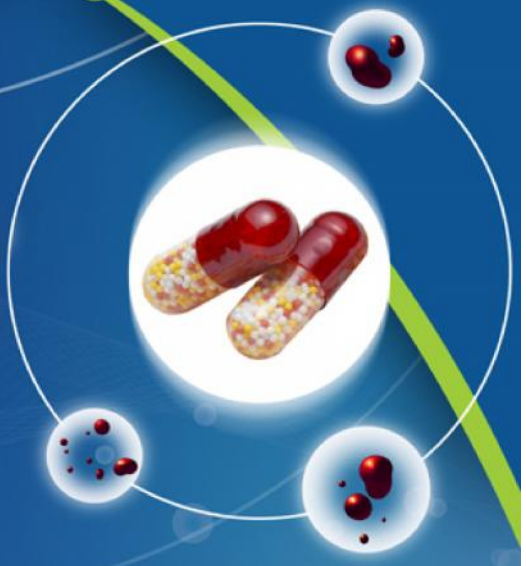
ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD



Volume - 03 Issue - 03 MAY-JUN 2015

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

A REVIEW ON PHARMACOLOGY OF TACROLIMUS IN RENAL TRANSPLANT PATIENTS

Sharma Anu*, Saini Priyanka, Chhimwal Jyoti, Sharma Samiksha, Khan Mohd. hahid

Department of Pharmacology, Kota College of Pharmacy, Kota, Rajasthan

Received: April 2015 ***Revised and Accepted: May 2015***

ABSTRACT

Solid organ transplantation provides a life saving treatment for patients with end stage kidney diseases. But total success after transplantation is hugely dependent on proper course of immunosuppressive therapy. Tacrolimus, a macrolide immunosuppressant agent, is indicated for the prophylaxis of organ rejection in patients receiving allogenic liver or kidney transplantation. The clinical practice still struggles with the shortcomings of the drug: the significant inter- and intraindividual variability of their pharmacokinetics, the unpredictability of their pharmacodynamics effects, as well as complexity of interactions with other agents in transplant recipients. This article briefly reviews the pharmacological aspects of tacrolimus as they relate to the mode of action and pharmacokinetics as well as drug interactions and adverse drug reaction.

Keywords*: Drug interactions, Adverse drug reaction, tacrolimus, and renal transplant*

INTRODUCTION

Tacrolimus is a macrolide immunosuppressant that has been shown to be safe and effective for the prevention of rejection after organ transplantation [1]. Immunosuppressant's drugs are used to dampen the immune response in organ transplantation [2].

It has been used in thousands of allograft recipients and has become the standard immunosuppressive drug of choice in numerous transplant centres [3]. Tacrolimus was first approved by the Food and Drug Administration (FDA) in 1994 for use in liver transplantation; this has been extended to include kidney, heart, and other organs. It has similar immunosuppressive properties to cyclosporine, but is much more potent [4].

**For Correspondence:*
Anu Sharma
Kota College of Pharmacy
Mail id:annusharma.sharma111@gmail.com

Immunosuppressant drugs greatly decrease the risks of rejection, protecting the new organ and preserving its function. These drugs act by blocking the immune system so that it is less likely to react against the transplanted organ.

RENAL TRANSPLANT

Kidney transplantation is the organ transplant of a kidney into a patient with ESRD (End stage renal disease). The majority of renal transplant recipients are on dialysis (peritoneal or hemodialysis) at the time of transplantation [5]. Transplant rejection occurs when transplanted tissue is rejected by the recipient's immune system, which destroys the transplanted tissue. Transplant rejection can be lessened by determining the molecular similitude between donor and recipient and by the use of immunosuppressant drugs after transplantation. Tacrolimus is mainly used to suppress the immune system from rejecting the donor kidney. These medicines must be taken for the rest of the patient's life. The use of cyclosporine or tacrolimus has improved the outcomes of transplantation significantly. Patient and graft survival rates have improved

secondary to lower incidence of acute rejection episodes and severe infectious complications [6]. Although cyclosporine, considered a breakthrough immunosuppressive when first discovered in the 1980s, it causes nephrotoxicity and can result in iatrogenic damage to the newly transplanted kidney [7].

