International Journal of Clinical Trials
Patel L et al. Int J Clin Trials. 2022 Nov;9(4):263-267
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20222626

Original Research Article

Real-world utilization and acceptance of tacrolimus-based immunosuppression in solid organ transplant recipients in India

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Received: 28 September 2022
Revised: 04 October 2022
Accepted: 06 October 2022

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ABSTRACT

Background: The objectives of the study were to describe the demographics and utilization pattern of tacrolimus (TAC)-based immunosuppressive regimens in recipients with solid organ transplant in India.
Methods: This real-world, multicenter (134 centers), retrospective analysis included data of solid organ transplant recipients between 2010 and 2022 who had received TAC-based immunosuppressive therapy. The study data was collected between April 2021 and March 2022.
Results: Data of a total of 1022 recipients with kidney transplant (KT, n=899) or liver transplant (LT, n=123) who received TAC-based immunosuppression was analyzed. The mean age of recipients among KT and LT was 41.04±10.62 and 42.88±11.32 years, respectively. The most common diseases leading to end stage organ failure were diabetes (24.7%), hypertension (15.8%), concomitant diabetes and hypertension (14.9%), chronic kidney disease (9.2%), nephrotic syndrome (5%), and end stage renal disease (ESRD, 4.4%) in KT recipients, whereas for LT, the common indications were liver cirrhosis (32.5%), hepatitis B viral infection (11.4%), alcoholic liver disease (10.6%), fatty liver disease (12, 9.8%) and non-alcoholic steatohepatitis (NASH, 5.7%). The source of transplant was living donor in majority of both KT (91.2%) and LT (77.2%) recipients. The most common induction regimen in KT was anti-thymocyte globulin (ATG), TAC, mycophenolate mofetil (MMF), and steroid (ATG+TAC+MMF+steroid, 42.3%) whereas in LT, it was TAC+MMF+steroid (67.5%); TAC+MMF+steroid was most common maintenance regimen (KT: 91.1%, LT: 78%).
Conclusions: Tacrolimus-based immunosuppression is widely used in the recipients of solid organ transplantation, including KT or LT in real-world clinical practice in India.

Keywords: Tacrolimus, Immunosuppression, Transplant, KT, LT, Kidney

INTRODUCTION

In India, organ transplantation has a high demand due to its large population base and high incidences of both communicable and noncommunicable diseases among its population.[1]

India has the third largest number of transplants among countries.[1] Studies have shown that solid organ transplants (SOT) may save the lives of patients who are suffering from terminal organ failure and lead to an improved quality-of-life.[2] A wide gap exists between patients who need transplants and the organs that are available in India. An estimated 17 people die every day waiting for an organ transplant.[3] In India, kidney transplant (KT) and liver transplants (LT) are the two most common solid organ transplants performed.[1]

Outcomes in SOTs have improved greatly with the use of immunosuppressive agents. Over the years, significant advancements in the immunosuppressive medications and regimens have subsequently resulted in improved

outcomes.[4] It has been described that the calcineurin inhibitors are the cornerstone of immunosuppressive therapy in solid organ transplants. The advent of calcineurin inhibitors has resulted in a dramatic advancement in the immunosuppressive regimen for recipients of SOTs, resulting in long-term survival and meaningful functional recovery.[4]

Tacrolimus (TAC), a calcineurin inhibitor agent, is a macrolide antibiotic. Tacrolimus is derived from *Streptomyces tsukubaensis,* which binds to FK506-binding protein 12 (FKBP12) to form a complex that inhibits calcineurin.[5] The US Food and Drug Administration (FDA) has approved tacrolimus for organ rejection prophylaxis in several transplants including liver, kidney, lung and heart.[5] Several studies have described the role of TAC-based immunosuppression in solid organ transplants.

