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Immunosuppression with Sirolimus after Solid Organ Transplantation in Children

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Immunosuppressive therapy is an essential component of the management of children who have received a solid organ transplant. The calcineurin inhibitors, cyclosporine and tacrolimus, have been the primary immunosuppressive agents used in children for the past two decades; however, each is associated with a significant number of adverse effects. Sirolimus was introduced in the United States in 1999 as an adjunct or alternative to traditional therapies.¹⁻³ It has proven to be effective in preventing acute rejection while producing fewer adverse effects, including renal dysfunction. Since 2000, sirolimus has been studied in children after kidney, liver, intestine, and heart transplantation. This issue of *Pediatric Pharmacotherapy* will review these papers and the potential role of sirolimus in the pediatric transplant population.

Mechanism of Action

Sirolimus, initially known as rapamycin, is a macrolide immunosuppressive agent with a unique mechanism of action. It is a fermentation product isolated from a strain of *Streptomyces hygroscopicus* found in soil samples from Rapa Nui (Easter Island). Sirolimus inhibits T-lymphocyte activation and proliferation, as well as antibody production. It binds to FK-binding protein-12 (FKBP-12) to form a complex which binds to and inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase. The resulting inhibition of mTOR suppresses cytokine-driven T-cell proliferation resulting in inhibition of the progression from the G₁ to the S phase of the cell cycle.¹⁻³

Clinical Experience in Children

Several case series have been published describing the use of sirolimus in pediatric transplant patients.⁴⁻¹¹ It has been used both in combination with a calcineurin inhibitor or with a mycophenolate/steroid regimen. In 2001, Sindhi and colleagues evaluated the efficacy and safety of sirolimus in 50 children (ages 19 days-21 years) with transplants, including 26 liver, 5

heart, 5 intestine, 9 liver/intestine, 1 lung, 1 bone-marrow, 1 liver/kidney, 1 multiorgan transplant, and 1 unspecified.⁵ Forty-two children received sirolimus as rescue therapy after failing or developing toxicity to traditional immunosuppressive agents; the remaining eight children receiving sirolimus as primary therapy. Sirolimus was initiated at 1 to 2 mg/m² given orally once daily. The mean period of follow-up was 204 days (range 18-800 days).

Of the 42 children given sirolimus as rescue therapy, 33 (80%) had resolution of their indication for rescue. In the primary treatment group, 7/8 (88.5%) had no episodes of rejection. The mean sirolimus trough concentration was 6.9±5.5 ng/mL. Nine children (18%) discontinued sirolimus because of adverse effects, primarily anemia and leucopenia. In 23 children who were given sirolimus after developing tacrolimus-induced nephrotoxicity, serum creatinine decreased from a mean of 1.73±0.6 to 1.2±0.8 mg/dL. Overall, 38 of the 50 children (76%) experienced benefit. Forty-one (82%) remained on therapy at the conclusion of the study, with 33 receiving a combination of tacrolimus and sirolimus and eight receiving sirolimus alone.⁵

Several other investigators have evaluated sirolimus in pediatric renal transplants.⁶⁻⁸ Vilalta and colleagues gave six children (2 to 18 years of age) sirolimus as primary therapy in combination with cyclosporine, mycophenolate, and methylprednisolone.⁶ The goal of this regimen was early withdrawal of cyclosporine, to minimize the risk of nephrotoxicity. Sirolimus was initiated at 1.15 mg/m² daily and adjusted to maintain trough concentrations between 4 and 12 ng/mL. Therapeutic levels were reached between days 3 and 5. Cyclosporine was withdrawn during the first week after transplantation, as soon as sirolimus levels were at goal. No rejection episodes were reported, and all patients had normal creatinine values within 14 days of transplantation.

In 2002, Sindhi's group published additional experience with sirolimus in 45 pediatric liver transplants.⁹ Fifteen children were given sirolimus as primary therapy and 30 as rescue therapy. When sirolimus was used as primary immunotherapy, six of the 15 children did not require steroids and another five tolerated early steroid withdrawal. In 12 of the 15 rescue patients who were receiving tacrolimus, the addition of sirolimus allowed for the elimination of tacrolimus. The mean sirolimus trough concentrations in the primary and rescue groups were 5.28 ng/mL and 5.1 ng/mL, respectively.

Sirolimus has also been used to prevent or improve the nephrotoxicity associated with calcineurin inhibitors in liver transplant patients, by allowing a reduction in cyclosporine or tacrolimus dose. Casas-Melley and coworkers conducted a retrospective review of 38 pediatric liver transplant patients (mean age 8.6 years) treated with sirolimus between January 2000 and February 2003.¹² In a subset of 11 children with renal impairment after tacrolimus use, the authors found a significant improvement in serum creatinine levels when sirolimus was added and the tacrolimus dose reduced (0.8 mg/dL on sirolimus compared to 1.3 mg/dL at baseline).

