Clinical Pharmacokinetics and Therapeutic Drug Monitoring of Sirolimus

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ABSTRACT

Background: Sirolimus is a novel macrocyclic antibiotic that has an immunosuppressive mechanism of action distinct from that of cyclosporine and tacrolimus.

Objective: The objective of this report is to provide an overview of the clinical development of sirolimus with emphasis on the mechanism of immunosuppressive activity, prevention of acute renal allograft rejection, clinical pharmacokinetics, concentration-effect relationships, and therapeutic drug monitoring (TDM).

Results: Pharmacokinetic studies in adult renal transplant patients have shown that sirolimus may be characterized as a drug with rapid absorption (t_{max} = 1 to 2 hours), low systemic availability (F = 14%), linear dose proportionality (2 to 24 mg), extensive partitioning into formed blood elements (B/P = 36), large apparent volume of distribution (1.7 L/kg), prolonged terminal half-life (62 hours), and large intersubject (CV = 52%) and intrasubject (CV = 26%) variability in oral-dose clearance. Results from phase III pivotal trials showed that sirolimus (2 or 5 mg/d) reduced acute renal graft rejection (generally, $P < 0.01$) without TDM. Although TDM may not be required for a regimen consisting of full-dose cyclosporine and corticosteroids with sirolimus 2 mg/d (4 hours after cyclosporine), it may be warranted in patients (1) with hepatic impairment, (2) who are young children, (3) who are receiving concurrent doses of strong CYP3A/p-glycoprotein inhibitors or inducers, (4) in whom cyclosporine dosing is markedly reduced or discontinued, and (5) who are at a high risk for rejection. A whole-blood sirolimus therapeutic window of 5 to 15 ng/mL (measured by microparticle enzyme immunoassay) is recommended for patients at standard risk of rejection. The large intrapatient variability observed in trough sirolimus concentrations indicates that dose adjustments should be optimally based on more than a single trough sample. Because of the time required to reach steady state, sirolimus dose adjustments would optimally be based on trough levels obtained ≥5 to 7 days after a dose change.

Conclusions: The effective use of sirolimus in an immunosuppressive regimen for the prevention of acute renal allograft rejection requires an understanding of the drug's clinical pharmacokinetics, concentration/adverse-effect relationship, concentration-efficacy relationship, and TDM.

Key words: sirolimus, rapamycin, drug monitoring, pharmacokinetics, pharmacodynamics.
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INTRODUCTION

Sirolimus* is a novel macrocyclic antibiotic that was isolated from soil collected on Rapa Nui (Easter Island).[1,2] The drug is a fermentation product of the actinomycete *Streptomyces hygroscopicus* and was originally shown to exhibit antifungal, antitumor, and immunosuppressive activity in animal models.[3] More recently, sirolimus has been developed for the prophylaxis of acute rejection in renal transplant patients. Approval for this indication was obtained from the US Food and Drug Administration in 1999 based on dose-controlled trials in renal transplant patients.

The present report provides an overview of the clinical development of sirolimus, with emphasis on (1) mechanism of immunosuppressive activity; (2) prevention of acute rejection in renal allograft patients; (3) clinical pharmacokinetics in healthy volunteers and renal allograft patients; (4) concentration-effect relationships in renal allograft patients; and (5) the utility of therapeutic drug monitoring (TDM).

MECHANISM OF ACTION

Sirolimus is a potent immunosuppressive agent whose mechanism of action differs from that of calcineurin-inhibiting agents such as cyclosporine and tacrolimus.[4] A lipophilic macrocyclic lactone, sirolimus contains a 31-membered macrolide ring ($C_{51}H_{79}NO_{13}$), the chemical structure of which has been confirmed by its complete organic synthesis.[5] Sirolimus modulates the immune response by inhibiting the activity of a regulatory protein critical to the coordination of events required for cells to move from the G_1 to the S phase of the cell cycle.[6] The mechanism of sirolimus is unique in that this regulatory protein is not targeted by cyclosporine or other agents currently used in transplantation. Cyclosporine and tacrolimus achieve their effects by inhibiting calcineurin and reducing interleukin-2 (IL-2) expression; sirolimus inhibits IL-2–mediated signal transduction but has no effect on calcineurin activity.[4]

The macrocyclic immunosuppressive agents sirolimus, cyclosporine, and tacrolimus bind to specific cytosolic proteins (immunophilins) to achieve their immunosuppressive activity.[7] The complexes of cyclosporine and tacrolimus, with their respective immunophilins (cyclophilin and FK-binding protein), inhibit calcineurin, a Ca^{2+}/calmodulin-dependent serine/threonine phosphatase required for production of IL-2 and early activation of T lymphocytes (ie, the transition from the G_0 to G_1 phase of the cell cycle). Sirolimus also binds to FK-binding protein, but unlike the tacrolimus/FK-binding protein complex, the sirolimus/FK-binding protein complex has no effect on calcineurin activity.[7] Rather, this complex binds to a specific cell-cycle-regulatory protein called mTOR (the mammalian target of rapamycin) and inhibits its activation.[8] Inhibition of mTOR suppresses cytokine-driven (IL-2, IL-4, and IL-15) T-lymphocyte proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.[9]

The immunosuppressive effect of sirolimus is synergistic with that of cyclosporine both in vitro and in vivo, and has an adverse-effect profile that largely differs from that of other immunosuppressive agents. Because sirolimus and

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cyclosporine have synergistic immunosuppressive properties and different adverse-effect profiles, they can be combined in an immunosuppressive regimen.

