DESCRIPTION

Tacrolimus is a macrolide lactone with potent immunosuppressive activity, isolated from Streptomyces tsukubaensis. Chemically, Tacrolimus is \((\cdot) - (3S, 4R, 5S, 8R, 9E, 12S, 14S, 15R, 16S, 18R, 19R, 26aS) - 8 - Allyl - 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24, 25, 26, 26 a - hexa-decahydro - 5,19 - dihydroxy - 3-\[(E) - [1R, 3R, 4R] - 4 - hydroxy - 3 - methoxycyclohexyl\] - 1 - methylvinyl\]-14, 16 - dimethoxy - 4,10, 12, 18 - tetramethyl - 15, 19 - epoxy - 3H - pyrido [2,1-c][1,4] oxazacyclotricosine \(\cdot\) 1, 7, 20, 21(4H,23H) - tetrone monohydrate. Tacrolimus has an empirical formula of \(\text{C}_{44}\text{H}_{69}\text{NO}_{12}\cdot\text{H}_{2}\text{O}\) and a formula weight of 822.05.

PanGraf 0.5 is a pink/ transparent, size "5" hard gelatin capsule containing white to off-white powder.
PanGraf 1.0 is a blue/ transparent, size "5" hard gelatin capsule containing white to off-white powder.
PanGraf 5.0 is a white / white, size "4" hard gelatin capsule containing white to off-white powder.

COMPOSITION

PanGraf 0.5
Each hard gelatin capsule contains:
Tacrolimus
equivalent to Anhydrous Tacrolimus........... 0.5 mg

PanGraf 1.0
Each hard gelatin capsule contains:
Tacrolimus
equivalent to Anhydrous Tacrolimus........... 1.0 mg

PanGraf 5.0
Each hard gelatin capsule contains:
Tacrolimus
equivalent to Anhydrous Tacrolimus........... 5.0 mg

CLINICAL PHARMACOLOGY
Mechanism of action
Tacrolimus exerts potent inhibitory effect on T-lymphocyte activation. It binds to immunophilins FK506 binding proteins (FKBP-12) and a complex of FKBP-12, calcium, calmodulin and calcineurin is formed, inhibiting phosphatase activity of calcineurin. This prevents dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT) and inhibits transcription of early T-cell activation gene, Interleukin-2, Tumour Necrosis Factor (TNF-α) and proto-oncogenes; suppressing expression of IL-2 and IL-7 receptor. This results in inhibition of T-lymphocyte activation. Tacrolimus also inhibits the mixed lymphocyte reaction, generation of cytotoxic T-cells and T-cell dependent B-cell activation.¹

PHARMACOKINETICS

Absorption of Tacrolimus after oral administration is incomplete and variable with oral bioavailability of 4 - 93% and mean bioavailability of 25%. Food appears to reduce the absorption and relative bioavailability of Tacrolimus. In most cases, Cmax is achieved after 0.5 to 1 hr. However, the overall mean time to Cmax is about 2 hrs. Tacrolimus is 72-99% plasma protein bound over a concentration range of 5-50 ng/ml. At concentration above 50 ng/ml, the plasma protein binding becomes saturable. It also binds to erythrocytes and lymphocytes. The distribution of Tacrolimus between whole blood and plasma depends on several factors such as hematocrit, temperature, time of plasma separation, drug concentration and plasma protein concentration. It is mainly metabolized (>99%) in liver by a cytochrome isoenzyme (P450 CYP3A) to at least 15 compounds. The main metabolite is 13-O-demethyltacrolimus and an active metabolite 31-O-demethyltacrolimus. Tacrolimus has an elimination half-life of 4 - 41 hrs with mean t1/2 of 12 hrs. The main route of elimination of Tacrolimus metabolites is biliary and less than 1% is excreted unchanged in urine. Fecal elimination accounts for more than 92% of the drug.

Special population

Pediatric: Children require higher mg/kg doses than adults because of higher clearance than adults.²

Hepatic impairment: In mild hepatic dysfunction, the mean clearance of Tacrolimus has not been reported to be substantially different from that in normal volunteers. However, clearance of Tacrolimus is decreased in patients with marked hepatic impairment compared to those with normal hepatic function.

