Sirolimus: A New Immunosuppressant

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Abstract

Though organ transplantation has evolved in many ways over the years, it is not without the disadvantage of causing rejections. Cyclosporin, azathioprine and corticosteroids are time tested and efficacious; however each is accompanied with its own array of disadvantages. Sirolimus is a relatively new immunosuppressant isolated from a macrolide antibiotic. It may have a beneficial role in prophylaxis of rejection as well as treatment of refractory rejection. It also has antifungal, antitumor and anti-smooth muscle proliferative roles.

INTRODUCTION

With new advances in the field of transplantation and treatment modalities to overcome rejection episodes, there is always a quest for an agent that is devoid of the disadvantages of the drugs currently in use. Sirolimus (Rapamycin) is a new immunosuppressant that has been approved by the US FDA and is gaining popularity. It was discovered by Suren Sehgal, an Indian scientist, 25 years ago in Easter Island (Rapa Nui to native islanders), hence its original name Rapamycin. It is a macrolide antibiotic produced by the fungus Streptomyces hygroscopicus. Although initially isolated as an antifungal agent with potent antifungal activity, subsequent studies revealed impressive antitumor and immunosuppressive activities. In this article, we have attempted to review the profile of this drug and its perspective in renal transplantation.

MECHANISM OF ACTION

As we understand, allograft rejection is a T cell mediated process. T-cell receptor (TCR) of the recipient recognizes HLA antigens directly on the surface of donor cells or indirectly after the donor HLA antigens have been processed and presented by recipient antigen presenting cells (APC). Antigen recognition is not enough to activate T cells. Interaction of other molecules (costimulatory molecules) on the surface of the T cell and APC is necessary. Once this happens, a series of intracellular events takes place. The T-cell leaves the quiescent phase G0 and enters the first phase of cell cycle G1. There is transcription of cytokine genes including genes for IL-2 and its receptor.

IL-2 and other growth factors promote the activation of mammalian target of Rapamycin (mTOR). Activation of mTOR propels the cell cycle progression from G1 to S phase. In the S phase, the cell doubles its DNA content, undergoes mitotic division leading to clonal expansion and proliferation of T-cells and the entire cascade of allograft rejection is thus perpetuated.

Sirolimus (SRL) is a carbocyclic lactone-lactam macrolide antibiotic (Fig. 1). It binds to the immunophilin FKBP12 and interferes with the function of mTOR, thus blocking the progression from G1 to the S phase of the cell cycle (Fig. 2).

PHARMACOKINETICS

Absorption

Sirolimus is available in oral solution and tablet form. It is rapidly but poorly absorbed after oral administration with an estimated bioavailability of 15%. Fatty meals

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significantly reduce the absorption. Knowing that food reduces the absorption, it may be more appropriate to prescribe the drug without food. The time of maximum concentration (t_{max}) was 0.5-2 hours after a dose of 3-15 mg/m² in one study and 0.8-2.3 hours in another study.\(^2,3\)

**Distribution**

Sirolimus is extensively distributed into tissues. The apparent volume of distribution is large and variable, ranging from 5.6 to 16.7 L\(^3,4\) in stable renal allograft recipients. Sirolimus is primarily bound to red blood cells (95%). Distribution among other components is 3% plasma, 1% lymphocytes and 1% granulocytes.\(^5\)

**Metabolism and Excretion**

Sirolimus is a substrate for CYP3A4 system in both liver and small intestine.\(^6\) It is mostly metabolized by O-methylation and/or hydroxylation. The metabolites have less than 10% of immunosuppressant activity and are excreted in bile and faeces.\(^5\) The t\(_{1/2}\) ranges from 57-62 hours, hence once a day dosage is adequate.\(^1\) In the plasma, Sirolimus is extensively bound to plasma proteins (92%), mainly serum albumin. Sirolimus has a large inter patient variability in clearance. One study demonstrated clearance between 96.7 and 310 ml/hr/kg.\(^4\) Liver disease significantly reduces its clearance. One-third of the recommended dosage should be given to patients with mild to moderate hepatic dysfunction.\(^7\)

