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Study and Reporting of Adverse Drug Reaction Patterns Among Organ Transplant Patients Receiving Tacrolimus Therapy in a Real World Post-Marketing Experience

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Abstract

With the availability of many immunosuppressive drugs for treatment of solid organ transplantation increase to a life span of patients who is receiving tacrolimus separately for End Stage of liver, heart and lung, kidney. But after all success of solid organ transplantation is purely dependent on proper course of immunosuppressive therapy. Tacrolimus is lactones antibiotic isolated from the fermentation of streptomyces tstkubaeis. This calcineurin inhibitor widely used for its immunosuppressive properties to increase patient survival and prevent graft function, organ rejection in solid organ transplant and graft-versus-host disease in transplant patients suppresses to enzyme for the growth of B cells and T cells. It was first approved for use to prevent graft rejection in 1994 for liver transplantation and in 1997 for kidney transplantation. The outcomes of this drug have varied due to differences in induction and maintenance therapy, drug dosing and monitoring. The aim of this study of an assessment and reporting of adverse drug reaction was to analyze the case reports of literature critically, conducted to monitor and evaluated the adverse events (AEs) and adverse drug reactions (ADRs) of immunosuppressive drug regimens, its causality, severity in therapy which is used various organ transplant patients and to document the pharmacotherapeutic actions taken for its management.

1 Introduction

Immunosuppressant drugs are a class of drugs that suppress, or reduce, the strength of the body's immune system. Some of these drugs are used to make the body less likely to reject a transplanted organ, such as a liver, heart or kidney, pancreas, bone marrow. These drugs are called anti-rejection drugs. Immunosuppressive drug Tacrolimus are given to organ transplant recipients in two phases' induction and maintenance therapy. the induction phase usually include short courses of various antibodies against T lymphocytes, along with high dose of steroids. These are 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[1]. The aim of maintenance immunosuppression is to avoid acute rejection, interstitial fibrosis and tubular atrophy and to improve overall graft and patients survival. The use of antibody therapy to provide enough immunosuppression is to delay the initiation of therapy with nephrotoxic calcineurin inhibitors. Immunosuppressant drugs are used to treat autoimmune diseases. With an autoimmune disease, the immune system attacks the body's own tissue. Because immunosuppressant drugs weaken the immune system, they suppress this reaction. This helps reduce the impact of the autoimmune disease on the body. Autoimmune diseases treated with immunosuppressant drugs. Almost every organ transplant patients who receives an organ transplant must take immunosuppressant drugs due to immune system sees a transplanted organ as a foreign mass. Drugs allow the transplanted organ to remain healthy and free from damage. Immunosuppressant drugs weaken immune system to reduce body's reaction to the foreign organ. National and international

transplant registries report 1-year graft survival rates of around 85% after kidney, liver and heart transplantation[2- 4]. Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects. The adverse effect is all unwanted effects, unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with labeling or market authorization, or expected from characteristics of the drug. Serious adverse effect as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening. The successes of the solid organ transplants depends on the ability of potent immunosuppressive agents to prevents and treat allograft rejection. Tacrolimus is the key immunosuppressant used to prevent allograft rejection in transplant recipients. Immunosuppressive drugs that effectively prevent organ rejection has led to transplantation being the pre-ferred treatment for end-stage. Tacrolimus is a macrolide with potent immunosuppressant activity, isolated from *Streptomyces tsukubaensis.* It prolongs the survival of the host and transplanted graft in different transplant model of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea and limbs (Table 1).

Tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell mediated reaction such as allograft rejection, delayed type hypersensitivity, collagen induced arthritis, experimental allergic encephalomyelitis and graft versus host disease. Tacrolimus were published in liver and kidney transplant recipients In 1994 showing a significant reduction in the incidence of acute rejection[5,6]. Calcineurin inhibitors are considered the mainstay of immunosuppression in renal transplantation[7]. Tacrolimus forms a complex with FK506 binding protein (FKBP12), which inhibits the enzymatic phosphates activity of calcineurin. Excessive use of immunosuppressive agents increases the malignant complications, metabolic and risk of infectious while subtherapeutic levels allow acute rejection and organ failure. In particular use of calcineurin inhibitors, high levels adverse effect nephrotoxicity exhibited. As with azathioprine, MMF can reduce nephrotoxicity by sparing the use of CNIs[8.] Tacrolimus more effective than other immunosuppressive drug in preventing acute rejection and allograft since tacrolimus was licensed for liver and kidney transplantation in the 1990s, and know most of the component of about 90% of immunosuppression regimens for kidney or liver transplant recipients in the US[9-10]. Excessive immunosuppression increases the risk of infectious, metabolic, and malignant complications, nephrotoxicity.

1.1 Mechanism of action

Tacrolimus is an immunosuppressant. It is a microclide lactone with potent in vitro and in vivo immunosuppressive activity. Studies suggest that tacrolimus inhibits the formation of cytotoxic lymphocytes which are regarded as being primarily responsible for graft rejection.Tacrolimus suppresses T –cell activation and T-helper-cell dependent B-cell proliferation, as well as formation of lymphokines such as interleukin-2 receptor[11- 15].

Table 1: Immunosuppressive agents used in solid organ transplantation

Type of Immunosuppressive agents	Drug used in this class
Calcineurin inhibitor	Tacrolimus, Cyclosporine
Anti-proliferative	Mycophenolate mofetil, Mycophenolate sodium, Azathioprine
Corticosteroid	Prednisolone, Prednisone, Methyl prednisolone
Polyclonal anti-lymphocyte antibodies	ALG, ATG, ALS

Tacrolimus inhibit the synthesis of interleukin-2 (IL-2) and numerous other cytokines that are important mediators in graft rejection, these agents bind to different immunophilins,tacrolimus complexes with FK506 binding protein[16], these drugs as immunophilin inhibits the activity of enzyme calcineurin and due to this issue, interrupts the calcium-dependent signal-transduction pathway in T cells[17,18,19]. As a consequence of calcineurin inhibition, transcription of early T-cell–activation genes is suppressed, affecting production of IL-2 and other cytokines such as IL-3, interferon and tumor necrosis factor. In addition, calcineurin inhibition modulates cyclic adenosine monophosphate responsive element binding protein activity[20] (Fig 1).

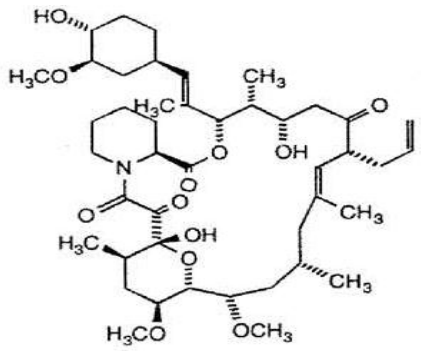

Fig 1: The chemical structure of Tacrolimus

1.2 Side effects

Tacrolimus are associated with a range of agent-specific side effects are nephrotoxicity, neurotoxicity, Immunosuppressive potency, diabetogenic, hepatotoxicit. Many of the important side

effects of Tacrolimus are dose dependent and relate to the sites where Tacrolimus concentrations are highest, notably in the brain and the kidney[21] Hypertension is a common adverse effect of Tacrolimus . Mild or moderate hypertension is more frequently reported than severe hypertension. It may cause hyperkalemia, potassium-sparing diuretics should be avoided.

Tacrolimus shows many dose-related side effects are associated with nephrotoxicity and this is one of the most important side effects particularly after renal transplantation. It is due impart due to severe vasoconstriction of the afferent arteriole, with concomitant reduction in renal blood flow and glomerular filtration rate[22-24]. These changes are reversible with discontinuation of the tacrolimus. In the longer-term Tacrolimus cause chronic non-reversible changes that are characterised by interstitial fibrosis and obliterative arteriolar changes due to fibrous intimal thickening[25]. Although tacrolimus are nephrotoxic, recent studies suggest this may be less of a problem with tacrolimus[26-28].