Renal insufficiency: Clearance of Tacrolimus is similar in patients with renal insufficiency and healthy volunteers.

Gender: No study has been reported in literature to evaluate the effect of gender on Tacrolimus pharmacokinetics. However, kinetic studies on kidney and liver transplant patients indicated no gender based differences.

CLINICAL STUDIES

There has been a large number of studies reported in literature that have evaluated the efficacy and safety of Tacrolimus in solid organ transplant. A study conducted with Tacrolimus in Indian population has shown that the daily dose requirements have ranged from 0.21±0.05 to 0.18±0.04mg/kg. The corresponding blood trough levels of the patients administered Tacrolimus have ranged from 13.48±6.90 to 14.44±7.81ng/ml at 3 months.³ A long-term study has also demonstrated the superior efficacy and safety profile of Tacrolimus from Cyclosporine in terms of a reduced incidence of treatment failure and significantly improved graft survival rates as has been reported in literature.⁴ It has also been seen that the rate of biopsy proven acute rejection and corticosteroid resistant rejection have been significantly lower with Tacrolimus.⁵ Tacrolimus when used in combination with Sirolimus has provided a very effective and safe regimen in terms of patient and graft survival rates.⁶ However, the best results in terms of graft survival and delayed graft function have been achieved with Tacrolimus in combination with Mycophenolate or
Azathioprine. Tacrolimus when compared with Cyclosporine in liver transplantation at 1 year has also shown that the clinical outcome has been better with Tacrolimus based immunosuppression than with Cyclosporine.

INDICATIONS AND USAGE

Tacrolimus is indicated for prophylaxis of organ rejection in patients receiving allogenic renal or liver transplants.

CONTRA-INDICATIONS

Tacrolimus is contraindicated in patients with hypersensitivity to Tacrolimus.

WARNINGS

1. Administration of Tacrolimus may cause diabetes mellitus and may require treatment.
2. Tacrolimus can cause neurotoxicity and nephrotoxicity when used in high doses.
3. Tacrolimus should not be used simultaneously with Cyclosporine. Either of the two should be discontinued at least 24 hours prior to initiating the other.
4. Patients should be monitored closely for the evaluation of rejection, toxicity, dose adjustments and compliance.
5. Mild to moderate hyperkalemia may occur and may require frequent monitoring and treatment.
6. Patients receiving Tacrolimus are at high risk of lymphomas, malignancies and infections due to oversuppression of immune system. Therefore, combination immunosuppressants should be used with caution.

PRECAUTIONS

Repeated laboratory tests like serum creatinine, potassium and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

General: Mild to moderate hypertension is a common adverse effect. Antihypertensive therapy may be required in some patients.

Patients with hepatic impairment: Lower dosage should be used in patients with compromised hepatic function.

Patients with renal impairment: Lower dosage should be used in patients if graft becomes compromised.

Hypertrophic cardiomyopathy: Hypertrophic cardiomyopathy has been observed in infants and children. Dosage reduction or discontinuation of therapy is required.

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Tacrolimus should be used in pregnancy only if the benefits outweigh potential risks to fetus.

Nursing mothers: Since Tacrolimus is excreted in human milk, nursing should be avoided.

DRUG/FOOD INTERACTIONS
As Tacrolimus is metabolized by cytochrome P450 CYP3A enzyme, potential drug interactions are numerous.

**Increased Tacrolimus Blood Concentration**
Calcium channel blockers, Antifungal agents, Macrolide antibiotics, Corticosteroids, Cyclosporine, Prokinetic agents, Omeprazole, Bromocryptine, Protease inhibitors etc. increase blood concentration of Tacrolimus. Monitoring of blood concentration of Tacrolimus and dosage adjustment is recommended.

**Decreased Tacrolimus Blood Concentration**
Anticonvulsants, Anticoagulants, Antacids, Rifabutin and Rifampicin decrease Tacrolimus blood concentration.
Interaction studies with drugs used in HIV therapy have not been conducted.

**Increased Renal Toxicity**
Nephrotoxic drugs like Acyclovir, Aminoglycosides, Amphotericin B, ACE inhibitors, Cisplatin, Cyclosporine and NSAIDs have a potential for additive or synergistic toxicity with Tacrolimus. Care should be taken when these drugs are co-administered with Tacrolimus.

**Vaccines**
Tacrolimus may reduce the efficacy of vaccines and recipients of Tacrolimus should not receive live attenuated vaccines.

**Food**
Food decreases the rate and extent of absorption of Tacrolimus. Absorption for this drug is greatest under fasted conditions. Grapefruit juice is reported to increase Tacrolimus blood trough concentration and should be avoided.

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**ADVERSE REACTIONS**

Tacrolimus shows adverse events common to other immunosuppressive therapies viz. neurotoxicity, nephrotoxicity, increased risk of infection and malignancy, diabetes mellitus and a lymphoproliferative disorder related to Epstein-Barr virus. The most common adverse events reported are:

**Nervous system** - Tremor, Headache, Paresthesia, Dizziness, Insomnia, Seizures, Coma and Delerium with high plasma concentrations of Tacrolimus.

**Gastrointestinal** - Diarrhea, Constipation, Nausea, Vomiting and Dyspepsia.

**Cardiovascular** - Hypertension, Chest pain.

**Urogenital** - Creatinine increased, Urinary tract infection.

**Metabolic and Nutritional** - Hyperkalemia, Hyperglycemia (new onset post transplant diabetes mellitus), Hyperlipidemia, Hypophosphatemia, Hypomagnesemia, Hyperglycemia, Diabetes mellitus, Hypokalemia, Edema

**Hemic and Lymphatic** - Anemia, Leukopenia

**Respiratory system** - Dyspnea

**Musculoskeletal** - Arthralgia, Back pain

**Skin** - Rash, Pruritus

**Miscellaneous** - Infection, Peripheral edema, Asthenia, Abdominal pain, Fever.

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**OVERDOSE AND TREATMENT**
There is a very limited experience of Tacrolimus overdose. Acute overdose does not show any special adverse effect. However, it is expected that they shall be consistent with reported adverse effects of Tacrolimus.

**Overdose Management**

It is expected that Tacrolimus is not dialysable to any significant extent. Although use of charcoal is reported, it is not supported by experience. General supportive measures and treatment of specific symptoms should be followed in all cases.

**DOSAGE AND ADMINISTRATION**

In renal transplantation, Tacrolimus oral therapy should be started as soon as patient is able to tolerate oral dose, at a dosage of 0.2 mg/kg/day in adults as 2 divided doses taken every 12 hrs. The initial dose of Tacrolimus may be administered within 24 hours of transplantation, but preferably until renal function has recovered. The recommended target whole blood trough concentrations is between 7-20ng/ml for 0-3 months and 5-15ng/ml for 4-12 months. Pediatric patients may require higher dosage.

In liver transplantation, therapy should be started at oral dose of 0.10 - 0.15 mg/kg/day administered in two divided daily doses every 12 hrs. Most patients are stable when whole blood trough concentrations are maintained between 5-20ng/ml.

Dosage adjustments are made on the basis of clinical assessment of rejection, tolerability and on blood concentration of Tacrolimus.

**Replacement /Concomitant administration with Cyclosporine**

Tacrolimus and Cyclosporine should not be administered concomitantly. Either of the two should be discontinued at least 24 hours before initiating the other.

**Adjunct therapy**

Concomitant use of corticosteroids and other immunosuppressants such as Mycophenolate mofetil or Azathioprine is recommended during early post transplant. However, lower maintenance doses of steroid are required due to steroid sparing effect of Tacrolimus.

**Blood Concentration Monitoring**

Monitoring of Tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, and addition or discontinuation of potentially interacting drugs and the posttransplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulant is not recommended because of the tendency to form clots on storage.

**STORAGE INSTRUCTIONS**

Store at a temperature below 25° C, protect from light and moisture.

KEEP OUT OF THE REACH OF CHILDREN.
REFERENCES

3. Efficacy and tolerability of Tacrolimus in patients of renal transplantation in Indian population. Data on file