



Immunosuppressants, Oral

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Prophylaxis Against Organ Rejection			Rheumatoid Arthritis	Refractory Plaque Psoriasis
		Heart	Kidney	Liver		
azathioprine (Azasan®) ¹	Salix		X adjunctive		X	
azathioprine (Imuran®) ²	generic		X adjunctive		X	
cyclosporine (Sandimmune®) ³	Novartis, generic	X adjunctive	X adjunctive	X adjunctive		
cyclosporine, modified (Gengraf®, Neoral®) ^{4,5}	Abbott, Novartis, generic	X adjunctive	X adjunctive	X adjunctive	X refractory	X
everolimus (Zortress®) ⁶	Novartis		X adjunctive*	X adjunctive		
mycophenolate mofetil (CellCept®) ⁷	Roche, generic	X adjunctive	X adjunctive	X adjunctive		
mycophenolate sodium (Myfortic®) ⁸	Novartis, generic		X adjunctive			
sirolimus (Rapamune®) ⁹	Wyeth, generic		X adjunctive			
tacrolimus (Prograf®, Hecoria™*) ^{10,11}	Astellas, Novartis, generic	X adjunctive	X adjunctive	X adjunctive		
tacrolimus extended-release (Astagraf XL™) ¹²	Astellas		X adjunctive			

Oral immunosuppressants included in this table when used in the setting of organ transplant are rarely utilized as single agents but rather are used in various combinations along with corticosteroids and other appropriate agents based on product labeling, established literature and local protocols.

*Novartis discontinued Hecoria in late 2014. The product remains in pharmacies until the supply has been exhausted.

OVERVIEW

The ultimate goal of immunosuppressive therapy after organ transplantation is to prevent organ rejection, prolong graft and patient survival by providing an environment of permanent acceptance or tolerance where the new organ is recognized as “self” by the host’s immune system. The sequence of events in graft rejection is (1) recognition of donor’s histocompatibility differences by the recipient’s immune system, (2) recruitment of activated lymphocytes, (3) initiation of immune effector mechanisms, and (4) destruction of the graft. These events can take place at varying rates and may involve differing effects or mechanisms. Therefore, rejection of the transplanted tissue can take place at any time following surgery.

Rejection can be classified as hyperacute, acute cellular, or chronic. Hyperacute rejection may occur when donor-specific antibodies are present in the recipient at the time of transplant. It often occurs within minutes of transplant but may occur anytime within the first two weeks following surgery. Alloreactive T lymphocytes that appear in circulation infiltrate the allograft through the vascular endothelium and mediate acute cellular rejection. This type of rejection may occur as early as a few

days postoperatively; however, it can occur anytime after transplantation. The process of chronic rejection is poorly understood, although it may simply be a slow form of cellular rejection. The clinical presentation of chronic rejection is dependent on the organ grafted and generally presents as normal organ aging. The onset of chronic rejection is very slow, and the changes in organ function are not usually reversible.

There are no published US guidelines dedicated to the role of immunosuppressants post-transplant; however, these agents have been in the marketplace long enough to establish their place in therapy. The drugs and dosing used in the maintenance of transplanted organs varies, but the regimens generally follow the same principles. Following induction therapy at the time of surgery, transplant recipients are started on drug regimens that consist of several categories. Antiproliferative agents, such as azathioprine (Azasan, Imuran) and mycophenolate (CellCept, Myfortic), are used as adjunctive therapy. Sirolimus (Rapamune) and everolimus (Zortress) are proliferation inhibitors with mechanisms of action different from that of mycophenolate. They may be used in order to decrease the doses of calcineurin inhibitors, such as cyclosporine (Gengraf, Neoral, Sandimmune) or tacrolimus (Prograf, Hecoria, Astagraf XL), which are typically included in the regimen but can have serious adverse events at higher therapeutic concentrations.

Azathioprine is indicated for the treatment of rheumatoid arthritis (RA), although use should be reserved for those patients with a severe, active, erosive disease that has not responded to aspirin, nonsteroidal anti-inflammatory agents (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs). According to the 2012 update to the 2008 guidelines from the American College of Rheumatology, initial therapy for RA should include early use of a DMARD with consideration given to an NSAID and/or low-dose corticosteroids, as adjuncts. These guidelines contain additional recommendations in various scenarios.^{13,14} Similar to 2008, azathioprine, cyclosporine, and gold were not included in the recommendations for RA based on their infrequent use and lack of new data.

Cyclosporine has also been used for the treatment of severe, refractory plaque psoriasis in patients unresponsive to other therapies and as a bridging agent during the induction of other maintenance agents.¹⁵

Pharmacology¹⁶

Drug	Mechanism of Action
azathioprine (Azasan/Imuran)	Azathioprine acts as a suppressor of delayed hypersensitivity and cellular cytotoxicity to a greater extent than it acts as a suppressor of antibody responses. Azathioprine inhibits purine metabolism; inhibits the synthesis of DNA, RNA, and proteins; interferes with cellular metabolism; and inhibits mitosis.
cyclosporine (Sandimmune, Gengraf, Neoral)	Cyclosporine specifically and reversibly inhibits immunocompetent lymphocytes in the G ₀ and G ₁ phase of the cell cycle. The T helper cell is the main target; however, the T-suppressor cell may be targeted as well. In addition, cyclosporine inhibits lymphokine production and release.
everolimus (Zortress)	Everolimus inhibits antigenic- and interleukin (IL-2 and IL-15)-stimulated activation and proliferation of T- and B-lymphocytes. In cells, everolimus binds to FKBP-12 to form an immunosuppressive complex that binds to and inhibits the mammalian target of rapamycin (mTOR), a key regulatory kinase. Consequently, subsequent protein synthesis and cell proliferation are inhibited. The everolimus:FKBP-12 complex has no effect on calcineurin activity.
mycophenolate (CellCept, Myfortic)	Mycophenolate mofetil is a prodrug that is immediately and completely hydrolyzed to the active metabolite, mycophenolate (mycophenolic acid), a reversible and uncompetitive inhibitor of inosine monophosphate dehydrogenase. It inhibits the <i>de novo</i> synthesis of the guanosine nucleotide without incorporation into DNA and exerts a potent cytostatic effect on B and T lymphocytes.
sirolimus (Rapamune)	Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine stimulation by a unique mechanism. Sirolimus also binds to FKBP-12 to generate an immunosuppressive complex that has no effect on calcineurin. This complex binds to and inhibits the activation of mTOR, resulting in suppression of cytokine-driven T cell proliferation and inhibition of the progression from the G ₁ to the S phase of the cell cycle.
tacrolimus (Prograf, Hecoria, Astagraf XL)	Tacrolimus inhibits T lymphocyte activation possibly by binding to an intracellular protein, FKBP-12, forming a complex. Calcium, calmodulin, and calcineurin are formed and the phosphatase activity of calcineurin is inhibited. This effect may prevent the dephosphorylation and translocation of activated T cells, a nuclear component thought to initiate gene transcription for the formation of lymphokines.

