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A comprehensive review on immunosuppressant agent: Tacrolimus

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ABSTRACT

An immunosuppressive drug with great potency, tacrolimus (FK 506), has been shown to be effective in both in-vivo and in-vitro studies. As a calcineurin inhibitor, tacrolimus is also effective. The pharmacokinetics profile of tacrolimus is very variable across and within patients as a result of its low solubility. Numerous formulation strategies, including complexation with cyclodextrins, solid dispersions, oily solutions, liposomes, etc., have been researched to increase this agent's oral administration. Tacrolimus can be used to treat severe autoimmune disorders such atopic dermatitis and rheumatoid arthritis, and it has been given for patients who have undergone liver, intestine, lung, and heart transplants. Because it has a superior safety profile and a higher rate of long-term survival in patients than other immunosuppressants, tacrolimus is used the most commonly..

Keywords: *Immunosuppressant, Pharmacogenomics, Tacrolimus, Calcineurin inhibitor*

1. INTRODUCTION

Immunosuppressive drugs are used in immunosuppressive therapy to prevent the rejection of transplanted organs and tissues (e.g. bone marrow, heart, kidney, liver), treat autoimmune diseases or diseases that are most likely of autoimmune origin e.g. rheumatoid arthritis, multiple sclerosis, myasthenia gravis, psoriasis, vitiligo, granulomatosis with polyangiitis, systemic lupus erythematous, systemic sclerosis /scleroderma, sarcoidosis, focal segmental glomerulosclerosis, Crohn's disease, Behcet's Disease, pemphigus, ankylosing spondylitis and ulcerative colitis. They are also used to treat some other non-autoimmune inflammatory diseases e.g. long term allergic asthma control. Organ transplantation is a critically important procedure, which requires immune modulation by using immunosuppressants[1].

Various formulation approaches have been investigated for immunosuppressants therapy.

Immunosuppressant drugs like Cyclosporine (Neoral®, Gengraf®, and Sandimmune®), Tacrolimus (Prograf®, FK506), Mycophenolate Mofetil (CellCept®), Azathioprine (Imuran®) and Sirolimus (Rapamune®) are used in market[2,43,44].

Clinical trials have shown that immunosuppressive medications are effective in treating illnesses such severe auto-immune disorders and acute immunological rejection of organ transplants[2]. However, these treatments put patients at a significantly increased risk of infection and cancer since they must be used for the rest of their lives and non-specifically depress the whole immune system[3,42]. The specific calcineurin inhibitors and glucocorticoids are nephrotoxic and diabetogenic, respectively, limiting their effectiveness in a number of clinical contexts. Reactive T-cell-targeted monoclonal and polyclonal antibody preparations are crucial adjuvant treatments that offer a rare chance to directly target immune-reactive cells[4, 7]. Finally, the arsenal of immunosuppressive

agents has been increased by more recent small compounds and antibodies. Sirolimus, Everolimus, and anti-CD25 (interleukin-2 receptor [IL-2R]) antibodies in particular target growth-factor pathways, significantly reducing clonal spread[36].

Biochemistry of Immunosuppresant drug: Tacrolimus

Tacrolimus (also known as FK-506 or Fujimycin) is an immunosuppressive drug whose main use is after organ transplant

procedures to reduce the activity of the patient's immune system and so

the risk of organ rejection[5,6]. It was discovered in 1984 from the fermentation broth of a Japanese soil sample that contained the bacteria Streptomycin tsukubaensis[7,8]. Tacrolimus appears as white to almost white crystalline powder and is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform. It has melting point and partition coefficient at 127 - 129°C and > 1000 (in n-octanol/water) respectively. Tacrolimus is chemically known as a macrolide. It reduces peptidyl- prolylisomerase activity by binding to the immunophilin FKBP-12 (FK506 binding protein) creating a new complex. This FKBP12-FK506 complex inhibits calcineurin which inhibits T-lymphocyte signal transduction and IL-2 transcription[9,27]. Structure of Tacrolimus is shown in Figure 1

