Active surveillance for adverse events among patients who underwent renal transplantation: A prospective observational study

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Abstract

Aim: Renal transplantation is the treatment of choice for end-stage renal disease patients. Renal transplant recipients, however, have to be on lifelong therapy with immunosuppressants, which are associated with a number of adverse events (AEs). The safety profile of these immunosuppressants is not clear with respect to the Indian population. This study was conducted to find the frequency and pattern of all AEs experienced by Indian renal transplant recipients during the initial 3 months posttransplantation.

Methods: Adults undergoing their first renal transplantation were enrolled in the study. All enrolled subjects were followed up for a maximum period of 3 months. All AEs were graded for severity and classified according to the Common Terminology Criteria for AEs criteria.

Results: Ninety-eight renal transplant recipients enrolled in the study. There was a loss of follow-up of 7%. Five subjects died during the study. Subjects experienced an average 9 AEs during the study. There was no difference in frequency of AEs between those on tacrolimus and cyclosporine. Most commonly observed AEs belonged to “Investigational” and “Metabolism and Nutrition” system organ classes. The most common AE was hypokalemia. New-onset diabetes after transplantation (NODAT) developed in 28% of subjects. There were 27 episodes of acute nephrotoxicity.

Conclusion: The incidence of NODAT in the Indian population is substantially higher than that observed in the Western population. The incidence of nephrotoxicity may indicate higher sensitivity of the Indian population to calcineurin inhibitors.

Keywords: Calcineurin inhibitor, diabetes, mycophenolate, nephrotoxicity, renal transplantation, tacrolimus

INTRODUCTION

Chronic kidney disease (CKD) is increasingly being recognized as a global public health problem. The incidence of CKD and end-stage renal disease (ESRD) continues to rise.[1] The prevalence of CKD in the Indian population is not accurately known, though a number of studies in different parts of the country have been done. The estimate...
for various parameters of CKD range from 0.8% for elevated serum creatinine (more than 1.8 mg/dL) to 10% for microalbuminuria in the Indian population.

Although options of maintenance dialysis are available, renal transplantation is the treatment of choice for ESRD patients. To prevent rejection of the graft, immunosuppressive drugs have to be taken by the recipient throughout his lifetime. A combination of a calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate (mycophenolate mofetil or mycophenolate sodium), and prednisolone with or without induction therapy is the current standard of care in these patients.

These immunosuppressive regimens are associated with a number of adverse events (AEs) that include renal toxicity, hyperglycemia, hypertension, osteoporosis, hyperplasia of gums, and hirsutism among others. Inadequate dosing, on the other hand, can result in rejection of the graft. Information on the safety profile of these drugs in the Indian context is inadequate.

The current study was undertaken to find the frequency and pattern of AEs experienced by patients in the initial 3 months postrenal-transplantation surgery.

**METHODS**

This prospective study was conducted at the All India Institute of Medical Sciences (AIIMS), New Delhi, India. Permission from the Institutional Ethics Committee was obtained before commencement of the study. This study was conducted according to the principles of Declaration of Helsinki. This study was not registered with any clinical trials registry since this is a purely observational study.

All adults undergoing first renal transplantation from January 15, 2011, to June 30, 2012, were enrolled. Informed consents were taken from all participants before enrollment in the study. After the surgical procedure, subjects were admitted to the Kidney Transplant Unit (KTU) for 1–2 weeks and thereafter attended the outpatient department (OPD), once a week.

The starting dose of tacrolimus was 0.15 mg/kg per day in two divided doses. Cyclosporine-A was administered at a dose of 6 mg/kg per day in two divided doses. Subsequently, tacrolimus was titrated to a trough level of 8–10 ng/ml, cyclosporine to a C2 level of 1000–1200 ng/ml and the changes in dose made appropriately. Mycophenolate was administered at a dose of 1 g/day in two divided doses for mycophenolate mofetil and 1440 g/day in two divided doses for mycophenolate sodium. All patients received an initial bolus of 500 mg of methylprednisolone followed by oral prednisolone at a dose of 20 mg/day and subsequently tapered from the 2nd week by 2.5 mg every 2 weeks to 10 mg/day by month 3.