TACROLIMUS

Tacrolimus is a macrolide immunosuppressant produced by Streptomyces tsukubaensis that is used after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. Immunosuppressant's are drugs which inhibit cellular/humoral or both immune response and have their major use in organ transplantation.

Discovery

Tacrolimus, also known as FK506 or Prograf, is a macrolide compound that was isolated by Fujisawa researchers from the culture broth of a soil microorganism *Streptomyces tsukubaensis* near Mount Tsukuba, Japan in 1984, the marked immunosuppressive properties of tacrolimus were confirmed following extensive *in vitro* and *in vivo* testing [8], thereby identifying what would become a cornerstone of immunosuppressive prophylaxis after solid organ transplantation.

Tacrolimus was first launched in Japan in 1993, for prevention of allograft rejection in liver or kidney transplant patients. In the US, tacrolimus (Prograf) was approved for prevention of rejection in liver transplant recipients in 1994, and in kidney transplant recipients in 1997. In 2003, tacrolimus was used as initial immunosuppression in 67% of kidney recipients and 89% of liver recipients (UNOS United Network for Organ Sharing 2004). It wasn't until the mid-1990s that tacrolimus became available in Europe [9].

Tacrolimus is a potent immunosuppressive agent that is effective in allograft prophylaxis after organ transplantation. While it has been shown to be 10 to 100 times more potent than Cyclosporin [10], tacrolimus has significantly reduced the incidence and severity of acute rejection rates in organ transplantation [11]. In addition, patients receiving tacrolimus therapy require less concomitant corticosteroid therapy thus reducing the risk of adverse corticosteroid-associated side effects [12].

Pharmacokinetic and pharmacodynamics

Mechanism of action

The exact mechanism by which tacrolimus produces immunosuppressant remains unknown, it appears to act through inhibition of T-lymphocyte activation. Tacrolimus binds to an intracellular protein, FKBP-12, and forms a complex with calcium, calmodulin, and calcineurin. The resulting complex inhibits the phosphatase activity of calcineurin, which prevents the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT). NF-AT is believed to initiate gene transcription for the formation of lymphokines such as interleukin-2 and gamma interferon. The clinical result of inhibition of NF-AT is immunosuppression. Tacrolimus is administered orally as well as by i.v. infusion. Oral absorption is variable and decreased by food. It is metabolized by CYP3A and excreted in bile with a longer t½ of 12 hour [2].

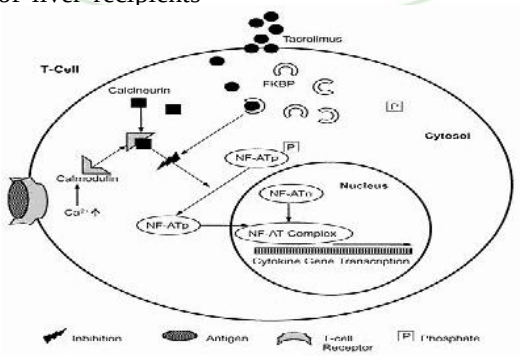


Fig no.1: Mechanism of action

Pharmacokinetic

Tacrolimus is orally administrated and also in sterile solution for injection (5 mg/ml). Immunosuppressive activity resides primarily in the parent drug. Whole blood, rather than plasma, is the most appropriate sampling compartment to describe tacrolimus pharmacokinetics. Target concentrations in many centres are 200–400 ng/ml in the early preoperative period and 100–200 ng/ml 3 months after transplantation. GI absorption is incomplete and variable. Food decreases the rate and extent of absorption. Plasma protein binding of tacrolimus is 75–99%, involving primarily albumin. Tacrolimus is extensively metabolized in the liver by CYP3A, with a t1/2 of ~12 hours; at least some of the metabolites are active.

