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A Review on Tacrolimus: A Potent Immunosuppressive Agent

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Abstract

Tacrolimus (FK 506) is a highly potent immunosuppressive agent and has proven activity in both in-vivo and in-vitro experiments. Tacrolimus is also a calcineurin inhibitor. Because of its poor solubility, Tacrolimus has a large inter-/intra-patient variability in its pharmacokinetics profile. To improve oral delivery of this agent, there are several formulation approaches such as oily solution, solid dispersions, complexation with cyclodextrins, liposomes *etc.* that have been investigated. Tacrolimus has been prescribed for liver, intestinal, lung and heart transplant recipients and can be used to manage severe autoimmune conditions, such as atopic dermatitis and rheumatoid arthritis.Tacrolimus is used most frequently in comparison to other immunosuppressant because it offers better safety profile with increased long-term survival in patients.

Keywords: Biosynthesis, Chemistry, Immunosuppressant, Pharmacogenomics, Tacrolimus.

Introduction

Immunosuppressive drugs are used to dampen the immune response in organ transplantation and autoimmune disease[1]. In transplantation, the major classes of immunosuppressive drugs used today are: glucocorticoids, calcineurin inhibitors, anti-proliferative/antimetabolic agents and biologicals (monoclonal antibodies).

Immunosuppressive drugs have been clinically successful in treating conditions such as acute immune rejection of organ transplants and severe auto-immune diseases[2]. However, such therapies require lifelong use and non-specifically suppress the entire immune system, exposing patients to considerably higher risks of infection and cancer. The calcineurin inhibitors and glucocorticoids, in particular, are nephrotoxic and diabetogenic, respectively, thus restricting their usefulness in a variety of clinical settings[3]. Monoclonal and polyclonal antibody preparations directed at reactive T-cells are important adjunct therapies and provide a unique opportunity to target specifically immune-reactive cells[4,7]. Finally, newer small molecules and antibodies have expanded the arsenal of immunosuppressive. In particular, mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) and anti-CD25 (interleukin-2 receptor [IL-2R]) antibodies (basiliximab, daclizumab) target growth-factor pathways, substantially limiting clonal expansion and thus potentially promoting tolerance. In the future decade, many more selective therapeutic agents under development are expected to revolutionize immunotherapy[27,28]

Chemistry of Tacrolimus

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[7, 8].

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[45]. 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.[7, 8, 9.] Structure of Tacrolimus is shown in Figure 1.

Mechanism of Action:

Tacrolimus binds with intracellular protein FKBP-12, which is used to block the activation of T-lymphocytes[5].Due to this blockage, there are two consequent process happened. One is calcium, calmodulin and calcineurin are formed and the other process is inhibition of the phosphatase activity of calcineurin[5,8].

The bioavailability of Tacrolimus is high but the therapeutic window is narrow[31], because of the narrow therapeutic window the marked whole blood trough levels result in efficacy and toxicity[32]. The Mechanism of Action is depicted in Fig.2.

Biosynthesis

There are several possible ways of biosynthesis of Tacrolimus[26, 27].The biosynthesis of methoxylmalonyl CoA to Acyl Carrier protein is proceeded by five enzymes (fkbG, fkbH, fkbI, fkbJ, and fkbK). Allylmalonyl-CoA is also able to be replaced by propionylmalonyl-CoA[28, 30]. The process of L-pipecolic acid synthesis is NRPS enforced by fkbP enzyme[22, 29]. After synthesizing the entire subunits, the molecule is cyclized. After the cyclization, the pre-tacrolimus molecule goes through the post-synthase tailoring steps such as oxidation and S-adenosylmethionine. Particularly fkbMenzyme is responsible of alcohol methylation targeting the alcohol of DHCHC starter unit (Carbon number 31 depicted in brown), and fkbD enzyme is responsible of C9 (depicted in green). After these tailoring steps, the tacrolimus molecule becomes biologically active [30, 32.] Biosynthesis of Tacrolimus are elaborated in Figure 3.

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[10, 12]. Tacrolimus gets excreted from the bile and urine, 30.7% - 92.6% from the bile and 1.1% - 2.3% from the urine[11].

Pharmacokinetics

Tacrolimus is more water-soluble than cyclosporine and undergoes more predictable, though poor, absorption from the gut. It has a highly variable half-life (4–41 hours) and it is metabolized by the liver[36]. Monitoring of the trough blood concentration of Tacrolimus is essential for appropriate dose adjustment, especially early in treatment.