PHARMACOKINETICS 17,18,19,20,21,22,23,24,25,26,27,28,29

Drug	Half-life (hr)	Metabolites	Excretion (%)	Target Drug Concentrations	
azathioprine (Azasan/Imuran)	5	6-mercaptopurine 6-thioinosinic acid	Hepatic Renal (1–2)	Not measured	
cyclosporine (Sandimmune)	19	--	Biliary Renal (6, 0.1 unchanged)	100–200 ng/mL (may vary depending on specific organ transplanted)	
cyclosporine, modified (Gengraf/Neoral)	8.4	--	Biliary Renal (6, 0.1 unchanged)	100–200 ng/mL (may vary depending on specific organ transplanted)	
everolimus (Zortress)	30	--	Fecal 80 Renal 5	3–8 ng/mL whole blood trough concentrations using LCMSMS	
mycophenolate mofetil (CellCept)	17.9	mycophenolic acid MPA-O-glucuronide MPA-acyl glucuronide	Fecal 6 Renal 93	Not measured	
mycophenolate sodium (Myfortic)	8–16	MPA-O-glucuronide MPA-acyl glucuronide	Renal <60 (3 unchanged)	Not measured	
sirolimus (Rapamune)	57–63 (up to 72 in males)	Hydroxysirolimus Demethylsirolimus hydroxy-demethyl-sirolimus	Fecal 91 Renal 2.2	Adult	Pediatric
				High immunologic risk: 10-15 ng/mL	≥ 13 years old and >40 kg: 16-24 ng/mL for 12 months, then 12–20 ng/mL thereafter
				Low to moderate immunologic risk: Following cyclosporine withdrawal: 16–24 ng/mL for 12 months, then 12-20 ng/mL thereafter	≥ 13 years old and <40 kg: 16–24 ng/mL for 12 months, then 12–20 ng/mL thereafter
tacrolimus (Prograf, Hecoria)	11.3	13-demethyl tacrolimus di-demethyl-tacrolimus	Renal <1 unchanged Bile extensive	Adult	Pediatric
				Kidney transplant, Month one to three: 7–20 ng/mL Month four to 12: 5–15 ng/mL	--
				Liver transplant, Month one to 12: 5–20 ng/mL	Liver transplant, Month one to 12: 5–20 ng/mL
				Heart transplant, Month one to three: 10–20 ng/mL ≥ Month four: 5–15 ng/mL	--

Pharmacokinetics (continued)

Drug	Half-life (hr)	Metabolites	Excretion (%)	Target Drug Concentrations	
tacrolimus extended-release (Astagraf XR)	32–48	13-demethyl tacrolimus 31-demethyl tacrolimus	Fecal 93 Urine: 2	with basiliximab induction without induction	Day 1–60: 5–17 ng/mL Month 3–12: 4–12 ng/mL Day 1–60: 6–20 ng/mL Month 3–12: 6–14 ng/mL

Because the rate and extent of absorption of mycophenolate mofetil and mycophenolate sodium delayed-release products are not equal, these products should not be used interchangeably without health care provider supervision.

Because the various cyclosporine products, including some nonproprietary products, are not bioequivalent to each other due to differences in the rate and extent of absorption, these products should not be used interchangeably without health care provided supervision.

Tacrolimus extended-release capsules are not interchangeable with tacrolimus immediate-release capsules

Patients with malabsorption may have difficulty in achieving therapeutic cyclosporine levels with Sandimmune soft gelatin capsules or oral solution.

CONTRAINDICATIONS/WARNINGS^{30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45}

Azathioprine is contraindicated in the treatment of RA in pregnant women. The risk of neoplasia is increased dramatically in patients with RA previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan, or others).

Azathioprine is metabolized to 6-mercaptopurine (6-MP) and then undergoes two major inactivation routes. One route is thiol methylation, which is catalyzed by the enzyme thiopurine S-methyltransferase (TPMT) to form an inactive metabolite. TPMT activity is controlled by a genetic polymorphism. Approximately ten percent of Caucasians and African-Americans have one non-functional TPMT allele and 0.3 percent of this population have two TPMT non-functional alleles. Patients with one non-functional TPMT allele (intermediate TPMT activity) may be at increased risk of myelotoxicity at conventional doses of azathioprine. Patients with two non-functional TPMT alleles are at an increased risk of developing severe, life-threatening myelotoxicity when receiving conventional doses of azathioprine. Testing for TPMT genotype is recommended in patients who are to receive azathioprine.

Cyclosporine products are contraindicated in psoriasis or RA patients with abnormal renal function, uncontrolled hypertension, or malignancies. Cyclosporine products are also contraindicated if given to psoriasis patients concomitantly with PUVA or UVB, methotrexate, or other immunosuppressive agents, coal tar or radiation therapy due to the risk of fatal malignancies and/or infections.

All immunosuppressants in this category carry warnings, including black box warnings, regarding the risk of development of serious infections, especially for transplant recipients. Fungal, viral, bacterial, and protozoal infections should be treated aggressively as infections may be fatal. Activation of latent viral infections should be monitored. Polyomavirus, especially BK virus, activation may result in serious and sometimes, fatal outcomes. Reduction of immunosuppressant dosage or use of other drugs should be considered as well. Immunosuppressant labeling also contains a black box warning that only individuals well versed in the management of systemic immunosuppressive therapy who are capable of monitoring these agents appropriately should prescribe them. These agents may also increase the risk of lymphoma or other neoplasias, particularly those of the skin. Patients should be warned to avoid

excess ultraviolet light exposure. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents.

Azathioprine (Azasan, Imuran) labeling contains an additional black box warning regarding reports of hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease. Azathioprine may cause severe leukopenia, thrombocytopenia, macrocytic anemia, or severe bone marrow depression. These hematologic toxicities are dose-related and seem to be more severe in renal transplant patients who are undergoing organ rejection.

The black box warnings for cyclosporine products reminds practitioners that the bioavailability of cyclosporine (Sandimmune) is not equal to that of cyclosporine; modified (Gengraf, Neoral) and appropriate monitoring should take place if a product change is necessary. Because the absorption of cyclosporine soft gelatin capsules and oral solution can be erratic, prescribers are also warned to monitor cyclosporine concentrations at repeated regular intervals to make sure therapeutic concentrations are maintained.

Cyclosporine products have the potential for thrombocytopenia and microangiopathic hemolytic anemia, hyperkalemia, hyperuricemia, hepatotoxicity, convulsions, encephalopathy, and anaphylaxis. Recommended doses of cyclosporine may cause systemic hypertension and nephrotoxicity. This risk increases as the dose and duration of therapy increases. Monitor renal function during therapy, as renal dysfunction, including structural kidney damage, is a potential adverse effect of cyclosporine. Since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used to treat hypertension.