**Drug Interactions**

As sirolimus is a substrate for CYP3A4 isoenzyme, other drugs (including cyclosporin and tacrolimus) which are metabolized by this isoenzyme affect its levels. Concomitant use of sirolimus and cyclosporin could in fact increase plasma levels of the latter. Other drugs which increase sirolimus levels and hence enhance its adverse effects are calcium channel blockers (verapamil, diltiazem), antifungals (ketoconazole, fluconazole, itraconazole), macrolide antibiotics (erythromycin, clarithromycin) and danazol. Drugs that decrease sirolimus levels by inducing CYP3A4 are antiepileptics (carbamazepine, phenytoin, phenobarbitone), rifampicin, St John’s wort (used for depression).

Cisapride should not be used with sirolimus because it increases the risk of cardiac toxicity. Administration of HMG CoA reductase inhibitors with sirolimus has been well tolerated. Acyclovir, digoxin, glyburide, nifedipine, prednisolone, sulfamethoxazole-trimethoprim, ethinyl estradiol-norgestrel may all be co-administered without any dose adjustment.

**Dosage**

Sirolimus is available as an oral solution and as tablets of 1mg, 2 mg and 5 mg strengths. The solution should be taken with water or orange juice. Its dose should be taken around 4 hours after the dose of cyclosporin as the latter increases the levels of sirolimus.\(^7\) Generally a loading dose of 6 mg followed by a maintenance dose of 2 mg is recommended. Recommended trough levels: 12-20 ng/ml (HPLC-UV).

**Special Groups**

1) **Paediatrics**: Grimm *et al* studied the pharmacokinetics of sirolimus in children of different age groups. Children demonstrated higher apparent clearance (485 ± 199 ml/hr/kg) compared with adolescents (376 ± 262 ml/hr/kg) and adults (208 ± 95 ml/hr/kg). The mean half-life was also shorter in children (49.1 ± 41 hours) as compared to adolescents (70.3 ± 106 hours) and adults (62 ± 16 hours).\(^8\) This suggests that children may require higher doses than adolescents or adults, corrected for body surface area or weight.

2) **Geriatrics**: No significant differences in the pharmacokinetics of older patients more than 65 years have been identified.

3) **Hepatic impairment**: A decrease in the dosage is required in patients with mild to moderate hepatic impairment as discussed above.

**Sirolimus As An Immunosuppressant**

Sirolimus may have a promising role in prophylaxis of rejection, treatment of refractory acute rejections and chronic allograft dysfunction, as substantiated by various studies.

**Prophylaxis**

Often cadaveric kidneys may be injured by hypotension and cardiac arrest, which may contribute to delayed graft function. Calcineurin inhibitors (CNI) may compound the nephrotoxicity. In such cases, antilymphocyte preparations provide a 2-week window for recovery of renal functions. However antilymphocyte preparations have various adverse effects. Hence sirolimus may prove to be useful in this regard to provide a window of time free of cyclosporin, and cyclosporin may be introduced later when serum creatinine values...
are less than 2.5 mg/dl.

Sirolimus exerts a synergistic effect in preventing acute rejection episodes when combined with cyclosporin, and may also enable early withdrawal of cyclosporin (CSA). When combined with cyclosporin, an acute rejection rate of 12-21.8% has been observed. In a trial by Kahan wherein the concentrations of cyclosporin and sirolimus were tightly controlled, rates of acute rejection were less than 10%. However when sirolimus is combined with cyclosporin, a worse renal function is noted at one year i.e. it may increase the nephrotoxicity of cyclosporin. Therefore, these two drugs must not be combined for more than 2 or 3 months i.e. cyclosporin should be discontinued after 2 or 3 months.

Two phase III double blind multi center studies in 1295 patients (US trial and Global trial) followed patients for 24 months. The US trial compared SRL 5 mg and 2 mg with azathioprine while the Global trial compared the same with placebo. Baseline immunosuppression was CSA and steroids in both groups. There was a durable benefit of SRL in reducing the incidence of biopsy proven rejection episodes and this effect was dose dependent - patients receiving 5mg/day had lower failure rates in both studies. At 24 months, the US trial showed that the 2mg/day dose was as effective as azathioprine whereas the Global study showed that 2 mg of SRL was superior to placebo in preventing rejection episodes. The benefits were achieved without the disadvantages of overimmunosuppression i.e. occurrence of malignancies or opportunistic infections were similar compared to placebo or azathioprine.

