Panacea Journal of Medical Sciences 2020;10(3):320–324

Content available at: https://www.ipinnovative.com/open-access-journals

Panacea Journal of Medical Sciences

Journal homepage: www.ipinnovative.com

Original Research Article

Prescription pattern and safety of immunosuppressive drugs in patients of renal transplant in IGIMS Patna - An observational study

Shambhu Kumar Yadav[1], Manish Kumar[1], Sukalyan Saha Roy[1], Saajid Hameed[1,*], Lalit Mohan[1], Harihar Dikshit[1]

[1]*Dept. of Pharmacology, Indira Gandhi Institute of Medical Sciences, Department of Pharmacology Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India*

ARTICLE INFO

Article history:
Received 12-05-2020
Accepted 09-06-2020
Available online 29-12-2020

Keywords:
Renal transplant
Immunosuppressant
ADR

ABSTRACT

Objective: Survival of post renal transplant patients has been improved by the suppression of the recipient's immune system by immunosuppressive agents. However, various adverse drug reactions are also associated with immunosuppressive agents. Keeping this in mind, present study was planned to study the prescriptions pattern of immunosuppressant drugs and to study adverse drug reactions associated with immunosuppressant drugs.

Materials and Methods: It was an observational and cross-sectional study. We have collected reported ADRs, prescriptions, IPD files and laboratory reports of 40 patients who had already undergone renal transplant prior to start of this study and 10 patients who undergone renal transplant after start of this study.

Result: Most patients were prescribed prednisolone + tacrolimus + MMF as immunosuppressive regimen (70%) followed by prednisolone + cyclosporine + MMF (22%). Prednisolone was prescribed to all patients. Tacrolimus was prescribed to 72% of patients. Total 78 ADRs were reported from 50 patients in our study (incidence rate 68%). Drug MMF was mostly associated with ADRs (35.90%) followed by tacrolimus (29.49%), prednisolone (19.23%) and cyclosporine (15.38%). Most of the ADRs was mild (65.38%) while only one ADR was severe.

Conclusion: Corticosteroid continues to be mainstay of therapy in post renal transplant patients. Calcineurin inhibitors were exclusively associated with nephrotoxicity. MMF was associated with most ADRs followed by tacrolimus. Most of the ADRs were mild and treated symptomatically.

1. Introduction

Kidney transplant is essential in case of ESRD (End Stage Renal Diseases) to improve survival and quality of life and reduce health care cost. But it also challenges nephrologist in preventing rejection of the graft and to use immunosuppressant judiciously to avoid their adverse effect and to also avoid infection common in immunocompromised host. Chronic kidney disease is also associated with altered intestinal transport mechanisms and this can affect the oral bioavailability of immunosuppressive drugs.[1] So there is more risk of adverse reactions.[2]

Survival of post renal transplant patients has been improved by the suppression of the recipient's immune system by immunosuppressive agents.[3] However, various adverse drug reactions are also associated with immunosuppressive agents.[4] Chronic allograft nephropathy is significantly affected by various factors such as Calcineurin nephrotoxicity, drug induced hypertension and non-compliance to immunosuppressive therapy.[5] Furthermore, it has been demonstrated from results of various studies that quality of life in renal transplant patient is significantly associated with immunosuppressive ADRs.[6–8]

ADRs are one of the important issue which needs attention while treating the patients with drugs. They

* *Corresponding author*.
E-mail address: saajid36@gmail.com (S. Hameed).

https://doi.org/10.18231/j.pjms.2020.066

are having great effect on life of patients. Mechanism of action of immunosuppressant i.e. suppression of the immune system is the leading factor for various adverse drug reaction. And the ongoing crisis that the patient suffers by End Stage Renal Disease (ESRD) adds to the problem. Calcineurin inhibitors are associated with a number of potentially serious adverse effects, including nephrotoxicity, diabetes, hypertension, and neurotoxicity which contributes to morbidity and mortality after transplantation.[9–13] Cyclosporine has become less relevant in the modern era of organ transplantation. So 92% of kidney transplant recipients are now being prescribed tacrolimus as the first-line calcineurin inhibitor.[14] Combined therapy with tacrolimus and mycophenolic acid may be associated with high risk of BK virus infection,[15] which can lead to failure of the transplanted kidney. Everolimus have beneficial effect on renal function and may reduce the occurrence of malignancy[16,17] but it can cause impaired wound healing, mouth ulcers, stomatitis, arthralgia, hyperlipidaemia, and anemia.[18–21] In spite of the numerous side effects, most transplant patients are maintained on long-term low-dose steroids.[22]

2. Materials and Methods

2.1. Study site/place

Renal Transplant Unit of IGIMS, Patna.