The neurotoxicity of tacrolimus may manifest in many ways, is more common and is exacerbated in the presence of low serum magnesium concentration[29]. Headache and tremor may occur, worse one to two hours following administration when the plasma concentration of the drugs are highest. Insomnia is also common. Agitation, convulsions, psychosis, hallucinations, encephalopathy and impaired consciousness are less common[30].The metabolic effects of Tacrolimus include diabetogenesis, which is two to four times more common with Tacrolimus than cyclosporine, and may also reflect different sensitivity to the diabetogenic effects of corticosteroids[31]. Hyperkalaemia, hyperuricaemia and hyperlipidaemia are the other common metabolic side effects and the latter may occur less frequently with tacrolimus.

2 Material and Methods

In various study the patients with solid organ transplantation who received tacrolimus mainly on the case report of literature and procedure of inclusion studies was based on the methods of a Non interventional prospective, observational case series, cohort technique study & descriptive analysis of the data was done. The study was performed for solid organ transplantation patient's case report and characteristic summary of product were included in the study.

2.1 Data Selection

Sources: In various Medical literatures published in any language on tacrolimus, mycophenolate mophetile identified using Pubmed, Medline and EMBASE, supplemented by Emtree & the ADR terms used in summary tabulation are coded as per medical dictionary for regulatory activities (MedDRA). Add other references were determined from the lists of published articles. unpublished data , including contributory bibliographical information, was the drug.

Search strategy: PUBMED, search term's were Tacrolimus or Prograf, FK-506,pangraf,Tacrofort,Tagraf and transplantation or graft rejection or transplant rejection.EMBASE search terms were tacrolimus and transplantation or graft rejection or transplant rejection,advers event of tacrolimus used in organ transplantation. MEDLINE search for English language articles published reports Tacrolimus Prograf, Tacrofort, Pangraf, Tagraf, Tacrofort, Tacpan, Panolimus search terms were Tacrolimus or FK 506 and transplantation' or 'transplant-rejection searches were latest updated .

Selection: Studies in patients with kidney, liver, heart, renal, pancreas or bone marrow transplantation who received tacrolimus. An appropriate statistical methodology was preferred.

2.2 Methodology

A total no of incident as AEs and ADRs included the pattern non serious listed, non serious unlisted ADRs, serious listed and serious unlisted ADRs. Tacrolimus package insert and information about pharmacovigilance program the case report as received from literature were entered in the data base using the dictionary that has hierarchical structure arranged by system-organ class.

Case report were scrutinized and the data was collected in a specially designed performa which included the following details: Exhaustive literature survey and detail study of case reports. Identification of suspected ADR reporting in case report.Interpretation and coding of adverse reaction descriptions as per MedDRA. Individual case causality assessment.This study were examined the case reporting patterns for known adverse drug interactions in the time period.

3 Results and Discussion

Patient Demographics: Out of total case reports of patients find out, Male predominates over female (Fig.2).

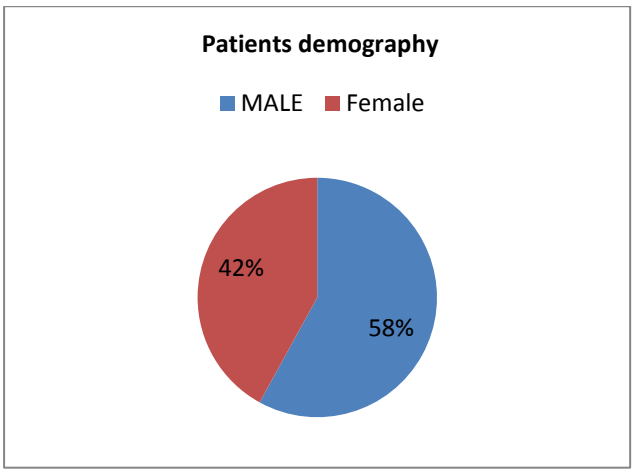

Fig 2: Shows the age distribution pattern of study population

In this study, among 83 case report patients who were developed ADRs, (58%) were males and (42%) were females (Fig.3).

