### Perioperative Implications

- Risk primarily related to emergent cases based on half-life.
- Caution with the concomitant use of hypotensive agents.
- Precautions to prevent reflux and regurgitation.
- Pts on regular sildenafil for pulm vasodilation will have significant pulm Htn that is often assoc with significant underlying lung disease and right ventricular dysfunction.
- Pts on regular sildenafil for pulm vasodilation may require aggressive periop management of severe pulm Htn to maintain adequate cardiac output. Adequate pulm vasodilation may require periop therapy with IV inodilators such as milrinone and/or inhaled selective pulm vasodilators such as NO or prostacyclin.
- A randomized trial of preop sildenafil did not show reduction in pulm vascular resistance.

### Drug Interactions

- Concurrent use of nitrates may cause hypotension.
- Drug interactions with cytochrome P450 inhibitors (e.g., ketoconazole, erythromycin, cimetidine) can be expected; during concomitant therapy a lower dose is suggested.

# Statins

Frederic T. Billings IV

### Uses

- Incidence in USA: Estimated 20 million
- Primary indications include:
  - Hyperlipidemia: HMG-CoA reductase inhibitors (statins) are powerful drugs for lowering LDL cholesterol concentrations, and certain statins—atorvastatin in high doses and rosuvastatin—increase concentrations of healthy HDL cholesterol.
  - Primary and secondary prevention of CV disease: CV benefits (reduction in myocardial infarction and stroke) in pts with hypercholesterolemia. Benefits also in normocholesterolemic pts with elevated markers of inflammation (e.g., CRP, Jupiter trial).
  - Unproven benefits: Conflicting data on effect of statins to reduce risk of sepsis, thrombotic disease, acute kidney injury following surgery or radiocontrast administration, ARDS, or mortality in ICU patient populations. Recent (2010–2015) multicenter clinical trials testing the impact of statins on these acute illnesses have largely been negative despite prior promising data.

### Perioperative Risks

- Myopathy: Incidence among nonoperative chronic statin users is 2–11% for myalgias, 0.5% for myositis, <0.1% for rhabdomyolysis. Incidence increased in severe renal insufficiency (CrCl <30 mL/min). Reversible following statin discontinuation.
- Hepatic dysfunction: Incidence of persistent elevations in aminotransferases is 0.5–3%; it is 0.1% for a 10-fold increase in alanine aminotrasferase. Effect is reversible following statin discontinuation.
- The incidence of myopathy and transaminitis increases when cytochrome P-450 3A4 inhibitors—including cyclosporine, tacrolimus, azole antifungals, fenofibrates, protease inhibitors, and macrolide antibiotics—are used together with statins that are extensively metabolized by cytochrome P-450 3A4 (lovastatin, simvastatin, and to a lesser extent atorvastatin).
- Lipophilic statins may be associated with more adverse events than hydrophilic statins.
- Data do not suggest, however, that periop statin use increases risk of periop myopathy or hepatic dysfunction.

### Overview/Pharmacology

- Statins inhibit the reduction of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Statins primarily inhibit hepatocyte cholesterol synthesis and increase LDL receptor transcription and hepatic LDL cholesterol uptake. Consequently statins reduce systemic concentrations of LDL cholesterol by 25–55%. Plasma HDL cholesterol levels may rise by 8–10% with atorvastatin and rosuvastatin.
- The reduction in intracellular isoprenoid synthesis, which reduces prenylation of small GTPases (e.g., Rac, Rho), may mediate the beneficial pleiotropic (non-lipid-lowering) effects of statins observed in preclinical studies and small human studies. These effects include stabilization of atherosclerotic plaque, reduction of inflammation, reversal of endothelial dysfunction (through upregulation of eNOS), decreased thrombogenicity, and reduced generation of reactive oxygen species (through inhibition of NADPH-oxidase assembly). These effects are observed within 6–18 h in rodents and cells.
- Statins are orally administered once daily, and peak plasma concentrations are achieved in 1–3 h.
- The hepatic cytochrome P-450 system metabolizes most statins to active and inactive metabolites, and statins are primarily excreted in bile.