Each subject was approached daily when he was admitted to KTU, and once a week when he attended the OPD. Investigations were performed daily in KTU, and once weekly when attending the OPD. Participants were followed for a maximum of 3 months. Only those patients who were lost to follow-up or expired were not followed up to 3 months.

Each subject was enquired about any symptom in general; leading questions were asked later. Further, results of all investigations performed during the study were also noted. If a participant failed to turn up, he/she was contacted telephonically.

Laboratory investigations from day 1 posttransplant were captured and were reported as AEs after comparing with day 1 values.

AE is defined as “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment” International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E2A). New-onset diabetes after transplantation (NODAT) is the emergence of diabetes mellitus in those after transplantation who had no history of diabetes mellitus before transplantation.

Causality assessment of each AE was performed using the WHO-UMC causality assessment scale. The severity of the event was also graded using the Common Terminology Criteria for AEs (CTCAEs) Version 4. Statistical analysis and all visualizations were performed using the Software, R version 3.2.0 (April 04, 2015).

**RESULTS**

There were a total of 98 participants in the study. The baseline characteristics of these participants are displayed in Table 1.

The underlying renal disease was not classified in the majority of subjects. The details are given in Table 2.

Out of the total of 98 subjects, 97 received renal allografts from live donors, and one subject underwent deceased donor transplantation.

Out of the 98 subjects, 29 had a human leukocyte antigen (HLA) mismatch of 0/6 and 13 subjects had an HLA
mismatch of 6/6. HLA mismatches of 1–5 were seen in 8, 13, 17, 7, and 11 subjects, respectively.

Of the 98 participants, there was loss of follow-up in seven participants. Eighty-six participants completed the follow-up period of 3 months, and five participants died during the study.

**Immunosuppressive regimen**
 Of the 98 subjects, 84 were under an immunosuppressive regimen consisting of mycophenolate mofetil, tacrolimus, and prednisolone. The rest of the 14 patients were under a regimen of enteric-coated mycophenolate sodium, cyclosporine, and prednisolone. Induction therapy was not administered to the participants.

**Adverse events**
 A total of 837 AEs were observed, which means a subject experienced on an average, 9 AEs in the first 3 months posttransplantation. The mean number of AEs experienced by patients on a tacrolimus and cyclosporine-based regimen was 8.4 and 9, respectively. There was no significant difference in frequency of AEs between the two groups (P > 0.05 with unpaired t-test). All AEs were graded on severity according to CTCAE, version 4. Twenty one % of all AEs were of Grade 3. Four AEs were of Grade 4. Most AEs occurred during the initial few days posttransplantation [Figure 1]. Nearly 45% of all AEs occurred in the 1st week. More than 20% of all AEs were high grade (Grade 3 and higher). All AEs were assessed for causality using the WHO-UMC Causality assessment algorithm. Nearly 97% of all AEs were categorized as “possible” and the remaining were categorized as “probable.”

**Mortality**
 Five participants died during the study. One subject died within 24 h of transplantation consequent to an acute coronary event. Two subjects died as a result of surgical complications. One subject died as a result of a number of complications (acute on chronic graft dysfunction, cytomegalovirus (CMV), and BK virus (BKV) infections). One subject had graft failure and was on hemodialysis and died outside the hospital.

**Adverse events-system organ class wise**
 All AEs were classified into system organ classes (SOCs) according to CTCAE, Version 4. More than half of all AEs belonged to the two SOCs, investigational (28%) and metabolism and nutritional disorders (27%) combined. The distribution of AEs based on SOC is described in Table 3.

**Immune-system disorders system organ class**
 Graft biopsies were done in 13 participants. Biopsy proven acute rejection (BPAR) was diagnosed in 6 participants. One episode occurred within the 1st week posttransplantation. Two episodes occurred in the 2nd and 3rd weeks posttransplantation. Three episodes occurred after the 1st month. All these episodes were treated with...
boluses of injection methyl prednisolone for 3 days with subsequent increase in immunosuppressive therapy.

