Respiratory Medicine (2004) **98**, 892–897

respiratoryMEDICINE

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

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Received 14 July 2003; accepted 17 December 2003

KEYWORDS
Sirolimus;
Transplantation;
Immunosuppression;
Rejection

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.

Introduction

Lung and heart transplantation has become an accepted treatment modality for end-stage organ disease.[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,[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.[3–7]

Immunosuppressive properties of sirolimus

The immunosuppressive properties of SRL have been confirmed in both in vitro and clinical studies.

Abbreviations: CI, calcineurin inhibitor; CsA, cyclosporine; SRL, sirolimus; Tac, tacrolimus

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0954-6111/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2003.12.016

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.[3,4] It also exerts an independent action on antigen- and cytokine-induced B-cell proliferation,[5] and it decreases the synthesis of immunoglobulin.[6] In animal studies, rats treated with SRL at various doses showed a longer duration of graft viability and longer survival than nonimmunosuppressed controls.[7,8] SRL has been found to inhibit cytokine expression, especially IL-10, more effectively than CsA[9] 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.[10] This was also true for SRL and Tac with regard to mouse heart tissue allografts.[11]

Sirolimus in heart and lung transplantation

Several multicenter prospective randomized trials conducted in the United States ($n = 719$),[12] globally ($n = 576$),[13] and in Europe ($n = 83$)[14] 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[15–17] and 86 heart transplant recipients.[15,18–22] SRL was tested in these trial 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 immunosuppressant agent in transplant recipients with renal impairment and as primary immunosuppressant immediately after lung transplantation.[17]

Sirolimus as a treatment for graft rejection

Cahill et al.[16] 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 difference in the change in rate of forced expiratory volume in 1 s (FEV_1) 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.[18] 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,[19] 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.[20] 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.

Reference	Organ	No of patients	Indication	Follow-up (mos)	Results	Rejection	Adverse events	Outcome
Snell et al.[15]	Lung	20	RF	1	5 ceased	2 acute	35 infections (16 pts)	7 died
	Heart	5			dialysis, 15/20 improved Cr	1 chronic		
Cahill et al.[16]	Lung	12	BOS/BO	6	Stable lung function Improvement in high-risk pts		Anemia edema malignancy	All alive
Haddad et al.[17]	Heart	2	Refractory rejection	10	Lower rejection rate		NA	All alive
Zakliczynsi et al.[19]	Heart	20	Induction IS	9	No RF lower Cr	No increased rejection	No more infections	3 died (2 controls)
Mueller et al.[20]	Heart	25	Primary IS	16 + /-5	22 pts tolerated	No increase	1 neurological 2-RF High cholesterol	All alive
Groetzner et al.[21]	Heart	25	RF	9 + /-5	Improved Cr; 3 ceased dialysis	No rejection	Stable graft function	All alive
Griffith et al.[22]	Heart	9	High risk (all RF, 4/9 MV)	5	Normal graft and renal function	2 in first 2 weeks	Prolonged serious drainage edema	All alive
Kink-Biggs et al.[17]	Lung	15	Primary IS	6	No more infections	Low incidence	Bronchial dehiscence	4 died

BO, bronchiolitis obliterans; BOS, bronchiolitis obliterans syndrome; Cr, creatinine; IS, immunosuppresion; 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.[15] 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.[21] 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.[22] 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 serous 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-immunosuppresssion. 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,[23,24] but there was no significant difference in the incidence rates of moderate or severe opportunistic or common transplant-related infections. In a global study,[13] 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.[25–27]

More recently, King-Biggs et al.[17] 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.[17]

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.[28] 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 withcomination of SRL and CsA or Tac and when there are sign of toxicity.[29]

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 CI. 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