### Pharmacokinetics

| Statin | Dose (mg) | Elimination Half-Life, hr | Protein Binding | Solubility | Cytochrome P-450 Isozyme | Active Metabolites | Renal Excretion, % |
|---|---|---|---|---|---|---|---|
| Atorva- | 10–80 | 15–30 | 80–90 | Lipophilic | 3A4 | Yes | 2 |
| Fluva– | 20–80 | 0.5–2.3 | >99 | Lipophilic | 2C9 | No | <6 |
| Lova– | 20–80 | 2.9 | >95 | Lipophilic | 3A4 | Yes | 10 |
| Prava– | 10–40 | 1.3–2.8 | 43–55 | Hydrophilic | | No | 20 |
| Rosuva– | 5–40 | 19 | 88 | Hydrophilic | 2C9 | No | 10 |
| Simva– | 10–80 | 2–3 | 94–98 | Lipophilic | 3A4, 3A5 | Yes | 13 |

### Assessment Points

| System | Effect | Assessment by Hx | PE | Test |
|---|---|---|---|---|
| HEPAT | Transaminitis | Asymptomatic | None | LFTs |
| MS | Myositis | Myalgia, cramps, aches | Muscle tenderness | Creatinine kinase |

**Key References**: Chan WW, Wong GT, Irwin MG: Perioperative statin therapy, *Expert Opin Pharmocother* 14(7):831–842, 2013; Lewicki M, Ng I, Schneider AG: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass. *Cochrane Database Syst Rev* (3):CD010480, 2015.

### Perioperative Implications

- Pts with coronary disease or a coronary disease risk equivalent (DM, symptomatic carotid artery disease, peripheral arterial disease, abd aortic aneurysm, chronic kidney disease, or multiple risk factors that confer a 10-y risk of CHD greater than 20%) should receive chronic statin therapy. Therefore pts on statin therapy should be examined preop for coronary and peripheral vascular disease.
- Concern for statin accumulation and muscular and hepatic side effects among pts receiving major surgery led the ACC/AHA/NHLBI to recommend short-term periop discontinuation of statin administration. Periop observational studies, however, have not assoc statin use with an increased risk of myopathy or rhabdomyolysis, and preoperative cessation of statin therapy (withdrawal) was associated with CV harm in some studies of pts undergoing cardiac and major vascular surgery.
- Some randomized trials and large observational studies suggest beneficial pleiotropic effects of statins administered in the periop period. Trials of statin use in critically ill pts have demonstrated no effect on ARDS, pneumonia, or sepsis.
- In the DECREASE III trial, 497 vascular surgery pts were randomly assigned to either 80 mg of extended-release fluvastatin daily or placebo at least 30 d before the procedure and continued for at least 30 d after surgery. The primary endpoint of myocardial ischemia within 30 d of surgery occurred significantly less often in the fluvastatin group (10.8% vs. 19.0%; hazard ratio 0.55, 95% CI 0.34–0.88). The secondary endpoint of the composite of death from CV

causes and myocardial infarction also occurred significantly less often in the fluvastatin group (4.8% vs. 10.1%; hazard ratio 0.47, 95% CI 0.24–0.94). There was no evidence of an increase in skeletal muscle or hepatic injury in the fluvastatin group. (Note: Recent concern regarding the quality of the DECREASE trials has questioned these results.)

- Among percutaneous coronary intervention pts, statin therapy administered 12 h before catheterization reduced composite of myocardial ischemic events and death in several placebo controlled RCTs.
- Statin therapy is recommended as early as possible before surgery for pts undergoing elective major vascular surgery who have not been receiving a statin.
- Statin therapy should not be discontinued for fear of side effects in the periop period in statin-usings.
- Physician-scientists hope that pleiotropic effects of statin therapy will provide periop protection for heart, brain, and kidney. As yet, there are no data to support this indication for statin use.

# Tacrolimus (FK-506)

Aisling Conran | Lee A. Fleisher



## Uses

- Rescue of primary immunosuppressant Rx following liver, lung, heart, pancreas, and limb transplant.
- Approximate number of candidates: 3000 awaiting liver transplant and 9000 awaiting kidney transplant in USA; 15,000 living liver transplant and 50,000 kidney transplant recipients are chronically receiving immunosuppressants.
- Has been used to suppress the inflammation associated with ulcerative colitis.

