Role of sirolimus, a novel immunosuppressive drug in heart and lung transplantation

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Summary

Lung and heart transplantation has become an accepted therapeutic option for patients with end-stage disease. However, the calcineurin-inhibitor-based immunosuppression often causes renal impairment. Therefore, sirolimus, a novel immunosuppressive agent, may serve as an alternative or complementary agent to calcineurin inhibitors. The aim of this review was to summarize the role of sirolimus in lung and heart transplantation. Although only a few, small studies have been conducted so far, the drug’s mechanisms of action and low-toxicity profile make it a highly promising option.

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Introduction

Lung and heart transplantation has become an accepted treatment modality for end-stage organ disease.\textsuperscript{1} However, despite the use of traditional immunosuppressive maintenance therapy, which consists of cyclosporine (CsA) or tacrolimus (Tac), azathioprine or mycophenolate mofetil, and steroids, acute rejection occurs frequently, especially in the first weeks and months after transplantation. Although these rejection episodes usually resolve, they are associated with substantial morbidity and an increased incidence of chronic rejection. Because acute rejection occurs far more often after lung transplantation than after any other form of solid organ transplantation,\textsuperscript{2} substantial efforts have been invested to develop new immunosuppressant drugs with minimal toxic side effects.

This work reviews the evidence supporting the use of a recently approved immunosuppressive drug, sirolimus (SRL), in heart and lung transplantation.

Mechanism of action

SRL has a similar molecular structure to Tac and also binds to FK binding protein 12 (FKBP12) complex. In contrast to CsA and Tac, the SRL-FKBP12 complex has no effect on calcineurin phosphatase. Instead, it binds to one or more proteins known as mammalian "targets of rapamycin" (mTOR), and subsequently inhibits both DNA and protein synthesis, resulting in arrest of the cell cycle in late G1 as it progresses to the S phase.\textsuperscript{3-7}

Immunosuppressive properties of sirolimus

The immunosuppressive properties of SRL have been confirmed in both in vitro and clinical studies.
SRL inhibits T-cell proliferation induced by cytokines such as interleukin (IL)-1, -2, -3, -12 and -15, alloantigens and mitogens in a dose-dependent manner. It also exerts an independent action on antigen- and cytokine-induced B-cell proliferation, and it decreases the synthesis of immunoglobulin. In animal studies, rats treated with SRL at various doses showed a longer duration of graft viability and longer survival than nonimmunosuppressed controls. SRL has been found to inhibit cytokine expression, especially IL-10, more effectively than CsA and to be 20 to 100 times more potent than CsA in preventing acute allograft rejection. When SRL was combined with CsA, cardiac and kidney allograft survival was longer than with either drug alone, suggesting a synergistic effect. This was also true for SRL and Tac with regard to mouse heart tissue allografts.

Sirolimus in heart and lung transplantation

Several multicenter prospective randomized trials conducted in the United States (n = 719), globally (n = 576), and in Europe (n = 83) have found SRL to be an effective immunosuppressive agent in renal transplant recipients. However, its role in human heart and lung transplantation has been investigated so far only in small prospective, uncontrolled studies (Table 1) with a total of 38 lung transplant recipients and 86 heart transplant recipients. SRL was tested in these trials as a potential treatment for acute or chronic graft rejection in patients with either refractory rejection (rescue therapy) or bronchiolitis obliterans syndrome (BOS), as an alternative immunosuppressive agent in transplant recipients with renal impairment and as primary immunosuppressant immediately after lung transplantation.

Sirolimus as a treatment for graft rejection

Cahill et al. in an observational controlled study, treated 12 lung transplant recipients with bronchiolitis obliterans with a combination of SRL, calcineurin inhibitor (CI), and prednisone for 24 weeks. After SRL was initiated, 58% of the patients required a reduction in the dose of CI to maintain appropriate CI trough concentrations. Nevertheless, serum creatinine levels rose in 75%. Unexpected adverse effects included anemia of chronic disease (normal iron stores with no evidence of bleeding), (100%), edema (50%), and malignancy (17%). For the whole group, there was no decrease in the change in rate of forced expiratory volume in 1 s (FEV1) or forced expiratory flow from the first to third quarters (FEF 25–75%) with SRL, though individual responses varied. SRL did not affect the decline in pulmonary function, but in those with rapidly declining pulmonary mechanics, SRL administration resulted in stabilization or improvement of pulmonary function. The authors concluded that until optimal dosing strategies and a more complete adverse-effect profile are established, combination therapy should be utilized cautiously in this patient population.

