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Augmented Tacrolimus Toxicity - A Consequence of Concomitant Drug-Drug Interaction in Adult Kidney Transplant Recipients

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Abstract: ***Introduction**: Adult kidney transplant recipients(KTRs) require long term immunosuppressant drugs to ensure graft viability in vivo. Along the course of their disease and its management, their quality of life is riddled by intermittent illnesses that crop up. The concomitant medicationsused to treat these ailments pave way to a multitude of possible drug interactions, resulting either in immunotherapeutic ineffectiveness or toxicity. This study intends to determine the Temporal/ Causal relationship, Preventability and Severity of ADRs reported following administration of concomitant medicaments in adult KTRs. **Methodology**: Adult KTRs on triple regimen of maintenance immunosuppression regime (Tacrolimus + MMF + Prednisolone) were monitored between 3months – 2 years of post transplant status. Adverse reactions reported/ documented during this period were analysed. Therapeutic drug monitoring of Tacrolimus was performed as per the treating Nephrologists recommendations.Qualitative Analysis of Causality by Naranjo Algorithm; Preventability by Modified Schumock & Thorton criteria and Severity by Hartwig's Scale were performed. **Results**: On an average, each recipient encountered four adverse events. Of the total of 64 documented adverse reactions analysed, 11 (17%) events had definite causality attributable to immunosuppressants. Five reports of Tacrolimus induced neurotoxic tremors were assessed definitely preventable. Concurrent administration of Calcium Channel Blocker (Amlodipine), Antibiotics (Erythromycin, Ciprofloxacin) and Antifungal (Fluconazole) could have paved way for the occurrence of these ADRs.*

Keywords: Tacrolimus, Adverse Drug Reaction, Therapeutic Drug Monitoring, Drug interactions

1. Introduction

End Stage Renal Disease (ESRD) is a rapidly emerging public health problem with an annual incidence of 1,00,000 patients in India.[1] Renal Transplantation is the most opted definitive treatment modality in management of ESRD.[2] A successful renal transplant has an advantage over maintenance dialysis in terms of Quality of Life and Survival benefit.[3,4]

In order to ensure a successful renal transplantation and graft viability in- vivo, lifelong immunosuppressant pharmacotherapy becomes mandatory. Level „A" evidence from various Randomized Clinical Trials have established Tacrolimus as a safe, effective and pharmaco-economic immunosuppressive agent for primary prevention of graft rejection following renal transplantation.[5]

The currently acclaimed regimen for maintenance immunosuppression in renal transplant recipients uses a combination of Tacrolimus+Mycophenolate mofetil+Steroid. This triple regimen rationally lowers the systemic overexposure to Tacrolimus, produces better graft survival rates [6] and also paves way for steroid sparing strategies in selected patients with low immunologic risk on a long run. [7]

Introduction of Therapeutic Drug Monitoring guidelines in individualization of dosage regimens and maintaining ascribed levels of specific immunosuppressant agents has been a boon to renal transplant recipients, with regards of decreasing incidence of subtherapeutic/toxic levels of immunosuppressant drug in their system.[8]

In spite of application of rational drug therapeutics in management of ESRD, the health related Quality of Life during the post transplantation period is riddled by intercurrent infections, adverse drug reactions and graft dysfunction. [9] The pharmacological interventions used to tackle these hurdles pave way to multitude of drug interactions, resulting either in drug toxicities/ adverse events/ graft dysfunction. In certain circumstances, the drug related events could negatively impact the patient"s health condition. In such instances, there always remains a rhetorical query about the 5Ws and 2Hs of the incurred event.

Hence the current study was undertaken to determine the Temporal/ Causal relationship, Preventability and Severity of ADRs during the maintenance phase of Tacrolimus based triple regimen immunosuppression in adult kidney transplant recipients. The sole intent of this study was to uncover possible concomitant medication induced ADRs that could be of valuable feedback to revise treatment/ follow up protocols and aid in minimising ADRs.