Tacrolimus is indicated for the prophylaxis of solid-organ allograft rejection in a manner akin to cyclosporine and as rescue therapy in patients with rejection despite —therapeutic levels of cyclosporine. Dosages are intended to achieve blood trough levels of 5–15-ng/ml. Nephrotoxicity, neurotoxicity, GI complaints, hypertension, hyperkalemia, hyperglycaemia, and diabetes are all associated with tacrolimus use. Tacrolimus has a negative effect on pancreatic β cells, and glucose intolerance and diabetes mellitus are well-recognized complications of tacrolimus-based immunosuppression. As with other immunosuppressive agents, there is an increased risk of secondary tumours and opportunistic infections. Because of its potential for nephrotoxicity, tacrolimus blood levels and renal function should be monitored closely, especially when tacrolimus is used with other potentially nephrotoxic drugs. Co administration with cyclosporine results in additive or synergistic nephrotoxicity; therefore, a delay of at least 24 hours is required when switching a patient from cyclosporine to tacrolimus [13].

Adverse Effects

- Hypertension
- Hyperkalameia
- Nephrotoxicity
- Neurotoxicity
- Malignancies
- Serious infection

Nephrotoxicity

Tacrolimus can cause renal impairment character by increases in serum creatinine as a result of a reduced glomerular filtration rate, particularly when used in high doses. These changes have been observed to be dose dependent and improvements have been associated with reduced dosing. The mechanism leading to these changes is not fully understood. Use of tacrolimus with sirolimus in heart transplantation patients in a US study was associated with increased risk of renal function impairment, and is not recommended. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. Care should be taken in using tacrolimus with other nephrotoxic drugs. In particular, tacrolimus should not be used simultaneously with cyclosporine. Tacrolimus should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporine concentrations, dosing with the other drug usually should be further delayed [14].

Hyperkalaemia

Mild to severe Hyperkalaemia was reported in patients treated with tacrolimus, especially in patients with renal impairment. Patients may require treatment, and should avoid high dietary potassium intake. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus therapy.

Hypertension

Hypertension is a common adverse effect of tacrolimus therapy. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating tacrolimus-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction.

Neurotoxicity

Neurological and CNS disorders have been reported with tacrolimus therapy. Symptoms include tremor, headache, and changes in motor function, sensory function or mental status, insomnia, seizures, coma and delirium. Patients experiencing such events should be carefully monitored. In cases of severe or worsening neurological disorder, adjustment of the immunosuppressive regimen should be considered [15].

Malignancies

As with other potent immunosuppressive compounds, patients treated with tacrolimus are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Serious Infections

Patients receiving tacrolimus are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic. These infections may lead to serious, including fatal, outcomes. Because of the danger of over suppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution [16].

Drug Interactions

Based on available literature, it is a common assumption that cyclosporine and tacrolimus drug interactions are similar [17]. The pharmacokinetic profiles of drug are significantly affected by complementary influence of both CYP3A4 and P-glycoprotein. It is interesting that drugs that competitively inhibit CYP3A4 activity also usually act as P - glycoprotein inhibitors, therefore increasing the bioavailability of calcineurin inhibitors and their potential for toxicity. One commonly encountered example is Ketoconazole [18]. On the other hand, other drugs, like phenobarbital, known to induce CYP3A4 levels via activation of gene transcription also tend to up-regulate levels of P-glycoprotein, [19] decreasing the overall bioavailability of calcineurin inhibitors. This, in turn, can lead to occurrence of rejection. In addition, the complicity of the interactions is enhanced by the fact that significant age-, gender-, and ethnicity-related differences in the profile of various drug interactions with calcineurin inhibitors have been noted [20-23].