2.2. Study duration

Months from December 2019 to May 2020

2.3. Materials

Prescriptions of patients who have undergone Renal transplant.

2.4. Study design

It was an observational and cross-sectional study. We have collected reported ADRs, prescriptions, IPD files and laboratory reports of 40 patients who had already undergone renal transplant prior to start of this study and 10 patients who undergone renal transplant after start of this study. ADRs reports were collected from ADR monitoring centre (AMC), Department of Pharmacology, IGIMS, Patna. Study was started after approval from Institutional Ethics Committee of IGIMS, Patna.

According to WHO, any ADR that resulted in death, a life-threatening situation, persistent or substantial disability/ incapacity, hospital admission, or prolonged hospital stay is considered as serious.[23]

2.5. Inclusion criteria

Patients who have undergone renal transplant and were on maintenance immuno-suppressive therapy.

2.6. Exclusion criteria

Patients already having immunodeficiency disease.

2.7. Statistical analysis

Results obtained from this study were presented in tabular form and data were interpreted by using Microsoft Excel 2007 software.

3. Results

4. Discussion

In our study, more male patients (62%) have undergone renal transplant than females (38%). Most of patients were >45 years old (62%). Most common cause of End Stage Renal Disease (ESRD) was Diabetes mellitus (38%) followed by hypertension (26%). Namazi et al. found in their study that 72.5% of total patients were men. They found only 2 patients (1.67%) were $\geq$ 65 years of age. Most common cause of ESRD in their study was hypertension (29.86%) followed by nephrolithiasis (13.89%), and glomerulonephritis (11.11%).[24] Love et al. found in their study that 69.2% of total patients were male and 52.52% of total patients were between 46 to 75 years of age. Most common cause of ESRD in their study was Diabetes Mellitus followed by hypertension.[25]

Most patients were prescribed prednisolone + tacrolimus + MMF as immunosuppressive regimen (70%) followed by prednisolone + cyclosporine + MMF (22%). Prednisolone was prescribed to all patients. Tacrolimus was prescribed to 72% of patients. Namazi et al. found in their study that combination therapy of prednisolone/cyclosporine/ mycophenolate mofetil (69.17%) was most prescribed immunosuppressive regimen. In their study, all patients were prescribed prednisolone and nearly all patients (97.5%) received cyclosporine as part of their immunosuppressive treatment and 25% were treated with azathioprine.[24]

Total 78 ADRs were reported from 50 patients in our study. These ADRs were reported from 34 patients. So, incidence rate of patients affected due to ADR was calculated to be 68%. Incidence rate = (Total number of patients reported ADRs/ Total number of patients) x 100.

Love et al.[25] found in their study that the incidence rate of ADR was 75.78%. When we compared our findings with other ADRs monitoring studies, we found our incidence rate to be quite high. Benkirane et al[26] and Nicholas moore[27] found in their study that incidence rate of ADR was only 15.5% and 9.42% only. The reason for these differences could be many pathological change that develop

Table 1: Demographiccharacteristics of Renal transplant patients

Characteristics		Number of Patients (%) N=50	Frequency of ADR (%) N=78
Sex	Male	51 (65.38)	51 (65.38)
	Female	27 (34.62)	27 (34.62)
Age	<15	0 (0)	0 (0)
	15-30	9 (11.54)	9 (11.54)
	31-45	19 (24.36)	19 (24.36)
	46-60	38 (48.72)	38 (48.72)
	61-75	12 (15.38)	12 (15.38)
Causes of End Stage Renal Disease	CKD associated with Diabetes Mellitus	19 (38)	
	CKD associated with Hypertension	13 (26)	
	CKD associated with both DM and HTN	9 (18)	
	CKD associated with autoimmune disease	3 (6)	
	Other	6 (12)	

Table 2: Immunosuppressive treatment given to Renal transplant patients (n=50)