Everolimus (Zortress) has a black box warning for increased incidence of kidney graft thrombosis, and prescribers are cautioned to use reduced doses of cyclosporine in combination with everolimus to reduce nephrotoxicity. Use of everolimus in heart transplantation is not recommended due to increased mortality. Patients who have hypersensitivity reactions to sirolimus (Rapamune) should not take everolimus.

The use of everolimus has been associated with angioedema, impaired wound healing and fluid accumulation, hyperlipidemia, non-infectious pneumonitis, diabetes mellitus, and male infertility. The concomitant use of everolimus with cyclosporine may increase the risk of thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Monitor hematologic parameters. Everolimus should not be administered earlier than 30 days after liver transplant due to an associated increase in hepatic artery thrombosis reported with mammalian target of rapamycin (mTOR) inhibitors.

Cases of interstitial lung disease (ILD) have occurred in patients receiving everolimus. Most cases generally resolve on drug interruption; however, fatal cases have occurred. A diagnosis of ILD should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been ruled-out through appropriate investigations.

Mycophenolate (CellCept, Myfortic) labeling contains a black box warning for the potential risk for miscarriage or congenital abnormalities if taken during pregnancy. Patient counseling and contraception is recommended for women of child bearing potential. If hormonal contraception is utilized (e.g., birth control pill, transdermal patch, vaginal ring, parenteral options), an additional

barrier contraceptive method must be used due to the potential for mycophenolate to interfere with the metabolism of these agents.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolic acid (MPA) derivatives in combination with other immunosuppressive agents. Patients receiving mycophenolate may develop severe neutropenia [Absolute neutrophil count (ANC) less than $0.5 \times 10^3/\text{mCL}$]. Patients should be monitored for blood dyscrasias and if they occur, therapy should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately.

Agranulocytosis and cases of pure red cell aplasia (PRCA) have also been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of tacrolimus or tacrolimus extended-release (ER) should be considered.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate mofetil and mycophenolate sodium (MMF, MPA CellCept, Myfortic). Hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia were the most frequent clinical features observed. PML may be due to activation of Polyomavirus; e.g., JC virus. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune functions. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms taking mycophenolate mofetil or mycophenolate (CellCept, Myfortic) and consultation with a neurologist should be considered as clinically indicated.

Viral reactivations of hepatitis B (HBV) or hepatitis C (HCV) as well as cytomegalovirus (CMV) have been reported in patients treated with immunosuppressants, including mycophenolate (CellCept, Myfortic). Consideration should be given to reducing immunosuppression in patients who develop evidence of new or reactivated viral infections.

Mycophenolate should be used with caution in patients with active serious digestive system disease. Gastrointestinal bleeding has been observed as well as rare cases of gastrointestinal perforation.

Sirolimus (Rapamune) carries a black box warning advising that the safety and efficacy of sirolimus in liver and lung transplant patients have not been established; therefore, use is not recommended. In a study in *de novo* liver transplant patients, the combination of sirolimus and tacrolimus (Prograf) was associated with excess mortality and graft loss. Many of these patients had evidence of infection at or near the time of death. In this and another study in *de novo* liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increased risk of hepatic artery thrombosis (HAT). Most cases of HAT occurred within 30 days post-transplantation and led to graft loss or death. When sirolimus has been used as part of an immunosuppressant regimen for lung transplant cases, bronchial anastomotic dehiscence, mostly fatal, has been reported. Sirolimus must be protected from light.

The safety and efficacy of sirolimus without concurrent cyclosporine treatment in renal transplant patients have not been adequately studied; therefore, it is not recommended. Sirolimus may increase serum cholesterol and triglyceride concentrations necessitating treatment. Sirolimus has also been associated with angioedema, impaired or delayed wound healing, fluid accumulation, and proteinuria.

Tacrolimus (Prograf, Hecoria, Astagraf XL) may also cause insulin-dependent post-transplant diabetes mellitus in as many as 11 to 22 percent of transplant patients. Tacrolimus can also induce nephrotoxicity, which was reported in about 36 to 59 percent of transplantation patients. To avoid nephrotoxicity, cyclosporine, in particular, should not be used within 24 hours of tacrolimus. Approximately 55 percent of liver transplant patients developed neurotoxicity including tremor and headache, and other changes in motor function, mental status, and sensory function in two randomized studies. Mild to severe hyperkalemia was reported in eight to 45 percent of transplant recipients after treatment with tacrolimus.

Tacrolimus has been associated with myocardial hypertrophy, particularly in those with high drug trough concentrations. It is reversible in most cases following dose reduction or discontinuation.

Tacrolimus ER(Astagraf XL) may prolong the QT/QTc interval and may cause Torsade de Pointes. Tacrolimus ER should be avoided in patients with congenital long QT syndrome. Consideration for obtaining electrocardiograms and monitoring serum electrolytes should be given in patients with congestive heart failure, bradyarrhythmias or those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation as well as patients with hypokalemia, hypocalcemia or hypomagnesemia.

Coadministration of tacrolimus (Prograf, Hecoria, Astagraf XL) with strong CYP3A4-inhibitors (list not inclusive: grapefruit juice, protease inhibitors, azole antifungals, verapamil, diltiazem, nifedipine, macrolide antibiotics, chloramphenicol) or strong CYP3A4-inducers (list not inclusive: rifampin, rifabutin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) is not recommended without dosing adjustments of tacrolimus and close monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions. This is especially important with drugs that prolong the QT interval. In such cases monitoring for QT prolongation is also recommended.

The use of live vaccines should be avoided during treatment with any of the agents in this review.

Tacrolimus ER (Astagraf XL) is contraindicated in patients with hypersensitivity to tacrolimus. Tacrolimus ER may be associated with the development of hypertension. Selection of an appropriate antihypertensive agent should take into consideration the risk of potentiating hyperkalemia, as well as the risk of calcium channel blockers altering tacrolimus blood concentrations.

Tacrolimus has been associated with gastrointestinal perforation, all reported cases have been considered to be a complication of transplant surgery or accompanied by infection, diverticulum or malignant neoplasm.

All of the warnings associated with tacrolimus are applicable to tacrolimus ER.

An additional black box warning for tacrolimus ER is the risk of increased mortality in female liver transplant recipients. A clinical trial involving 471 liver transplant patients randomized to either tacrolimus ER (Astagraf XL) or tacrolimus (Prograf) demonstrated a ten percent higher mortality among the 76 female patients (18 percent) treated with tacrolimus ER (Astagraf XL) compared to the 64 female patients (eight percent) treated with tacrolimus at 12 months. Use of tacrolimus ER is not recommended in liver transplantation.

Tacrolimus ER (Astagraf XL) capsules are not interchangeable or substitutable with tacrolimus immediate-release capsules. There have been reports of medication and dispensing errors during post-

marketing surveillance. Cases of graft rejection have occurred that may have been related to the medication error and the resulting under-or over-exposure to tacrolimus.

Risk Evaluation and Mitigation Strategy (REMS)⁴⁶

Mycophenolate-containing products (CellCept, Myfortic) REMS requirement consists of a Medication Guide, elements to assure safe use, such as healthcare provider training and communications, and assessments of the REMS.