Intas Pharmaceuticals Limited, Ahmedabad, India has developed a formulation of tacrolimus which is bioequivalent to the innovator tacrolimus. Intas' tacrolimus met the narrow therapeutic index bioequivalence criteria of European medicines agency (EMA, 90-111%), which is stringent than the bioequivalence criteria of Indian market (80-125%). The bioequivalence study comparing Intas' tacrolimus (test) with innovator (reference) concluded that the test and reference formulations of tacrolimus 0.5 mg and 5 mg capsules were well tolerated and met the requirements of the European regulatory bioequivalence guidelines. There were no relevant differences in the safety profiles of the test and reference formulations.[6] The current study was conducted to evaluate the real-world usage pattern of Intas' tacrolimus-based immunosuppression in SOTs and to describe the disease characteristics and demographic pattern of recipients undergoing SOTs.

METHODS

Study design

This retrospective analysis involved data of recipients of SOTs and who had received TAC-based immunosuppression in India between 2010 and 2022. All treatment decisions were at the investigator's discretion, including individual dose, duration of treatment, and method and frequency of clinical assessments, in accordance with local labelling information and standard clinical practice.

The current study collected data between April 2021 and March 2022 on transplant recipients' characteristics, as well as treatment utilization patterns. The characteristics including age, gender, and treatment-related parameters were collected. The data collected included age, sex, medical history, diseases leading to end stage organ failure, type of SOT, details of transplant (date, organ transplanted, donor source, etc), and details of treatment such as TAC-based induction and maintenance immunosuppression regimens, were collected.

Sample size and statistical analysis

This was a real-world study and data was collected retrospectively without any predetermined sample size. No hypothesis was tested in this study and only the observations from transplant recipients records were collected and analyzed. Demographic and baseline characteristics were summarized using descriptive statistics. Categorical variables were summarized with frequency and percentage. Continuous variables were summarized with count, mean, standard deviation, etc. Graphical presentation of data was done using bar chart as appropriate. Statistical analyses were performed using Microsoft excel (Microsoft Corp., USA).

Ethics statement

The study protocol was approved by the ACEAS independent ethics committee, Ahmedabad, India. This study was performed in accordance with International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) and ethical principles of Declaration of Helsinki. Since this study involved data retrieval from medical records only, an informed consent was not obtained.

RESULTS

A total of 1022 recipients with KT (n=899) or LT (n=123) who received TAC-based immunosuppression were included. The demographic characteristics of organ recipients are summarized in Table 1. Majority of KT and LT recipients were males (82.8% and 83.7%, respectively). The mean age of recipients among KT and LT was 41.04±10.62 and 42.88±11.32 years, respectively.

Table 1: Demographic characteristics.

Parameters	KT (N=899)	LT (N=123)
Age in years, mean ± SD (range)	41.04±10.62 (9-72)	42.88±11.32 (3-66)
Height in cm, mean ± SD (range)	163.0±12.4 (55-190)	164.5±10.96 (94-187)
Weight in kg, mean ± SD (range)	66.69±14.07 (21.8-168)	65.31±11.32 (14.2-88)
Gender of transplant recipients, n (%)		
Men	744 (82.8)	103 (83.7)
Women	155 (17.2)	20 (16.3)

Disease leading to end stage organ failure

Kidney transplantation

The most common diseases leading to end stage kidney disease in KT recipients were diabetes (24.7%, n=222), hypertension (15.8%, n=142), concomitant diabetes and

hypertension (14.9%, n=134), chronic kidney disease (9.2%, n=83), nephrotic syndrome (5%, n=45), and end stage renal disease (ESRD, 4.4%, n=40) (Figure 1).

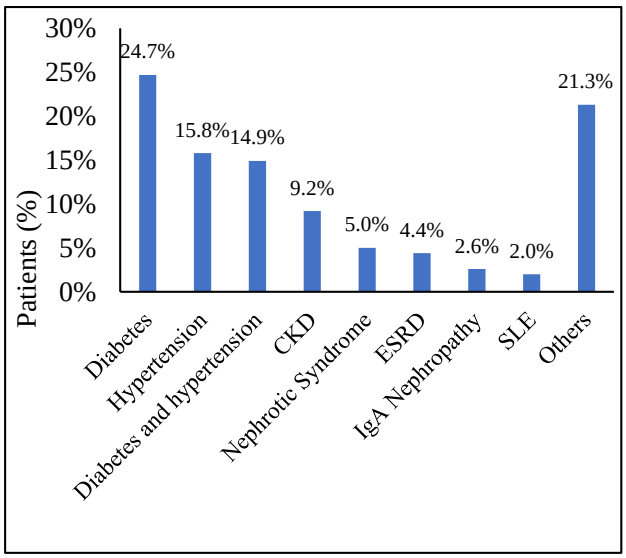

Figure 1: Disease leading to end stage kidney failure requiring KT.