2. Methodology

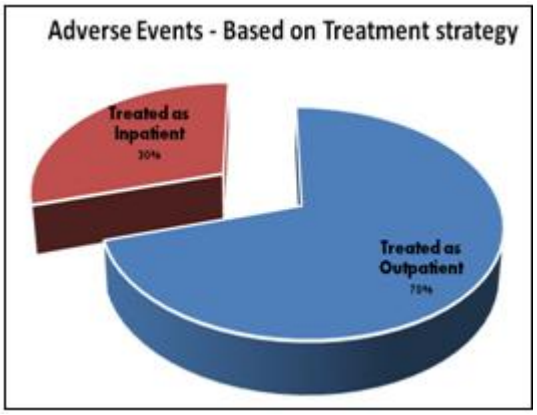
This prospective/retrospective cohort study was carried out after prior approval from the Institutional Ethics Committee. The study was conducted among adult kidney transplants attending our renal transplant outpatient facility receiving triple regimen of immunosuppressant therapy with (Tacrolimus+ MMF + Prednisolone) during 3months- 2 years post transplantation status. Adverse reactions reported/ documented during this period were collected from hospital medical records and individual patient case records.

Therapeutic drug monitoring of Tacrolimus was performed as per the treating Nephrologists recommendations.

Collected data was charted onto Microsoft Excel sheets. Temporal associations of the recorded ADRs were analysed. Qualitative Analysis of Causality was performed by applying the Naranjo Algorithm; Preventability was analysed by Modified Schumock & Thorton criteria and Severity was graded by Hartwig"s Scale was performed. Literature search was conducted to provide valuable insight regarding possible drug interactions between the triple drug immunosuppressant regime and other concomitant medications that were used in a case by case manner.

3. Results

In our study we observed a total of 64 adverse events among our study population of the 15 renal transplant recipients during the 90 to 720 day post renal transplant phase of maintenance Tacrolimus based triple therapy.



All the 64 ADRs were analysed. 30% (19) Adverse reactions required hospitalization and In-patient care for their resolution. The other 70% (45) ADRs were managed in the Out-patient facility.

On an average, each renal transplant recipient encounters four adverse events (three treated as Out-patient; one as In-patient) during our observation period of 90 to 720 days post transplant status. Temporal incidence of adverse events managed as Outpatient and Inpatient were found clustered around 223-281days and 255-465days post transplant respectively.

1) WHO-ART based SOC spectrum of Adverse Reactions:

All adverse events were classified into the System Organ Classes (SOC) WHO-ART terminology.[10]

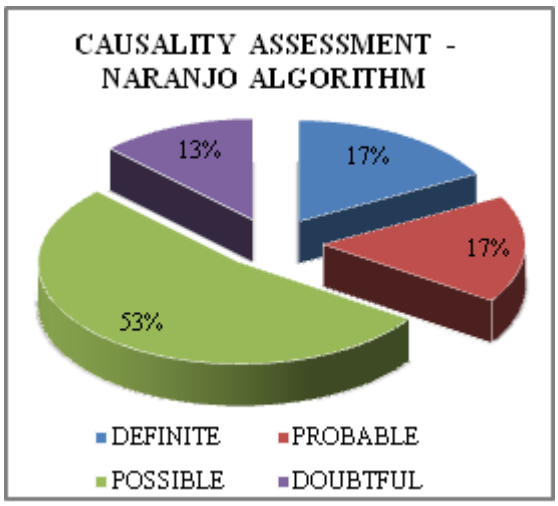
Among the most common adverse events treated in out-patient clinics, Respiratory Illnesses, Dermatological conditions (dermatophytoses, eczema), Gastrointestinal disturbances and Resistance mechanism disorders (Abscess-Brain, Oropharyngeal candidiasis, systemic mycosis) were reported.

Four events of renal transplant rejection were treated as In-patient emergencies and grouped under secondary term events in the SOC classification. Two patients were diagnosed with Tuberculosis (classified as "Body as whole – general disorder") and were started on Rifampicin free Anti-tubercular drug regimen along with Ofloxacin.