Biopsy revealed one episode each of acute tubular necrosis (ATN), transplant glomerulopathy, acute tubular injury, drug-induced acute interstitial nephritis (AIN), and three nonspecific changes. The patient who was diagnosed with drug-induced AIN was administered methyl prednisolone and responded well. The patient diagnosed with ATN was treated with injection rabbit-anti-thymocyte globulin due to suspicion of acute rejection and subsequent lowering of dose of tacrolimus.

In addition, acute cellular rejection was suspected in three patients and was administered methyl prednisolone without confirmation with a biopsy.

**Investigation system organ class**

About 28% of all AEs observed, were investigational abnormalities. These AEs were incidentally discovered not due to complaints by patients but observed from laboratory investigations.

The most frequently observed “investigational” AEs were “total protein decreased,” “alanine aminotransferase increased,” and “aspartate aminotransferase increased.” Most AEs of this SOC were of the milder Grade 1 (signifying asymptomatic or mild symptoms). Around 20% of AEs of this SOC, however, were severe in grade (Grade 3 and 4).

**Metabolism and nutrition disorders system organ class**

AEs of this SOC were also seen very frequently (27.9% of all AEs). Hypokalemia was the most frequently observed AE (48 episodes) overall. The other AEs of this SOC that were observed with high frequency were “hypocalcemia,” “hyponatremia,” “hypoalbuminemia,” “hypophosphatemia,” “NODAT,” “hyperkalemia,” and others, in decreasing order of frequency. The majority of adverse drug reactions (ADRs) of this SOC were mild (Grade 1).

**New onset diabetes after transplantation**

This is a known ADR of calcineurin inhibitors (CNIs). There were 24 cases of NODAT in the course of the study. This means that 28% of those who were non-diabetics before transplantation developed diabetes mellitus subsequent to transplantation. Four of the 14 patients (28.5%) on cyclosporin-based therapy and 20 of the 84 patients (23.8%) on tacrolimus-based therapy developed NODAT. There was no significant difference between the two groups. Similarily, out of the 12 subjects who were positive for hepatitis-c before the study, four developed NODAT. However, all 12 hepatitis-C-positive subjects were under a cyclosporine-based immunosuppressive therapy. Of the 24 patients who developed NODAT, only one patient had a history of methylprednisolone administration for the management of rejection. Furthermore, among the nine patients who were administered methylprednisolone for the management of acute cellular rejection, only one patient developed NODAT.

**Gastrointestinal disorders system organ class**

Gastrointestinal disorders were also observed in high frequency. A total of 71 gastrointestinal AEs were observed during the study. Dyspepsia, diarrhea, abdominal pain, and constipation were the most commonly observed gastrointestinal AEs (decreasing orders of frequency) in the study. There were 21 episodes of diarrhea reported during the study. All these episodes were mild to moderate in grade (Grade 1 or 2).

**Renal and urinary disorders system organ class**

Perhaps the most clinically relevant AEs are those that affect the renal graft.

This SOC includes CNI nephrotoxicity, which affects the renal graft and is a well-known adverse effect of tacrolimus and cyclosporine.

A total of 27 episodes of nephrotoxicity were observed during the study. The diagnosis of CNI toxicity was confirmed in all episodes with serum drug (tacrolimus or cyclosporine) levels, which was further corroborated when the toxicity was reversed when the regimen was appropriately modified. Biopsy was not performed for the diagnosis of CNI nephrotoxicity.

Thirteen episodes of transient deterioration of renal function were reported for which no apparent cause was
attributable. The serum drug levels in these patients were either in the normal range, or there was no information of drug levels. There was also spontaneous improvement noticed despite no alteration in the dosage regimen. Further, two episodes of acute tubular injury and one episode of AIN were also observed.

**Infections and Infestations system organ class**

Another area of concern is infections due to immunosuppression. The most frequently observed infections in this study were urinary tract infections (16 episodes), Enteric infections (15 episodes), and rhinitis (11 episodes). There were three episodes of CMV infection; one each of BKV, herpes zoster, herpes labialis, herpes stomatitis, recurrent varicella zoster, lower respiratory tract infection, and lung abscess.

