Sirolimus: Mammalian Target of Rapamycin Inhibitor to Prevent Kidney Rejection

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Lifelong administration of multiple immunosuppressants is usually required to maintain function of a transplanted kidney. Selection of immunosuppressant agents has been geared toward preventing acute rejection and minimizing drug-induced side effects. In recent years, a number of new immunosuppressant agents have been approved for the prevention of acute rejection resulting in improved graft and patient survival, as well as improved function of the transplanted kidney. The opportunity to individualize immunosuppressant regimens based upon patient demographics and immunologic characteristics has expanded with the recent approval of sirolimus for prevention of acute rejection in renal transplant recipients.

Mechanism of Action

The mechanism of action of sirolimus is distinct from that of other commonly used immunosuppressants. Sirolimus and its O-alkylated analogue SDZ RAD bind to immunophilins known as FK 506 binding proteins (FKBP), specifically FKBP12. These sirolimus-FKBP complexes then bind to mammalian target of rapamycin, an intracellular enzyme that modulates lymphocyte cellular division and proliferation (Sehgal, 1998; Vasquez, 2000). While calcineurin inhibitors, like cyclosporine and tacrolimus, interfere with T-cell activation by blocking the production of interleukin-2 (IL-2), sirolimus predominantly inhibits T-cell proliferation by blocking T-cell responsiveness to IL-2. However, sirolimus does not block the IL-2 signals that lead to T-cell apoptosis, a process believed to be essential in the development of allograft tolerance. Additionally, sirolimus decreases immunoglobulin production by B-cells (American Society of Transplantation, 2000).

Clinical Trials

The safety and efficacy of sirolimus in combination with cyclosporine to prevent acute rejection of a transplanted kidney has been established in randomized, multicentered clinical studies. Combination immunosuppressant therapy of sirolimus, cyclosporine (at full or reduced dose), and steroids resulted in a lower incidence of biopsy proven rejection in kidney transplant recipients compared to transplant recipients who received cyclosporine, steroids, and placebo (Khan, Julian, Pescovitz, Vanrenterghem, & Neylan, 1999). In phase III clinical trials, cyclosporine, corticosteroids, and either sirolimus (2 or 5 mg/day doses), azathriopine, or placebo were administered to 1,296 kidney transplant recipients. The incidence of acute rejection of the transplanted kidney was significantly lower among patients receiving sirolimus as part of their immunosuppressant regimen compared to those receiving azathriopine or placebo (Food and Drug Administration, 2000).

Although tacrolimus and sirolimus bind to the same immunophilin, their mechanism of action differs. The combination of tacrolimus and sirolimus is synergistic in pre-clinical models permitting the use of lower dosages of tacrolimus that may reduce or eliminate some of the adverse effects of tacrolimus. McAlister and colleagues (2000) reported only one episode of rejection, attributed to noncompliance, in 32 liver, kidney, and kidney-pancreas transplant recipients receiving a combination of sirolimus, low dose tacrolimus, and low dose steroid with early withdrawal for immunosuppression. Currently, studies are being conducted to determine the effect of tacrolimus-sirolimus combinations on kidney transplant graft function, patient and graft survival, and adverse effects.

Although current immunosuppressive regimens based upon cyclosporine or tacrolimus are very effective at reducing the incidence of acute rejection and preventing loss of the transplanted kidney from acute rejection, these drugs are known to compromise renal function. Subsequently, investigations comparing sirolimus versus cyclosporine as a base therapy for immunosuppression have been undertaken with similar outcomes in patient survival, kidney graft survival, and incidence of rejection being reported (Groth et al., 1999; Kreis et al., 2000). Compared to recipients receiving cyclosporine, the sirolimus group exhibited lower serum creatinine levels and better glomerular filtration rates in the early post-transplant period (1-2 months posttransplant), with significant differences sustained at 12 months posttransplant (Kreis et al., 2000).

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The Medication Review section of the *Nephrology Nursing Journal* presents information on medications administered to individuals with nephrologic disorders. Readers wishing to contribute to this column should contact Kim Bremer, department editor, for assistance. For specific guidelines, see any February issue of the *Nephrology Nursing Journal*. The opinions and assertions contained herein are the private views of the contributors and do not necessarily reflect the views of the American Nephrology Nurses' Association.

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Drug Interactions/Contraindications

Like tacrolimus and cyclosporine, sirolimus is metabolized by the cytochrome P450 3A4 isoenzyme. Concomitant administration of cyclosporine (modified) and sirolimus in stable renal transplant recipients resulted in markedly increased sirolimus peak and trough blood concentrations (Kaplan, Meier-Kriesche, Napoli, & Kahan, 1998) prompting a recommendation that sirolimus be administered 4 hours after cyclosporine (modified) when used in combination. Co-administration of sirolimus and ketoconazole is not recommended as ketoconazole increases sirolimus blood concentration levels. A similar relationship was observed when sirolimus was administered with diltiazem. Rifampin has been demonstrated to lower sirolimus exposure. Agents that alter cyclosporine levels may also alter sirolimus levels. Increased sirolimus levels may result with concomitant administration of nicardipine, verapamil, danazol, clarithromycin, erythromycin, allopurinol, metoclopromide, fluconazole, itraconzole, and grapefruit juice. Reduced sirolimus levels may occur with concomitant administration of carbamazepine, phenobarbital, phenytoin, mafcillin, octreotide, and ticlopidine. No clinically significant drug interactions have been reported with the use of sirolimus and acyclovir, digoxin, glyburide, nifedipine, norgestrel, ethinyl estradiol, and trimethoprim-sulfamethoxazole (Kelly, Gruber, Behbod, & Kahan, 1997; Vasquez, 2000).