Immunosuppressive Regimen	Number of Prescriptions (%)
Prednisolone + Tacrolimus + Mycophenolate mofetil (MMF)	35 (70)
Prednisolone + cyclosporine + Mycophenolate mofetil (MMF)	11 (22)
Prednisolone + Cyclosporine	3 (6)
Prednisolone + Tacrolimus	1 (2)
Immunosuppressive drugs	
Prednisolone	50 (100)
Cyclosporine	14 (28)
Mycophenolate mofetil	46 (92)
Tacrolimus	36 (72)

Table 3: Adverse Drug Reactions (ADRs) in Renal Transplant Patients (n=78)

ADRs	No of ADRs (%)	Drugs Involved (n)
Nephrotoxicity	6 (7.69)	Tacrolimus (4), Cyclosporine (2)
Diarrhoea	4 (5.13)	Tacrolimus (2), MMF (2)
Thrombocytopenia	4 (5.13)	MMF (4)
Headache	3 (3.85)	Tacrolimus (3)
Leukopenia	5 (6.41)	MMF (1), Prednisolone (2), Cyclosporine (2)
Oral Candidiasis	7 (8.97)	MMF (3) , Prednisolone (2), Cyclosporine (2)
UTI	7 (8.97)	MMF (2), Prednisolone (4), Cyclosporine (1)
Wound healing complication	8 (10.26)	Tacrolimus (2), Prednisolone (6)
Metabolic acidosis	2 (2.56)	MMF (2)
Anaemia	10 (12.82)	MMF (10)
Pancytopenia	2 (2.56)	MMF (2)
Hyponatremia	8 (10.26)	Tacrolimus (8)
Leukopenia	2 (2.56)	MMF (1), Prednisolone (1)
Hepatotoxicity	5 (6.41)	Cyclosporine (5)
Hyperkalaemia	4 (5.13)	Tacrolimus (4)
CMV	1 (1.28)	MMF (1)

Table 4: Frequency of ADRs among Immunosuppressive drugs (n=78)

Drugs	No of ADRs (%)
Prednisolone	15 (19.23)
Cyclosporine	12 (15.38)
Mycophenolate mofetil	28 (35.90)
Tacrolimus	23 (29.49)
Total	78

Table 5: Severity assessment of ADRs (n=78)

Grade	Number of ADRs (%)
Mild	51 (65.38)
Moderate	36 (46.15)
Severe	1 (1.28)

Table 6: Actions taken after ADRs (n=78)

Action Taken	Number of ADRs (%)
Drug withdrawn	3 (3.85)
Dose reduced	21 (26.92)
Symptomatic	39 (50)
No action	15 (19.23)

in patients due to End Stage Renal Disease (ESRD).

Calcineurin inhibitors are well known for nephrotoxicity as their common adverse effect and this was also found in our study as all reports of nephrotoxicity was found in patients receiving cyclosporine or tacrolimus. Similar results were found in studies of Robert F. English et al[28] and Busauschina A. el al.[29]

In renal transplant patients, infection is one of the leading cause of morbidity and mortality. It is also considered as the main cause of death in the early period after renal transplant.[30–32] In our study, 7 cases of oral candidiasis, 7 cases of UTI and 8 cases of wound healing complications were found. In a study done by Namazi et al.[24] the prevalence of infectious episodes was 26.67%.

Drug MMF was mostly associated with ADRs (35.90%, mostly Anaemia, Thrombocytopenia and pancytopenia etc.) followed by tacrolimus (29.49%, mostly Nephrotoxicity, Hyponatremia, Hyperkalaemia etc.), prednisolone (19.23%, mostly wound healing complication, UTI, Oral Candidiasis, Leukopenia etc.) and cyclosporine (15.38%, mostly Hepatotoxicity, nephrotoxicity, Leukopenia, Oral Candidiasis etc.).

Most of the ADRs were found in age-group 46-60. Patients of old age were mostly affected by ADRs and poor prognosis. Oral Candidiasis, Urinary Tract Infection, Wound healing complication were most common ADRs. Most of the ADRs were mild (65.38%) while only one ADR was severe. 50% of ADRs were treated symptomatically. Responsible drug was withdrawn in only 3 cases. Similar results were found in other studies.[25]

5. Conclusions

Most common immunosuppressive regimen prescribed was prednisolone + tacrolimus + MMF. Among these corticosteroids were mainstay of therapy. Mycophenolate Mofetil (MMF) was associated with most ADRs followed by tacrolimus. Most of the ADRs were mild and treated symptomatically. To decrease the rate of ADRs that are preventable, we can adopt various strategies such as regular follow-up of patients, periodic monitoring of cyclosporine level and it's dose adjustment according to monitoring findings, taking care of clinically significant drug interactions, prescribing much safer immunosuppressive regimens (eg. cyclosporine conversion to tacrolimus or sirolimus, preferring steroid-sparing protocol) and educating patients.