DRUG INTERACTIONS^{47,48,49,50,51,52,53,54,55,56,57,58}

Avoid the concomitant use of azathioprine (Azasan, Imuran) and mercaptopurine due to the potential for severe myelosuppression. Coadministration of azathioprine and any agent, which may affect leukocyte production, should be cautioned as this combination may lead to exaggerated leukopenia, especially in renal transplant patients. Anemia and severe leukopenia are also possible with concomitant use of Angiotensin Converting Enzyme (ACE) inhibitors and azathioprine. Concomitant allopurinol administration requires azathioprine dose reduction by 66 to 75 percent. Cases of severe pancytopenia have been reported in Hepatitis C patients receiving ribavirin in conjunction with azathioprine. Patients receiving this combination should have complete blood counts monitored weekly for the first month, twice monthly for the second and third months and then monthly thereafter.

Azathioprine may inhibit the anticoagulant effect of warfarin.

Concomitant use of cyclosporine products (Sandimmune, Gengraf, Neoral) with other nephrotoxic drugs may potentiate renal dysfunction, especially in dehydrated patients. Because cyclosporine is extensively eliminated by cytochrome P450 3A4 and P-glycoprotein (P-gp), monitoring of circulating cyclosporine concentrations and appropriate dosage adjustments are essential when used concomitantly with other drugs that are inducers or inhibitors of CYP3A4 or P-gp. Drugs that are known to increase cyclosporine concentrations include (list not all-inclusive): calcium channel blockers (diltiazem, nifedipine, verapamil), azole antifungals, macrolide antibiotics, quinupristin/dalfopristin, methylprednisolone, allopurinol, amiodarone, bromocriptine, colchicine, danazol, protease inhibitors, imatinib, metoclopramide, nefazodone and oral contraceptives. Grapefruit juice is also known to increase blood concentrations of cyclosporine. Drugs or dietary supplements known to decrease cyclosporine concentrations include (list not all-inclusive): rifampin, carbamazepine, phenobarbital, phenytoin, bosentan, octreotide, terbinafine, ticlopidine and St. John's Wort. In RA patients coadministered diclofenac or methotrexate with cyclosporine, the AUC of diclofenac and methotrexate each was significantly increased. Orlistat decreases cyclosporine absorption and its use should be avoided in patients receiving oral cyclosporine. Frequent gingival hyperplasia has been reported with the concurrent administration of nifedipine and cyclosporine.

Cyclosporine itself is also an inhibitor of CYP3A4 and of Pgp, and therefore, may increase plasma concentrations of co-administered medications that are substrates for these metabolic pathways. Cyclosporine may decrease the clearance of (list not all-inclusive): digoxin, colchicine, ambrisentan, prednisolone, HMG-CoA reductase inhibitors (statins), aliskiren, repaglinide, NSAIDs, sirolimus, and etoposide.

CYP3A4 and P-glycoprotein (P-gp) are the primary elimination pathways of everolimus (Zortress), so concurrent therapy with potent inducers or inhibitors of CYP3As or P-gp may affect blood

concentrations of everolimus. This includes cyclosporine, a 3A4 inhibitor with which everolimus may be administered, according to the indication. Everolimus itself may inhibit 3A4 and 2D6 enzymes.

Mycophenolate products (CellCept, Myfortic) should not be given with azathioprine because these agents all work to inhibit purine metabolism and could potentially cause bone marrow suppression. Mycophenolate concentrations may be decreased by antacids; therefore, do not administer concurrently.

Coadministration of PPIs (e.g., lansoprazole, pantoprazole) to patients receiving CellCept brand of mycophenolate has been reported to reduce mycophenolic acid (MPA) exposure by approximately 30 percent in patients; maximum concentration was decreased by 30 to 70 percent. This may possibly be due to decreased MPA solubility at an increased gastric pH. Although clinical relevance has not been established, PPIs should be used with caution when coadministered.

Mycophenolate is not recommended to be coadministered with cholestyramine or other agents that may interfere with enterohepatic recirculation. MPA exposure was decreased by as much as 40 percent. Cyclosporine also interrupts the enterohepatic recirculation of MPA, while tacrolimus does not interfere with this process. When MPA is administered concomitantly with cyclosporine or tacrolimus, patients should be monitored for MPA adverse events and have their dose of MPA reduced, if needed.

It is recommended that calcium free phosphate binders, such as sevelamer, are administered two hours after mycophenolate mofetil (CellCept) dose to minimize the impact on the absorption of MPA. A 67 percent reduction in MPA exposure was reported with concomitant administration of mycophenolate mofetil and rifampin; concurrent use is not recommended.

Rifampin should not be given concomitantly with MPA unless the benefit outweighs the risk of decreased exposure to MPA. The combination of metronidazole and norfloxacin reduced MPA exposure by one-third, and therefore, this combination is not recommended to be given concomitantly with MPA.

Because sirolimus is known to be a substrate for cytochrome CYP 3A4 and P-glycoprotein (P-gp), coadministration of sirolimus with strong inhibitors or inducers of CYP3A4 and/or P-gp is not recommended.

To prevent an additive or synergistic impairment of renal function, tacrolimus (Prograf, Hecoria, Astagraf XL) should be coadministered cautiously with other agents that may cause renal impairment, such as aminoglycosides, amphotericin B, and cisplatin. Tacrolimus is primarily metabolized by the CYP3A enzyme systems; therefore, substances known to inhibit these enzymes may decrease metabolism or increase bioavailability and drugs known to induce these enzyme systems may result in an increased metabolism or decreased bioavailability of tacrolimus. Coadministration of tacrolimus with strong CYP3A4-inhibitors (e.g., grapefruit juice, protease inhibitors, such as ritonavir, nelfinavir, telaprevir, and boceprevir, azole antifungals, calcium channel blockers, such as verapamil, diltiazem, nifedipine and nifedipine, macrolide antibiotics, chloramphenicol, cimetidine, amiodarone, bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol and methylprednisolone) or strong CYP3A4-inducers (e.g., rifampin, rifabutin, phenytoin, carbamazepine, phenobarbital, or St. John's wort) is not recommended without dosing adjustments of tacrolimus and close monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions. This is especially important with drugs that prolong the QT interval, such as protease inhibitors and some

antifungal agents. In such cases, monitoring for QT prolongation is also recommended. When voriconazole or posaconazole is initiated in patients already taking tacrolimus, the tacrolimus dose should be reduced to one-third of the original dose and subsequent dosing be based on monitoring of tacrolimus whole blood trough concentrations. Coadministration of magnesium and aluminum hydroxide antacids also increase tacrolimus concentrations and monitoring of tacrolimus whole blood concentrations are recommended when these agents are used concomitantly with tacrolimus.

Lansoprazole and omeprazole may compete with tacrolimus for metabolism through the CYP3A4 system and may substantially increase tacrolimus whole blood concentrations.

