A study of adverse events associated with the use of 
Immunosuppressive agents in kidney transplanted Patients

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Abstract
Introduction: Kidney transplantation provides a life 
saving treatment for patients with End Stage Renal 
Disease (ESRD). But total success after transplantation is 
hugely dependent on proper course of immunosuppressive 
therapy. The rationale behind this study was to monitor, 
analyse, and evaluate the AEs and ADRs associated with 
immunosuppressive drugs and to document the 
pharmacotherapeutic actions taken for its management.
Methodology: The study was Retrospective and medical 
data of all patients (as per inclusion/exclusion criteria) 
admitted during the Study Period was analysed.
Results: A total of 95 patients were enrolled in the study and 
incidence rate of patient affected due to ADR was found to be 
75.78 % and overall 352 AEs were documented. Causality and 
Severity assessment of ADRs were done which showed 
Probabale (47), and Moderate (47) respectively. Out of 84 
ADRs, 80 ADRs were Not preventable. Furthermore 
significant relation was observed (p<0.005) among various 
factors, drugs and suspected ADRs.
Conclusion: The results of this study show that 
immunosuppressive drugs may cause serious and frequent 
adverse effects. So, special monitoring and regular follow up 
of patients are required to minimise the risk and frequency of 
these adverse effects.

Key words:
Immunosuppressive Drugs, Adverse Effects

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Introduction:
Kidney transplantation (KT) is treatment of choice 
for patients suffering from End Stage Renal Disease, 
(ESRD). But to prevent the patient life, after
transplantation the foremost requirement is a well defined immunosuppressive therapy. By various epidemiological studies it has been found that in 2004 a total of 26,539 solid organ transplantations were performed in which Kidney transplants were most common; 9,025 from cadaveric donors and 6,646 from living donors.[1] Because of long term graft survival and graft function, KT is more cost effective alternative to a regular dialysis process to which a patient with chronic kidney disease or ESRD need to go frequently. Currently in the United States, more than 100,000 persons are living with functioning kidney transplant, this number represents 27% of the nearly 350,000 persons enrolled in the US ESRD program.[2] There are many factors which cause permanent renal failures in human beings and these are listed in Table 1.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Patients, No.</th>
<th>Patients With Functioning Transplants, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>102.9</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70.4</td>
<td>16</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>48.1</td>
<td>45</td>
</tr>
<tr>
<td>Cystic kidney</td>
<td>13.0</td>
<td>52</td>
</tr>
<tr>
<td>Other urologic causes</td>
<td>6.1</td>
<td>30</td>
</tr>
<tr>
<td>Other causes</td>
<td>12.3</td>
<td>37</td>
</tr>
<tr>
<td>All</td>
<td>346.5</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 1: Causes of Chronic Renal Failure and Percentage of Functioning Renal Transplants in the United States (1997).[2]

Immunosuppressive agents
As clear from their names these are the agents which suppress the immune system in human beings. It is generally achieved by depleting lymphocytes, diverting lymphocyte traffic, or blocking lymphocyte response pathways. Immunosuppressants generally have multiple actions including therapeutic effect (suppressing rejection), infection or cancer (secondary effect of immunosuppression) and toxicity to other tissues. [3]

Classification of Immunosuppressive Drugs
They include small molecule drugs, depleting and non depleting protein drugs (polyclonal and monoclonal antibodies), fusion proteins, intravenous immunoglobulin, and glucocorticoids. The Table 2 shows the classification of immunosuppressive agents which are generally used in solid organ transplantation.[4]

- **Calcineurin inhibitors (Specific T-cell inhibitors)**
  - Cyclosporine, Tacrolimus

- **Drugs acting on Target of Rapamycin**
  - Sirolimus

- **Antiproliferative Drugs**
  - Azathioprine, Mycophenolate mofetil (MMF), Methotrexate.

- **Antibodies**
  - Muromonab CD3, Antithymocyte globulin (ATG).

- **Corticosteroids**
  - Methyl prednisone, Prednisolone.

