Chapter

# 2 Sirolimus: Evolving Trends

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## INTRODUCTION

The widespread use of solid organ transplantation has become a necessity in end-stage kidney, liver and heart disease. The series of immunosuppressives are increasingly used since 1970 to protect against acute and chronic graft rejection in the transplant population. The conventional nonspecific immunosuppression with corticosteroids and azathioprine is inproved with the use of more direct-acting and efficacious Cyclosporine (Cys) in 1980. However Cys is nephrotoxic and thus have the limitation of prolonged use. The 'newer' agents with greater advantages include tacrolimus (Tac), mycophenolate mofetil (MMF) and monoclonal antibody preparations. But these are found to have suboptimal pharmacokinetics, adverse effect or drug interactions. Sirolimus (SRL) is the most recent immunosuppressive to protect against transplant rejection and is recommended for combined use with Cys and corticosteroids.

SRL is a carbocyclic lactone-lactam macrolide antibiotic prepared through natural fermentation from the soil actinomycete streptomyces hygroscopicus and is discovered 25 years ago. Its original name was rapamycin[1,2].

## MECHANISM OF ACTION

SRL has immunosuppressive, antifungal and antitumor activity[3,4]. This molecule belongs to a class of agents that binds to cytosolic proteins (immunophilins) to exert immunosuppressive effect. It binds to FK binding protein (FKBP) and inhibits the mammalian target of rapamycin (m TOR) unlike Cys and Tac which inhibit calcineurin. It inhibits cellular response to IL-2 and $G_1$–S phase of cell cycle. However, Cys and Tac inhibit production of IL-2 and $G_0$–$G_1$ phase of cell cycle[5,6].

SRL inhibits "third signal" of T-cell proliferation induced by cytokines such as IL-1, IL-2, IL-3, IL-12, IL-15, alloantigens amd mitogens in a dose dependent manner. This inhibition prevents the cell entering the cell cycle and proliferating. Moreover it inhibits B-cell proliferation and decreases synthesis of immunoglobulins. An alternative m TOR inhibitor, everolimus is also available as immunosuppressant.

## PHARMACOKINETICS

SRL is rapidly but poorly absorbed after oral administration with estimated bioavailability of 15%[7]. This has high lipophilicity and 95% of this drug is bound to red blood cells which contains excessive FKBP. SRL is 100 times more potent than Cys because of increased binding to red cells than lymphocytes.

Like Cys and Tac, SRL undergoes extensive metabolism by CYP3A4 system both in the liver and small intestine. The terminal half-life of SRL is long ranging from 57 to 62 hours, suggesting once – daily dosing is adequate[7].

SRL is primarily eliminated 91% in the faces and only 2% in the urine. It is extensively metabolized in the liver; hence, dosage modification is necessary in patient with hepatic dysfunction and not in those with renal dysfunction.

## DRUG INTERACTIONS

Since SRL is extensively metabolized by CYP3A4 enzyme system, those enzyme inducers like rifampicin and phenytoin and enzyme-inhibitors like azoles,

erythromycin alter the drug concentration[8]. The concomitant use of SRL and statins results in reversible rhabdomyolysis because of common metabolic pathway of CYP3A4. The co-administration of propofol and SRL enhance the hyperlipidemic effect. In vitro and vivo studies the combination of SRL and Cys or Tac have synergistic effect[9-11].

## INDICATIONS

### Renal Transplant

#### *SRL helps in primary immunosuppression following renal transplant*

The Rapamune US study[12] in 719 Afro-American patients on baseline Cys and steroid therapy following transplant are grouped with add-on SRL in uptitrated dosage in one arm and same with azathioprine in another arm. They observed treatment failure, graft loss or patient death were statistically lower in the SRL arm than azathioprine arm.

The Rapamune global study[13] was conducted in Australia, Canada, Europe and US in 576 patients who received Cys and steroid as baseline immunosuppressants. This is a comparative evaluation between SRL in escalating dose in one group and placebo in another group. The composite end point of acute rejection was significantly lower with SRL group than with placebo group.

Data from these studies[12,14] show that SRL decreases the incidence of acute rejection compared with azathioprine or placebo in kidney transplant patients but does not change patient or graft survival over the first two years after transplant.

#### *Refractory rejection*

It is usually defined as patients with ongoing rejection (Banff Class IIB or III) despite the use of high dose steroids and polyclonal and mouse anti $CD_3$ monoclonal antibodies. SRL has been successfully used in this area of renal transplant. Between 6-12 months following initiation of SRL therapy, refractory rejection was reversed in 90% patients[15]. Hence SRL should be recommended as rescue therapy in refractory rejection.

#### *Corticosteroid Sparing*

In Cys based immunosuppression in low risk renal transplant patients the addition of SRL may allow reduction or withdrawal of corticosteroids. In one study[16] of 35 cadaver donor recipients steroids were successfully withdrawn in 27 patients.