Consumption of alcohol with tacrolimus ER (Astagraf XL) may increase the rate of release or alter the pharmacokinetic properties of tacrolimus, and therefore, alcoholic beverages should not be consumed with tacrolimus ER (Astagraf XL).

ADVERSE EFFECTS

Drug	Headache	Nausea	Vomiting	Diarrhea	Rash	Tremor	Liver toxicity	Other common effects
azathioprine (Azasan, Imuran) ^{59,60}	nr	reported	reported	reported	reported	nr	reported	leukopenia, thrombocytopenia
cyclosporine (Sandimmune*) ⁶¹	2–15	2–10	2–10	3–8	nr	12–55	4–7	gum hyperplasia, hypertension, renal dysfunction, hirsutism
everolimus (Zortress) ⁶²	18	29	15	19	1–10	8	1–10	constipation, peripheral edema, anemia
mycophenolate mofetil (CellCept) ⁶³	16.1–54.3	19.9–54.5	32.9–33.9	31–51.3	22.1	24.2–33.9	24.9	leukopenia, anemia, infection
mycophenolate sodium (Myfortic) ⁶⁴	3–20	24.5–29.1	23	21.4–23.5	3–20	3–20	nr	leukopenia, anemia, infection
sirolimus (Rapamune) ⁶⁵	34	25–31	nr	25–35	10–20	nr	nr	peripheral edema, hypertension, lipid abnormalities
tacrolimus (Prograf, Hecoria) ^{66, 67}	37–64	32–46	14–27	37–72	10–24	48–56	6–36	hypertension, abnormal renal function, insomnia
tacrolimus extended-release (Astagraf XL) ^{68**}	12 (10)	15 (13)	13 (13)	27 (31)	nr	18 (17)	nr	new onset diabetes, infections, constipation

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

The adverse event data presented here indicates occurrence in transplant (renal, hepatic, cardiac) patients only.

* The package inserts for Gengraf and Neoral reference the adverse event data from studies using Sandimmune.

** The control arm for the Astagraf XL studies was tacrolimus immediate-release (Prograf).

SPECIAL POPULATIONS^{69,70,71,72,73,74,75,76,77,78,79,80}

Pediatrics

Safety and efficacy of azathioprine (Azasan, Imuran) and everolimus (Zortress) have not been established in the pediatric population.

Cyclosporine (Sandimmune) has been given to patients as young as six months of age without unusual adverse effects; however, there are no adequate, well-controlled studies in children. Cyclosporine, modified (Gengraf, Neoral) has been given to transplant recipients as young as one year of age without unusual adverse effects. Cyclosporine whole blood concentrations should be measured and dosages adjusted accordingly. The safety and efficacy of these products have not been established in children less than 18 years old with juvenile RA or psoriasis.

Safety and efficacy of mycophenolate mofetil (CellCept) have not been established in children receiving heart or liver transplants. Mycophenolate sodium (Myfortic) has established safety and efficacy in patients five to 16 years old who are stable renal transplant recipients.

Safety and efficacy of sirolimus (Rapamune) have not been established in children younger than 13 years of age or in children younger than 18 who are considered to be at high immunologic risk.

Safety and efficacy of tacrolimus (Prograf, Hecoria) in pediatric kidney or heart transplant patients have not been established. There is limited data on the use of tacrolimus (Prograf and Hecoria) in pediatric liver transplantation. However, tacrolimus use after pediatric liver transplantation has been successful. Pediatric liver transplant patients generally required higher doses of tacrolimus to maintain blood trough concentrations of tacrolimus similar to adult patients. The safety and efficacy of tacrolimus ER (Astagraf XL) in pediatric kidney transplant patients less than 16 years of age has not been established.

Pregnancy

Azathioprine can cause fetal harm when administered to pregnant women; therefore, azathioprine has been labeled Pregnancy Category D.

Mycophenolate products are Pregnancy Category D. While there are no adequate, well-controlled studies in pregnant women, the use of mycophenolate is associated with an increased risk of first trimester miscarriage and congenital malformations such as external ear and facial abnormalities and anomalies of the distal limbs, heart, esophagus, and kidney.

Cyclosporine products, everolimus, sirolimus, and tacrolimus have been labeled Pregnancy Category C.

Renal Impairment

The dose of azathioprine should be decreased for moderate to severe renal failure.

Patients with renal impairment should receive doses of tacrolimus at the lowest value of the recommended initial dosing range.

Hepatic Impairment

Patients taking everolimus who have moderate hepatic impairment should decrease the everolimus dose by half. There is no information available for patients with severe hepatic impairment.

For patients with mild or moderate liver impairment, it is recommended that the maintenance dosage of sirolimus be reduced by approximately one-third, and the maintenance dose should be reduced by one-half in those with severe liver impairment. However, it is not necessary to reduce the loading dose of sirolimus.

Patients with hepatic impairment should receive doses of tacrolimus at the lowest value of the recommended initial dosing range.

Race

The data in kidney transplant patients indicate that African- American patients required a higher dose of tacrolimus (Prograf, Hecoria) and tacrolimus ER (Astagraf XL) to attain comparable trough concentrations compared to Caucasian patients. In addition African-American and Hispanic kidney transplant patients are at an increased risk of new onset diabetes after transplantation and on tacrolimus therapy.

DOSAGES^{81,82,83,84,85,86,87,88,89,90,91,92}

Drug	Initial Dose	Maintenance Dose	Pediatric Dose	Availability
azathioprine (Azasan)	Transplant: 3–5 mg/kg once daily RA: 1 mg/kg (50-100 mg) once or twice daily	Transplant: 1–3 mg/kg once daily RA: 1–2.5 mg/kg once or twice daily	--	75, 100 mg tablets
azathioprine (Imuran)	Transplant: 3–5 mg/kg once daily RA: 1 mg/kg (50-100 mg) once or twice daily	Transplant: 1–3 mg/kg once daily RA: 1–2.5 mg/kg once or twice daily	--	50 mg tablet
cyclosporine (Sandimmune)	15 mg/kg four to 12 hours prior to transplant 14–18 mg/kg once daily for one to two weeks	Transplant: 5–10 mg/kg once daily monitor whole blood trough levels with approximate range of 100–200 ng/mL	Same as adult, may require higher doses	100 mg/mL solution 25, 100 mg soft gelatin capsules
cyclosporine, modified (Gengraf, Neoral)	Transplant: 15 mg/kg divided twice daily four to 12 hours prior to or immediately post transplant	Transplant: 5–10 mg/kg/day; divided twice daily, monitor whole blood trough levels with approximate range of 100–200 ng/mL	Same as adult	25, 100 mg capsules (Gengraf) 25, 100 mg soft gelatin capsules (Neoral) 100 mg/mL solution
	Psoriasis / RA: 2.5 mg/kg divided twice daily	Psoriasis / RA: 2.5–4 mg/kg divided twice daily	--	

Dosages (continued)