A recent paper from the researchers at the University of Toronto describes their experience with sirolimus in pediatric heart transplant recipients.¹³ Sixteen patients (ages 5 to 18 years) were treated, with a median time of introduction of 2.7 years post-transplant (range 1 month to 8.2 years). Fifteen of the patients were receiving steroids, 15 were receiving tacrolimus, and 11 were receiving mycophenolate. The average daily maintenance dose of sirolimus to achieve trough concentrations within the desired range of 5 to 15 mcg/mL was 0.25 mg/kg (7 mg/m²). The six patients given sirolimus for rejection showed improvement in subsequent biopsies. Two of the three patients treated for tacrolimus-induced nephrotoxicity showed improvement in glomerular filtration rate after tacrolimus was reduced or removed. Adverse effects included hyperlipidemia (38%) abdominal pain (31%), mouth ulcers (26%), anemia or neutropenia (12.5%), pericardial effusion (6%), and interstitial lung disease (6%). Three children required discontinuation due to adverse effects. The authors concluded that sirolimus was a valuable agent for the management of pediatric transplant patients with rejection or in patients with adverse effects to other agents.¹³

Pharmacokinetics

After oral administration, sirolimus is rapidly absorbed, with an average time to peak serum

concentrations in adults of 1 hour after initial dosing and 2 hours after repeated dosing. Systemic bioavailability is approximately 14% with the oral solution. Bioavailability with the tablet is 27% higher than that with the oral solution, indicating that the formulations are not bioequivalent. The two products have been found to be clinically equivalent at the 2 mg dose. Administration with food produces variable effects. Bioavailability of the oral solution is decreased when administered with a high-fat meal, but when the tablets are taken with a high-fat meal, bioavailability is increased.^{2,3}

Sirolimus is widely distributed, with a mean volume of distribution of 12±8 L/kg. It is highly bound (92%) to serum proteins, primarily albumin. Sirolimus is a substrate for cytochrome P450 3A4 (CYP3A4) in the intestinal wall and liver and undergoes counter-transport by P-glycoprotein. It is extensively metabolized through O-demethylation and hydroxylation, forming seven major metabolites. The mean elimination half-life for sirolimus in adult renal transplant patients is 62±16 hours.^{2,3}

The pharmacokinetic profile of sirolimus has also been studied in pediatric patients.¹⁵ Data from several small trials have demonstrated a more rapid clearance in younger children. In a study of 21 transplanted children receiving sirolimus and tacrolimus, the mean half-life of sirolimus was 11.8±5.5 hours, significantly shorter than that reported in adults.⁴ These results were replicated in a recent trial of 13 children, where the mean terminal half-life was found to be 10.8 hours after 1 month of sirolimus use and 12.1 hours after 3 months.¹⁶

In 2005, Filler and colleagues reported their experience adding sirolimus to a tacrolimus-based regimen in eight children with renal transplants.⁸ The children were included in the treatment protocol after developing chronic nephropathy with their tacrolimus regimen. Sirolimus was initiated at 0.13±0.05 mg/kg/day (3.51±1.26 mg/m²/day) given in two divided doses. After adding sirolimus, tacrolimus concentrations decreased, requiring dosage adjustment. The mean sirolimus trough concentration was 6.19±1.36 ng/mL, with a mean half-life of 17.5±6.9 hours, significantly longer than previously reported in children. The authors suggested this difference in half-life may be the result of an interaction with tacrolimus.

Drug Interactions

Administration of sirolimus with CYP3A4 inhibitors will result in a decrease in metabolism and an increase in sirolimus concentrations.

Drugs known to inhibit CYP3A4 include:

bromocriptine	ketoconazole
cimetidine	metoclopramide
cisapride	nicardipine
clarithromycin	telithromycin
clotrimazole	telithromycin
danazole	troleandomycin
erythromycin	verapamil
fluconazole	voriconazole
itraconazole	all protease inhibitors

Grapefruit juice also reduces CYP3A4 activity and should not be administered with sirolimus. In contrast, concomitant use with CYP3A4 inducers, such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's wort, may increase the rate of CYP3A4 activity and reduce sirolimus concentrations.^{2,3}

Sirolimus concentrations may also be increased with concomitant administration of cyclosporine or diltiazem. It is recommended that sirolimus be administered 4 hours after cyclosporine to minimize variations in trough sirolimus concentrations.^{2,3}

Adverse Reactions

The most frequently reported adverse effects associated with sirolimus include hypertension (39-49% of adult patients in clinical trials), hyperlipidemia (38-57%), diarrhea (32-42%), anemia (27-37%), fever (23-34%), thrombocytopenia (13-30%), hypokalemia (11-21%), leukopenia (9-15%), rash (10-20%), and leukopenia (9-15%). In most cases, these adverse effects are dose or concentration-dependent.^{2,3} A similar adverse effect profile has been described in pediatric studies.^{4,15}