Topical Tacrolimus is sufficiently absorbed when the skin is inflamed. After an application of 0.03% to 0.3% ointment, the peak levels are reached after 3 to 6 hours of application, which may vary from 0.05 to 0.25 ng/mL[19]. Although topical Tacrolimus penetrates less readily in the intact or healing skin, its absorption is far better than that of cyclosporine A, as the latter has a larger molecular weight (1202.635) compared with Tacrolimus (mol weight 822.05). Whole blood level may be monitored, however, to avoid exceeding the safe limit of 5 to 20 ng/mL, which is considered safe according to results from transplant recipients. The absorption ofthedrug may vary due in part to poor aqueous solubility of the drug in gastric secretions[43],.

The elimination half-life in adult healthy volunteers, kidney transplant patients, liver transplants patients, and heart transplant patients are approximately 35, 19, 12, 24 hours, respectively. The

elimination half-life in pediatric liver transplant patients was 11.5±3.8 hours, in pediatric kidney transplant patients was 10.2±5.0 (range 3.4-25) hours.

Pharmacodynamics

Within lymphocytes, Tacrolimus exert immunosuppression by several pathways, including inhibiting the calcineurin and the c-Jun N-terminal kinase (JNK) and p38 pathways, and inducing the increased expression of transforming growth factor-ß1 (TGF-ß1)[14,15]. The majority of studies on the pharmacodynamic effects of Tacrolimus have focused on their role in T cells. The involvement of natural killer (NK) cells in transplant rejection is not very well defined. However, Tacrolimus has been found to inhibit NK cell degranulation in a dose-dependent manner[17.]

Pharmacogenomics of Tacrolimus

The majority of pharmacogenetic studies on Tacrolimus have focused on the effects of variants in the *CYP3A4*, *CYP3A5* and *ABCB1* genes because of the central role the enzymes and transporters they code for play in Tacrolimus and cyclosporine disposition[44]. However, a few studies have examined:

- The influence of single nucleotide-polymorphisms (SNPs) within the gene encoding the pregnane X receptor (*NR1I2*), which regulates the expression of multiple genes including *CYP3A* and *ABCB1*.[18]
- A couple of studies have examined SNPs in the *POR* gene, which encodes for CYP450 oxidoreductase, a protein responsible for transferring electrons from NADPH to CYP450 enzymes, enabling their activity.[19]
- Several studies have also looked at variations in the TGF-ß1 gene (*TGFB1*), the cyclophilin A gene (*PPIA*), and the *CYP2C8* gene; CYP2C8 is involved in the metabolism of arachidonic

acids (AAs) into epoxyeicosatrienoic acids (EETs), metabolites implicated in maintaining normal renal function[20]

- Despite these numerous studies, only the **3* allele in the *CYP3A5* gene has shown strong associations with Tacrolimus pharmacokinetics[21]
- Some study was based on patients treated with the twice daily formulation of Tacrolimus (Prograf®) .A new prolonged release once daily formulation of Tacrolimus (Advagraf®) has been approved for the prevention of renal allograft rejection.Thepharmacogenetics of tacrolimus could differ between the two formulations however this study reports a two fold higher clearance in CYP3A5 expressers compared to non-expressers[33]. This suggests that previous works describing the pharmacogenetics of the twice daily formulation could be useful to identify the polymorphisms implicated in dose requirements in patients treated with the once daily formulation.[34]
- Some Study demonstrates that patients expressing CYP3A5 need more Tacrolimus to reach target tacrolimuspredose concentration. In addition, tacrolimus exposure is lower in these patients in the early phase after kidney transplantation.[35]

Very little consistent evidence has emerged for factors affecting Tacrolimus pharmacodynamics or cyclosporine pharmacokinetics and pharmacodynamics[16,24]. The overall inconsistency of these studies may be related to ethnic variability, small numbers of patients, non-specific pharmacokinetic assays, variation in when outcomes are measured, and the impact 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 ethnicity and donor genotype into account may help resolve some of this variability[20]

Tacrolimus Drug Interactions

Tacrolimus blood/ plasma levels Drugs that alter/impair renal function should be used with caution as Tacrolimus impairs the renal system[16]. Furthermore, since Tacrolimus produces immunosuppression, the use of live vaccines should be avoided.[22, 23] Drug interaction with Tacrolimus explained in Table 1.

Unwanted effects

Tacrolimus causes hypertension, hirutism and gingivalhyperplasia[28]. Effects that are more common with Tacrolimus include.

- Pleural and pericardial effusions;
- Cardiomyopathy in children, who should be monitored by echocardiography[30].

Side Effects: The most common Side effect associated with the use of Tacrolimushas 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[25].

Dosages

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

- 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].
- 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. 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[21].

- It is not recommended for use in pregnancy and lactation, as its safety has not yet been established. Although results of combining topical tacrolimus with UV light has been found to be encouraging in vitiligo, carcinogenic adverse effects cannot be ruled out, and long-term follow-up is still required[22].