#### *Cyclosporine Sparing*

An open-label study[17] evaluated SRL-based versus Cys-based immunosuppression in combination with MMF in 78 patient and graft survival was 97.5% and 92.5% versus 95% and 89.5% in the SRL and Cys arms respectively. No statistical difference was noted in this small sample size. Renal function as assessed by GFR was higher in SRL group. This supports the hypothesis that SRL may be used as primary immunosuppressant in renal transplantation.

### Liver Transplant

Preliminary data[18] on use of SRL in liver transplant in three arm regimens is observed as (a) primary immunosuppression with low-dose Tac and steroid (b) abrupt or tapered switching from Tac or Cys to SRL due to calcineurin inhibitor toxicity (c) with Tac for chronic rejection. The conclusions drawn by author suggest that SRL is effective in liver transplant and allows for reduction in Cys and Tac dosing; however one should be cautions about excessive immunosuppression in patients receiving long-term calcineurin inhibitor therapy. However larger double blind randomized controlled study need to be done to confirm its long term usefulness.

### Cardiac Transplant

One multicentric, randomized, clinical study[19] used SRL in treatment of International Society for Heart and Lung Transplantation (ISHLT) grade 2 or 3A rejection in 60 heart transplant patients. Reversal of rejection to either ISHLT grade 0 or 1 was considered a treatment success.

The authors concluded that though SRL is useful to control moderate acute rejection; but effectiveness and adverse effects are dose-dependent.

### Lung Transplant

Limited data are available regarding its (SRL) use in lung transplant. In one abstract[20] it was observed that SRL can be used as primary immunosuppressant when patients develop adverse effects due to calcineurin inhibitors. The drug's mechanism of action and low toxicity profile make it a highly promising option.

### Autoimmune Disease

SRL blocks the proliferation of T and B cells in response to Cytokines and hence it is considered of some value in rheumatoid arthritis, systemic lupus

erythematosus, psoriasis, dermatomyositis, uveoretinitis. Nadiminti et al observed a successful outcome with SRL in an young patient of dermatomyositis[21].

Topically applied SRL penetrates normal skin and may have some antipsoriatic and immunosuppressive activity[22].

### Coronary Revascularization

Rates of angiographic restenosis and target lesion revascularization are found to be higher in small vessels (< 2.5mm in diameter) than in larger vessels 6 months after percutaneous transluminal coronary angioplasty or stenting and 1 year after stenting as in diabetes, complex and long lesions. The SRL-eluting Cypher stent is confirmed to be superior to the bare Bx Velocity stent to prevent late restenosis following angioplasty[23]. SRL and Paclitaxel eluting stent are equally effective for prevention of post angioplasty restenosis[24].

## DOSAGE AND ADMINISTRATION

Due to the long half-life of SRL the recommended regimen is a 6 mg loading dose followed by maintenance dose of 2 mg/d. A 15mg loading dose and 5 mg maintenance dose were also used in Phase III clinical studies[25]. It is only available in liquid form. SRL and Cys should be given four hours apart due to pharmokinetic interaction between the two. The Cys dosage should be reduced by 45% if it is coprescribed with SRL. SRL oral solution should be mixed in at least 2 ounces of water or orange juice (not grape juice) in a plastic or glass cup and stirred vigorously for one minute before consumption. SRL is contraindicated in patients with macrolide hypersensitivity. Since most patients will be receiving SRL 2 mg/day, routine drug monitoring may not be required. The therapeutic drug monitoring is only recommended in early period of post-transplantation when SRL is combined either with Cys or Tac and when there is toxicity. The safe therapeutic blood level of SRL should be between 3.5 and 15 ng/ml.

## TOLERABILITY

The major clinical side effects of SRL therapy are myelosuppression and hyperlipidemia. The hypertriglyceridemia and hypercholesterolemia due to overproduction of lipoprotein or due to decreased lipolysis are reversible on withdrawal of the drug. It can also be managed by dose reduction and/or the addition of antihyperlipidemic agents. The myelosuppression is also reversible. Headache, epislaxis, diarrhea, stomatitis acne and polyarthralgia are also reported.

In a global study[26], the incidence of post-transplantation lymphoproliferative disorders was 1.4% which was slightly higher than found in other groups. Several studies reported unexplained interstitial pneumonitis associated with SRL treatment in renal and liver transplant recipients[27].

## CONCLUSION

SRL is an unique and potent immunosuppressive agent available for use in solid organ transplantation, antiimmune disorders, and in-site drug eluting stent angioplasty. It possesses a pharmacokinetic and drug interaction profile similar to that of Cys and Tac. The mechanism of action is somewhat different than traditional calcineurin inhibitors.

SRL demonstrated safety and efficacy in large phase III clinical research studies. Acute rejection is significantly reduced, but patient and graft survival are not significantly increased. It is found to be useful in refractory and chronic rejection.

SRL use has been reported to have adverse effects like bone marrow suppression and hyperlipidemia but nephrotoxicity and neurotoxicity are rare. This drug is available in liquid form and dose is initiated as a bolus with 6 mg/d followed by maintenance dose of 2 mg/d. It may be co-prescribed with Cys and/or Tac as they have synergistic effect. The cost-effectiveness and economic analyses have yet to be completed.

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