Dosage

Label recommendations for sirolimus are a 6 mg loading dose as soon as possible after transplantation (24-48 hours posttransplant) followed by a daily maintenance dose of 2 mg daily by mouth. In children 13 years or older who weigh less than 40 kg, the initial dose is 3 mg/m^2 with a recommended maintenance dose of 1 mg/m^2/day (Wyeth-Ayerst, 1999). The safety and efficacy of sirolimus in children less than 13 years of age has not been established. Precise guidelines for therapeutic drug monitoring of sirolimus are being developed. High performance liquid chromatography (HPLC-UV) and HPLC-mass spectroscopy are the preferred assays for determining sirolimus blood concentrations. Recently, concentrated-controlled dosing for sirolimus was recommended (Kahan et al., 2000). Five to seven days after initiating sirolimus, serum trough levels should be obtained using the HPLC-UV assay. Blood for sirolimus trough levels should be drawn 22-24 hours after the previous dose, preferably before 10 am, so it is important to instruct the patient to hold the next dose of sirolimus until the sample is obtained. A sirolimus trough level should be checked 5-7 days after a dose change. Once the patient is stabilized, sirolimus levels only need to be drawn every 2-3 months. The dose should be adjusted based on the trough levels. When used in combination with other immunosuppressant agents, a target trough level of 5-15 ng/ml is recommended. In studies where sirolimus was employed as a base agent for immunosuppression, the average maintenance dose of sirolimus ranged from 6 to 9 mg/day with sirolimus target trough levels of 30 ng/ml during the first 2 month posttransplant and 15 ng/ml thereafter (Groth et al., 1999; Kreis et al., 2000).

Cost

The approximate cost of sirolimus is $328.80 for 30 pouches with each pouch containing 2 mg/ml. Cost varies depending upon dose ordered. Overall immunosuppression cost will depend upon whether sirolimus is employed as an adjunct immunosuppressant with either tacrolimus or cyclosporine as base therapy, whether reduced doses of the base immunosuppressant can be used, or whether sirolimus is employed as the base immunosuppressant agent.

Dialyzability

The effect of dialysis on sirolimus levels has not been established. The lipophilic nature of sirolimus makes it unlikely to be effectively removed with dialysis (Vasquez, 2000). Sirolimus is primarily bound to red blood cells with approximately 3% free in plasma, so negligible amounts may be removed with plasmapheresis.

Common Adverse Reactions

Sirolimus therapy is associated with adverse reactions that are different from those for other immunosuppressive therapies. Key adverse reactions observed in sirolimus plus cyclosporine-treated patients are increased blood lipids, including triglycerides and cholesterol, and reduced platelet and white blood cell counts. The increased triglycerides and cholesterol can be treated successfully with the use of lipid and/or cholesterol-lowering drugs. The reduced platelet and white blood cell counts normally respond to a reduction in sirolimus dose. Other adverse reactions include hypertension, rash, acne, arthralgia, diarrhea, and hypokalemia. These reactions are dose related (Kelly, 1999).

Nursing Considerations

Preliminary evidence suggested that African-Americans exhibit a reduced rate and extent of sirolimus absorption. When sirolimus was used in combination with low dose cyclosporine, African-Americans exhibited a higher rate of rejection than Caucasians; thus African-Americans receiving sirolimus and cyclosporine combination immunosuppressant therapy may need to be maintained at higher levels than Caucasian transplant recipients (American Society of Transplantation, 2000).

It is recommended that sirolimus be administered 4 hours after the morning dose of cyclosporine to minimize potential toxicities. Dosing with respect to food should be consistent to minimize variability in oral absorption. Sirolimus is available in a bottle or pouch. A table form of sirolimus was recently approved by the Food and Drug Administration. The prescribed amount of sirolimus should be mixed in a glass or plastic container with at least two ounces (1/4 cup, 60 ml) of water or orange juice. Grapefruit and Seville orange juice should not be used as it increases the bioavailability of the medication. When using the pouch, squeeze the entire contents of the pouch into the glass or plastic container.

Sirolimus should be stored protected from light and refrigerated at 2-8° C (36-46° F). Once the bottle is opened, the contents should be used within 1 month. If necessary, patients may store both pouches and bottles at

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room temperature up to 25° C (77° F) for several days, but no longer than 30 days. Sirolimus oral solution provided in bottles may develop a slight haze when refrigerated. Each amber syringe used to draw up the dose of sirolimus should be discarded after each use (Wyeth-Ayerst, 1999).

Summary

Current immunosuppressive therapies are effective but can be associated with significant adverse reactions. Sirolimus works differently from the immunosuppressants currently available, and except for increased lipid levels, the adverse reaction profile of sirolimus does not appear to overlap to any great extent with that associated with cyclosporine or tacrolimus. While additional research is needed, the initial clinical data in kidney recipients suggest that sirolimus, in combination with cyclosporine or tacrolimus, might have the potential to reduce the frequency of rejection episodes, permit reductions in cyclosporine or tacrolimus dosage, and permit steroid withdrawal (Kelly, 1999).

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