Table 2: Classification of immunosuppressive agents[4]

General approach of immunosuppressive therapy
Generally the multi drug regimen is followed which allow the use of low doses of individual agents, thus reducing the severity of dose related adverse effects. The protocols and individual drug regimen tend to be centre specific which may vary to different hospitals. The centre specific protocols generally combine a drug from two or three of the following classes: calcineurin inhibitors, antimetabolites or sirolimus, and corticosteroids.

When rejection is suspected the graft biopsy is generally done to confirm that and empirical treatment is started which involves high doses of corticosteroids mainly 500mg to 1000mg of methyl prednisolone i.v. for one to three doses. If sign and symptoms seem to be improved then induction therapy is modified to provide greater level of overall immunosuppressant.[6]

Types of Immunosuppressive therapies
Immunosuppressive therapies can be sub-divided in to following types.
1. Induction Therapy
2. Maintenance Therapy
3. Therapy for Acute rejection.

Induction Therapy
The main aim of this therapy is to provide high level of immunosuppression, as to prevent the graft from body early immune response. It consists of one of two perioperative immunosuppressive strategies:
A. The provision of highly intense level of immunosuppression either universally on the basis of patient risk factors like age, race etc.
B. The use of antibody therapy to provide enough immunosuppression is to delay the initiation of therapy with nephrotoxic calcineurin inhibitors.
The above (B) practice is generally followed in renal transplanted patients in whom newly transplanted kidney is highly susceptible to nephrotoxic injury, where in liver and heart transplanted patients the rationale of using this practice is to protect them with pre-existing renal insufficiency from further injuries.[5]

Maintenance Therapy
The goal of this therapy is to provide low or moderate level of immunosuppression while saving graft from rejection. Therapy typically involves a calcineurin inhibitor, glucocorticoids and anti-proliferative drug like mycophenolate mofetil.[6]

Anti-Rejection Therapy
The prime aim of this therapy is to minimize the immune response so that to prevent the graft from injury. The therapy generally started with pulse therapy of methyl prednisolone, with or without subsequent increase in doses of ongoing immunosuppressive regimen of patient.
Generally the acute rejection is reversed with three to four doses of methyl prednisolone but some cases are less responsive to this therapy so subsequently antibodies like Anti Thymocyte Globulin (ATG) or Muromonab.[1]

Objectives:
1. Primary Objective:
   ➢ To study the pattern of adverse events associated with use of immunosuppressive agents.
   ➢ To carry out the causality, preventability and severity of reported Adverse Drug Event.
2. Secondary Objectives
   ➢ To observe the actions taken by the medical practitioner for managing ADRs.
   ➢ To study the prescribing pattern of immunosuppressive drugs

Rationale of the Study
Since immunosuppressive agents are fore most and lifelong requirement after a transplant and as they suppress the immune system so, these drugs are associated with ample of adverse effects so the purpose of the study was to determine the types of adverse events with immunosuppressants in patients with KT and also to determine the frequency of the adverse events and further to extract Adverse Drug Reactions (ADRs) from the documented Adverse Events (AEs). Besides this, the study also focused on prescribing pattern of these drugs and management of the ADRs.

Material And Methods

Material
Various scales have been used in the study which is following:
1. Naranjo Scale
2. Modified Schumock and Thorton Scale
3. Modified Hartwig and Seigel scale
4. Case Record Form
5. SPSS version 20.0

Methods

Study Design:
The study was Retrospective, in which data of all the in-patients (as per inclusion/exclusion criteria) was recorded from the Medical Record Department who were admitted during the study period. The permission for this had been granted by the hospital administration.
Study Site:
The study was undertaken at a Tertiary Care Hospital, New Delhi.

Study Duration:
The study was conducted over a period of Nine months i.e. from August 2011 to April 2012.

Study Population:
The study population was selected by following inclusion and exclusion criteria.

1. Inclusion criteria
   - Kidney transplanted patients receiving immunosuppressive agents.

2. Exclusion Criteria
   - Patients with Hyperacute rejection.

Sample Size: 95 patients

Data collection and analysis:
The data was collected in a well designed Case Record Form (CRF), in which all the essentials particulars have been included to ease the further analysis of the data.