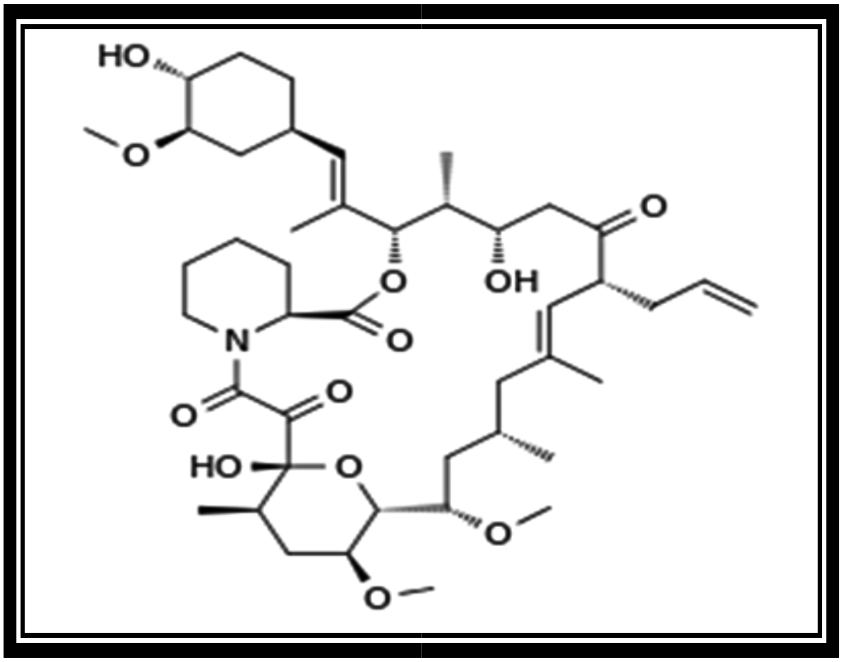

Figure 1: Structure of Tacrolimus[7, 8, 9]

Biosynthesis of Tacrolimus

Tacrolimus can be biosynthesized in a variety of methods. Five enzymes (fkbG, fkbH, fkbI, fkbJ, and fkbK) are involved in the biosynthesis of methoxyl malonyl CoA to Acyl Carrier protein. Propionylmalonyl-CoA can also take the place of allylmalonyl-CoA. By activating the fkbP enzyme, the L-pipecolic acid production pathway is NRPS enforced[27,28,41]. The molecule is cycled once the whole subunits have been created. The pre-tacrolimus molecule undergoes the postsynthase tailoring processes after the cyclization, including oxidation and S-adenosyl methionine. Particularly, the fkbM and fkbD enzymes are in charge of the alcohol methylation that targets the alcohol of the DHCHC starting unit (Carbon number 31 is shown in brown), while C9 is handled by the fkbM enzyme (shown in green). The tacrolimus molecule becomes physiologically active following these modifications[30,32,36]. Biosynthesis of Tacrolimus are elaborated in Figure 2.

