CHAPTER 34

TACROLIMUS

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INTRODUCTION

Tacrolimus (also FK-506 or fujimycin) is a 23-membered macrolide lactone derived from the fermentation broth of a Japanese soil sample that contained the bacterium *Streptomyces tsukubaensis*. It is an immunosuppressive drug that used mainly for allogeneic organ transplant to lower the risk of organ rejection.[1] Tacrolimus was discovered in 1987; the name tacrolimus is derived from 'Tsukuba macrolide immunosuppressant.[2] The discovery of tacrolimus was preceded by the discovery of rapamycin (sirolimus) on Rapa Nui (Easter Island) in 1975 and it was among the first macrolide immunosuppressants discovered.[3] In 1994, tacrolimus was first approved for use in liver transplantation by Food and Drug Administration; this has been extended to include kidney, heart, small bowel, pancreas, lung, trachea, skin, cornea, bone marrow, and limb transplants.

Structure and physical properties

Tacrolimus has a molecular weight of 822 kDa with the empirical formula of $C44H69NO12•H_2O$ (Figure 1). It appear as white crystals or crystalline powder, insoluble in water, slightly soluble in saturated hydrocarbons, and highly soluble in lipids and other organic solvents.[4]

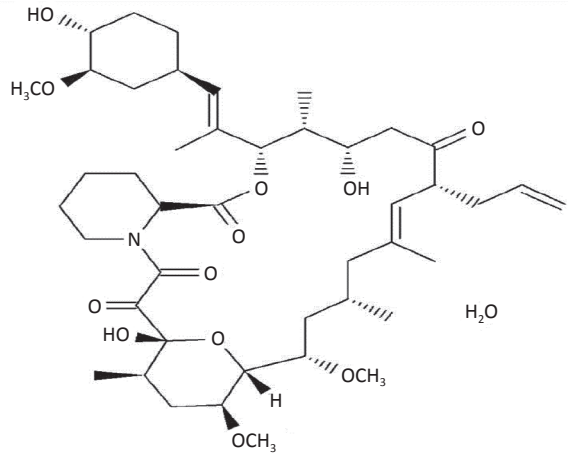


Figure 1. Structure of tacrolimus.

Mechanism of Action

Calcineurin inhibitors exert their cellular effects through binding to proteins called immunophilins. FK binding proteins, a family of cytoplasmic proteins present in most cells, bind tacrolimus with high affinity. The drug-receptor complex specifically and competitively binds to and inhibits a calcium and calmodulin dependent phosphatase called calcineurin.[5] In the process of T-cell activation calcineurin dephosphorylates inactive nuclear factor of activated T cells (NFAT). Nuclear factor of activated T cells can cross over from cytoplasm into the nucleus only in dephosphorylated form. After entering the nuclear membrane, NF-AT forms a complex with a nuclear subunit of NF-AT. This complex then binds to the promoter regions of several genes, such as interleukin (IL)-2, IL-3, IL-4 and tumour necrosis factor (TNF)-α.[6] Tacrolimus enters the T cells and then binds to immunophilins to form a complex that binds competitively and blocks calmodulin. This process prevents the dephosphorylation of the nuclear factor of activated T (NF-AT) cells and blocks the cascade of cytokine gene transcription involved in T-cell activation. Ultimately, proliferation of lymphocytes is reduced (Figure 2). Although some inhibition of T-suppressor and T-cytotoxic cells also seems to occur, tacrolimus acts mainly on T-helper cells. In addition, tacrolimus also inhibits T cell-dependent B cell responses.

Besides the interference with calcineurin/NFAT pathways, tacrolimus has been also shown to block both the Jun N terminal kinase and p38 signaling pathways, which are necessary for activation of AP-1 among other transcription factors.[7] Interference of tacrolimus with both calcineurin/NFAT pathways and Jun N terminal kinase and p38 signaling pathways, two distinct mechanisms of T-cell activation, contributes to the high specificity of immunosuppressive properties of calcineurin inhibitors.[4]

Additional immunomodulatory effects of tacrolimus include the inhibition of mast cell adhesion, interfering with IgE receptor-mediated histamine and serotonin release from basophils and mast cells, the down-regulation of the expression of IL-8 receptor and FCRI on Langerhans' cells, and decreasing intercellular adhesion

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, and abdominal discomfort. Rarely, tacrolimus may cause increase in liver enzyme which is reversible with dose reduction or drug discontinuation.

Dermatologic: Skin tingling, acne, localized flushing (following ethanol consumption), folliculitis, urticaria, rash, pustular rash, vesiculobullous rash, contact dermatitis, cyst, eczema herpeticum, fungal dermatitis, sunburn, alopecia, dry skinan alopecia. Calcineurin-inhibitor pain syndrome (symmetrical pain in the lower limbs, usually involving the bones of the feet, ankles, and knees) is another side effect which may be associated with tacrolimus.

Contraindications and precautions

Hypersensitivity to tacrolimus or polyoxyl castor oil products (used as solvents for injection preparation of the drug) is a contraindication to its use. Intravenous tacrolimus should be used only if the oral route is not feasible.

The following conditions should be take into account during folow-up in patients started on tacrolimus therapy:

- Anaphylaxis (If iv injection will be used)
- Cardiovascular: Myocardial hypertrophy, prolongation of the QT/QTc and torsade de pointes may ocur.
- Diabetes mellitus (post-transplant): Monitor blood glucose frequently.
- Gastrointestinal perforation: Gastrointestinal perforation may ocur.
- Hyperkalemia: Monitor serum potassium levels and avoid use of agents potentially have hyperkalemic effect.
- Hypertension
- Infections
- Malignancy
- Nephrotoxicity
- Neurotoxicity
- **Pure red cell aplasia (PRCA):** PRCA has been reported in patients receiving tacrolimus. Discontinuation of therapy should be considered with diagnosis of PRCA.
- Drug-drug/drug-food interactions

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