As with any immunosuppressive agent, the use of sirolimus places patients at increased risk for infection and the development of lymphoma. Other rare adverse reactions with sirolimus include anaphylaxis and other hypersensitivity reactions. Interstitial lung disease has been reported in both adult and pediatric patients treated with sirolimus. Some of these cases have resulted in patient death. In addition, bronchial anastomotic dehiscence, usually fatal, has been reported in adult lung transplant patients receiving sirolimus.^{2,3,17}

Concomitant use of sirolimus and calcineurin inhibitors may also increase the likelihood for adverse effects. Close monitoring is needed for patients receiving these combinations, with adjustment and/or discontinuation of one of the drugs if necessary. Adult patients receiving sirolimus in combination with tacrolimus after

liver transplantation have been found to be at greater risk for hepatic artery thrombosis, graft loss, and death.^{2,3}

Although the incidence of nephrotoxicity with sirolimus appears to be less than that reported with calcineurin inhibitors, it remains a significant concern, particularly when these agents are used in combination.^{2,3} Butani reported proteinuria in 12 of 13 children receiving sirolimus after renal transplantation.¹⁸ The mean interval to presentation was 1 month, with an increase in the urine protein to creatinine ratio (Up/c) of 1.1 to 3.9 within 5 months of starting therapy. Angiotensin receptor blockers were effective in reducing the Up/c to a mean of 2.2 at follow-up.

Dosing Recommendations and Availability

The recommended dosing regimen for sirolimus in adult renal transplant patients is a loading dose of 6 mg followed by a maintenance dose of 2 mg given once daily.^{2,3} In pediatric patients, a loading dose of 3 mg/m² may be given, with a maintenance dose of 1 mg/m²/day.²⁻¹⁶ Dosage adjustments should be made to maintain whole blood sirolimus trough concentrations within the desired range. For patients receiving sirolimus with a calcineurin inhibitor and a corticosteroid, a therapeutic range of 5-12 ng/mL is recommended. If the regimen does not include a calcineurin inhibitor, a higher range (12-24 ng/mL) should be used.^{1,2}

Once a dose adjustment has been made, patients should remain on the new dose for 7 to 14 days until steady-state has been reached before making further changes. In patients for whom a considerable increase in sirolimus concentration is needed, a loading dose may be calculated by the following equation²:

$$\text{sirolimus loading dose} = 3 \times (\text{new maintenance dose} - \text{current maintenance dose})$$

Sirolimus (Rapamune[®], Wyeth Pharmaceuticals) is available in 1 and 2 mg tablets, as well as a 1 mg/mL oral solution. The oral solution is provided in 60 mL amber glass bottles with disposable amber oral syringes and caps. The solution should be refrigerated at 2-8° C. Once opened, the bottle should be used within one month. If necessary, the solution may be stored at room temperature for a period of no more than 15 days.²

To prepare a dose of the oral solution, the desired volume should be drawn up in the amber oral syringe and emptied into a glass or plastic cup. It should then be mixed with at least 60 mL

(2 oz) of water or orange juice, stirred, and given. The cup should then be rinsed with another 120 mL (4 oz) of water or orange juice and the patient given the rinse solution. Sirolimus should not be mixed with any other liquids. Neither the tablets nor the oral solution should be administered with grapefruit juice. Because of the variability in absorption when given with food, it is recommended that sirolimus be administered at consistent times in relation to meals.²

Summary

Sirolimus may provide a useful addition or alternative to the calcineurin inhibitors for chronic immunosuppression in children with solid organ transplants. While small case series have shown it to be effective and produce less nephrotoxicity, it has been associated with a wide range of adverse effects. Additional prospective studies are needed to establish its role in transplant management.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/27/06:

1. Eye lubricant gel (GenTeal[®] Severe 0.3%) was added to the Inpatient Formulary for use in ophthalmologic examinations using the RetCam II in neonates at risk for retinopathy of prematurity.
2. Leuprolide acetate injectable suspension (Eligard[®]) was added to the Inpatient and Outpatient Formularies for the palliative treatment of advanced prostate cancer.
3. The restriction on the use of bevacizumab (Avastin[®]) was amended to include use in non-squamous cell non-small cell lung cancer patients without brain metastases, a history of DVT/PE, or who do not require warfarin.
4. The restriction on bortezomib (Velcade[®]) was amended to reflect the current FDA indication for multiple myeloma patients who have received at least one prior therapy.
5. The restriction for porfimer sodium (Photofrin[®]) was amended to include use in endobronchial non-small cell lung cancer.
6. The restriction on rituximab (Rituxan[®]) was amended to include use for refractory kidney transplant rejection, ABO incompatible kidney transplant, and positive cross-match kidney transplant.

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