Sirolimus (Rapamycin)

Clinical Use: Monitor immunosuppressive therapy following organ transplant.

Clinical Background

Sirolimus (rapamycin, Rapamune) is an immunosuppressant that inhibits cytokine-stimulated T-cell proliferation. Sirolimus initially binds to FK-binding protein-12 (FKBP-12). This sirolimus-FKBP-12 complex in turn binds to a specific cell cycle regulatory protein, the mammalian target of rapamycin (mTOR) kinase, thereby inhibiting mTOR action. mTOR inhibition prevents cell cycle progression from G1 to S phase in T-cells and, thus, T-cell proliferation. mTOR inhibition is a different mechanism of action than that of calcineurin-inhibiting agents such as cyclosporine (CsA), a fact that may account for the synergistic effect of sirolimus/CsA combined therapy following renal transplant. Sirolimus is currently recommended for use in conjunction with cyclosporine (and corticosteroids) to reduce or prevent graft rejection by the host. Sirolimus dose-related side effects include increased serum levels of cholesterol, triglycerides, and creatinine and decreased glomerular filtration rate. Hypertension, rash, anemia, arthralgia, diarrhea, hypokalemia, leukopenia, and thrombocytopenia also may occur.

Sirolimus bioavailability and clearance are dependent on intestinal and hepatic metabolism by cytochrome P-450 (CYP) 3A4 enzyme and on countertransport by the multidrug efflux pump p-glycoprotein in the intestine. Pharmacokinetic studies reveal an approximate 4.5-fold range in interindividual behavior (see Table) and a correlation between trough blood concentrations and both efficacy and toxicity. The pharmacokinetics are altered during drug coadministration. For example, when sirolimus is administered concomitantly with the microemulsion formulation of CsA rather than administered 4 hours apart, sirolimus trough levels increase. Furthermore, diltiazem and ketoconazole increase sirolimus C_{max} while rifampin decreases the C_{max}. Hence, therapeutic drug monitoring (TDM) may be needed to achieve the best clinical outcome in selected cases (see below) even though routine TDM is not an absolute requirement.

Individuals Suitable for Testing

Patients who have had an organ transplant and:

- have hepatic impairment
- are receiving concurrent doses of strong CYP3A and p-glycoprotein inhibitors or inducers
- in whom CsA doses are markedly reduced or discontinued
- have had marked changes in the relative timing of administration of sirolimus and CsA
- are at high risk for rejection
- need to be monitored for adherence to the drug regimen

Pediatric patients are also candidates for testing after organ transplant.

Specimen Requirements

2 mL refrigerated whole blood (EDTA, lavender-top tube)
The optimal time for specimen collection is 0.5 to 1 hour before the next oral dose. This will yield the trough level.

Method

- Liquid chromatography with UV detection
- Extraction of sirolimus from whole blood
- Further extraction with 1-chlorobutane under alkaline conditions
- Reconstituted dry residue analyzed via HPLC
- Limit of Quantitation: 2.5 ng/mL

Reference Range

3.0 - 18.0 ng/mL (trough levels)

Interpretive Information

Steady state trough sirolimus levels below 3.0 ng/mL may place the patient at risk for host-graft rejection. Conversely, levels above 18.0 ng/mL are more likely to be associated with adverse events. As mentioned above, levels may be affected by drug coadministration and pharmacokinetics. Since 5 to 7 days are required to reach steady state after a dose adjustment, evaluation of multiple trough levels that were obtained greater than 7 days after the last dose change is recommended prior to a subsequent dose change.

Interindividual Pharmacokinetic Variability

Oral Solution	**Oral clearance rate (Cl/F)**
Tablet	**208 ± 95 mL/h/kg**
	139 ± 63 mL/h/kg
Time to peak concentration (t_{max})	
1.4 ± 1.2 h	**Apparent oral steady-state volume (V_{ss}/F)**
3.46 ± 2.40 h	**12.0 ± 4.6 L/kg**
Terminal half-life ($t_{1/2}$)	**Not established**
62.3 ± 15.2 h	
Not established	