CKD, chronic kidney disease; ESRD, end stage renal disease, IgA, immunoglobulin A, SLE, systemic lupus erythematosus.

The most common diseases leading to end stage liver disease in LT recipients were liver cirrhosis (32.5%, n=40), hepatitis B viral infection (11.4%, n=14), alcoholic liver disease (ALD, 10.6%, n=13), fatty liver disease (9.8%, n=12) and non-alcoholic steatohepatitis (NASH, 5.7%, n=7) (Figure 2).

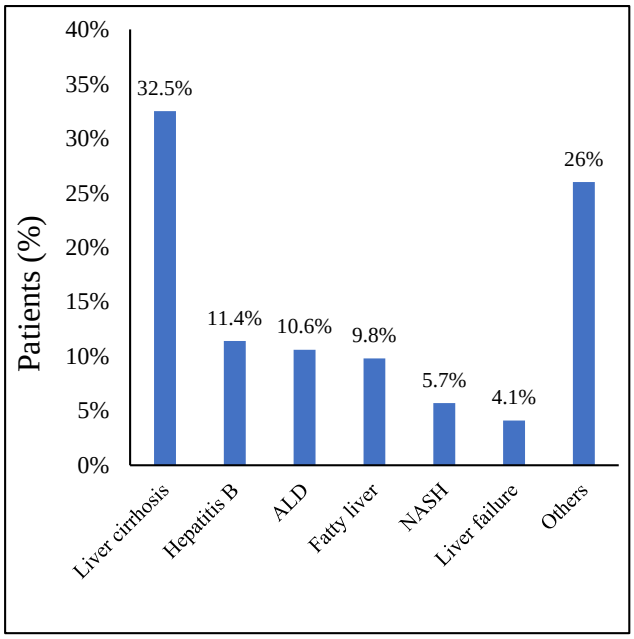

Figure 2: Disease leading to end stage liver failure requiring LT.

ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis

Donor source of transplant

The donor source of transplant was living donor in majority of both KT and LT. In KT, 91.2% transplants were from living donors whereas 8.8% transplants were from deceased ones. In LT, 77.2% transplants belonged to live donors whereas 22.8% transplants were from deceased ones (Table 2).

Table 2: Characteristics of donors.

Parameter	KT (N=899)	LT (N=123)
	n (%)	n (%)
Donor source		
Deceased	79 (8.8)	28 (22.8)
Living donor	820 (91.2)	95 (77.2)

Agents used for immunosuppression

Induction immunosuppression

The most common induction regimen used in KT recipients was anti-thymocyte globulin (ATG), TAC, mycophenolate mofetil (MMF), and steroid (ATG+TAC+MMF+steroids) in 381 (42.3%) recipients followed by TAC+MMF+steroids in 327 (36.4%) recipients and basiliximab+TAC+ MMF+steroids in 62 (6.9%) recipients. The most common induction regimen used in LT recipients was TAC+MMF+steroids in 83 (67.5%) recipients followed by ATG+TAC+MMF+steroids in 15 (12.2%) recipients (Table 3).

Maintenance immunosuppression

The most common maintenance regimen used was TAC+MMF+steroids in KT (91.1%, n=819) and LT (78%, n=96) recipients; cyclosporine+MMF+steroids was the other used maintenance regimen in 0.8% recipients each in the KT and LT.