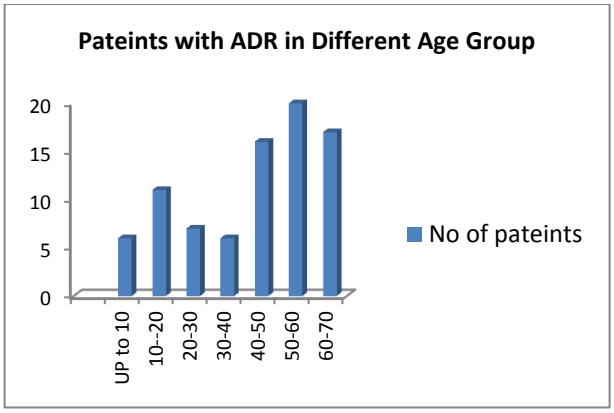

Fig 3: Patients with Adverse Drug Reactions in Different Age Groups

ADRs are one of the prime concerns to deal with while treating the patients with tacrolimus drugs. They are favoring a important role on patients' life both by in terms of quality of life and financially impact. As in our study the immunosuppressive drugs calcineurin inhibitors tacrolimus were identified 253 adverse drug reactions. all pivotal ADRs compared the investigational agent with calcineurin inhibitor tacrolimus 83 case reports studies was shown that 253 adverse drug reaction inclusion sources of literatures of the total 253 ADRs 102 were serious unaspected,142 serious listed, 8 were non serious unlisted,1 were non serious listed. These ADRs were not preventable.

The results of this study shown that immunosuppressive drug tacrolimus may cause serious and frequent adverse effects. So, special monitoring and regular follow up of patients are required to minimize the risk and frequency of these adverse effects. This review focuses on reported results of tacrolimus in organ transplantation. One safety concern of aspergillosis infection has been identified from two case reports. Three case reports of potential drug interaction were find out from case reports literature during the study period of these, one case find out to interaction tacrolimus and ranolazine is unlisted as per the reference safety information. There were eight case reports in paediatric age group. Of these case reports, three was reported with fatal outcome.

Six case reports associated with the tacrolimus exposure during pregnancy were findout during the study period.The maximum numbers of ADRs associated with the use of tacrolimus were identified from the SOC "Gastrointestinal disorders" with a total of 33 ADRs (13.04 %). The second maximum numbers of ADRs associated with use of tacrolimus were identified from SOC "Infections and infestations" with 29 ADRs (11.46 %).The third maximum numbers of ADRs associated with use of tacrolimus were findout from SOC "General disorders and administration site conditions" with 23 ADRs (9.09 %) (Fig.4 - Fig.7).