PRECLINICAL DATA

In mice, rats, rabbits, pigs, and primates, sirolimus has been shown to prolong survival after organ grafts,[10] and in some models, to induce tolerance. Little toxicity has been noted at immunosuppressive doses, except for a species-specific toxicity in dogs involving gastrointestinal lesions and vasculitis extending throughout the gastrointestinal tract. Studies in pigs revealed that at sirolimus blood levels of 7 to 8 ng/mL, renal allografts survived after cessation of sirolimus treatment.[10]

CLINICAL STUDIES

Phase II Pilot Studies

In phase II multicenter clinical trials, sirolimus was effective in preventing acute rejection when used with cyclosporine or as primary immunosuppressive therapy. The first of 3 phase II trials[11] demonstrated that prophylactic treatment of cadaveric or living-unrelated, primary renal allograft recipients with full-dose cyclosporine and corticosteroids and fixed-dose sirolimus significantly reduced the incidence of the first biopsy-confirmed acute rejection episode over 6 months compared with full-dose cyclosporine and corticosteroids plus placebo ($P = 0.018$). Patients receiving full-dose cyclosporine had target cyclosporine concentrations of 200 to 350 ng/mL during month 1, 200 to 300 ng/mL during months 2 and 3, and 150 to 250 ng/mL during months 4 to 12. Sirolimus also was effective with reduced-dose cyclosporine in nonblack patients. Patients receiving reduced-dose cyclosporine had target cyclosporine concentrations of 100 to 175 ng/mL during month 1, 100 to 150 ng/mL during months 2 and 3, and 75 to 125 ng/mL during months 4 to 12.

The second phase II study conducted in renal transplant recipients[12] was an open-label, concentration-controlled assessment of sirolimus versus cyclosporine, with concomitant administration of azathioprine and corticosteroids in both treatments. The third phase II study conducted in renal transplant recipients[13] was also concentration-controlled and compared sirolimus with cyclosporine during concomitant administration of mycophenolate mofetil and corticosteroids in both treatments. In the latter 2 phase II trials comparing sirolimus with cyclosporine,[12,13] the incidences of biopsy-proven acute rejection episodes (over 12 months), as well as graft and patient survival, were similar between treatments within studies. The safety profiles of the cyclosporine- and sirolimus-treated groups were different, however, and sirolimus-treated patients exhibited a trend toward better renal function (ie, 13% lower serum creatinine level, 17% higher glomerular filtration rate, and 22% lower uric acid level over 1 year in the second trial[12]).

Phase III Clinical Trials

Two phase III multicenter clinical trials[14,15] have shown that sirolimus 2 or 5 mg/d plus cyclosporine and corticosteroids significantly reduced the incidence of acute rejection (over 6 months) compared with regimens consisting of either cyclosporine plus corticosteroids (2 mg, $P = 0.076$; 5 mg, $P = 0.001$)[14] or cy-

closporine, azathioprine plus corticosteroids (2 mg, $P < 0.01$; 5 mg, $P < 0.001$).[15] Based on these results, a loading dose of 6 mg on day 1 followed by a maintenance dose of 2 mg once daily is the recommended sirolimus regimen for most adult renal transplant patients.

PHARMACOKINETIC STUDIES

The pharmacokinetic characteristics of sirolimus, administered as an oral solution, have been studied in various populations, including healthy subjects,[16] pediatric patients undergoing dialysis,[17] patients with hepatic impairment,[18] and stable/de novo renal transplant recipients receiving oral cyclosporine and corticosteroids.[18–24]

Absorption

Sirolimus is absorbed rapidly; mean peak whole-blood sirolimus concentrations (C_{max}) occur ~1 hour after administration of single doses[16] and 2 hours after multiple doses[20] in stable renal transplant patients. The systemic availability (F) of sirolimus is ~14%.[23] The low bioavailability of sirolimus after oral administration can be attributed to extensive intestinal[25] and hepatic[26] metabolism by the cytochrome P-450 (CYP) 3A enzyme family and to countertransport by the multidrug efflux pump p-glycoprotein in the intestine.[25,27] Linear dose proportionality, after single oral doses, has been observed in both healthy adult subjects (0.5–17 mg)[16] and renal allograft patients (2–24 mg).[17,18] In 22 healthy adult subjects receiving sirolimus and a high-fat breakfast (54.7% fat), C_{max} was decreased 34%, time to peak concentration (T_{max}) was increased 3.5-fold, and total exposure (area under the curve [AUC]) was increased 35% compared with fasting values.[28] To minimize variability, sirolimus should be administered consistently with or without food.[24]

Distribution

Sirolimus is partitioned extensively into formed blood elements, as shown by a mean whole blood–plasma ratio of ~36 in renal allograft patients.[16–18] The free fraction in plasma is ~8%,[18] with 40% of sirolimus associated with lipoproteins and 60% associated with lipoprotein-free plasma.[29] After multiple-dose administration in stable renal allograft patients, the mean oral-dose apparent steady-state volume of distribution (V_{ss}/F) of whole-blood sirolimus was ~12 L/kg.[20] After correction for systemic availability (F = 0.14), the apparent volume of distribution in renal allograft patients is ~1.7 L/kg.

Elimination

Sirolimus undergoes extensive oxidative metabolism after incubation with human liver microsomes to yield multiple demethylated, monohydroxylated, dihydroxylated, and didemethylated metabolites.[30] Many of the same metabolites have also been observed in the whole blood of renal allograft patients receiving multiple concomitant oral doses of sirolimus, cyclosporine, and corticosteroids. The immunosuppressive activity of the sirolimus metabolites is low. Based on a human lymphocyte proliferation assay,[31] hydroxylated sirolimus and demethylated sirolimus show ~7% and 10%, respectively, of the activity of sirolimus. After a single oral dose of carbon 14–labeled sirolimus in healthy volunteers, little radioactivity was excreted in urine (2.2%), and 90%