Limitations of Tacrolimus

Tacrolimus doesn't bear a smoother pharmacokinetic profile and thus it leads to a great bunch of hurdles for researchers to target adequate amount of drug to the action site[18]. Apart from its poor bioavailability, nephrotoxicity is also of great concern simultaneously. All these limitations can be well addressed through targeted drug delivery system likely in a smarter way. Such limitations bearing Tacrolimus are discussed below[18, 19]

- Biopharmaceutical issues: Tacrolimushas poor biopharmaceutical properties like lower water solubility ranging from4 to 12 µg/mL as well as lesser bioavailability ~21% only because of considerable first pass e□ect through CYP-450 3A4 gene in gut as well as liver and drug absorption is further hindered due to e□ux by P-glycoprotein[19]
- Variability issues: Tacrolimus takes about 2hrs for complete body release and displays more intra and inter individual variability (89%, 25% average) in renal transplant patients.
- Toxicity issues: 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 e□ects like neurotoxicity (tremor, seizure and encephalopathy) are also common[22,23].

- Immunosuppression: Immunosuppressants have common side e□ect of global immunosuppression due to lack of target–specificity, complex mechanism of actions leading to recurrence of infection especially in case of cancer or polyomavirus-associated nephropathy[24].

Others: Diabetes mellitus, diarrhea, pruritus, alopecia orhypertension can be observed. The occurrence of all these side e□ects further relies on nature of medication, duration of treatment, finally disease[25]. It also relies on transplanted organ dosage and age factor of patients.

Contraindications and precautions of Tacrolimus:

The following conditions are contraindicated with this Tacrolimusdrug:

- Breast-feeding, Hepatic disease, Immunosuppression, Infants, Infection, Neoplastic disease, such as: Skincancer and Lungcancer[30]Oliguria, Pregnancy, QTinterval prolongation[32]Sunlight (UV) exposure,Grapefruit juice.

Summary of 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[38]. 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[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[39].

Currently there is a requirement for Tacrolimus formulations and/or dosage forms having higher bioavailability and better pharmacokinetic properties[40,41]. Higher bioavailability alongwith an extended release dosage form will enable decreasing the number of dosage units to be taken by the patients, for e.g. once daily dosage without the threat of lack of effectiveness due to low doses in the past. Moreover, the variations in the plasma drug concentration against time profile will also be decreased significantly[44]. Increased bioavailability will also lead to more reproducible release profile.

The biggest issue with modified or extended release dosage forms of Tacrolimus is the complication in getting a desired and adequate absorption in the lower part of the gastrointestinal tract as the oral formulations reaching to the colon may get excreted before any significant release of the drug[45]. Moreover, due to the higher expenditure of genotypic tests and the wide availability and usage of monitoring of therapeutic drug levels, it is inconvenient for many persons and/or institutions to carry out the genotyping of all the transplant patients[46].

Conclusion

From the current trends, in case of transplant recipients, Tacrolimus has become an important therapeutic option for the optimal individualization of immunosuppressive therapy especially.

- Tacrolimus is used most frequently in comparison to other immunosuppressant because it offers better safety profile with increased long-term survival in patients.
- Tacrolimus has proved to be a promising drug since 19th century especially as an immunosuppressant in organ transplantation and has been explored in different areas of medication, but its efficacy and toxicity issues needs to be dealt properly with more precision and accuracy.
- 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/intrasubject 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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Table 1: Drug Interactions with Tacrolimus[16, 22, 23]

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

Table 2: Formulation of Tacrolimus[33]

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

Figures:

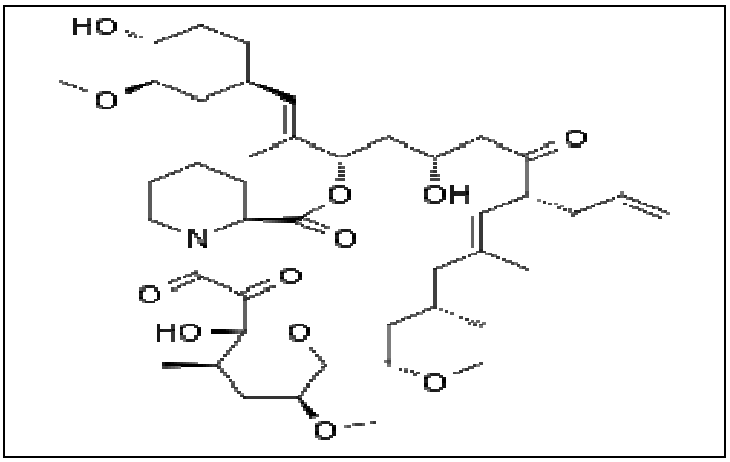

Figure 1: Structure of Tacrolimus[7,8,9]

