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Tacrolimus Toxicities in Clinical Practice: A Case-Based Perspective

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ABSTRACT

Tacrolimus is a calcineurin inhibitor used as an immunosuppressant and is used in various conditions like prevention of organ transplant rejection, atopic dermatitis and psoriasis. In our set of series we are mainly focusing on toxicities like AKI (acute kidney injury), thrombotic microangiopathy, acute pancreatitis, hypomagnesemia and PRES (Posterior reversible encephalopathy) and hyperkalemia which are some of the major reactions and needs quick intervention. Even though most of the reactions are preventable they should be timely detected and stopped if not may also be fatal. Even though tacrolimus is crucial and cannot be avoided it would be better if given in reduced doses and also avoid longer duration of treatment. Hence monitoring of tacrolimus induced adverse drug reactions may help in getting a picture on avoiding it and help increase patient efficacy and adherence during treatment.

KEYWORDS: AKI (Acute Kidney Injury), PRES (Posterior reversible encephalopathy) ADR (Adverse drug reactions).

INTRODUCTION

Tacrolimus is a calcineurin inhibitor which comes under immunosuppressive agents. It plays a crucial role in post- transplant care and prevention of graft rejection and graft versus host disease. Its main mechanisms of action include calcineurin inhibition and suppression of T- cell lymphocyte activation making it indispensable in both solid organ and hematopoietic stem cell transplantation. However, the disadvantage is its use is limited to narrow therapeutic index and wide inter individual variability in pharmacokinetics which needs close monitoring so as to avoid toxicity. While it is well tolerated in some individuals, many adverse drug reactions have been reported which may vary from acute, preventable reactions to life-threatening reactions that can lead to death which may include nephrotoxicity, neurotoxicity, electrolyte disturbances, metabolic complications and hematological complications. The risk of the occurrence of toxicity is further amplified by drug- drug interactions, comorbidities and genetic polymorphisms that can affect the drug metabolism.

This case series defines in detail five clinically significant and diverse adverse drug reactions attributed to Tacrolimus which includes Acute kidney injury, Thrombotic Microangiopathy, Acute Pancreatitis, Posterior reversible encephalopathy syndrome with Hypomagnesemia and Hyperkalemia. All the mentioned reactions were reported to the Pharmacovigilance programme of India under the WHO-Uppsala monitoring Center. Thus, further systemically assessed for causality, severity, type, preventability and outcome by using relevant scales like WHO-UMC causality scale, Rawlin and Thompson

classification, Modified Hartwig classification and Siegel scale and Schumock and Thornton Preventability scale. The main aim through this case series in to highlight the importance of tacrolimus induced toxicities and the importance of vigilant monitoring to ensure patient safety and optimal therapeutic outcomes

Case studies

Case Report 1-Tacrolimus induced Acute Kidney Injury

The 23 year old male presented to the Hematology Outpatient (OP) Department with complaints of delayed developmental milestones, pallor, fatigue, fever and rashes all over the body and was admitted for further evaluation on 16th January 2025. He has a K/C/O Pancytopenia, Severe Aplastic Anemia, Purpuric lesion. He was diagnosed with Familial Platelet Disorder with Myeloid malignancy having RUNX1 mutation, Febrile Neutropenia, Mucositis and Left Upper DVT. The patient was on the following medications T. Acyclovir 400 mg 1-0-1 for 1 week, T. Fluconazole 400 mg 1-0-0 for 1 week, C. Tacrolimus 1 mg 1-0-1, T. Fopymin 1 mg for 1 week and T. Shelcal M 1 tab 1-0-0. This patient was given C Tacrolimus 1 mg 1-0-1 from the Haematology department. He thus developed an Acute kidney injury on 21st March 2025 with Serum Creat- 2.89, Uric acid- 11.24 and Tacrolimus levels of 20.7. During regular investigations the deranged blood levels were seen. Thus , the dose was reduced to 0.5 mg.The underlying condition was thus resolving.