SOC of ADRS	Treated As Outpatient	Treated As Inpatient
Application site disorder	1	0
Body as whole- general disorders	3	3
Central and peripheral nervous system	5	1
Collagen disorders	0	2
Gastrointestinal disorders	6	1
Metabolic & nutritional disorders	1	0
Musculoskeletal disorders	1	1
Psychiatric disorders	1	0
Resistance mechanism disorders	6	2
Respiratory system	13	1
Secondary terms- events	0	5
Skin & appendage	7	0
Vascular (extra-cardiac)	0	3
Vision disorders	1	0
TOTAL:	45	19

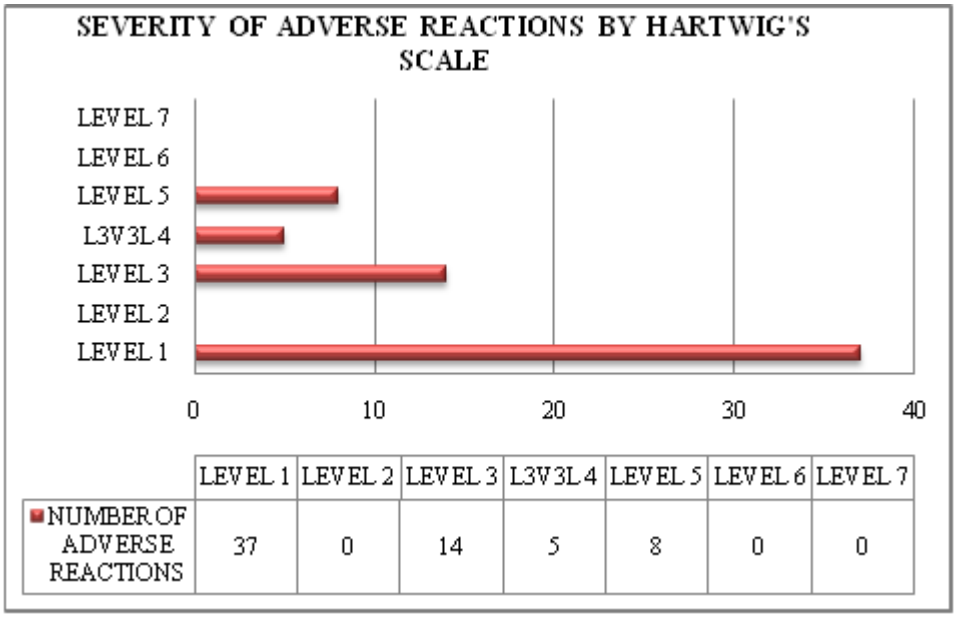
2) Causality Assessment

Definite causality relationship was established using Naranjo Algorithm between 17% (11) of the collected Adverse events to Immunosuppressant regimen. These reports included five reports each of fine tremors & renal transplant rejection and one report of lung cavity – fungal. Adverse events especially infectious conditions namely parasitic/ protozoal/ viral/ fungal/ tubercular diseases fell under „probable" causality scale when Naranjo Algorithm was applied.



3) Severity Assessment

A majority of the collected Adverse events (57.81%) were assessed to be of Level-1 severity, implying that the adverse event did not require any change in the treatment profile of the transplant recipient