**DISCUSSION**

This is the first time that a pharmacovigilance study has been done in patients undergoing renal transplantation in the Indian context and all AEs regardless of clinical severity have been captured.

Although the incidence of BPAR in this study of 6.1% appears to be low, it cannot be compared to previous studies which report more than 10% at 6 months, since these studies are not comparable due to the differences in follow-up period and other methodological differences. This also might be due to predominance of live related renal donors at our center and subsequently low level of HLA mismatches and low panel-reactive antibodies levels.

However, the incidence of NODAT according to our study was substantially higher at 28%, and this too is based on data for only up to 3 months posttransplantation. According to evidence published outside India, the incidence of NODAT ranges from 4% to 25%. This variation being probably due to different criteria used for the diagnosis of NODAT.\[5-8\] According to a meta-analysis, the incidence of NODAT was found to be 12.9% among those under a tacrolimus-based regimen within 1 year posttransplantation. However, the criteria used to define NODAT in this meta-analysis were the requirement of insulin therapy for at least 30 days in those with no history of diabetes. Further, evidence suggests that risk of NODAT increases progressively with time.\[9\]

There are a couple of studies conducted in India to find out the prevalence of NODAT. One of these, a retrospective study reported incidences of glycemic metabolic abnormalities and drug therapy requiring hyperglycemics of 54.5% and 32.7%, respectively. The other Indian study\[11\] reported an incidence of NODAT at 16.7% at 1 year among patients on a tacrolimus-based therapy. In this study, the criteria was the requirement of any antidiabetic pharmacotherapy (oral or insulin therapy) among those with no history of diabetes.

The high incidence of NODAT could partly be explained by higher prevalence of patients with hepatitis C infection.\[12\]

Since genetic predisposition to NODAT is well known, preliminary data from our and various other studies from our country would suggest that our population is genetically predisposed to NODAT. This, however, needs to be confirmed by larger multicenter studies. This is particularly important since NODAT is associated with increased risk for graft-related complications such as rejection, graft loss, and infections and may reduce survival of graft recipients.\[17-20\]

The incidence of renal toxicity due to calcineurin inhibitors as confirmed by biopsy or elevated drug levels associated with renal dysfunction in our study was nearly 28% which appears substantial in spite of using CNIs in the recommended dosages. Although there is no similar data from other centers in our country, this might indicate higher sensitivity of our population to CNI toxicity. This would indicate need for larger multicentric trials to establish ideal CNI levels in our population. A few studies have reported that CYP3A4 and CYP3A5 gene polymorphisms may be associated with tacrolimus levels. This may have to be explored in the Indian population.

There were 8 episodes of opportunistic infections in our study population. According to previous studies, the incidence of opportunistic infections over the 1st year posttransplantation was around 25%.\[21\] No direct comparison is possible since the data of our study is based only on the initial 3 months posttransplantation.

In this study, there were 71 episodes of gastrointestinal events, which appears to be higher as compared to previous studies.\[21\] The incidence of diarrheal episodes though does not appear to be high.

This study has tried to capture all AEs, irrespective of severity and grade. According to previous studies, AEs belonging to “Metabolism and Nutrition” were the most frequent in the early posttransplantation period. A similar picture was observed in our study in which “Investigational” and “Metabolism and Nutrition” adverse effects were observed most frequently, especially in the 1st week posttransplantation. This study shows
that a lot of laboratory abnormalities occur in the initial weeks posttransplantation. However, there seem to be no short-term implications of these abnormalities. This is expected since the kidney is responsible for regulation of electrolytes, and the fact that it is in the immediate postsurgical period.

**CONCLUSION**

In this prospective study, conducted on Indian renal transplant recipients, we found that “Investigational” and “Metabolism and Nutrition” AEs were most commonly seen, but were less relevant since they resolved spontaneously.

This study indicates that the incidence of NODAT is higher among Indian recipients. Further, risk factors of NODAT will also have to be studied so as to devise ways to reduce or manage its occurrence.

In view of the significant problem of calcineurin-induced nephrotoxicity, we need to revisit the dose of calcineurin inhibitors, and further studies may be required to explore this aspect.

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**Conflicts of interest**

There are no conflicts of interest.

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