Case Report 2-Tacrolimus induced Thrombotic Microangiopathy

This 44 year old male came to the Emergency Department with complaints of fever, oral bleeding and anemia and was admitted for further evaluation under Clinical Haematology Department on 5th February 2025. He has a K/C/O Pancytopenia, Acute Febrile Illness. He was thus diagnosed with Aplastic Anemia with Post Allogeneic Stem Cell Transplantation,Disseminated Candidemia, Bilateral Pneumonia. The patient was thus started on Inj. Caspofungin, Inj. Meropenam, C. Tacrolimus 1 mg 1-0-1, T. Methylpred 30 mg 1-0-0 for 3 days. Post transplant he developed Thrombotic microangiopathy on 2nd March 2025. The drug was thus stopped in view of the adverse drug reaction and he was treated with T. Methylpred 32 mg and other supportive measures on 4th march 2025, thus the underlying condition was resolved.

Case Report 3-Tacrolimus induced Acute pancreatitis

A 63 year old female came to the OutPatient (OP) Department with complaints of fever, chills, abdominal pain and nausea and was admitted under the Nephrology Department on 23th December 2023. She has K/C/O Type II Diabetes, Hypertension, Chronic kidney Disease, Cushingoid features. She was on Tacrolimus previously in June 2020 and developed Acute pancreatitis, the drug was stopped and restarted on the present admission. She was treated with T. Aldactone 25 mg 1-0-0, T. Torsemide 20 mg 1-0-0, T. Cilnidipine 20 mg 1-0-0, C. Tacrolimus 1 mg 1-0-1. She re-developed Acute pancreatitis using C. Tacrolimus ,the drug was thus stopped on 25th December 2025. Her blood investigations showed Creatinine- 13.14 mg/dl, Reticulocyte- 3.36. She was thus treated with IV fluids and given supportive care and her underlying condition was resolving

Case Report 4 -Tacrolimus induced PRES and Hypomagnesemia

A 19 year old female presented to the Emergency Department with complaints of loose stools with abdominal pain. No history of fever, chest pain, palpitation or any bleeding manifestations.She has K/C/O Hypoplastic MDS -Post Allogenic Stem Cell Transplantation from MSD, (DOT29/04/2025) ,GVHD Prophylaxis - and was on Tacrolimus + Methotrexate.. Urinary Tract Infection- E. coli,metabolic syndrome with DM& SHTN. She was treated with T. Nitrofurantoin 100 mg 1-0-1,T. Valganciclovir 900

mg 1-0-1 ,T. Pentids 400mg 1-0-1 ,T. Aciclovir 400mg OD x 1 weekT. Fluconazole 400mg OD ,T. Prednisolone 60 mg 1-0-0,,C. Cyclosporine 100 mg BD T. Fopymin 1 tab OD,T. Magvion 400mg TDS ,T. Pantop D 40/30mg 1-0-0 ,Inj. NPH 10-0-12 Units BD ,Inj . H Actrapid acc to GRBS

Post transplant, she was initiated on T. tacrolimus for GVHD prophylaxis from 30/april/2025. She developed hypomagnesemia during hospital stay and was managed accordingly with IV and oral corrections. The laboratory data showed magnesium 1.29 mg/dl on 29/may/2025.The suspected drug is continued and hypomagnesemia is possibly induced by Tacrolimus.

On 12/06/2025, she developed a shivering of whole body with frothing from mouth for 5 minutes followed by confusion. A tongue bit was also present. She was shifted to HDU for further evaluation and management. An urgent neurology opinion was sought .Hence her Tacrolimus was changed to cyclosporine suspecting CNI induced tremors and the event was resolving.