In other trials, when used independently with other drugs (mycophenolate mofetil and steroids), sirolimus had almost the same efficacy as cyclosporin in preventing acute rejection episodes (41% for sirolimus versus 38% for cyclosporin).

Two prospective randomized phase II trials using therapeutic dose monitoring compared the effects of cyclosporin and sirolimus. One study used either cyclosporin or sirolimus with steroids and azathioprine, and the other with mycophenolate mofetil (MMF) and steroids. In both the studies renal function was better at one month in the sirolimus group (n=24) and only in 67% of the patients in the MMF group (n=12). Baseline immunosuppression consisted of cyclosporin and prednisolone in both the groups. Further trials using sirolimus in refractory rejection are warranted.

Chronic allograft nephropathy

Since CNI nephrotoxicity is an important component of chronic allograft nephropathy, attempts have been made to replace cyclosporin with sirolimus. One such study included 50 patients of whom 48 had CNI nephrotoxicity and 2 had thrombotic microangiopathy. Thirty two patients had an initial improvement in renal function (probably as a result of improved renal perfusion due to CNI withdrawal) and subsequent deterioration due to progression of rejection. Further trials would be required to establish a definitive role of sirolimus in chronic allograft nephropathy and chronic rejection.

Adverse Effects

The main adverse effects are shown in Table 1
Table 1: Adverse effects of sirolimus

<table>
<thead>
<tr>
<th>Effect</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>1. Hyperlipidemia</td>
<td>50%</td>
</tr>
<tr>
<td>2. Myelosuppression (dose dependent)</td>
<td></td>
</tr>
<tr>
<td>3. Opportunistic infections : HSV, Pneumonia</td>
<td></td>
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<tr>
<td>4. Interstitial pneumonitis</td>
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<tr>
<td>5. Hypokalemia</td>
<td></td>
</tr>
<tr>
<td>6. Proteinuria</td>
<td></td>
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<tr>
<td>7. Dermatologic :</td>
<td></td>
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<tr>
<td>Acne lesions</td>
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</tr>
<tr>
<td>Skin rash</td>
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<tr>
<td>8. Miscellaneous :</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td></td>
</tr>
<tr>
<td>Delayed wound healing</td>
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<tr>
<td>Wound hematoma</td>
<td></td>
</tr>
<tr>
<td>Insomnia, tremor</td>
<td></td>
</tr>
<tr>
<td>Asthenia, headache, epistaxis</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
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<tr>
<td>Arthralgia</td>
<td></td>
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<tr>
<td>Lymphocele</td>
<td></td>
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<tr>
<td>Lower limb edema</td>
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</table>

**Metabolic**

i) **Hyperlipidemia**: Hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) develops in 50% of the cases. This is reversible and can be managed by dose reduction and/or antihyperlipidemic agents.12 Two prospective trials which compared sirolimus with cyclosporin in regimens using azathioprine and steroids (Groth et al)14 and mycophenolate mofetil and steroids (Kreis H et al)15 found that there was a higher incidence of both hypertriglyceridemia (51% versus 12% and 73% versus 50%) and hypercholesterolemia (44% versus 14% and 65% versus 45%) in the sirolimus groups in the two studies respectively. The differences were maximum at month 2 and decreased by month 6. In the second trial the serum triglyceride and cholesterol were not significantly different in the two groups at month 12.