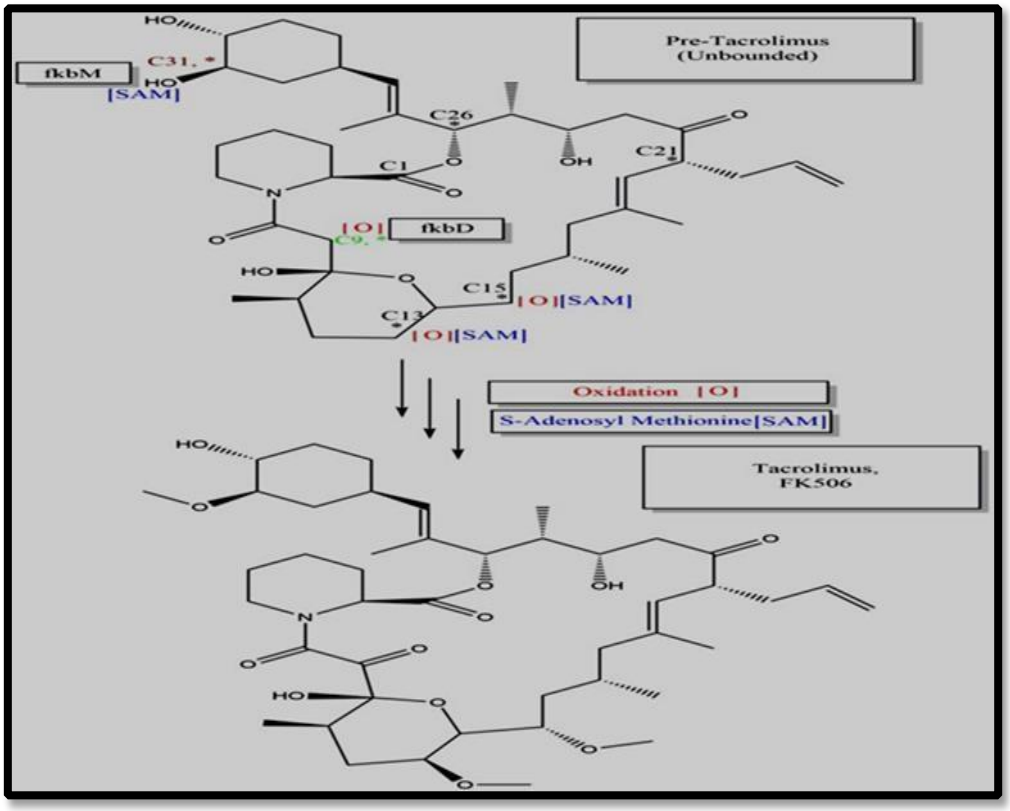

Figure 2: Biosynthesis of Tacrolimus[30,32]

Pharmacokinetics

Compared to cyclosporine, tacrolimus has a higher water solubility and absorbs from the stomach more consistently, albeit poorly. It is metabolized by the liver and has a half-life that varies greatly (4–41 hours)[10,11,36]. For the right dosage modification, particularly early in the course of treatment, monitoring of the trough blood concentration of Tacrolimus is crucial.

When the skin is irritated, topical tacrolimus can be absorbed well. The peak values, which can range from 0.05 to 0.25 ng/mL19 following the administration of 0.03% to 0.3% ointment, are attained after 3 to 6 hours of treatment. Despite the fact that topical Tacrolimus enters the skin less readily in healthy or healing skin, its absorption is much better than that of cyclosporine A since the latter has a higher molecular weight (1202.635) than Tacrolimus (822.05)[12,13,16]. To prevent going above the 5–20 ng/mL safe limit, which has been determined to be safe based on outcomes from transplant patients, whole blood levels may be monitored. The drug's low aqueous solubility in gastrointestinal secretions can affect how well it is absorbed, among other factors[24,29]. Approximately 35, 19, 12, and 24 hours, respectively, are the half-lives of elimination in adult healthy volunteers, kidney transplant recipients, liver transplant recipients, and heart transplant recipients.

Pharmacodynamics

Tacrolimus inhibits the calcineurin, c-Jun N-terminal kinase (JNK), and p38 pathways in lymphocytes and increases the production of transforming growth factor-ß1 (TGF-ß1)[10,16]. The majority of research on Tacrolimus' pharmacodynamic effects has been on how they affect T cells. Natural killer (NK) cell role in transplant rejection is not fully understood[24,25]. However, it has been discovered that Tacrolimus inhibits NK cell degranulation in a dose-dependent manner.

Pharmacogenomics of Tacrolimus

Most of Tacrolimus pharmacogenetic investigations have concentrated on the consequences of variations in the CYP3A4, CYP3A5, and ABCB1 genes because of the crucial role the enzymes

and transporters they code for play in Tacrolimus and cyclosporine disposition[13,14,44]. Few studies, however, have looked at:

The effect of single nucleotide polymorphisms (SNPs) on the pregnane X receptor gene

(NR1I2), which controls the expression of other genes, including CYP3A and ABCB1[23].