Collected data was analyzed for types of AEs and ADRs. The causality assessment was done by using Naranjo Scale. The severity and preventability assessment was done by using Modified Hartwig and Seigel scale and Modified Schumock and Thorton Scale. The data was evaluated statistically using SPSS to determine the association between the most frequent ADRs and drugs and with co-morbid conditions. A p-value of less than 0.05 was considered as statistically significant.

Results

Patient Demographics:
Out of total patients enrolled, Male predominates over female.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>66 (69.2)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (30.8)</td>
</tr>
</tbody>
</table>

Table 3: Gender Distribution

Age and Weight distribution

Table 4 and 5 shows the age and weight distribution pattern of study population, the most frequent subjects were in 46-60 years and 61-70 kg weight respectively.

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>1 (1.05)</td>
</tr>
<tr>
<td>15-30</td>
<td>22 (23.15)</td>
</tr>
<tr>
<td>31-45</td>
<td>24 (25.2)</td>
</tr>
<tr>
<td>46-60</td>
<td>38 (40)</td>
</tr>
<tr>
<td>61-75</td>
<td>10 (10.52)</td>
</tr>
</tbody>
</table>

Table 4: Age Distribution

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>6 (6.31)</td>
</tr>
<tr>
<td>51-60</td>
<td>14 (14.73)</td>
</tr>
<tr>
<td>61-70</td>
<td>41 (43.15)</td>
</tr>
<tr>
<td>71-80</td>
<td>27 (28.42)</td>
</tr>
<tr>
<td>81-90</td>
<td>7 (7.36)</td>
</tr>
</tbody>
</table>

Table 5: Weight Distribution

Co-morbidity:
Following Co-morbidities were found among the study population

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (HTN) (Only)</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes Mellitus (DM) (Only)</td>
<td>15</td>
</tr>
<tr>
<td>DM + HTN</td>
<td>20</td>
</tr>
<tr>
<td>DM + Hypothyroidism</td>
<td>4</td>
</tr>
<tr>
<td>DM + HTN + Hypothyroidism</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 6: Co-morbidity in KTs patients

Indications for Kidney Transplants (KTs):
These were the etiologies for KTs in which most frequent was Diabetes induced nephropathy (37.98%), followed by Hypertension induced nephropathy (29.47%).

<table>
<thead>
<tr>
<th>Indications</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM related Chronic Kidney Diseases (CKD)</td>
<td>36</td>
<td>37.98</td>
</tr>
<tr>
<td>HTN related CKD</td>
<td>28</td>
<td>29.47</td>
</tr>
<tr>
<td>DM + HTN related CKD</td>
<td>22</td>
<td>23.15</td>
</tr>
<tr>
<td>Autoimmune CKD</td>
<td>6</td>
<td>6.31</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>3.15</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Table 7: Indication for KTs
Figure 1: KT’s Indications

Incidence Rate

Among the study population 352 AEs were documented out of which 84 ADRs were extracted out. These ADRs were reported in 72 patients so; Incidence rate of patient affected due to ADR was calculated to be 75.78%.

Incidence of patients affected due to ADRs:

- Total number of patients reported ADRs
- Incidence rate among Males was found more (78.78%) than compare to females (68.96%).

Types and Frequency of ADRs:

- Out of 352 AEs, 84 ADRs were extracted out after causality assessment.
- The ADRs have been categorized according to their frequency and incidence rate of patients affected.
- ADRs with Frequency 1 and Incidence Rate 1.35%

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Frequency</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Transplant Lymphoproliferative disorder (PTLD)</td>
<td>Cyclosporine + MMF + Prednisolone</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Sirolimus</td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>Leg Cellulitis</td>
<td>Tacrolimus + MMF + Prednisolone</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>MMF</td>
<td></td>
</tr>
</tbody>
</table>

Table 8: ADRs with Frequency 1

ADR with Frequency 2 and Incidence Rate 2.77%

Table 9: ADRs with Frequency 2

ADR with Frequency 3 and Incidence Rate 4.16%

Table 10: ADRs with Frequency 3

Other ADRs which were having higher frequencies and incidence rates are tabulated here.

Table 11: ADRs with Higher Frequencies

Frequency of ADRs in Different Age groups:

As age plays a major role in happening of ADRs in patients so, ADRs are categorized according to the Age group in which mostly affected group was 46-60 years followed by 31-45 years. No ADR was found in age group below 15 years.