Table 3: Most common immunosuppression regimens.*

Regimens	KT (N=899)	LT (N=123)
	n (%)	n (%)
Induction regimens		
ATG+TAC+MMF+steroid	381 (42.3)	15 (12.2)
TAC+MMF+steroid	327 (36.4)	83 (67.5)
Basiliximab+TAC+MMF+steroid	62 (6.9)	-
Maintenance regimens		
TAC+MMF+steroid	819 (91.1)	96 (78)
Cyclosporine+MMF+steroid	7 (0.8)	1 (0.8)

*Data not presented for other regimens. ATG-anti-thymocyte globulin, MMF-mycophenolate mofetil, TAC-tacrolimus.

DISCUSSION

This retrospective study reports a preliminary assessment of the real-world usage of tacrolimus-based immunosuppression therapy in recipients of solid organ transplants in India. This study provides a sneak peak in to the demographics and characteristics of recipients of KT and LT at various centers across India and utilization patterns of TAC-based immunosuppression regimens as induction as well as maintenance therapies.

KT was performed in 88% of the total 1022 transplants included in this study, and 12% received LT. These finding are in line with a review performed by Ramesh and Pal which suggested KT as the most common transplants in India followed by LT.[1] An estimated 220,000 people require KT in India as per literature which suggests an unmet need in KT. The number of KTs performed in India are at second place after the USA across the globe.[7]

In India, currently, 90% of KT recipients receive grafts from living donors while 10% grafts are from deceased donors. The current study reported that 91.2% of the KTs were performed from live donors.[7] In recent years, the transplant rate from deceased donors has shown a heartening growth. Deceased donor transplants have increased in India from 196 in 2012 to 570 in 2015.[7] In 2019, a total of 9751 KTs were performed, of which 11.7% were deceased donor KTs and 88.3% were living donor KTs. Of these KTs, majority of the transplant recipients were males (72%) and females constituted 28%.[1] Similarly, in our study, the majority of KT recipients were males (82.8%).

LT is the second most common SOT performed in India.[1] As per Government of India estimates, 0.2 million patients die due to liver failure or liver cancer in a year, of which timely LT can save the lives of about 10-15% patients.[8] In 2019, a total of 2592 LTs were performed, of which 23.1% were deceased donor LTs and 76.8% were living donor LTs. Overall, a total of ~7500 LTs were performed in India till 2016, of which ~80% were from living donor and the remaining were from the deceased donors.[9] A previous study reported that majority of LT recipients were males (74.4%) and females constituted 25.7%.[1] Similarly, in our study, majority of the LT recipients were males (83.7%).

The most common diseases leading to end stage organ disease were diabetes, hypertension, concomitant diabetes and hypertension, chronic kidney disease, nephrotic syndrome, and ESRD in KT recipients. In a retrospective study from India, Jha et al reported that the most common native kidney diseases in KT recipients included diabetic kidney disease, glomerulonephritis and chronic tubulointerstitial disease.[10] In a review, Kelly and Sibal reported that chronic liver failure secondary to cholestatic liver disease and biliary atresia are common indications for LT.[11] In the current study, liver cirrhosis, hepatitis B infection, alcoholic liver disease, fatty liver disease, and NASH were the common indications for LT. Liver cirrhosis, hepatitis infections, alcohol abuse, hepatocellular carcinoma, cholestatic liver disease, and acute hepatic failure are the most common indications for LT as per published literature.[12,13]

The availability of better immunosuppressive regimens has led to a paradigm shift in the transplant outcomes with a lesser incidence of post-transplant complications.[7] TAC, and mycophenolic acid/mycophenolate mofetil (MPA/MMF) with corticosteroids are the commonly used immunosuppressive regimens in KT.[14] European liver transplant registry (ELTR) has reported that TAC-based immunosuppression is associated with improved outcomes in LT recipients.[15] Induction therapy is used to prevent the risk of acute graft rejection, and usually consists of ATG and corticosteroids.[16] In our study, ATG in combination with TAC+MMF+steroid was the most common induction regimen and TAC+MMF+steroid as most common maintenance regimen in KT recipients. In LT recipients, TAC+MMF+steroid was the most common induction and maintenance regimen in our study.