Case Report 5 - Tacrolimus induced Hyperkalemia

The 33 year old female presented to the Nephrology Outpatient (OP) Department for review. She has a medical history of Hypertension, Uncontrolled Diabetes,Hypertriglyceridemia, Chronic kidney disease - stage IV with Creatinine about 3.8, Anemia and 2 induced abortion in 2022 and 2023 respectively . Renal biopsy showed Mild global glomerulosclerosis in the background of near normal glomeruli in 2018 ,Rituximab 500MG 3 DOSES taken in January 2023 .She was on T. Acidose DS 1gm twice daily ,T. Arkamin 100ugm twice daily ,T. Cellcept 500mg twice daily, T. Dapaflin 10mg once daily which was now stopped,C. Dilzem CD 120a 5mg once daily,INJ H. Mixtard (30/70) 14 - 10 - 0 U SC twice daily,T. Wysolone 2.5mg and T. Shelcal CT 1 - 0 - 0 on alternate days. In February 2024, the patient was started on treatment with Tacrolimus 1 mg twice daily . On 4 th August 2024,The patient developed hyperkalemia with a potassium value of 5.7 mEq/L , hence the drug was withdrawn by treating physician suspecting probable Tacrolimus induced hyperkalemia and was thus treated with IV fluids and given supportive care and her underlying condition was resolving.

DISCUSSION

Tacrolimus, a calcineurin-inhibitor used as an immunosuppressant, is known for its narrow therapeutic index and potential for multisystem toxicity. This case series consists of case reports of tacrolimus-induced ADRs, including AKI, hypomagnesemia, hyperkalemia, PRES, and acute pancreatitis,Thrombotic Microangiopathy.

Case report 1, depicts Tacrolimus induced acute kidney injury accounts for approximately 2.88 % of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [9]. This case of Tacrolimus-Induced Acute Kidney Injury (WHO –UMC ID: IN- IPC -301101701), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type A (Augmented ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 1, and the outcome of the reaction was determined by WHO criteria as "recovering." The ADR was found to have been Probably preventable according to the Schumock and Thornton Scale.

Case report 2, depicts Tacrolimus induced Thrombotic Microangiopathy which accounts for approximately 1.30 % of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [9]. This case of Tacrolimus-Induced Thrombotic microangiopathy Injury(WHO –UMC ID: IN- IPC -301042164), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type A (Augmented

ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 3, and the outcome of the reaction was determined by WHO criteria as "recovered." The ADR was found to have been Probably preventable according to the Schumock and Thornton Scale.

Case report 3, depicts Tacrolimus induced Acute pancreatitis which accounts for approximately 0.23 % of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [9]. This case of Tacrolimus-Induced Acute Pancreatitis WHO –UMC ID: IN- IPC -301087752), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type D (Delayed ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 3, and the outcome of the reaction was determined by WHO criteria as "recovering." The ADR was found to have been Probably preventable according to the Schumock and Thornton Scale.

Case report 4, depicts Tacrolimus-Induced PRES and Hypomagnesemia which accounts for approximately 0.88 % and 0.58 % of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [9]. This case of Tacrolimus-Induced PRES (WHO –UMC ID: IN- IPC -301106136), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type A (Augmented ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 3, and the outcome of the reaction was determined by WHO criteria as "recovering." The ADR was found to have been probably preventable according to the Schumock and Thornton Scale.

And this case of Tacrolimus induced Hypomagnesemia (WHO–UMCID:IN-IPC-301093102**)**, was reported by our AMC. The causality was determined as possible using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type A (Augmented ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 3, and the outcome of the reaction was determined by WHO criteria as "recovering." The ADR was found to have been Probably preventable according to the Schumock and Thornton Scale.

Case report 5, depicts Tacrolimus-Induced Hyperkalemia which accounts for approximately 0.96 % of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [9]. This case of Tacrolimus-Induced Hyperkalemia(WHO –UMC ID: IN- IPC -301017125), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type A (Augmented ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 3, and the outcome of the reaction was

determined by WHO criteria as "recovering." The ADR was found to have been Probably preventable according to the Schumock and Thornton Scale.