Table 12: Frequency of ADRs in different Age groups.
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Frequency of ADRs with Major Immunosuppressants:
Tacrolimus and MMF were having the higher numbers of ADRs though they were most frequently prescribed drugs which will be discussed in prescription pattern further in this article.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>40</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>4</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>22</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 13: Frequency of ADRs with Major Immunosuppressants

Analysis of ADRs:
ADRs were analyzed for their Causality, Severity and Preventability assessment by using various scales viz. Naranjo Algorithm for ‘causality’ assessment, Modified Hartwig and Seigel scale for ‘severity’ assessment, and Modified Schumock and Thornton scale for ‘preventability assessment.

Causality Assessment:
Most of the ADRs were ‘Probable’, means fair relationships with drugs actually exist, followed by Possible.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>4</td>
</tr>
<tr>
<td>Probable</td>
<td>47</td>
</tr>
<tr>
<td>Possible</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 14: Causality Assessment

Severity Assessment:
Mostly ADRs were Moderate, and One ADR was found to be severe in nature which was life threatening.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>49</td>
</tr>
<tr>
<td>Moderate</td>
<td>34</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 15: Severity Assessment

Preventability Assessment:
After preventability assessment, 95.23% of ADRs were found to be ‘Not preventable’.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely preventable</td>
<td>0</td>
</tr>
<tr>
<td>Probable preventable</td>
<td>4</td>
</tr>
<tr>
<td>Not preventable</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 16: Preventability Assessment

Relationship among Most Common ADRs with Major Immunosuppressants Prescribed:
A significant association was found among Tacrolimus and Major ADRs like Neurotoxicity, and Nephrotoxicity and Cyclosporine with Nephrotoxicity.
Drugs | Most Common ADRs | p-value, Chi-square
--- | --- | ---
Tacrolimus | Neurotoxicity | 0.048, 3.918
 | Nephrotoxicity | 0.001, 11.161
Cyclosporine | Nephrotoxicity | 0.000, 48.722
MMF | Anaemia | 0.797, 0.066
 | Pancytopenia | 0.787, 0.073
 | Thrombocytopenia | 0.678, 0.172

Table 17: Association of ADRs with immunosuppressants

Management of ADRs:
For managing ADRs, physicians gave symptomatic treatment in majority of cases besides continuing immunosuppressive therapy and drug withdrawn was only done in two cases.

<table>
<thead>
<tr>
<th>Action Taken</th>
<th>Frequency of ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Withdrawn</td>
<td>2</td>
</tr>
<tr>
<td>Dose Reduced</td>
<td>18</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>43</td>
</tr>
<tr>
<td>No Action Taken</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 18: Management of ADRs

Prescription pattern:
Immunosuppressive agents are prescribed as per departmental protocol and according to the type of therapy i.e. Induction, Maintenance etc. Here also, the Tacrolimus containing regimen was most frequent in both the therapies and Sirolimus was prescribed in few.

**Induction Therapy Regimen:**

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus + MMF + Prednisolone</td>
<td>75</td>
</tr>
<tr>
<td>Cyclosporine + MMF + Prednisolone</td>
<td>17</td>
</tr>
<tr>
<td>Sirolimus + MMF + Prednisolone</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 19: Prescription pattern for Induction therapy

**Maintenance Therapy Regimen:**

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus + MMF + Prednisolone</td>
<td>73</td>
</tr>
<tr>
<td>Cyclosporine + MMF + Prednisolone</td>
<td>15</td>
</tr>
<tr>
<td>Sirolimus + MMF + Prednisolone</td>
<td>5</td>
</tr>
<tr>
<td>Tacrolimus ± Sirolimus + Prednisolone</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 20: Prescription pattern for Maintenance Therapy

Discussion:
ADRs are one of the prime concerns to deal with while treating the patients with drugs. They are making a huge impact on patients’ life both by financially and in terms of quality of life. Immunosuppressive drugs act by suppressing the immune system of human beings which itself is the leading factor for various adverse drug reaction and moreover, therapy starts when body still needs to recover from its native kidney failure which also play the additive role in precipitating ADRs.