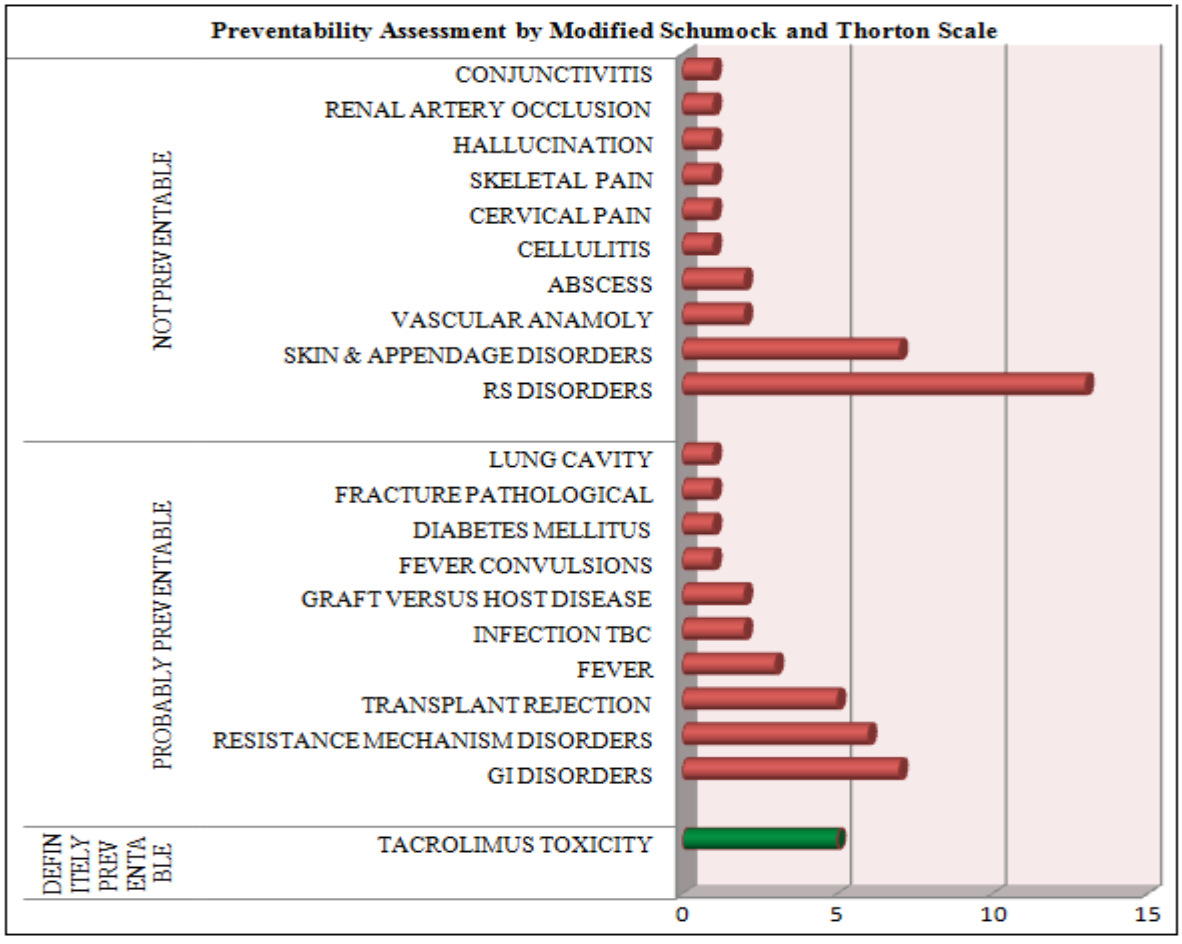


ADRs that fell under „Level-5"severity requiring intensive medical care included adverse events of transplant rejection, lung cavity, systemic mycoses and tuberculosis.

4) Preventability Assessment

When Modified Schumock and Thorton Scale of preventability analysis was performed, five reports of Tacrolimus induced neurotoxic tremors were assessed as "definitely preventable". The TDM reports taken immediately on instance of these events showed blood Tacrolimus levels >20ng/ml. (Normal Tacrolimus Therapeutic level: 5-20ng/ml).[11]

When the antecedent documented Tacrolimus levels in each of these five reports were checked, they were either in the normal or subnormal therapeutic levels. Hence we probed into the concurrent medications that could have affected Tacrolimus handling in the body. Relevant literature search was performed to check for previously reported citations of the possible concomitant drug interaction with tacrolimus.



Concurrent administration of Calcium Channel Blocker (Amlodipine), Antibiotics (Erythromycin, Ciprofloxacin) and Antifungal (Fluconazole) were noted in these records.