Drug	Initial Dose	Maintenance Dose	Pediatric Dose		Availability
everolimus (Zortress)	Kidney: 0.75 mg twice daily at the same time as cyclosporine Liver: 1 mg twice daily started at least 30 days post transplant at same time as tacrolimus	Adjusted to maintain a trough whole blood concentration of 3–8 ng/mL using an LCMSMS assay	--		0.25, 0.5, 0.75 mg tablets
mycophenolate mofetil (CellCept)	--	Renal transplant: 1 gram twice daily	Renal transplant: 600 mg/m ² twice daily (maximum 2 grams daily)		200 mg/mL suspension 250 mg capsule 500 mg tablet
		Cardiac transplant: 1.5 grams twice daily	--		
mycophenolate mofetil (CellCept)		Hepatic transplant: 1.5 grams twice daily	--		
mycophenolate sodium (Myfortic)	--	720 mg twice daily (empty stomach)	<u>>5 years of age:</u> 400 mg/m ² twice daily (maximum 720 mg twice daily)		180, 360 mg delayed release tablets
sirolimus (Rapamune)	High immunologic risk: Up to 15 mg loading dose then 5 mg daily in combination with cyclosporine and corticosteroids for at least 12 months	High immunologic risk: Adjust to a trough concentration of 10–15 ng/mL	--		1 mg/mL solution 0.5, 1, 2 mg tablets
	Low to moderate immunologic risk: 6 mg on day 1; then 2 mg daily in combination with cyclosporine and corticosteroids for two to four months	Low to moderate immunologic risk: Following cyclosporine withdrawal, adjust to trough concentration of 16–24 ng/mL for 12 months then 12–20 ng/mL thereafter	≥ 13 years old and > 40 kg: Same as adult	Adjust to trough level of 16–24 ng/mL for 12 months after cyclosporine withdrawal, then 12–20 ng/mL thereafter	
			≥ 13 years old and < 40 kg: 3 mg/m ² x1 then 1 mg/m ² /day	Adjust to trough level of 16–24 ng/mL for 12 months then 12–20 ng/mL thereafter	

Dosages (continued)

Drug	Initial Dose	Maintenance Dose	Pediatric Dose		Availability
tacrolimus (Prograf, Hecoria)	Kidney transplant: 0.2 mg/kg/day divided twice daily (in combinations with azathioprine)	Kidney transplant in combination with azathioprine: Month 1 to 3: dose to a trough concentration of 7–20 ng/mL Month 4 to 12: dose to a trough concentration of 5–15 ng/mL Kidney transplant in combination with MPA month 1–12 dose to a trough concentration of 4–11 ng/mL			0.5, 1, 5 mg capsules
	Liver transplant: 0.1–0.15 mg/kg/day divided twice daily	Liver transplant: Month 1–12: dose to a trough concentration of 5–20 ng/mL	Liver transplant: 0.15–0.2 mg/kg/day divided twice daily	Liver transplant: Month 1 to 12: Dose to a trough concentration of 5–20 ng/mL	
	Heart transplant: 0.075 mg/kg/day divided twice daily	Heart transplant: Month 1 to 3: Dose to a trough concentration of 10–20 ng/mL ≥Month 4: Dose to a trough concentration of 5–15 ng/mL			
tacrolimus extended-release (Astagraf XL)	with basiliximab induction: 0.15 mg/kg/day	0.15 mg/kg/day Day 1 to 60: dose to trough concentration of 5–17 ng/mL Month 3–12: dose to trough concentration of 4–12 ng/mL	-		0.5 mg, 1 mg and 5 mg extended-release capsules
	without induction: pre-operative: 0.1 mg/kg/day	post-operative: 0.2 mg/kg/day Dose to trough concentrations: Day 1 to 60: 6–20 ng/mL Month 3–12: 6–14 ng/mL			

Many immunosuppressive protocols require combinations of immunosuppressants with or without the addition of corticosteroids; please refer to product labeling for recommended combination regimens.

Do not crush, chew, or cut everolimus (Zortress), mycophenolate (CellCept, Myfortic), or sirolimus (Rapamune) tablets. Do not open mycophenolate (CellCept) capsules.

TPMT phenotype testing is recommended for patients receiving azathioprine.

Cyclosporine (Sandimmune) solution can be made more palatable by diluting it with milk, chocolate milk, or orange juice at room temperature. Cyclosporine (Gengraf, Neoral) solution can be made more palatable by diluting it with apple juice or orange juice at room temperature. Sirolimus solution should be diluted with water or orange juice before administering.

Sirolimus (Rapamune) oral solution must be protected from light.

CLINICAL TRIALS

Search Strategy

Due to the large number of studies identified for the immunosuppressants, this review focuses on head-to-head trials meant to determine safety or efficacy for FDA-approved indications only. This review is not meant to encompass all trials involving the use of immunosuppressants, such as the benefit of steroid-free regimens or the timing of initiating calcineurin inhibitors. Many of the trials performed with these agents are open-label trials due to the need for therapeutic concentration monitoring.

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Cardiac Transplant

cyclosporine (Sandimmune) versus tacrolimus (Prograf)

A single-center, randomized, prospective, open-label study was conducted to investigate whether trough concentration-adjusted mycophenolate mofetil is more efficacious in combination with tacrolimus or cyclosporine and to investigate the impact of either drug on mycophenolate mofetil dosage.⁹³ Immunosuppressive therapy consisted of tacrolimus (n=30) dosed to a target blood trough concentration of 10 to 15 ng/mL or cyclosporine (n=30) dosed to a target blood trough concentration of 100 to 300 ng/mL in combination with mycophenolate mofetil dosed to a target blood trough concentration of 1.5 to 4 mg/mL and corticosteroids. Investigators tracked acute rejection episodes (ARE), survival data, and adverse events. No difference was seen between the groups in baseline characteristics. Corticosteroids were withdrawn within six months of cardiac transplant in all patients. The tacrolimus-treated patients had a lower incidence of ARE per 100 patient days compared to cyclosporine (0.03 versus 0.15; p=0.00007). However, overall patient survival during follow-up was

similar (93 percent versus 90 percent) between the groups. Participants in the tacrolimus group required a lower mycophenolate mofetil dose to achieve the targeted blood concentrations. After two years, the mean graft vessel disease score was 1.85 ± 3.18 in the tacrolimus group versus 3.95 ± 4.8 in the cyclosporine group ($p=0.08$). A ten-year follow-up of this group of patients was published in 2013.⁹⁴ Survival for the tacrolimus plus mycophenolate mofetil (TAC/MMF) group was 96.7 percent at one year, 80 percent at five years and 66.7 percent at ten years. Survival in the cyclosporine plus mycophenolate mofetil group (CsA/MMF) was 90 percent at one year, 88.3 percent at five years, and 80 percent at ten years, none of these differences were statistically significantly different. Freedom from acute rejection episodes (ARE) was significantly higher in the TAC/MMF group (65.5 percent) versus the CsA/MMF group (21.7 percent, $p=0.004$). Freedom from cardiac allograft vasculopathy (CAV) after five and ten years was 64 percent and 45.8 percent in the in the TAC/MMF group compared to 36 percent ($p=0.085$) and eight percent ($p=0.003$) in the CsA/MMF group. There were no differences between the groups with regard to coronary angioplasty or stenting, renal dysfunction, diabetes mellitus, CMV infections, or malignancies.