Several studies have looked at SNPs in the POR gene, which produces the CYP450 oxidoreductase, a protein that transfers electrons from NADPH to CYP450 enzymes to enable their activation. Patients receiving the twice-daily version of Tacrolimus (Prograf®) were the subject of certain studies. For the purpose of preventing renal allograft rejection, a novel extended release once-daily formulation of tacrolimus (Advagraf®) has been authorized. The pharmacogenetics of tacrolimus may vary across the two formulations, however according to this study, CYP3A5 expressers had double the clearance of non-expressers. This implies that earlier research on the pharmacogenetics of the twice-daily formulation would be helpful in identifying the polymorphisms involved in dosage needs in individuals receiving the once-daily formulation[34,35].

The general lack of consistency in these studies may be attributed to factors such as ethnic variation, small patient populations, non-specific pharmacokinetic assays, variability in the timing of outcome measurements, and the influence of donor genotype, particularly in nephrotoxicity studies in kidney transplant patients or pharmacokinetic studies in liver transplant patients. Larger studies and meta-analyses that take donor genotype and ethnicity into consideration might aid in resolving some of this variability.

Clinical Pharmacology and Therapeutic action

Cytochrome P450 3A enzymes (CYP3A4 or CYP3A5) are responsible for the metabolism of

Tacrolimus. Hydroxylation and demethylation processes result in the biotransformation of Tacrolimus, with the metabolite of 13-demethyl tacrolimus[15,17,18]. Tacrolimus gets excreted from the bile and urine, 30.7% - 92.6% from the bile and 1.1% - 2.3% from the urine.

Tacrolimus Drug Interactions

Tacrolimus produces immunosuppression, the use of live vaccines should be avoided.

Tacrolimus blood/ plasma levels Drugs that alter/impair renal function should be used with caution

as Tacrolimus impairs the renal system[18,19]. Drug interaction with Tacrolimus explained[24,25] in Table 1.

Table 1: Drug Interactions with Tacrolimus

Drug-Drug Interactions	**Effect on Concentration of Tacrolimus**
Proton pump inhibitor: Lansoprazole, Omeprazole	More concentration of Tacrolimus
Calcium channel blockers: Diltiazem, Nicardipine, Nifedipine, verapamil	Lower concentration of Tacrolimus
Azole Antifungal: Ketoconazole	Lower concentration of Tacrolimus
Azole Antifungal, Clotrimazole, Fluconazole, Itraconazole, Voriconazole	More concentration of Tacrolimus
Antacid: Magnesium-Aluminium hydroxide	More concentration of Tacrolimus
GI Prokinetic Agents: Cisapride, metoclopramide	More concentration of Tacrolimus
Macrolide antibiotics: Erythromycin,clarithromycin, roleandomycin	Lower concentration of Tacrolimus
Anti-Arrhythmic Agent: Amiodarone	More concentration of Tacrolimus

Side Effects:

The most common Side effect associated with the use of Tacrolimus has been described in detail as given below:

Diarrhea, constipation, nausea, or vomiting, Heartburn, Stomach pain, Loss of appetite,

Headache, Uncontrollable shaking of a part of the body[20].

Tacrolimus causes hypertension, hirutism and gingival hyperplasia.

Effects that are more common with Tacrolimus include Pleural and pericardial effusions;

Cardiomyopathy in children, who should be monitored by echocardiography[21]

Dosages

Tacrolimus has been used in different dosage forms which is described as given below:

Topical Dosage Form:

The topical route is a preferred choice; however, due to the benign nature of these dermatomes, and the potentially serious side effects of oral/intravenous tacrolimus confine its use only in transplant patients[20,22]. Topically, tacrolimus has been used in 0.03% to 0.1% ointment. In pediatric patients aged 2 years and older, 0.03% is preferred, while in adults and geriatric patients 0.1% may be used 2 times a day.