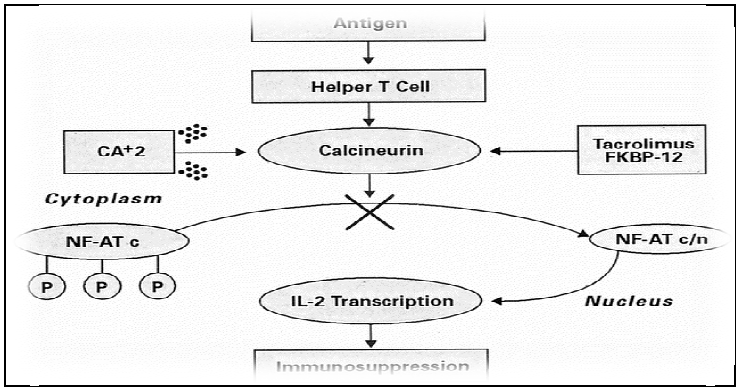

Figure 2: Mechanism of Action of Tacrolimus[31,32]

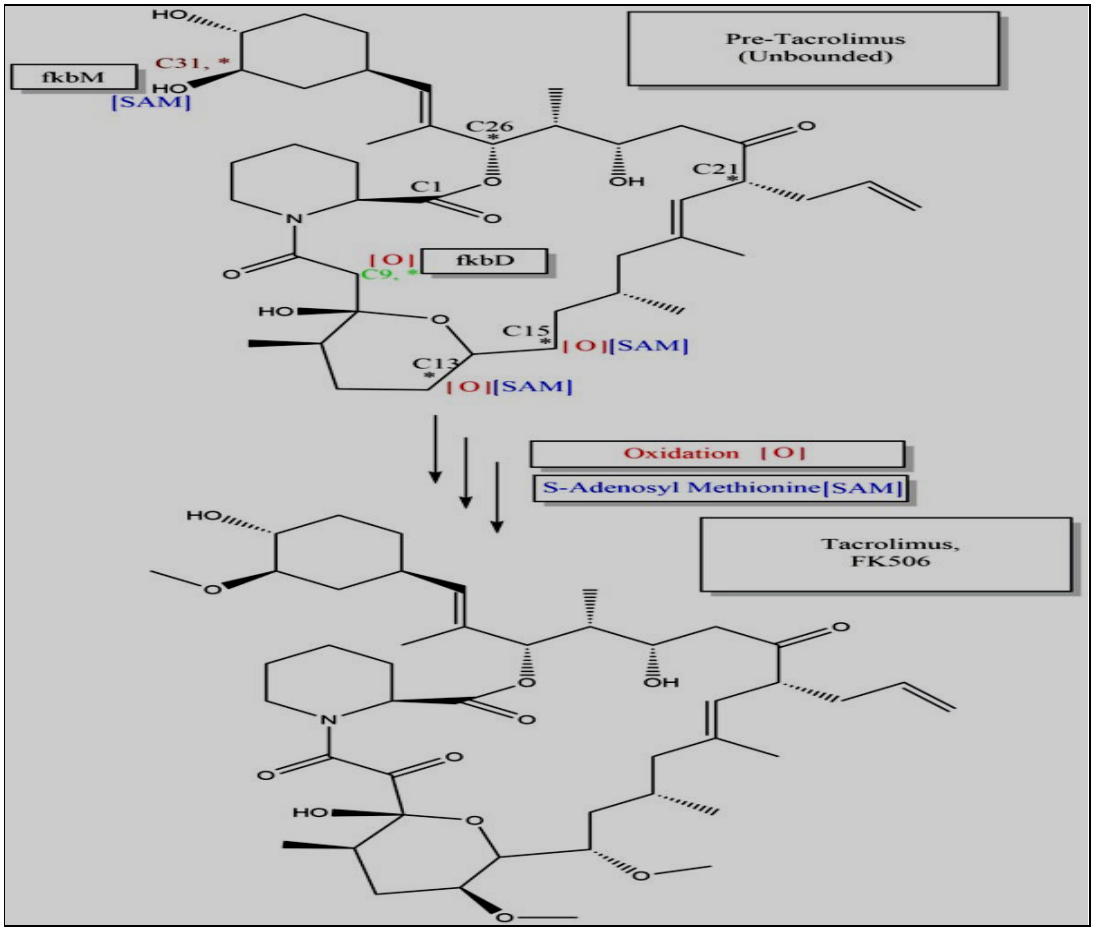

Figure 3: Biosynthesis of Tacrolimus[30,32]