Haddad et al. described two patients with chronic rejection of cardiac grafts who were refractory to the usual antirejection medications. In both cases, SRL proved successful in suppressing graft rejection, and these effects were maintained even after 10 months of SRL treatment despite significant decreases in the doses of the other immunosuppressant drugs.

SRL was also investigated for its ability to induce immunosuppression in heart transplant recipients in order to decrease the incidence of acute rejection and avoid early renal failure. In a prospective short-term pilot study, 42 patients were randomized to two groups before transplantation. The study group (n = 20) received SRL and low dose CsA, and the control group (n = 22) received high-dose CsA and azathioprine. Both groups also received prednisone. The duration of follow-up was 9 months. There were no episodes of acute renal failure in the study group, whereas two patients in the control group required hemodialysis. The number of episodes of rejection was similar in both groups, although the study group had a significantly lower biopsy score. The overall infection and mortality rates were similar as well. The combination of SRL and Tac was studied in a controlled, prospective trial in 25 heart transplant recipients. All but three patients tolerated the combination well. Only one acute rejection episode was noted, and there was no increase in the infection rate. The authors concluded that this combination may decrease the trough level of each of the drugs.

Together, these studies, although very small, suggest that a SRL-based regimen could be an effective alternative treatment for rejection in lung and heart transplant recipients.

Sirolimus as a treatment for renal failure

SRL has no renal toxicity, which is a common posttransplant problem associated with CI. In a
Table 1  Sirolimus-based immunosuppression in heart and lung transplantation: Review of the literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Organ</th>
<th>No of patients</th>
<th>Indication</th>
<th>Follow-up (mos)</th>
<th>Results</th>
<th>Rejection</th>
<th>Adverse events</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snell et al.</td>
<td>Lung</td>
<td>20</td>
<td>RF</td>
<td>1</td>
<td>5 ceased</td>
<td>2 acute</td>
<td>35 infections (16 pts)</td>
<td>7 died</td>
</tr>
<tr>
<td>Heart</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cahill et al.</td>
<td>Lung</td>
<td>12</td>
<td>BOS/BO</td>
<td>6</td>
<td>Stable lung function Improvement in high-risk pts</td>
<td></td>
<td>All alive</td>
<td></td>
</tr>
<tr>
<td>Haddad et al.</td>
<td>Heart</td>
<td>2</td>
<td>Refractory rejection</td>
<td>10</td>
<td>Lower rejection rate</td>
<td></td>
<td>NA</td>
<td>All alive</td>
</tr>
<tr>
<td>Zakliczynsi et al.</td>
<td>Heart</td>
<td>20</td>
<td>Induction IS</td>
<td>9</td>
<td>No RF lower Cr</td>
<td>No increased rejection</td>
<td>No more infections 1 neurological 2-RF High cholesterol</td>
<td>3 died (2 controls)</td>
</tr>
<tr>
<td>Mueller et al.</td>
<td>Heart</td>
<td>25</td>
<td>Primary IS</td>
<td>16+/−5</td>
<td>22 pts tolerated</td>
<td></td>
<td></td>
<td>All alive</td>
</tr>
<tr>
<td>Groetzner et al.</td>
<td>Heart</td>
<td>25</td>
<td>RF</td>
<td>9+/−5</td>
<td>Improved Cr; 3 ceased dialysis</td>
<td>No rejection</td>
<td>Stable graft function</td>
<td>All alive</td>
</tr>
<tr>
<td>Griffith et al.</td>
<td>Heart</td>
<td>9</td>
<td>High risk (all RF, 4/9 MV)</td>
<td>5</td>
<td>Normal graft and renal function</td>
<td></td>
<td>Prolonged serious drainage edema</td>
<td>All alive</td>
</tr>
<tr>
<td>Kink-Biggs et al.</td>
<td>Lung</td>
<td>15</td>
<td>Primary IS</td>
<td>6</td>
<td>No more infections</td>
<td>Low incidence</td>
<td>Bronchial dehiscence</td>
<td>4 died</td>
</tr>
</tbody>
</table>