## Perioperative Risks

- Htn: CCBs may be effective in treating tacrolimus-associated Htn, but care is required. Interference with tacrolimus metabolism may necessitate a reduction in dose.
- Nephrotoxicity: Do not administer concurrently with cyclosporine; administer cautiously with other potentially nephrotoxic drugs (e.g., aminoglycoside antibiotics).
- Hypersensitivity may occur with IV formulation; pts should be monitored for 30 min after injection.
- May result in opioid-induced hyperalgesia.

## Worry About

- Drug is metabolized by cytochrome P450 (3A) enzyme system. Other medications that inhibit or induce this enzyme may affect tacrolimus drug levels.

## Overview/Pharmacology

- General effect: Macrolide antibiotic with potent immunosuppressive properties, often used for rescue therapy in liver transplant pts with rejection refractory to other immunosuppressants.
- Tacrolimus is metabolized by the liver; metabolites are primarily excreted in bile; elimination half-life of 8.5 h is prolonged with hepatic dysfunction.
- CCBs, cyclosporine, erythromycin, antifungal agents, and metoclopramide may increase blood levels of tacrolimus as a function of P450 inhibition.
- Anticonvulsants (carbamazepine, phenobarbital, phenytoin) and rifampin may decrease blood levels of tacrolimus secondary to induction of the cytochrome P450 system.
- Adverse effects requiring dose adjustments include nephrotoxicity, neurotoxicity, alterations in glucose metabolism, infection, and susceptibility to malignancy.

## Drug Class/Mechanism of Action/Usual Dose

- Macrolide antibiotic, highly protein-bound (>75%), binds primarily to albumin and/or $\alpha_1$-glycoprotein.
- Tacrolimus binds to calcineurin, blocking production of interleukin-2 and thereby inhibiting further T-lymphocyte proliferation and immunosuppression.
- Dosing: IV 0.05–0.1 mg/kg per d; PO 0.15–0.3 mg/kg per d in 2 divided doses.

## Assessment Points

| System | Effect | Assessment by Hx | PE | Test |
|---|---|---|---|---|
| GENERAL | Hypersensitivity, rash | Observe 30 min; have epinephrine 1:1000 available | | |
| CV | Htn | | BP/HR | |
| RESP | Pleural effusion, dyspnea | | | |
| GI | Diarrhea, N/V, constipation, abnormal liver function, anorexia, abdominal pain | | | LFTs |
| RENAL | Abn kidney function, oliguria | | | BUN, Cr |
| ENDO | Hyperkalemia, hypokalemia, hyperglycemia | | | $K^+$, glucose |
| HEME | Anemia, leukocytosis, thrombocytopenia | | | CBC |
| CNS | Headache, tremor, insomnia, paresthesias, mental status changes, circumoral numbness | | Preop neurologic exam | |

**Key Reference**: Siniscalchi A, Piraccini E, Miklosova Z, et al.: Opioid-induced hyperalgesia and rapid opioid detoxification after tacrolimus administration, *Anesth Analg* 106(2):645–646, 2008.

## Perioperative Implications

### Preoperative Concerns

- Continue all immunosuppressants through the periop period.
- Monitor levels: Therapeutic range is 5–30 ng/mL; maintenance level is 5–10 ng/mL.

### Monitoring

- Consider frequent NIBP or arterial cath.

### Induction/Maintenance

- Inducers of P450 system include phenobarbital, phenytoin, isoniazid; some volatile anesthetics may result in increased metabolism of tacrolimus.

### Possible Drug Interactions

- CCBs, cyclosporine, erythromycin, antifungal agents, and metoclopramide may increase blood levels of tacrolimus as a function of P450 inhibition.
- Anticonvulsants (carbamazepine, phenobarbital, phenytoin), rifampin may decrease blood levels of tacrolimus secondary to induction of the cytochrome P450 system.
- Adverse effects requiring dose adjustments include nephrotoxicity, neurotoxicity, alterations in glucose metabolism, infection, and susceptibility to malignancy.

## Anticipated Problems/Concerns

- Hypersensitivity may occur with IV formulation.