The efficacy and safety of tacrolimus and cyclosporine were compared using 73 adult heart transplant patients in a single-center, prospective, randomized, open-label clinical trial.⁹⁵ At the time of transplantation, patients were randomly assigned to receive either tacrolimus ($n=43$) or cyclosporine ($n=30$). Ten tacrolimus-treated patients received the drug intravenously in the perioperative period, and all other patients received oral tacrolimus only. The mean follow-up was 27 months. The two groups had similar patient survival rates (tacrolimus 83 percent, cyclosporine 81 percent). Fewer tacrolimus-treated patients (79 percent) experienced acute rejection when compared to cyclosporine-treated patients (100 percent, $p=NS$). The two groups were also similar with regard to the number of infections, rate of dialysis, and insulin requirements; however, the proportion of patients requiring multiple antihypertensives was lower in the tacrolimus group (12.5 percent versus 50 percent at month six; $p=0.025$).

Patients were randomized in a 2:1 fashion to either oral tacrolimus ($n=54$) or cyclosporine ($n=28$).⁹⁶ The two groups had similar rejection and survival rates at one year. Kaplan-Meier estimates showed a freedom from rejection of 26.3 percent for the tacrolimus-treated participants and 18.5 percent for the cyclosporine-treated participants ($p=0.444$). Survival rates were 79.6 percent in the tacrolimus arm and 92.9 percent in the cyclosporine arm ($p=0.125$). At three of the five centers, patients were treated with antithymocyte globulin during the immediate postoperative period. Acute rejection-free rates were 49.2 percent and 26.7 percent for tacrolimus and cyclosporine, respectively ($p=0.08$); for those treated with thymoglobulin, rejection-free rates were 7.1 percent and 8.3 percent ($p=0.965$). Patient survival rates were 84.6 percent and 93.3 percent ($p=0.382$) versus 75 percent and 92.3 percent ($p=0.243$). No significant differences were found between the groups in the overall rates of infection, impaired renal function (31.5 percent versus 21.4 percent), or glucose intolerance (seven percent versus 4.3 percent). Fewer patients receiving tacrolimus needed antihypertensive therapy (59.5 percent versus 87.5 percent, $p=0.025$).

Cardiac transplant recipients ($n=95$) were randomized at a single center to either open -label cyclosporine or tacrolimus and were followed to determine the rate of cytomegalovirus (CMV) infection in each group.⁹⁷ All patients at highest risk of developing CMV (CMV recipients receiving CMV plus organs) received valganciclovir prophylaxis. CMV infection was considered as the detection of an increased viral load and/or the presence of CMV in histological samples, regardless of clinical symptoms. The rate of CMV infection overall (not just in highest risk patients) was higher in patients

treated with cyclosporine than in those treated with tacrolimus (45.1 percent versus 15.9 percent, $p=0.002$). The group of patients treated with cyclosporine had a shorter mean survival time free from CMV infection than patients treated with tacrolimus (900 days versus 1,440 days, $p=0.001$).

cyclosporine, modified (Gengraf/Neoral) versus tacrolimus (Prograf)

Tacrolimus ($n=157$) was compared to cyclosporine, modified ($n=157$), each in combination with azathioprine and corticosteroids, in a randomized controlled clinical trial of newly transplanted heart recipients.⁹⁸ Acute rejection episodes were assessed by protocol biopsies, which underwent local and blinded central evaluation. At 18 months, patient and graft survival was 92.9 percent in the tacrolimus-treated group compared to 89.8 percent in the cyclosporine-treated group. The incidence of first biopsy-proven acute rejection of grade $\geq 1B$ at month six, the primary end point was 54 percent in the tacrolimus arm versus 66.4 percent in the cyclosporine arm ($p=0.029$). The incidence of first biopsy-proven acute rejection of grade $\geq 3A$ at month six was 28 percent in the tacrolimus group and 42 percent in the cyclosporine group ($p=0.013$). Significant differences ($p\leq 0.05$) were seen between the groups for adverse events, such as new-onset diabetes mellitus (20.3 percent versus 10.5 percent), post-transplant arterial hypertension (65.7 percent versus 77.7 percent), and dyslipidemia (28.7 percent versus 40.1 percent) for tacrolimus versus cyclosporine, respectively.

Heart transplant patients were randomized to receive either tacrolimus ($n=33$) or cyclosporine, modified ($n=34$), each in combination with corticosteroids and azathioprine, without induction, in a five-year follow-up study.⁹⁹ Endpoints included survival, Grade $\geq 3A$ or treated rejection, angiographic cardiac allograft vasculopathy, renal dysfunction, use of two or more antihypertensive medications, incidence of diabetes, and lipid concentrations. Significant differences were seen only for the tacrolimus-treated arm: lower five-year mean triglyceride concentrations (97 ± 34 versus 172 ± 103 mg/dL, $p=0.011$) and average serum creatinine concentrations (1.2 ± 0.5 mg/dL versus 1.5 ± 0.4 mg/dL, $p=0.044$). The tacrolimus-treated arm showed a trend toward fewer patients requiring two or more antihypertensive drugs; however, this did not reach statistical significance.

A prospective, open-label, multicenter, 12-month study randomized 85 cardiac transplant recipients to receive either tacrolimus-based ($n=39$) or cyclosporine-based ($n=46$) immunosuppression.¹⁰⁰ Fifteen patients (18 percent) were given peri-operative muromonab (Orthoclone, OKT3) due to pre-transplant renal dysfunction, to delay treatment with tacrolimus or cyclosporine. All patients received a triple-drug protocol with identical adjunctive immunosuppressant agents. Endomyocardial biopsies were performed at weeks one, two, three, four, six, eight, ten, 12, 24, and 52. Patients were mostly male (87 percent), Caucasian (90 percent), had a mean age of 54 years, and primary diagnoses of coronary artery disease (55 percent), and idiopathic dilated cardiomyopathy (41 percent). Patient and allograft survival were not different between the treatment groups. Probability and overall incidence of each grade of rejection, whether treated or not, and the types of treatment required did not differ between the groups. At baseline and through 12 months of follow-up, serum cholesterol concentrations were higher in the cyclosporine group at three, six, and 12 months (239 versus 205 mg/dL, 246 versus 191 mg/dL, 212 versus 186 mg/dL, respectively, $p\leq 0.001$). No significant differences were seen in renal function, hyperglycemia, hypomagnesemia, or hyperkalemia during the first 12 months. More cyclosporine-treated patients developed new-onset hypertension requiring drug therapy (71 percent versus 48 percent, $p=0.05$). The incidence of infection was similar for the two groups.