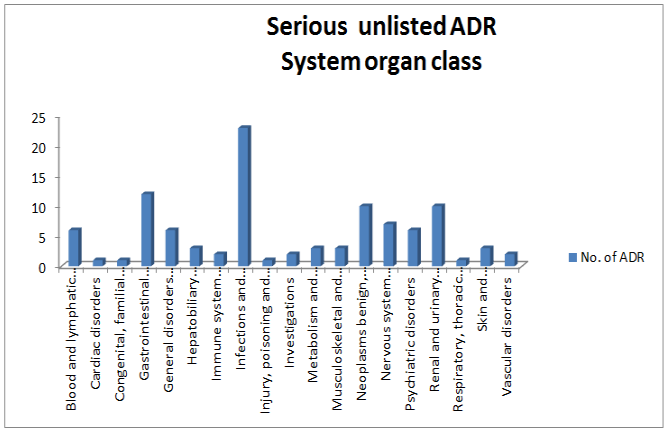

Fig 4: System organ class serious unlisted ADR

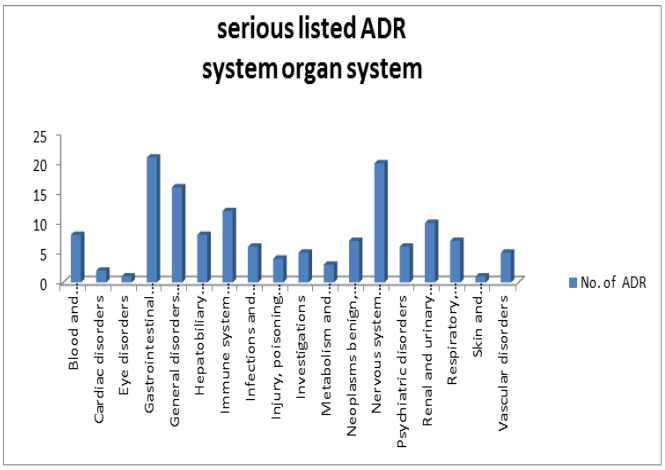

Fig 5: System organ class serious listed ADR

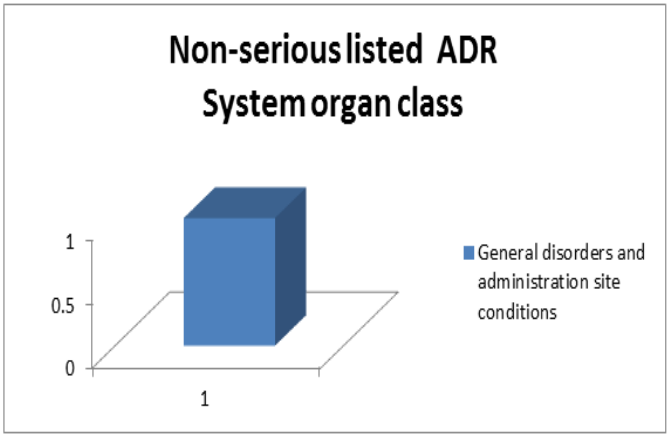

Fig 6: System organ class Non-serious listed ADR

4 Conclusion

Based upon this study, provides the generalized and preliminary information about the type and frequencies of ADRs associated with immunosuppressive drugs in solid organ transplantation of tacrolimus recipients patient with end stage renal disease. Overall safety profile evaluation for tacrolimus changed and

significant issues have arisen. As most of the ADRs were not preventable so, this shows that it's very difficult to avoid the occurrence of ADRs though physicians have done fair job in dealing with them either by providing symptomatic treatment or by modifying the doses and regimens.

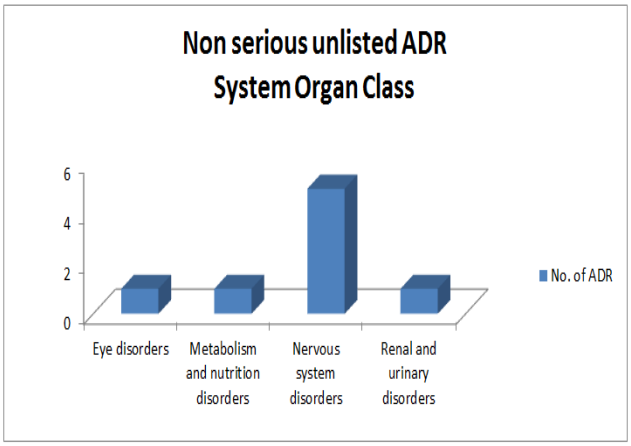

Fig 7: System organ class Non serious unlisted ADR

During the study period of this ADR, one safety concern of aspergillosis infection has been identified from two cases which would monitor in future, and based on cumulative experience will reassess the risk benefit profile of tacrolimus. This study is unique in its own, 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. Further development in both induction and maintenance immunosuppressive strategies is required to achieve an ideal regimen, which would prolong allograft survival with minimal complications as ADRs.

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6 Conflict of interest

The authors declared that there are no conflicts of interest.

7 Author's contributions

SS and CR performed the experimental work. PR carried out draft the manuscript.

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