Interaction of Calcineurin Inhibitors with Other Immunosuppressive Drugs

Corticosteroids, still a part of most immunosuppressive regimens, have been shown to be substrates, inhibitors, and inducers of CYP3A4 [24] as well as potent inducers of P-glycoprotein, [25] Depending on time of administration and sample collection, corticosteroids have been shown to either lower or increase tacrolimus requirements. The clinical importance of these interactions has been stressed but is not fully understood. In combination with mycophenolate mofetil, tacrolimus has been found to be associated with significantly higher mycophenolic acid (MPA) trough levels and exposure (AUC) than when it was coadministered with cyclosporine [26]. This finding has been attributed to cyclosporine decreasing rather than tacrolimus increasing the MPA exposure [27]. The reverse interaction is insignificant as the concentration of cyclosporine is approximately 100-fold higher at the interaction sites. Tacrolimus and sirolimus have been shown to inhibit each other's metabolism [28]. In addition, as far as the biological activity is concerned, tacrolimus and sirolimus have synergistic in vivo immunoinhibitory properties due the fact that both drugs inhibit separate steps in T-lymphocyte activation [29]. The combination of sirolimus with cyclosporine or tacrolimus has, therefore, a potential for lower toxicity through utilization of lower dosing regimens. Everolimus, which is the 40-*O*-hydroxyethyl derivative of sirolimus, is also a substrate of both CYP3A4 and P – glycoprotein and has, therefore, a

potential for competitive interactions with both calcineurin inhibitors [30]. for competitive interactions with both calcineurin inhibitors [30]. Since its biological activity is, as in case of sirolimus, synergistic to those of cyclosporine and tacrolimus, combining it with calcineurin inhibitors may lead to overall decrease in toxicity without affecting transplantation outcomes, although nephrotoxicity remains a significant problem even at low doses of calcineurin inhibitors [31].

Table no 1. Tacrolimus drug interaction [32**]**

Sr. no	**INTERACTION**	**DRUG**
1	Cyclosporin, Aminoglycosides, Amphotericin B, Cisplatin, NSAIDs, Vancomycin, Cotrimoxazole, Acyclovir, Gancyclovir Teicoplanin	Increased nephrotoxicity
2	Potassium-sparing diuretics	Increased risk of Hyperkalemia
3	Azole antifungal, Calcium-channel blockers, Cimetidine, Danazol, HIV-protease inhibitors, Macrolide Antibacterial Metoclopramide	Increased plasma concentrations and toxicity
4	Antacids, Rifampin, Rifabutin, Casofungin, Phenytoin, Phenobarbital Carbamazepine	Decrease tacrolimus plasma concentrations

CONCLUSION

The use of tacrolimus has greatly advanced our knowledge about the nature of many processes involved in immune response. On the other hand, we have also learned about the dark side of these drugs: the significant inter- and intra individual variability of their pharmacokinetics, the unpredictability of their pharmacodynamics effects, as well as complexity of interactions and adverse drug reaction with other agents in transplant recipients. This knowledge can also prevent the occurrence of similar such reactions in the future.