Current study findings interpretation require consideration in view of certain limitations, which include missing data, potential inconsistency in data entry as multiple study centers involved. The overall objective of study was to determine preliminary real-world patterns of utilization of tacrolimus-based immunosuppression in transplant recipients in India. Clinical efficacy and safety of tacrolimus in terms of dosage and drug levels was not a focus of this analysis, and future research is warranted to focus on these parameters.

CONCLUSIONS

This retrospective, observational study reports that tacrolimus-based induction and maintenance immune-suppression regimens are widely used in the real-world clinical practice, in Indian recipients of kidney transplants or liver transplants. There is a need for additional data with longer follow-up periods to explore clinical outcomes in various transplant recipients who may be prescribed tacrolimus-based immune-suppressive therapies.

ACKNOWLEDGEMENTS

The authors would like to thank the study investigators for their contribution.

Funding: Funding by Intas Pharmaceuticals Limited.
Conflict of interest: Dr. Deepak Bunger, Dr. Lav Patel, and Mr. Shreekant Sharma are employees of Intas Pharmaceuticals Limited, Ahmedabad, Gujarat, India
Ethical approval: The study was approved by the ACEAS Independent Ethics Committee, Ahmedabad, India

REFERENCES

1. Ramesh V, Pal C. Organ Donation and Transplantation in India in 2019. Exp Clini Transplantation. 2021;19:1313-21.
2. Grinyó JM. Why is organ transplantation clinically important? Cold Spring Harbor perspectives Med. 2013;3.
3. Health Resources and Service Administration, USA. Organ Donation Statistics. Available at: https://www.organdonor.gov/learn/organ-donation-statistics. Accessed on 25 September, 2022.
4. Enderby C, Keller CA. An overview of immunosuppression in solid organ transplantation. Am J Managed car. 2015;21:s12-23.
5. Prograf (tacrolimus). Northbrook, IL: Astellas Pharma US. 2013.
6. Mathew P, Mandal J, Patel K, Soni K, Tangudu G, Patel R et al. Bioequivalence of two tacrolimus formulations under fasting conditions in healthy male subjects. Clin Therap. 2011;33:1105-19.
7. Shroff S. Current trends in kidney transplantation in India. Ind J Urol. 2016;32:173-4.
8. Directorate General of Health Services. National Organ Transplant Programme. Available at: https://dghs.gov.in/content/1353_3_NationalOrganTransplantProgramme.aspx. Accessed on 25 September, 2022.
9. Narasimhan G, Kota V, Rela M. Liver transplantation in India. Liver Transplantation. 2016;22:1019-24.
10. Jha VK, Mahapatra D, Jairam A, Singh V. Demographic Characteristics, Outcome and Complications of Renal Transplantations at a Tertiary Care Center in South India. J Asso Physicians Ind. 2021;69:28-31.
11. Kelly D, Sibal A. Current status of liver transplantation. Ind J Pediatr. 2003;70:731-6.
12. Finotti M, Auricchio P, Vitale A, Gringeri E, Cillo U. Liver transplantation for rare liver diseases and rare indications for liver transplant. Translational Gastroenterol Hepatol. 2021;6:27.
13. Adam R, Karam V, Cailliez V, JG OG, Mirza D, Cherqui D et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation. Transplant Int. 2018;31:1293-317.
14. Hellemans R, Bosmans JL, Abramowicz D. Induction Therapy for Kidney Transplant Recipients: Do We Still Need Anti-IL2 Receptor Monoclonal Antibodies? Am J Transplantation. 2017;17:22-7.
15. Adam R, Karam V, Delvart V, Trunečka P, Samuel D, Bechstein WO et al. Improved Survival in Liver Transplant Recipients Receiving Prolonged-Release Tacrolimus in the European Liver Transplant Registry. Am J Transplantation. 2015;15:1267-82.
16. Wiseman AC. Induction Therapy in Renal Transplantation: Why? What Agent? What Dose? We May Never Know. Clin J Am Society Nephrol. 2015;10:923-5.

Cite this article as: Patel L, Sharma S, Bunger D. Real-world utilization and acceptance of tacrolimus-based immunosuppression in solid organ transplant recipients in India. Int J Clin Trials 2022;9(4):263-7.