	69,9	68,0	67,7
Creatinine clearance (mL/min)	Tacrolimus	75,5	78,0	79,5	80,3	81,8	82,4
	Cyclosporine	57,3	57,1	56,9	56,8	56,8	56,8
C_0 Tacrolimus (ng/mL)	Tacrolimus	11,8	12,4	11,3	10,4	9,2	8,5
Tacrolimus dose (mg/kg/j)		0,13	0,12	0,11	0,10	0,10	0,09
C_0/dose ratio		1,27	1,63	1,92	2,08	2,15	2,21
C_0 Cyclosporine (ng/mL)	Cyclosporine	---	164,0	159,0	153,0	144,0	135,0
C_2 Cyclosporine (ng/mL)		----	870,0	892,0	841,0	756,0	699,0

Cyclosporine dose (mL/j)			0,040	0,040	0,040	0,037	0,032
C_0 MMF (µg/mL)	Tacrolimus	2,39	2,87	3,08	3,32	3,54	3,71
MMF dose (mg/j)	Tacrolimus	1700	1600	1550	1500	1400	1308

Table-6: Comparisons by gender and age (Tacrolimus and Cyclosporine).

Immunosuppressive treatment/ covariable	Significant parameters	Periods concerned and p-values	Results
Tacrolimus – Sexe	C_0	J7 (0,001), 1M (0,02), 3M (0,01)	Early differences at 7days
	Creatinine	J7 (0,04), 1M ($<10^{-4}$), 3M (0,006)	Significant differences
	Dose	1M (0,004), 3M (0,01), 12M (0,01)	Significant differences
	Âge	J7 (0,003), 1M (0,003), 3M ($<10^{-3}$)	Significant differences
Tacrolimus – Âge	C_0	J7 ($<10^{-4}$), 1M (0,01)	Differences according to age
	Creatinine	1M (0,02), 3M (0,03)	Significant differences
	MMF	12M (0,006)	Late difference at 12M
	Dose	1M, 3M, 12M (all $<10^{-4}$)	Strong significant differences
Cyclosporine – Sexe	C0	3M (0,001)	Significant differences
	C2	3M (0,007)	Significant differences
Cyclosporine – Âge	Poids	J7 (0,002), 12M (0,03)	Significant differences
	C0	J7 (0,004)	Early significant differences

Table-7: Main correlations between biological, pharmacokinetic and clinical parameters.

Treatments for transplant patients	Parameters	Post-transplant periods and Coefficient (r)	Intensity
	C_0*vs.* C_2	1M 0,780), 3M (0,639), 12M (0,579)	Strong correlations
	C_0 *vs.* Urea	J7 (0,710), 2M (0,860), 12M (0,927)	Very strong correlations
Cyclosporine	C0 *vs.* Créatinine	1M (0,567), 2M (0,676), 12M (0,859)	Strong correlations at 12M
	C_2*vs.*Creatinine	2M (0,716), 3M (0,560)	Moderate correlations
	Weight *vs*. Kidney Function	3M (0,805), 6M (0,759)	Strong correlations
Tacrolimus	C_0 *vs* Dose	J7 - 12M	Weak positive correlation
	C_0 vs CKD-EPI	3M-12M	Weak positive correlation

Discussion: This study highlights the clinical, biological and pharmacokinetic characteristics of renal transplant patients treated with two calcineurin inhibitors such us tacrolimus and cyclosporine. The recipients were predominantly young men, with a mean age of 35.5 years, in contrast to the donors, who were older and predominantly female. This profile is consistent with epidemiological data reported in the literature[19], where the recipient population remains generally male and of working age. Although tacrolimus and cyclosporine share a common mechanism of action as calcineurin inhibitors, their tolerance profiles show notable differences. Neurologically, tremors were observed more frequently with tacrolimus (15.5%) than with

cyclosporine (8.3%), with no statistically significant difference ($p = 0.38$). These tremors, generally localised in the extremities, are consistent with data in the literature reporting that tremor is one of the most common neurotoxic effects of tacrolimus, often dose-dependent and associated with plasma concentrations above 15ng/mL, which are considered toxic[20]. Skin disorders were significantly more common with ciclosporin (36.1%) than with tacrolimus (5.8%), with a highly significant value ($p < 0.001$). Conversely, hair loss was reported only in patients taking tacrolimus (10%) and not in those taking cyclosporine ($p = 0.05$). These results highlight the specific dermatological profiles of each molecule, which is consistent with previous studies highlighting the frequency of hypertrichosis and acne with ciclosporin, and alopecia with tacrolimus[21].