5) Literature Search Results

Immunosupressant drugs in KTRs	Concomitant medication	Literature search results
Tacrolimus + MMF + Prednisolone	Amlodipine	P-glycoprotein and CYP3A4 interaction[12]
	Erythromycin	CYP3A4 inhibition[13]
	Ciprofloxacin	Pharmacodynamic interaction:decrease in IL-2 mediated immunosuppressive response [14]
	Fluconazole	CYP3A4 inhibition[13]

4. Discussion

In our study we found that the incidence of adverse events following immunosuppressant therapy had negatively impacted the Quality of Life (QOL) in renal transplant recipients. This finding is in concurrence with a cross sectional analysis conducted by Matas et. al among 4247 renal transplant recipients, where they established a strong association between the detrimental effect of adverse events on QOL of the subjects . [14]

In our current study, the renal transplant recipients were observed for incidence of adverse events during 90 to 720 days postoperative period. This time frame was set to eliminate influences of induction regimen drugs and immediate postoperative complications. Temporal incidence of adverse events on maintanence triple regimen drugs (Tacrolimus + MMF + Prednisolone) were found to be clustered around 7months to 1yr3months postoperative period. This period probably represents critical interaction of these drugs on the system and mandates stringent monitoring of renal transplant recipients.

As per the United Kingdom Renal Association guidance on monitoring of renal transplant recipients, the recommended frequency of clinic visits during our time frame (i.e, 3months to 2yrs) is fortnightly for 3months-6months, monthly for 6months -1year and once in 6 months for 1yr to 2 year duration post transplant. The guidelines also recommend a time scale for monitoring therapeutic drug levels of calcineurin inhibitors. [15] Our centre also adheres to these timelines of patient review and follow-up.

On analysing the individual adverse events on a case to case basis, we were able to identify that common ailments like Respiratory illnesses, Gastrointestinal disturbances, Dermatological ailments that are sporadic among general population were frequent among renal transplant recipients. Though these conditions were classifiable as Doubtful/Possible" causal relationship, „Level 1" severity and „Not Preventable" adverse events, the medications used to tide over these intercurrent illnesses can possibly alter the pharmacokinetic profile of Tacrolimus/MMF/Steroid.

Tacrolimus, a potent calcineurin inhibitor displays marked inter and intra-individual pharmacokinetic variability. It is metabolised by CYP3A4 enzymes and is prone for drug interactions. Patient specific optimization of dosage is guided by Therapeutic Drug Monitoring.[16] In our study we identified that Antimicrobial agents (i.e., Erythromycin, Ciprofloxacin and Fluconazole) that were used to tide over the intercurrent illnesses paved way for the incidence of Tacrolimus toxicity in the susceptible renal transplant recipients.

Amlodipine, a Dihydropyridine chemical class of Calcium Channel Blocker is considered as a first line agent in management of hypertension following renal transplant, especially in patients under calcineurin inhibitors therapy .[17] In spite of compelling indication for use of Amlodipine in treating hypertension in renal transplant recipients, a meta analysis comprising 21 trials did not validate these findings.[18] In our study, we encountered an incidence of Tacrolimus toxicity levels during precedent and concomitant use of Amlodipine. Dihydropyridine group of calcium channel blockers alleviate calcineurin inhibitor related bone pain[19] apart from the control of hypertension and associated left ventricular hypertrophyin renal transplant recipients. [20]

5. Conclusion

The clear cut distinction in addressing the causal relationship of an adverse event to the immunosuppressant agent used is nebulous in renal transplant recipients. High incidence of Adverse reactions in renal transplant recipients is probably a consequence of polypharmacy, drug interactions, co-morbidities and compliance issues. Prudent choice of concomitant medication is the key in preventing ADRs. For example: Calcium Channel Blocker (Amlodipine), Antibiotics(Erythromycin, Ciprofloxacin) and Antifungal (Fluconazole) were a few commonly encountered drugs that are known to alter pharmacokinetics of Tacrolimus. A personalized approach in the management of transplant recipients , though demanding in the clinical setting, can serve to address prevention or restriction of severity of Adverse reactions.

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