Table 1 : Causality assessment of tacrolimus induced adverse drug reactions

Patient No.	Adverse Drug Reaction	Causality Assessment			
		WHO-UMC scale	Rawlin and Thompson's classifications	Hartwig's Severity Assessment scale	Schumock and Thornton scale

1	Tacrolimus induced Acute kidney Injury	probable	Type A	Moderate level 1	Probably preventable
2	Tacrolimus induced Thrombotic microangiopathy	probable	Type A	Moderate level 3	Probably preventable
3	Tacrolimus induced Acute pancreatitis	probable	Type D	Moderate level 3	Probably preventable
4	Tacrolimus Induced PRES	probable	Type A	Moderate level 3	Probably preventable
5	Tacrolimus induced Hypomagnesemia	possible	Type A	Moderate level 3	Probably preventable
6	Tacrolimus-Induced Hyperkalemia	probable	Type A	Moderate level 3	Probably preventable

CONCLUSION

This case series depicts the wide range of clinically significant adverse drug reactions associated with Tacrolimus, an immunosuppressant with a narrow therapeutic index. The reported cases including acute kidney injury ,thrombotic microangiopathy ,neurotoxicity, metabolic disturbances, and electrolyte imbalances, emphasize the significance of therapeutic monitoring, awareness about potential toxicities, and individualized dosing of the drug. All ADRs were reported to the Pharmacovigilance Programme of India and assessed using standardized methods, emphasizing the need for active pharmacovigilance to ensure patient safety and optimize therapeutic outcomes in transplant and immunosuppressive therapy settings.

REFERENCES

1. 1.Dilibe A, Subramanian L, Poyser TA, Oriaifo O, Brady R, Srikanth S, Adabale O, Bolaji OA, Ali H. Tacrolimus-induced posterior reversible encephalopathy syndrome following liver transplantation. World J Transplant. 2024 Jun 18;14(2):91146. doi: 10.5500/wjt.v14.i2.91146. PMID: 38947962; PMCID: PMC11212591.
2. 2.Griffis OL, Thai SQ, Allison C, Baetz B, Mohammed A. The Association Between Tacrolimus Levels and Hyperkalemia in Allograft Recipients Who Underwent Heart or Lung Transplantation in New Orleans, USA Between 2013 and 2019: A Single-Center Retrospective Study. Ann Transplant. 2022 Aug 2;27:e935607. doi: 10.12659/AOT.935607. PMID: 35915576; PMCID: PMC9357348.
3. Xu M, Xu S, Yi X. A comparative analysis of drug-induced kidney injury adverse reactions between cyclosporine and tacrolimus based on the FAERS database. BMC Immunol. 2025 May 2;26(1):35. doi: 10.1186/s12865-025-00714-7. PMID: 40316906; PMCID: PMC12049015.
4. Tacrolimus: Transient thrombotic microangiopathy: case report. Reactions Weekly. 2020;1820(1):288. doi: 10.1007/s40278-020-83108-x. Epub 2020 Sep 5. PMCID: PMC7474494.

5. Kim Y, Choi CY, Sunwoo Y, Go C, Kim S, Eom SH, Shin S, Choi YJ. A Real-World Data Derived Pharmacovigilance Assessment on Drug-Induced Nephropathy: Implication on Gaps in Patient Care. Healthcare (Basel). 2023 Dec 31;12(1):95. doi: 10.3390/healthcare12010095. PMID: 38201001; PMCID: PMC10778829.
6. Munjal RS, Sharma J, Polishetti S, Valleru PS, Banker H, Bandhu Gupta R, Anamika F, Jain R. Beyond Immunosuppression: The Intricate Relationship Between Tacrolimus and Microangiopathy. Cureus. 2023 Nov 24;15(11):e49351. doi: 10.7759/cureus.49351. PMID: 38146570; PMCID: PMC10749684.
7. Tacrolimus: Nephrotoxicity: case report. Reactions Weekly. 2020;1815(1):296. doi: 10.1007/s40278-020-81622-4. Epub 2020 Aug 1. PMCID: PMC7393034.
8. The use of the WHO-UMC system for standardized case causality assessment [Internet]. Available from: https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf
9. VigiAccess [Internet]. www.vigiaccess.org. Available from: https://www.vigiaccess.org/
10. Adverse drug reactions [Internet]. Clinical Gate. 2015. Available from: https://clinicalgate.com/adverse-drug-reactions