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 α_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.