6. Source of Funding

No financial support was received for the work within this manuscript.

7. Conflict of Interest

The authors declare they have no conflict of interest.

References

1. Lemahieu WP, Maes BD, Verbeke K, Vanrenterghem YF. Alterations of CYP3A4 and P-glycoprotein activity in vivo with time in renal graft recipients. *Kidney Int*. 2004;66(1):433–40. doi:10.1111/j.1523-1755.2004.00750.x.
2. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. *Expert Opin Drug Metab Toxicol*. 2008;4(8):1065–74. doi:10.1517/17425255.4.8.1065.
3. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, et al. Pharmacotherapy: A Pathophysiologic Approach. New York: McGraw-Hill; 2008.
4. Rosenberger J, Geckova AM, Dijk JP, Roland R, Heuvel WJ, Groothof JWF, et al. Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients. *Clin Transplant*. 2005;19(1):70–6. doi:10.1111/j.1399-0012.2004.00300.x.
5. Taber DJ, Dupuis RE. Kidney and liver transplantation. In: KodaKimble M, Young L, Kradjan W, editors. Applied Therapeutics: The Clinical Use of Drugs. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 34–5.
6. Fallen M, Gould D, Wainwright SP. Stress and quality of life in the renal transplant patient: a preliminary investigation. *J Adv Nurs*. 1997;25(3):562–70. doi:10.1046/j.1365-2648.1997.1997025562.x.
7. Geest SD, Moons P. The patient's appraisal of side-effects: the blind spot in quality-of-life assessments in transplant recipients. *Nephrol Dial Transplant*. 2000;15(4):457–9. doi:10.1093/ndt/15.4.457.
8. Valderrábano F, Jofre R, López-Gómez JM. Quality of life in end-stage renal disease patients. *Am J Kidney Dis*. 2001;38(3):443–64. doi:10.1053/ajkd.2001.26824.
9. Almeida C, Silveira M, de Araújo V, de Lemos L, de Oliveira Costa J, Reis C, et al. Safety of Immunosuppressive Drugs Used as Maintenance Therapy in Kidney Transplantation: A Systematic