**Hypokalemia**: Hypokalemia has been reported more frequently with sirolimus as compared to CSA. This was mild and easily corrected with potassium supplements. There was evidence of excessive urinary excretion of potassium with an increase in TTKG indicative of an increased tubular secretion of K, in the presence of hypokalemia. This complication occurred in the first 3 months when sirolimus levels were higher.22

**Haematological**

Anemia, thrombocytopenia and leucopenia were mild and dose dependent. In a study of 16 patients divided into 4 groups receiving 5 mg/m², 10 mg/m², 15 mg/m² of sirolimus and placebo respectively, a single case of thrombocytopenia occurred in the 15 mg/m² group.23

**Infections**

Opportunistic infections: HSV and pneumonia have been reported. Interstitial pneumonitis has also been reported.24 Morelon E et al reported 3 cases of interstitial pneumonia in renal transplant recipients treated with sirolimus who had either exertional dyspnea (n=2) or were asymptomatic (n=1). X-ray of the chest had shown bilateral pulmonary infiltrates with a basilar and peripheral distribution. Bronchoalveolar lavage showed lymphocytic pneumonitis in 2 patients. There was no evidence of infection in any patient and transbronchial biopsy in 2 patients had shown non-specific lymphocytic interstitial changes. None were treated with antibiotics and all responded well when sirolimus was withdrawn.24

**Proteinuria**

Switching from CSA to SRL was complicated by the development of proteinuria in 32 cases of which 18 had nephrotic syndrome. Renal biopsy done in 15 patients showed FSGS in 5 cases which were absent before SRL was started. It is possible that CNI withdrawal leads to an increase in renal blood flow which unmasksm proteinuria in patients with pre-existing CNI related FSGS.21

**Dermatological**

Acne lesions manifesting as pustulous monomorphic lesions over scalp, face and trunk were found in all the 10 males in a study in which no females had similar skin lesions. Biopsy was normal in all patients and there was spontaneous resolution in 4-6 weeks.21

**Others**

Mild transient headache, nausea, dizziness, hypoglycaemia, epistaxis, delayed wound healing, lower limb edema, mouth ulcers and bone pain have been reported.

**USE OF SIROLIMUS IN NON TRANSPLANT SETTING**

**Prevention of stent restenosis**: Arterial injury is associated with activation of smooth muscle cells (SMC) within the vessel wall which migrate and proliferate to produce new blood vessels. This response is applicable to disease states like tumor growth and metastasis, diabetic retinopathy, arthritis, accelerated arteriopathy after cardiac transplantation and neointimal proliferation after balloon angioplasty (PTCA) and stent placement.26 Sirolimus has been proved to be a potent inhibitor of SMC proliferation and migration in view of its unique mechanism. Sirolimus-eluting coronary artery stents have reduced in-stent restenosis from about 30% to less than 5% in large clinical trials.27

Thirty patients with angina pectoris were treated with sirolimus coated BX-velocity stents-50% received a slow release formulation and 50% received a fast release formulation. After an 8 month follow up no patient had more than 50% intimal hyperplasia as measured by intravascular ultrasound or quantitative coronary angiography. Only 3 patients had more than 15% intimal
hyperplasia at 4 months. No complications like in-stent or edge restenosis, stent thrombosis, repeat revascularization, MI or death were observed. The absence of adverse effects at 8 months suggest that the use of sirolimus coated stents is feasible and safe.

The anti-proliferative action of sirolimus has also been used in the treatment of accelerated arteriopathy after cardiac transplantation and its use has been associated with a reduction in retinoblastoma protein phosphorylation.

Anti-tumor activity: Sirolimus inhibits the proliferation of transformed cell lines of lymphoid, CNS, hepatic, melanocytic, osteoblastic, myogenic, renal and connective tissue origin, as well as the proliferation of T and B cells transformed by HTLV-1 and EBV, respectively. It was found to be very active against B16 melanocarcinoma, EM ependymoblastoma, CD8 F1 mammary and colon 38 tumors. It was more active than 5FU and adriamycin in murine models of B16 and colon 38 tumors.

Anti fungal activity: Although sirolimus was found to have potent antifungal activities and its efficacy was comparable to Amphotericin B, its development as an antifungal was not pursued due to its potent immunosuppressive activity, which is an undesirable attribute of an anti-infective agent.

CONCLUSION

Sirolimus is a new potent immunosuppressant whose profile could offer an advantage over other currently used drugs in view of its absence of intrinsic nephrotoxicity and efficacy as good as cyclosporin. It could have both a steroid sparing as well as a cyclosporin sparing effect. However, we do not have enough experience with this drug at present.

REFERENCES