With regard to infectious complications, no difference signification was found between the two groups (5.3% vs. 8.3%; $p = 0.34$). Similarly, gastrointestinal disorders (diarrhoea and vomiting) were infrequent and comparable (4.8% vs. 2.8%; $p = 0.10$). These results are consistent with those of several previous studies showing that the frequency of infections and digestive disorders is more related to the cumulative dose of immunosuppressants than to the molecule used[22].

Biologically, the evolution of renal function during follow-up shows a gradual improvement with tacrolimus, contrasting with a slow but continuous deterioration in patients on cyclosporine. This difference suggests better renal tolerance of tacrolimus, which has been confirmed in several multicentre studies[23]. Pharmacokinetically, tacrolimus shows a gradual decrease in residual concentrations (C_0) in parallel with the reduction in daily dose (0.13 to 0.09 mg/kg/day). The C_0/dose ratio increases, reflecting stable exposure at decreasing doses, probably related to pharmacokinetic adaptation and optimal therapeutic adjustment over the course of follow-up. Mycophenolic acid administered in combination with tacrolimus shows a gradual increase in residual concentration (2.39 to 3.71 µg/mL) despite dose reduction. Under cyclosporine, C_0 and C_2 concentrations gradually decrease with dose, but renal function continues to deteriorate, suggesting molecule-specific nephrotoxicity, which is well documented in the literature[24]. The analysis of sociodemographic factors indicates that age and gender significantly influence residual concentrations and dosage regimen during the first year post-transplant, while renal function remains broadly comparable across categories. A strong correlation was observed between ciclosporinemia and urea at different follow-up times, suggesting a direct impact of treatment exposure on short- and medium-term renal status.

Conclusion

This study confirm that tacrolimus has better renal tolerance and a more stable pharmacokinetic profile, although it is more often associated with neurological effects and alopecia. Cyclosporine, on the other hand, remains effective but is associated with more pronounced cutaneous and renal toxicity. These observations highlight the need for individualised therapeutic monitoring in order to optimise the benefit/risk balance and improve long-term graft survival.

References

1. Collins, A., Foley, R., Chavers, B., Gilbertson, D., Herzog, C., Johansen, K., ... & Agodoa, L. (2014). US Renal Data System 2013 annual data report. *American Journal of Kidney Diseases*, 63(1), E1-E460.

2. Alechinsky-Yildiz, L., Colin, P., Couapel, J. P., De Saint-Aubert, N., Drouin, S., Droupy, S. (2018). Urologie: Réussir les ECNi. Elsevier Health Sciences.

3. Jha, V., Garcia-Garcia, G., Iseki, K., Li, Z., Naicker, S., Plattner, B., Yang, C. W. (2013). Chronic kidney disease: global dimension and perspectives. *The lancet*, 382(9888), 260-272.

4. Rekhif, Y. (2021). Organ donation in Algeria: limitations and prospects. *Pan African Medical Journal*, 39(1).

5. Atik, A., Tehir, M., Khemri, D., Bougroura, A., Ramdani, B., Bayahia, R. Benziane, A. (2017). Kidney transplantation in the Maghreb: current situation and prospects. *Néphrologie & Thérapeutique*, 13(5), 291.

6. Jurewicz, W. A. (2003). Tacrolimus versus ciclosporin immunosuppression: long-term outcome in renal transplantation. Nephrology Dialysis Transplantation, 18(suppl_1), i7-i11.

7. Ashraf, H., Solla, P., & Sechi, L. A. (2022). Current advancement of immunomodulatory drugs as potential pharmacotherapies for autoimmunity based neurological diseases. *Pharmaceuticals*, 15(9), 1077.

8. Rodrigo, E., San Segundo, D., Fernández-Fresnedo, G., López-Hoyos, M., Benito, A., Ruiz, J. C.Arias, M. (2016). Within-patient variability in tacrolimus blood levels predicts kidney graft loss and donor-specific antibody development. *Transplantation*, 100(11), 2479-2485.