1. Theodore J, Lewison N. Lung transplantation comes of age. *N Engl J Med* 1990;**332**:772–4.
2. Girgis RE, Tu I, Berry GJ, Reichenspurner H, Valentine VG, Conte JV, Ting A, Johnstone I, Miller J, Robbins RC, Reitz BA, Theodore J. Risk factors for the development of obliterative bronchiolitis after lung transplantation. *J Heart Lung Transpl* 1996;**15**:1200–8.
3. Sehgal SN. Rapamycin. Mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 1998;**31**:335–40.
4. Bertagnolli MM, Yang L, Herrmann SH, Kirkman RL. Evidence that rapamycin inhibits interleukin-12 induced proliferation of activated T lymphocytes. *Transplantation* 1994;**58**: 1091–6.
5. Aaguaard-Tillery KM, Jelinek D. Inhibition of human B lymphocyte cell cycle progression and differentiation by rapamycin. *Cell Immunol* 1994;**152**:493–507.
6. Kimm HS, Raskova J, Deglanns D. Effects of cyclosporine and rapamycin on immunoglobulin production by preactivated human B cells. *Clin Exp Immunol* 1994;**96**:508–12.
7. Zueng XX, Strom TB, Steele AW. Quantitative comparsion of rapamycin and cyclosporine effects on cytokine gene expression studied by reverse transcriptase-competitive polymerase chain reaction. *Transplantation* 1994;**58**:87–92.
8. Clanb R, Collier D, Lim S, Pollard SG, Samaan A, White DJ, Thiru S. Rapamycin for immunosuppressive in organ allografting. *Lancet* 1989;**2**:227.
9. Morris RE, Meiser BM. Identification of a new pharmacological action for an old compound. *Med Sci Res* 1989;**17**: 609–10.
10. Stepkowski SM, Kahan BD. Rapamycin and cyclosporine synergistically prolong heart and kidney allograft survival. *Transplant Proc* 1991;**23**:3262–4.
11. Morris RE, Meiser BM, Wu J, Shorthouse R, Wang J. Use of rapamycin for the suppression of alloimmune reactions in vivo: schedule dependence, tolerance induction, synergy with cyclosporine and FK 506 and effect on host-versus-graft and graft-versus-host reactions. *Transplant Proc* 1991;**23**: 521–4.
12. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomized multicenter study. The Rapamune US Study Group. *Lancet* 2000;**356**:194–202.
13. MacDonald AS, for the Rapamune Global Study Group. A worldwide phase III, randomised, controlled safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation* 2001; **71**: 271–80.
14. Kahan BD, Julian BA, Pescovitz MD, Vanrenterghem Y, Neylan J. Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in Caucasian recipients of mismatched primary renal allograft: a phase II trial. *Transplantation* 1999;**68**: 1526–32.
15. Snell GI, Levvey B, Chin W, Kotsimbos T, Whitford H, Waster KN, Richardson M, Williams TJ. Sirolimus allows renal recovery in lung and heart transplant recipients with chronic renal impairment. *J Heart Lung Transpl* 2002;**21**: 540–6.
16. Cahill BC, Somerville KT, Crompton J, O'Rourke M, Parker ST, O'Rourke MK, Stringham J, Karwande SV. Early experience with sirolimus in lung transplant recipients with chronic allograft rejection. *J Heart Lung Transpl* 2003;**22**: 169–76.
17. King-Biggs MB, Dunitz JM, Park SJ, et al. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. *Transplantation* 2003;**75**: 1437–43.
18. Haddad H, MacNeil DM, Howlett J, O'Neill B. Sirolimus. A new potent immunosuppressant agent for refractory cardiac transplantation rejection: two case reports. *Can J Cardiol* 2000;**16**:221–4.
19. Zakliczynski M, Nozynski J, Wojarski J, Zembala M. Prospective short-term pilot study of sirolimus as an induction of immunosuppression in heart transplant recipients. Abstract 138. The International Society for Heart and Lung Transplantation, Vienna, Austria, April 2003.
20. Mueller M, Groetzner MJ, Kaczmarek I, Reisch F, Schuster F, Landwehr P, Ueberfuhr P, Reichart B. Sirolimus in combination with tacrolimus for primary immunosuppression after orthotopic heart transplantation. Abstract 139. The International Society for Heart and Lung Transplantation, Vienna, Austria, April 2003.
21. Groetzner J, Kaczmarek I, Buehse L, Muller M, Landwehr P, Vogeser M, Meiser B, Reichart B. Calcineurin-inhibitor-free immunosuppression with mycophenolate mofetil and sirolimus after cardiac transplantation is safe and improves renal function significantly. Abstract 237. The International Society for Heart and Lung Transplantation, Vienna, Austria, April 2003.
22. Griffith BP, Augustine SM, Gottlieb WS, Drachenberg DC, Poston DR, Brown GJ. Rapamycin-based and late FK-506-light immunosuppression in heart transplant recipients. Abstract 137. The International Society for Heart and Lung Transplantation, Vienna, Austria, April 2003.
23. Groth CG, Backman L, Morales J-M, Calne R, Kreis H, Lang P, Touraine JL, Claesson K, Campistol JM, Durand D, Wramner L, Brattstrom C, Charpentier B. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. *Transplantation* 1999;**67**:1036–42.
24. Kreis H, Cisterne JM, Land W, Swuifflet JP, Abramowics D, Campistol JM, Morales JM, Grinoyo JM, Mourad G, Berthoux FC, Brattstrom C, Lebranchu Y, Vialtel P. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation* 2000;**69**:1252–60.

25. Morelon E, Stern M, Kreis H. Interstitial neumonitis associated with sirolimus therapy in renal transplant patients. *N Engl J Med* 2000;**343**:225–6.
26. Mahalati K, Murphy DM, West ML. Bronchiolitis obliterans and organizing pneumonia in renal transplantation recipients. *Transplantation* 2000;**69**:1531–2.
27. Kahan BD, Camardo JS. Rapamycin: results and future opportunities. *Transplantation* 2001;**72**:1181–93.
28. Kells PA, Gruber SA, Behbod F, et al. Sirolimus, a new, ptent immunosuppressive agent. *Pharmacolotherapy* 1997;**17**: 1148–56.
29. Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: a review of the evidence. *Kidney Int* 2001;**59**:3–16.