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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.

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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.

Cause	Patients, No.	Patients With Functioning Transplants, %
Diabetes	102.9	17
Hypertension	70.4	16
Glomerulonephritis	48.1	45
Cystic kidney	13.0	52
Other urologic causes	6.1	30
Other causes	12.3	37
All	346.5	29

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 immuneglobulin, 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.[1]

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 the 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.

Gender	Number (%)
Male	66 (69.2)
Female	29 (30.8)

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.

Age (in years)	Number (%)
<15	1 (1.05)
15-30	22 (23.15)
31-45	24 (25.2)
46-60	38 (40)
61-75	10 (10.52)

Table 4: Age Distribution

Weight (kg)	Number (%)
<50	6 (6.31)
51-60	14 (14.73)
61-70	41 (43.15)
71-80	27 (28.42)
81-90	7 (7.36)

Table 5: Weight Distribution

Co-morbidity:

Following Co-morbidities were found among the study population

Co-morbidity	Frequency
Hypertension (HTN) (Only)	42
Diabetes Mellitus (DM) (Only)	15
DM + HTN	20
DM + Hypothyroidism	4
DM + HTN + Hypothyroidism	5
Others	6

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%).

Indications	Frequency	Percent
DM related Chronic Kidney Diseases (CKD)	36	37.98
HTN related CKD	28	29.47
DM + HTN related CKD	22	23.15
Autoimmune CKD	6	6.31
Others	3	3.15
Total	95	100 %

Table 7: Indication for KTs

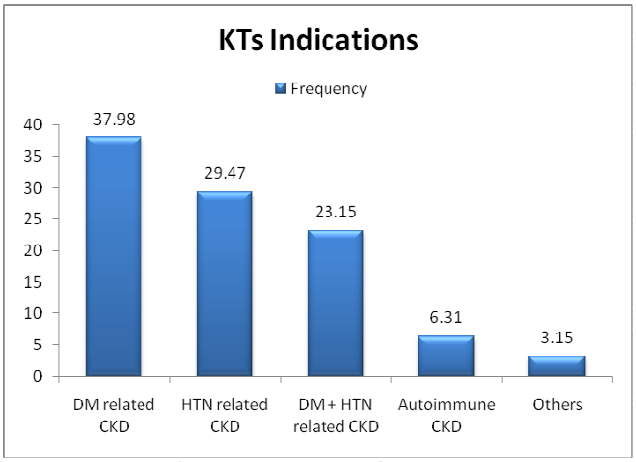

Figure 1: KT's Indications

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:

$$\frac{\text{Total number of patients reported ADRs}}{\text{Total number of patients}} \times 100$$

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 %

ADRs	Drugs involved
Post Transplant Lymphoproliferative disorder (PTLD)	Cyclosporine + MMF + Prednisolone
Hyperkalemia	Sirolimus
Itching	Tacrolimus
Leg Cellulitis	Tacrolimus + MMF + Prednisolone
CMV	MMF

Table 8: ADRs with Frequency 1

ADRs with Frequency 2 and Incidence Rate 2.77 %

ADRs	Drugs Involved
Hepatotoxicity	Tacrolimus
Leucopenia	Tacrolimus + MMF + Prednisolone
Oral Thrush	Tacrolimus + MMF + Prednisolone , Cyclosporine + MMF + Prednisolone
Metabolic Acidosis	MMF
Seizures	Tacrolimus
Wound Healing Complication	Sirolimus

Table 9: ADRs with Frequency 2

ADRs with Frequency 3 and Incidence Rate 4.16%

ADRs	Drugs Involved
Anaemia	Tacrolimus, MMF
Pancytopenia	MMF
Hyponatremia	Tacrolimus
Agitation	Prednisolone
UTI	Tacrolimus + MMF + Prednisolone
Sleeplessness	Tacrolimus
PTDM	Tacrolimus, Prednisolone

Table 10: ADRs with Frequency 3

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

ADRs	Frequency	Incidence Rate	Drugs Involved
Psychosis	4	5.55	Prednisolone
Headache	6	8.33	Tacrolimus
Thrombocytopenia	7	9.72	MMF
Diarrhea	8	4.05	Tacrolimus, MMF
Tremors	10	13.88	Tacrolimus
Nephrotoxicity	11	15.27	Tacrolimus, Cyclosporine

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.