9. Colombo, M. D., Perego, R., & Bellia, G. (2013). Cyclosporine associated of nephrotoxicity. *Open Journal of Nephrology*, 3(03), 168.

10. Lier, F., Piguet, V., Stoller, R., Desmeules, J., & Dayer, P. (2002). Therapeutics — neurotoxicity of calcineurin inhibitors and analogues. *French Journal of Internal Medicine (Médecine et Hygiène)*, 60(2387), 744–747.

11. Bencini, P. L., Tarantino, A., Grimalt, R., Ponticellp, C., & Caputo, R. (1995). Porokeratosis and immunosuppression. *British Journal of Dermatology*, 132(1), 74-78.

12. Djoudad, E., Bendifallah, B., Meknassi, D., Boudani, S., Meddahi, M., & Zerdoumi, F. (2021). *Post-renal transplantation diabetes: A retrospective study. Nephrology & Therapeutics*, 17(5), 393.

13. Elouaer, Y., Mars, M., Kammoun, K., Troudi, R., Chaker, H., Chaabouni, Y., … Hmida, M. B. (2018). *Overview of kidney transplantation at CHU Hédi Chaker Sfax: A report of 414 cases. Nephrology & Therapeutics*, 14(5), 428.

14. Heisel, O., Heisel, R., Balshaw, R., & Keown, P. (2004). New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *American Journal of Transplantation*, 4(4), 583-595.

15. Mudge, D. W., Atcheson, B. A., Taylor, P. J., Pillans, P. I., & Johnson, D. W. (2004). Severe toxicity associated with a markedly elevated mycophenolic acid free fraction in a renal transplant recipient. *Therapeutic drug monitoring*, 26(4), 453-455.

16. Johnston, A., & Holt, D. W. (1999). Therapeutic drug monitoring of immunosuppressant drugs. *British journal of clinical pharmacology*, 47(4), 339.

17. Vogeser, M., Shipkova, M., Rigo-Bonnin, R., Wallemacq, P., Orth, M., Widmann, M., & Verstraete, A. G. (2014). Multicenter analytical of automated electrochemiluminescent cyclosporine assay. *Therapeutic Drug Monitoring*, 36(5), 640–650.

18. Fung, A. W., Knauer, M. J., Blasutig, I. M., Colantonio, D. A., & Kulasingam, V. (2017). Evaluation of electrochemiluminescence immunoassays for immunosuppressive drugs on the Roche cobas e411 analyzer. *F1000Research*, 6, 1832.

19. Zannad, B., Fatma, L. B., Belkhiria, M., Rafrafi, N., Khedher, R., Jebali, H., Moussa, F. B. (2014). Overview of renal transplantat at Rabta University Hospital. *Nephrology & Therapeutics*, 10(5), 408-409.

20. Yahiaoui, N. (2011). Therapeutic monitoring of tacrolimus during the three months following transplantation: retrospective study of the 2010 and 2011 renal allograft cohort at Grenoble University Hospital.

21. Zahid, S., Elkhayat, S., Serghini, H., Baba, A., Medkouri, G., Chkairi, N., Ramdani, B. (2021). De novo diabetes after kidney transplantation: risk factors. *Revue Marocaine de Néphrologie*, 1(2), 128-133.

22. Raoundi, O., Flayou, K., En, N. F., Shimi, N., Ouzeddoune, N., Benamar, L., ... & Rhou, H. (2015). Kidney transplantation from living donors: experience of one centre. *Nephrology & Therapeutics*, 11(5), 416.

23. Laftavi, M. R., Alnimri, M., Weber-Shrikant, E., Kohli, R., Said, M., Patel, S., & Pankewycz, O. (2011). Low-dose rabbit antithymocyte globulin versus basiliximab induction therapy in low-risk renal transplant recipients: 8-year follow-up. In *Transplantation proceedings*, 43(2), 458-461. Elsevier.

24. Fantini, M. C., Becker, C., Kiesslich, R., & Neurath, M. F. (2006). Novel small molecules and drugs for immunosuppression. *Nature Clinical Practice Gastroenterology & Hepatology*, 3(11), 633-644.