REFERENCES

1. *Fitzsimmons W E, Bekersky I, Dressler D, Raye K, Hodosh E, and Mekki Q. Transplant. Proc 1998; 30: 1359–1364.*
2. *Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's pharmacological basis of therapeutics XI[th] edition, MC Graw hill, New York, 2006; 1004.*
3. *Staatz CE, and Tett SE. Clin. Pharmacokinet 2004; 43(10):623-653.*
4. *Shapiro R, Jordan M.L, Scantlebury VP, Vivas C, Gritsch HA, McCauley J, Ellis D, Gilboa N, Lombardozzi-Lane S, Randhawa P, Demetris AJ, Irish W, Hakala TR, Simmons RL, Fung JJ, Starzl TE. Tacrolimus in renal transplantation. Transplant Proc 1996; 28(4):2117-2118.*
5. *Crosson J T. Focal segmental glomerulosclerosis and renal transplantation. Transplant Proc 2007; 39(3):737-43.*
6. *Frohn C, Fricke L, Puchta JC, Kirchner H. The effect of HLA-C matching on acute renal transplant rejection. Nephrol Dial Transplant 2001; 16 (2):355-360.*
7. *Henry ML, Elkhammas EA, Davies EA, Ferguson RM. A clinical trial of cyclosporine G in cadaveric renal transplantation. Pediatr Nephrol 1995; 9 (Suppl): S49–51.*
8. *Medline Plus (2012). "Kidney Failure". National Institutes of Health. Retrieved 1 January 2013.*
9. *Pratschke JT, Steinmuller WO, Bechstein R, Neuhaus SG, Tullius S, Jonas G, Schumacher W, Luck M, et al. Orthotopic liver transplantation for hepatic associated metabolic disorders. Clin Transplant 1998; 12(3):228-32.*
10. *Goto S, Stepkowski SM, Kahan BD. Effect of FK 506 and cyclosporine on heart allograft survival in rats. Transplant Proc 1991; 23(1): 529-30.*
11. *Kaplan B, Schold J D, Meier-Kriesche HU. Long-term graft survivalwith neoral and tacrolimus: a paired kidney analysis. J Am Soc Nephrol 2003; 14(11): 2980-4.*
12. *Busuttil RW, and Holt CD. Tacrolimus (FK506) is superior to cyclosporine in liver transplantation. Transplant Proc 1997; 29(1-2): 534-8.*
13. *Huang AT, Mold NG, Zhang SF. Antithymocyte globulin stimulates human hematopoietic progenitor cells. Proc Natl Acad Sci USA 1987; 84 (16): 5942–5946.*
14. *Calne R Y, White DJ. The use of cyclosporin A in clinical organ grafting. Annals of surgery, 1982; 196(3), 330.*
15. *Tomlinson JE, McMahon AD, Chaudhuri R. Efficacy of low and high dose inhaled corticosteroid in smokers versus nonsmokers with mild asthma. Thorax 2005; (60): 282–287.*
16. *Green CJ. Experimental transplantation and cyclosporine. Transplantation, 1988; 46(2): 3S-10S*
17. *Moreno M, Latorre A, Manzanares C, et al. Clinical management of tacrolimus drug interactions in renal transplant patients. Transplant Proc 1999;3 1: 2252,*
18. *Labroo RB, Thummel KE, Kunze KL, et al. Catalytic role of cytochrome P4503A4 in multiple pathways of alfentanil metabolism. Drug Metab Dispos 1995; 23:490.*
19. *Schuetz EG, Beck WT, Schuetz JD: Modulators and substrates of P-glycoprotein and cytochrome P4503A co-ordinately up-regulate these proteins in human colon carcinoma cells. Mol Pharmacol 1996; 49:311.*
20. *Bleck JS, Thiesemann C, Kliem V, et al. Diltiazem increases blood concentrations of cyclized cyclosporine metabolites resulting in different cyclosporine metabolite patterns in stable male and female renal allograft recipients. Br J Clin Pharmacol 1996; 41:551.*
21. *Christians U, Jacobsen W, Benet LZ, et al. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet 2003; 41:813.*
22. *Mathis AS, DiRenzo T, Friedman GS, et al. Sex and ethnicity may chiefly influence the interaction of fluconazole with calcineurin inhibitors. Transplantation 2001; 71:1069.*
23. *Tuteja S, Alloway RR, Meier-Kriesche HU, et al. The effect of gender on ketoconazole induced changes in tacrolimus pharmacokinetics. Transplantation 2000; 69:S163.*
24. *Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. Drug Metab Rev 1997; 29:413.*
25. *Demeule M, Jodoin J, Beaulieu E, et al. Dexamethasone modulation of multidrug transporters in normal tissues. FEBS Lett 1999; 442:208.*
26. *Campana C, Regazzi MB, Buggia I, et al. Clinically significant drug interactions with cyclosporin. An update. Clin Pharmacokinet 1996; 30:141.*
27. *Filler G, Zimmering M, Mai I. Pharmacokinetics of mycophenolate mofetil are influenced by concomitant immunosuppression. Pediatr Nephrol 2000; 14:100.*
28. *Van Gelder T, Klupp J, Barten MJ, et al. Comparison of the effects of tacrolimus and cyclosporine on the pharmacokinetics of mycophenolic acid. Ther Drug Monit 2001; 23:119.*
29. *Kaplan B, Meier-Kriesche HU, Napoli KL, et al. The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. Clin Pharmacol Ther 1998; 63:48.*
30. *Crowe A, Lemaire M. In vitro and in situ absorption of SDZ-RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: comparison with rapamycin.*

31. *Nashan B. Early clinical experience with a novel rapamycin derivative. Ther Drug Monit 2002; 24:53.*

32. *Robert S, Gaston. Maintenance Immunosuppression in the Renal Transplant Recipient American Journal of Kidney Diseases2001; 38 (6): S25-S35.*