Oral Dosage Form:

Oral Tacrolimus has been used in psoriasis in the dosage of 0.1 mg/kg/body weight/d. The plasma levels effective in inducing and maintaining remission range from 0.5 mg to 1.4 ng/mL[20].

Limitations of Tacrolimus

Tacrolimus has poor biopharmaceutical properties like lower water solubility ranging from 4 to

12 µg/mL as well as lesser bioavailability ~21% only because of considerable first pass effect through CYP-450 3A4 gene in gut as well as liver and drug absorption is further hindered due to efflux by P-glycoprotein[19]

Tacrolimus takes about 2hrs for complete body release and displays more intra and inter individual variability (89%, 25% average) in renal transplant patients.

The most dominating one is the nephrotoxicity or renal impairment in organ transplanted subjects and it is the principle reason for patient non-compliance. Adverse effects like neurotoxicity (tremor, seizure and encephalopathy) are also common[22,23].

Contraindications and precautions of Tacrolimus:

The following conditions are contraindicated with this Tacrolimus drug:

Breast-feeding, Hepatic disease, Immunosuppression, Infants, Infection,

Neoplastic disease, such as: Skin cancer and Lung cancer Oliguria, Pregnancy[25,26]

Marketed Formulation of Tacrolimus

For oral administration, Tacrolimus is originally formulated and marketed as soft gelatine capsules comprising the equivalent of 0.5, 1 or 5 mg anhydrous Tacrolimus and marketed under the trade name Prograf®. The recommended initial oral dose is from about 0.1 to 0.2 mg/kg/day in patients. The dose aims at a certain trough plasma level from about 5 to about 20 ng/ml. Prograf® is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants[36,37]. Details of the clinical pharmacology, pharmacokinetics, and clinical studies are described in the label approved by FDA on Apr. 27, 2006 for Prograf®, NDA no 50708 which is hereby incorporated by reference. A new tablet formulation of tacrolimus was prepared and evaluated with pharmacokinetic study, research showed smaller inter-individual variability (IIV) in pharmacokinetic (PK) parameters than the conventional capsule formulation, while both

formulations were comparable PK and tolerability profiles[29,33]. These beneficial characteristics of the tablet formulation of tacrolimus was a useful alternative to the conventional capsule formulation in patients after organ transplantation, who are likely to have much larger IIV than healthy subjects[43,44].

Table 2: Marketed Tacrolimus formulation and it uses

Tacrolimus Formulation	Company Name and Country	Year	Use of Formulation in
Prograf	Astellas Pharma, Japan	1993	Kidney, Liver transplant Rejection
Prograf	Astellas Pharma Japan	1999	Atopic dermatitis
Prograf[38]	Astellas Pharma, Japan	2005	Rheumatoid Arthritis
Prograf	Astellas Pharma,U.S	2006	Heart transplant rejection
FK506	Senju Pharma	2007	Lupus nephrititis
Prograf[40]	Astellas Pharma	2008	Mysthenia Gravis
FK 506[33]	Senju Pharma	2009	Ulcerative colitis
Astagraf XL[33]	Astellas Pharma	2013	Extended release Formulation of prophylaxis of organ rejection
Envarsus XL[33]	Veloxis Pharma,U.S	2013	Extend release formulation of kidney Transplant Rejection.

2. CONCLUSION

According to the most recent developments, Tacrolimus has emerged as a key therapeutic alternative for the best possible individualized immunosuppressive treatment, particularly in the case of transplant patients.

Tacrolimus has been shown to be a promising drug since the 19th century, especially as an immunosuppressant in organ transplantation, and has been explored in different areas of medicine, but its efficacy and toxicity issues need to be dealt with properly with more precision and accuracy. Tacrolimus is used the most frequently in comparison to other immunosuppressants because it offers better safety profile with increased long-term survival in patients. The majority of work has been focused on enhancement of in-vitro solubility and absorption.

• There is no doubt that development of new formulations or analogues of Tacrolimus with better bioavailability and having low inter/intra-subject variability will be critical for future development of tacrolimus formulation. This will make the use of drug more effective and safe.

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