In our study, the Incidence rate of patient affected with ADRs was found to be 75.78% which is quite high, though comparison of this data cannot be done effectively because very little studies have been done so far for this class of drugs but when we compare with the other ADRs monitoring studies, our incidence rate is really high than the studies by Benkirane et al [7] and Nicholas Moore [8] which shows only 15.5% and 9.42% respectively. The main reason of these differences could be because of several pathological changes that occur in patient due to End stage Renal Disease (ESRD).

Calcineurin Inhibitors are famous for their nephrotoxic potential and this was also seen in our study where all reports of Nephrotoxicity was related to either Cyclosporine or Tacrolimus, studies from Robert F. English et al [9] and Busauschina A. et al [10] support this statement.

One of the serious and life threatening condition was PTLD which was observed in single patient who was receiving the immunosuppressive therapy for last four years, but this complication is result of overall immunosuppression as several studies have done on it and no one could blame a single immunosuppressant like in a study by Funch et al [11] on 108 PTLD cases where he concluded that MMF was not associated with increased risk in PTLD.
among patients who received triple immunosuppressive therapy.

A significant correlation of Neurotoxicity (p= 0.048) and Nephrotoxicity (p=0.001) with Tacrolimus and Nephrotoxicity (p=0.000) with cyclosporine was found out, as same has also been confirmed in other studies for respective drugs. Thrombocytopenia and Pancytopenia in our study was related to MMF though there was not a statistically significant relationship. A very few studies are there to support this, yet a global pharmacovigilance system says that 2.05% of transplanted patients experienced Pancytopenia with MMF and in those 65.28% experienced in initial days of therapy i.e. before one month as same in our study, in which most of the cases were observed during induction therapy.

After causality assessment, 47 ADRs were ‘Probable’, out of 84, and preventability assessment showed that most of the ADRs i.e. 80 were ‘Not Preventable’ which means that it’s very difficult to avoid ADRs with Immunosuppressive drugs. Forty Nine ADRs were ‘Mild’ in Severity followed by ‘Moderate which were thirty four. 

The above data cannot be compared with other studies as no study has been done so far of this kind. In management of ADRs, Symptomatic treatment was provided in majority of the cases i.e. in 43 cases out of 84, while Drug withdrawn was done only with two cases this shows that Immunosuppressive drugs are integral part of post-transplant therapy required to prevent graft rejection, so they are withdrawn when risk seriously outweighs the benefit or patient is not able to sustain with it.

The prescription pattern of immunosuppressive drug was as per the departmental protocol which has been shown in results; although Tacrolimus and Sirolimus combined immunosuppression was given in couple of patient. Among them one patient was less responsive to tacrolimus regimen so Sirolimus was added to his regimen but that lead to further increase in serum creatinine levels and wound healing complications so, Sirolimus was withdrawn later on. In another patient Sirolimus was introduced in Maintenance therapy replacing MMF because it induced the diarrhea but in this case no such complications were found. Two such studies are there which have different views regarding this combined immunosuppression as found in our study, one study by Smith K.D. et al [12] conclude that combined sirolimus and tacrolimus therapy leads to increased incidence of delayed graft function and retards wound healing. A different study conducted by McAlister VC et al [13] on thirty two recipients of liver, kidney, and pancreatic transplants who were treated with this combined immunosuppression experienced low rate of rejection and excellent graft function without drug related toxic effects.

Our study has its own limitations since it was retrospective, so the AEs or ADRs which were skipped by the physicians to write on medical sheets could not be documented and further patients could not be followed up further so the chronic effects of immunosuppression were not documented well.

Conclusion:
This study provides the generalized and preliminary information about the type and frequencies of ADRs associated with immunosuppressive drugs in KT's recipients. As most of the ADRs were not preventable so, this shows that its very difficult to avoid the occurrence of ADRs as most of them were Not-preventable though physicians have done fair job in delaing with them either by providing symptomatic treatment or by modifying the doses and regimens. This study is unique in its own, since very few studies have been done which covers all immunosuppressive regimens and drugs and AEs & ADRs related to them, and this study may be helpful for planning the induction therapies as ADRs occur more frequently during this time.
References: