Tacrolimus: A Patient Case Related to Mechanism of Action and Metabolism

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Abstract

Tacrolimus is a macrolide antibiotic drug that is an immunosuppressive agent used in organ transplant patients to prevent graft rejection (figure 1). Maintaining appropriate levels of drug in the body decreases the likelihood that the patient will reject their organ. The consequences of organ rejection may range from needing a new organ to life sustaining therapy and at worse, death.

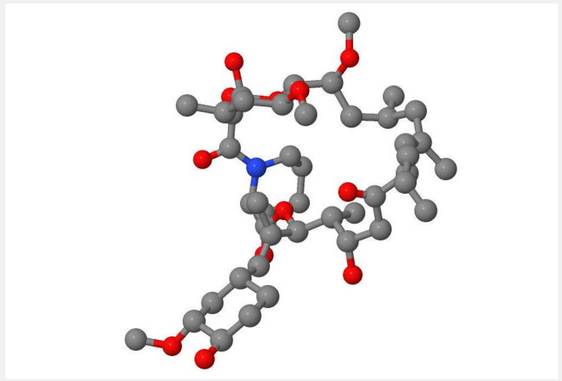

Figure 1 Tacrolimus Molecular Model. Model depicts Tacrolimus in the bound state within FKBP12. Each color represents an element (gray = carbon, red = oxygen, blue = nitrogen). Rendered in Jmol from 1FKJ.pdb.

Introduction

The immune system is an intricate defense mechanism to protect the body from harmful substances which have proteins coating their surfaces called antigens. When antigens enter the body, the immune system recognizes they are not from the body, labeling them as "foreign", and attacks them. When transplant patients receive an organ from another person, their body's immune system may recognize the transplanted organ as "foreign" due to the surface antigens, which can lead to rejection of the organ. To help prevent this reaction, organ donors are matched to the patient receiving the organ. The better the match, the more similar the antigens, the less likely the organ will be rejected. Transplant medications are also used to suppress the recipient's immune system. The goal is to prevent the immune system from attacking the newly transplanted organ. If these medicines are not used, the body will almost always launch an immune response and destroy the organ.

A 45 year old male presents to the Transplant Center at Froedtert Hospital in preparation for his kidney transplant. While reviewing the patient's medications, the pharmacist notices the patient is on omeprazole 40 mg once daily for a gastric ulcer. Omeprazole is a proton pump inhibitor (PPI) that competitively inhibits the cytochrome P450 3A4 and 2C19 liver enzymes that metabolize tacrolimus. This combination of medications results in a drug-drug interaction (DDI) that affects the concentration of tacrolimus[1] in the body. This project looks at how tacrolimus works and its DDI with omeprazole.

Molecular Story

Tacrolimus impairs immune function by inhibiting an immunophilin protein FKBP12. Normally, FKBP12 inhibits transforming growth factor β (TGF-β) receptors on immune T cells preventing a rise in p21, the Cdk2/cyclin E complex inhibitor. FKBP12 allows a T cell to enter the synthesis phase of the cell cycle. When tacrolimus binds to FKBP12 (figure 2), immune T cells will arrest in the G1 phase of the cell cycle preventing cell proliferation[2] (figure 3). Lower numbers of T cells means the immune system is not as efficient or effective at fighting off the foreign substances.

Tacrolimus bound to FKBP12 forms a complex that inhibits the enzyme calcineurin[3] (figure 4). The calcium-dependent serine threonine phosphatase enzyme called calcincurin, activates T cells after they have been presented foreign antigen[5]. By preventing T cell activation, tacrolimus further suppresses the organ recipient's immune response.

Tacrolimus is metabolized by CYP3A4 and is a substrate for CYP3A5 and p-glycoprotein; the source of many DDIs.
Metabolism forms a major metabolite 13-O-Demethyltacrolimus, which is created through O-demethylation by liver microsomes[6].

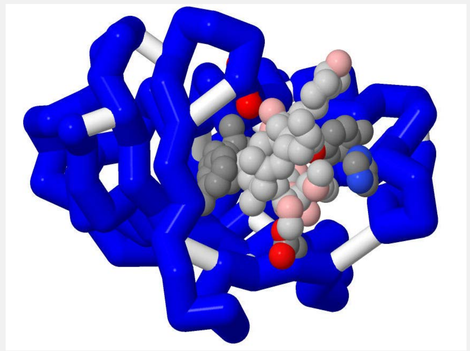

Figure 4 Tacrolimus Bound to FKBP12. Picture shows tacrolimus bound to the active site amino acids of FKBP12. The rest of the protein is depicted with a blue and white wireframe. The amino acids of the active site are discussed in Figure 2 and the color key depicting the elemental spheres are found in Figure 1. Rendered in Jmol from 1FKJ.pdb.

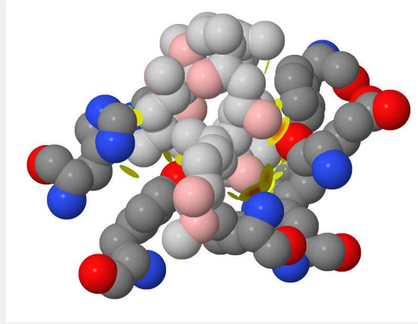

Figure 2 Tacrolimus Bound to FKBP12 Active Site. The picture shows the amino acids of the active site interacting with tacrolimus. The yellow to red discs depict the strength of the interaction between tacrolimus and the amino acids of the active site, yellow being a weak interaction and red being a strong interaction. Tacrolimus interacts with 7 amino acids of the active site (Glu 54, Tyr 82, Trp 59, Phe 46, Asp 37, Ile 56, and His 87). The other interaction discs depict interactions with water molecules. Water molecules are not shown. Color key can be found in Figure 1. Rendered in Jmol from 1FKJ.pdb.

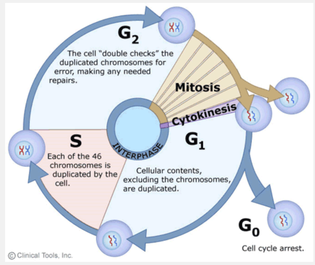

Figure 3. Cell Cycle[4] Diagram depicts the basic life cycle of a cell. G1 and G2 phases are times during which the cell builds up necessary supplies for the next step of the cycle.

Alternatively, tacrolimus could undergo O-demethylation at the 31 position by CYP3A4 metabolism to form 31-O-demethyltacrolimus. This metabolite is reported to have a similar effect to tacrolimus[7]. Since tacrolimus has such a small therapeutic window, any change in its metabolism greatly affects the drug's mechanisms for preventing graft rejection. When tacrolimus is used in combination with another medication that is metabolized by CYP3A4, in this case omeprazole, competitive inhibition of tacrolimus metabolism causes drug concentration to rise in the body to potentially toxic levels.

Resolving Drug-Drug Interactions

The clinical problem with tacrolimus is its metabolism by CYP450 enzymes. Numerous medications are CYP450 inducers or inhibitors. Tacrolimus has a narrow therapeutic window, so any change in its metabolism can lead to supratherapeutic or subtherapeutic concentrations in the blood, causing toxicity and/or rejection.

In order to prevent this interaction with inducers or inhibitors of CYP3A4, medicinal chemists could alter the 13 and 31 position of the tacrolimus molecule to reduce the metabolism by CYP3A4. This alteration could include replacing the methyl group at the 13 and/or 31 positions with an aromatic group, which would be harder to remove. This alteration would push the metabolism of tacrolimus from CYP3A4 to towards a different CYP450 enzyme or p-glycoprotein, thus preventing many of the DDIs that tacrolimus encounters with CYP3A4 metabolism. The addition of the aromatic group(s) would decrease its metabolism by CYP3A4 but still allow it to bind to the FKBP12 active site. Adding these groups has the potential to change the half-life of tacrolimus, thus dosing and/or frequency of taking the medication could change as well.

Current Solutions

In the previously mentioned case, the Froederdt pharmacist decided to discontinue the patient's omeprazole due to its competitive inhibition of CYP3A4. The pharmacist then recommended an alternative proton pump inhibitor, pantoprazole, that has no effect on CYP3A4 metabolism.

Summary

Tacrolimus can be used to suppress the immune system in organ transplant patients. Its high affinity for the protein FKBP12 allows it to inhibit the protein's function after binding has occurred. The inhibition of FKBP12 arrests T cells in the G1 phase of the cell cycle preventing proliferation. This action lowers the immune response that the body mounts against the transplanted organ. The metabolism of tacrolimus by CYP3A4 along with its narrow therapeutic window, causes many DDIs among common drugs that have an affect on CYP3A4. In the future, medicinal chemists should consider a way to alter tacrolimus' metabolism thus decreasing the amount of DDIs it has with other common drugs.

References

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