Review and Meta-Analysis. *Pharmaceuticals*. 2013;6(10):1170–94. doi:10.3390/ph6101170.
10. Nankivell BJ, Borrows RJ, Fung CS, O′Connell PJ, Chapman JR, Allen RDM, et al. Calcineurin Inhibitor Nephrotoxicity: Longitudinal Assessment by Protocol Histology. *Transplant*. 2004;78(4):557–65. doi:10.1097/01.tp.0000128636.70499.6e.
11. Nankivell BJ, P′Ng CH, O′Connell PJ, Chapman JR. Calcineurin Inhibitor Nephrotoxicity Through the Lens of Longitudinal Histology. *Transplant*. 2016;100(8):1723–31. doi:10.1097/tp.0000000000001243.
12. Borda B, Lengyel C, Várkonyi T, Kemény E, Ottlakán A, Kubik A, et al. Side effects of the calcineurin inhibitor, such as new-onset diabetes after kidney transplantation. *Acta Physiologica Hungarica*. 2014;101(3):388–94. doi:10.1556/aphysiol.101.2014.3.13.
13. Chepman JR. Chronic Calcineurin inhibitor Nephrotoxicity-Lest we forget. *Am J Transplant*. 2011;11(4):693–7.
14. Saran R, Li Y, Robinson B. US renal data system 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2015;66(1):S1–305.
15. Suwelack B, Malyar V, Koch M, Sester M, Sommerer C. The influence of immunosuppressive agents on BK virus risk following kidney transplantation, and implications for choice of regimen. *Transplant Rev (Orlando)*. 2012;26(3):201–11. doi:10.1016/j.trre.2011.05.002.
16. Lim WH, Eris J, Kanellis J, Bomiid ZP, and DW. et A systematic review of conversion from Calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. *Am J Transplant*. 2014;14(9):2106–19.
17. Lieberthal W, Levine JS. The Role of the Mammalian Target Of Rapamycin (mTOR) in Renal Disease. *J Am Soc Nephrol*. 2009;20(12):2493–502. doi:10.1681/asn.2008111186.
18. Zaza G, Tomei P, Ria P, Granata S, Boschiero L, Lupo A, et al. Systemic and Nonrenal Adverse Effects Occurring in Renal Transplant Patients Treated with mTOR Inhibitors. *Clin Dev Immunol*. 2013;2013:1–13. doi:10.1155/2013/403280.
19. Campistol JM, de Fijter J, Flechner SM, Langone A, Morelon E, Stockfleth E, et al. mTOR inhibitor-associated dermatologic and mucosal problems. *Clin Transplant*. 2010;24(2):149–56. doi:10.1111/j.1399-0012.2010.01232.x.
20. Bin W, Feng-Bo W, Lei Y, Yao T. Meta-analysis of immunosuppressive therapy with target-of-rapamycin inhibitor instead of Calcineurin inhibitor after kidney transplantation operation. *China Pharm*. 2011;22(34):3229–31.
21. Glover TE, Watson CJE, Gibbs P, Bradley JA, Ntzani EE, Kosmoliaptsis V, et al. Conversion From Calcineurin to Mammalian Target of Rapamycin Inhibitors in Liver Transplantation. *Transplant*. 2016;100(3):621–9. doi:10.1097/tp.0000000000001006.
22. Medscape;Available from: https://emedicine.medscape.com/article/430128-medication#3.
23. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Uppsala: Uppsala Monitoring Centre; 2000.
24. Namazi S, Sagheb MM, Karimzadeh I. Adverse Reactions of Immunosuppressive Drugs in Iranian Adult Kidney Transplant Recipients. *Exp Clin Transplant*. 2012;10(3):224–31. doi:10.6002/ect.2011.0100.
25. Love S, Lalit K, Lokesh S, Virendra Y, Binny T, Al HM, et al. A study of adverse events associated with the use of Immunosuppressive agents in kidney transplanted Patients. *Int J Drug Dev Res*. 2012;4(3):283–91.
26. Benkirane RR, R-Abouqal R, Haimeur CC, Kettani SSECE, Azzouzi AA, Alaoui AM, et al. Incidence of Adverse Drug Events and Medication Errors in Intensive Care Units. *J Patient Saf*. 2009;5(1):16–22. doi:10.1097/pts.0b013e3181990d51.
27. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol*. 1998;45(3):301–8. doi:10.1046/j.1365-2125.1998.00667.x.
28. English RF, Pophal SA, Bacanu SA, Fricker J, Boyle GJ, Ellis D, et al. Long-Term Comparison of Tacrolimus- and Cyclosporine-Induced Nephrotoxicity in Pediatric Heart-Transplant Recipients. *Am J Transplant*. 2002;2(8):769–73. doi:10.1034/j.1600-6143.2002.20811.x.
29. Busauschina A, Schnuelle P, van der Woude FJ. Cyclosporine nephrotoxicity. *Transplant Proc*. 2004;36(2):S229–33. doi:10.1016/j.transproceed.2004.01.021.
30. Fishman JA, Rubin RH. Infection in Organ-Transplant Recipients. *N Engl J Med*. 1998;338(24):1741–51. doi:10.1056/nejm199806113382407.
31. Schmidt A, Oberbauer R. Bacterial and fungal infections after kidney transplantation. *Curr Opin Urol*. 1999;9(1):45–9. doi:10.1097/00042307-199901000-00008.
32. Splendiani G, Cipriani S, Tisone G, Iorio B, Condo S, Vega A, et al. Infectious Complications in Renal Transplant Recipients. *Transplant Proc*. 2005;37(6):2497–9. doi:10.1016/j.transproceed.2005.06.012.

Author biography

Shambhu Kumar Yadav, Senior Resident

Manish Kumar, Associate Professor

Sukalyan Saha Roy, Assistant Professor

Saajid Hameed, Junior Resident

Lalit Mohan, Additional Professor

Harihar Dikshit, Professor and Head

Cite this article: Yadav SK, Kumar M, Roy SS, Hameed S, Mohan L, Dikshit H. Prescription pattern and safety of immunosuppressive drugs in patients of renal transplant in IGIMS Patna - An observational study. *Panacea J Med Sci* 2020;10(3):320-324.