BO, bronchiolitis obliterans; BOS, bronchiolitis obliterans syndrome; Cr, creatinine; IS, immunosuppression; MV, mechanically ventilated; Pts, patients; RF, renal failure.
study of 20 lung and five heart transplant patients with serious renal impairment who were being treated with CI, the addition of SRL led to a cessation of CI treatment in 48% and a substantive reduction in CI dose in the remainder. After 30 days, dialysis could be stopped in four of the five dialyzed patients, and elevated serum creatinine levels (mean 0.29 mmol/l) dropped in 15 of the 20 patients with this finding. The improvement in creatinine level after 30 days predicted the long-term value, whereas the starting value did not predict either the 30-day or the long-term value. There were two bouts of acute rejection and one bout of chronic rejection. Sixteen patients had 35 infectious complications and 17 patients had 24 episodes of potential SRL-related toxicity; all these events were level related and generally responded to a dose reduction or temporary cessation of the drug. However, the mortality rate was high (seven deaths) and despite the authors concluded that these deaths were related not directly to drug toxicity of SRL, it should be interpreted carefully. By the end of the study, 15 patients were still taking SRL. These findings indicate that SRL may serve as a useful alternative immunosuppressant in transplant recipients with renal impairment who require significant withdrawal of CI. Whether the resulting improvement in creatinine level can be maintained for the long term probably depends on the balance between the acute and chronic renal damage.

Groetzner et al. studied the impact of CI-free immunosuppression and SRL treatment on renal failure in 25 heart transplant recipients monitored for 9 months. They found that renal function improved significantly, and hemodialysis could be stopped in three dialyzed patients. No acute rejection was noted, and graft function remained stable.

Griffith et al. studied the effect of SRL in nine high-risk heart transplant recipients, of whom four were on mechanical ventilation. All had renal failure. Histological rejection requiring treatment occurred only in three patients within the first 2 weeks, and each was remarkably sensitive to a minimal steroid bolus. No rejection requiring treatment was seen in any patient after 2 weeks. All patients had normal graft and renal function at a median follow-up of 5 months (range 1–9). There was, however, prolonged serious drainage from the chest tubes and peripheral edema, which responded to aggressive diuresis. This study suggests that SRL may be effective in mechanically supported recipients with renal failure. Further studies using larger samples are still needed.

**Tolerability**

The main clinical side effects of SRL treatment are myelosuppression, hyperlipidemia, and over-immunosuppression. Headache, epistaxis, diarrhea, mild stomatitis, skin complaints, mild acne, and polyarthalgia have also been reported. The hypertriglyceridaemia and hypercholesterolaemia are reversible and can be managed by dose reduction and/or the addition of antihyperlipidemic agents.

Two studies reported a more frequent occurrence of herpes simplex virus infection and pneumonia with SRL than CsA, but there was no significant difference in the incidence rates of moderate or severe opportunistic or common transplant-related infections. In a global study, the incidence of posttransplantation 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.

More recently, King-Biggs et al. reported the occurrence of bronchial anastomotic dehiscence in lung transplant recipients when SRL was used as part of an immunosuppressive regimen, in combination with Tac and corticosteroids. In these cases, SRL was initiated at the time of transplantation in 15 lung transplant recipients. This complication was noted in four of 15 patients of whom three died.

**Therapeutic monitoring of SRL**

SRL, currently only available in liquid formulation, has a relatively low bioavailability (15%). It has a long half-life (63 h), justifying both a loading dose to rapidly attain steady-state concentrations and once daily dosing. SRL levels should be between 3.5 and 15 ng/ml. The successful reduction in acute rejection associated with fixed SRL doses of 2 and 5 mg/day in the US and Global trials suggests that while desirable, routine monitoring of SRL levels in such regimens is not essential, particularly at doses of 2 mg/day. However, monitoring is probably necessary to ensure safe, effective concentrations especially in the early period post transplantation, in patients that treat with combination of SRL and CsA or Tac and when there are sign of toxicity.

**Summary**

SRL is a potent novel immunosuppressive drug in humans. It has been successfully used with and
without CsA, and may serve as an alternative or complementary agent to CsA. Tac may also be an efficient and safe partner for SRL. Although only a few, small studies have been conducted so far in heart and lung transplant recipients, the drug’s mechanisms of action and low-toxicity profile make it a highly promising option. Recent cases of bronchial anastomotic dehiscence in de novo lung transplant recipients raise concerns about the role of SRL, when administered at the time of transplantation, in this patient group. Until large, prospective trials are conducted, SRL might be better used as a rescue therapy in lung transplant recipients or in transplant recipients with chronic impairment in renal function.

References