Age	Patients with ADRs (%)	Patients without ADRs (%)	Total
<15	0 (0%)	1 (100%)	100%
15-30	12 (54.54 %)	10 (45.45%)	100%
31-45	21 (87.50 %)	3 (12.50%)	100%
46-60	36 (94.73%)	2 (5.27 %)	100%
61-75	9 (90%)	1 (10%)	100%

Table 12: Frequency of ADRs in different Age groups.

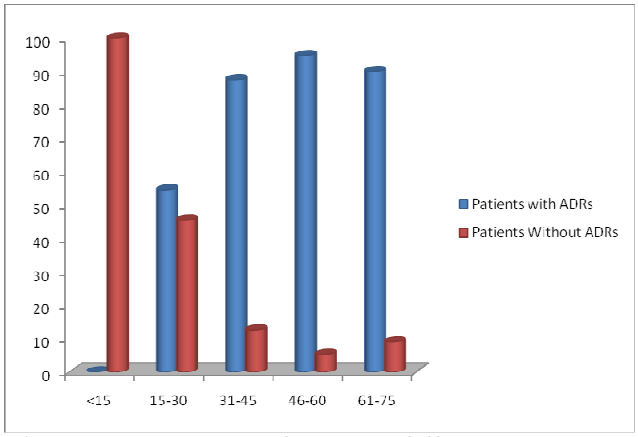

Figure 2: Frequency of ADRs in different age groups

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.

Drugs	Frequency
Tacrolimus	40
Sirolimus	4
Mycophenolate Mofetil	22
Cyclosporine	5
Prednisolone	13

Table 13: Frequency of ADRs with Major Immunosuppresants

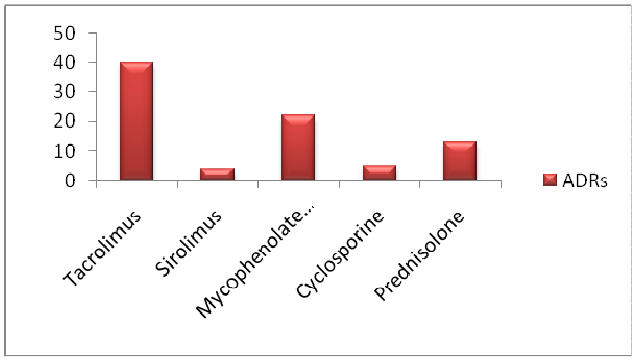

Figure 3: Frequency of ADRs with Major Immunosuppresants

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 Thorton scale for 'preventability assessment.

Causality Assessment:

Most of the ADRs were 'Probable', means fair relationships with drugs actually exist, followed by Possible.

Parameters	Frequency
Definite	4
Probable	47
Possible	33
Total	84

Table 14: Causality Assessment

Severity Assessment:

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

Parameters	Frequency
Mild	49
Moderate	34
Severe	1
Total	84

Table 15: Severity Assessment

Preventability Assessment:

After preventability assessment, 95.23% of ADRs were found to be 'Not preventable'.

Parameters	Frequency
Definitely preventable	0
Probable preventable	4
Not preventable	80
Total	84

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 immunosuppresants

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.

Action Taken	Frequency of ADR
Drug Withdrawn	2
Dose Reduced	18
Symptomatic	43
No Action Taken	21
Total	84

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:

Regimens	Number of Patients
Tacrolimus + MMF + Prednisolone	75
Cyclosporine + MMF + Prednisolone	17
Sirolimus + MMF + Prednisolone	3

Table 19: Prescription pattern for Induction therapy

Maintenance Therapy Regimen:

Regimens	Number of Patients
Tacrolimus + MMF + Prednisolone	73
Cyclosporine + MMF + Prednisolone	15
Sirolimus + MMF + Prednisolone	5
Tacrolimus ± Sirolimus + Prednisolone	2

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 acts 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 KTs 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.

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