Hepatic Transplant

cyclosporine versus tacrolimus (Prograf)

An open-label, multicenter trial randomized 478 adults and 51 children (≤ 12 years of age) to receive tacrolimus ($n=263$) or cyclosporine ($n=266$) following hepatic transplantation.¹⁰¹ Participants were followed for one-year post-transplant, with primary endpoints of one-year patient and graft survival. The secondary endpoints were the incidence of acute rejection, corticosteroid-resistant rejection, and refractory rejection, defined as continued rejection after two courses of corticosteroids and an intravenous course of muromonab. A Kaplan-Meier analysis showed patient-survival rates at day 360 of 88 percent for both the tacrolimus and cyclosporine groups ($p=0.85$), and graft-survival rates of 82 percent and 79 percent, respectively ($p=0.55$). One hundred fifty-four patients in the tacrolimus arm and 173 patients in the cyclosporine arm experienced acute rejection ($p\leq 0.002$), and 43 patients in the tacrolimus arm and 82 patients in the cyclosporine arm experienced corticosteroid-resistant rejection ($p\leq 0.001$). In addition, refractory rejection occurred in six and 32 patients, respectively ($p\leq 0.001$). Thirty-seven patients in the tacrolimus arm and 13 patients in the cyclosporine arm discontinued the study due to adverse events, primarily nephrotoxicity and neurotoxicity ($p\leq 0.001$).

Five hundred forty-five liver transplant recipients from eight European centers were randomized into an open-label trial to tacrolimus- or cyclosporine-based regimens.¹⁰² At 12 months post-transplant, tacrolimus was associated with a significant reduction in acute rejection (40.5 percent versus 49.8 percent, $p=0.04$), refractory acute rejection (0.8 percent versus 5.3 percent, $p=0.005$), and chronic rejection (1.5 percent versus 5.3 percent, $p=0.032$) episodes. These results were seen despite significantly lower corticosteroid usage in the tacrolimus arm. Tacrolimus-treated participants also experienced a lower incidence of infection. No difference was seen between the treatment arms in patient survival (tacrolimus 82.9 percent versus cyclosporine 77.5 percent) and graft survival (tacrolimus 77.5 percent versus cyclosporine 72.6 percent). Safety data were comparable with the most serious events being renal impairment, disturbances of glucose metabolism, and neurological complications.

A total of 529 liver transplant patients participated in a one-year, randomized, multicenter study with a four-year follow-up extension that compared the safety and efficacy of tacrolimus ($n=263$) to cyclosporine ($n=266$).¹⁰³ Participants were evaluated at three-month intervals to determine patient and graft survival rates, incidence of adverse events, and changes in laboratory and clinical profiles. Overall, patient and graft survival rates were comparable between the two groups (tacrolimus 79 percent and 71.8 percent; cyclosporine 73.1 percent and 66.4 percent, respectively). Hepatitis C-positive patients had improved survival with tacrolimus (78.9 percent tacrolimus group versus 60.5 percent cyclosporine group; $p=0.041$). The two groups had comparable incidences of late acute rejection, late steroid-resistant rejection and death or graft loss related to rejection. The safety profiles of both treatments were comparable.

The Randomized Evaluation of Fibrosis (REFINE) study was an open-label prospective, randomized, multicenter study.¹⁰⁴ Adult patients ($n=356$) who had received a liver transplant for hepatitis C virus (HCV) cirrhosis were randomized to cyclosporine or tacrolimus-based regimens. Patients then entered a 12-month treatment phase, with a follow-up assessment at 24 months posttransplant. The primary endpoint was the rate of fibrosis stage ≥ 2 using Ishak-Knodell scoring by 12 months after liver transplantation. A total of 71.6 percent of patients randomized to cyclosporine, compared to 67.5 percent of patients randomized to tacrolimus had fibrosis score ≥ 2 at month 12 (OR 1.11; 95% CI

0.56,2.21, $p=0.759$). Similarly, no significant between-group difference occurred at month 24 (OR 1.15; 95% CI 0.47,2.80, $p=0.767$) in these patients. However, in the subset of patients who did not receive corticosteroids, a fibrosis score ≥ 2 was significantly less frequent with cyclosporine versus tacrolimus at month 12 (18.9 percent versus 42.1 percent; $p=0.029$).

cyclosporine, modified (Gengraf/Neoral) versus tacrolimus (Prograf)

A prospective, randomized, intent-to-treat, four-year follow-up trial comparing cyclosporine, modified (n=50) to tacrolimus (n=49) was conducted to evaluate a multidrug approach that would reduce both early and long-term morbidity related to immunosuppression post-hepatic transplant without compromising efficacy.¹⁰⁵ The primary endpoints were rejection and infection, and the secondary endpoints were liver function, renal function, bone marrow function, cardiovascular risk factors, and the recurrence of hepatitis C. Study treatment was started on postoperative day two with mycophenolate mofetil. All patients received an identical steroid taper. Forty-six cyclosporine, modified patients and 44 tacrolimus patients completed the full four years of follow-up. The overall patient survival rate was 93 percent, and the overall graft survival rate was 89 percent. There were no significant differences seen between the study groups in four-year patient survival (cyclosporine, modified 96 percent versus tacrolimus 90 percent, $p=NS$), graft survival (cyclosporine, modified, 90 percent versus tacrolimus, 88 percent, $p=NS$), or rejection (cyclosporine, modified 34 percent versus tacrolimus 24 percent, $p=0.28$). There were no differences in infection rates. For patients with hepatitis C (n=37), there were also no differences in viral titers or Knodell biopsy scores; however, in the tacrolimus-treated patients, there was a lower rejection rate ($p=0.0097$) and a lower rate of hepatitis C recurrence ($p=0.05$). No difference was seen in the percent of patients weaned off steroids after four years or in the incidence of diabetes mellitus and hypertension. More patients in the cyclosporine, modified group had a twofold increase in creatinine when compared to the tacrolimus group (63 percent versus 38 percent, respectively, $p=0.04$).

A prospective randomized trial compared cyclosporine, modified (n=51) to tacrolimus (n=50) for primary immunosuppression.¹⁰⁶ One-hundred-one adult liver transplant patients were enrolled and followed for five years. At one, three, and five years, survival rates were 86 percent, 75 percent, and 72 percent, respectively with no significant difference between the two treatment arms. A total of thirty cases of acute rejection occurred with no significant difference between the two treatment groups. More cyclosporine patients reported serious adverse events than tacrolimus patients (48 versus 32 patients, respectively). More cyclosporine-treated patients (n=19) switched to the other calcineurin inhibitor than tacrolimus-treated patients (n=15). The switch was mainly due of lack of efficacy. There were no cases of chronic rejection in the tacrolimus arm. Four patients were switched from tacrolimus to cyclosporine, modified due to adverse effects. There was no difference between the two treatment groups in renal dysfunction, diabetes, hypertension, neurologic disorders, new-onset malignancies or infections, and there were no significant differences in survival or rejection among the intention-to-treat groups.

Cyclosporine, modified (n=250) was compared to tacrolimus (n=245) for safety and efficacy at three and six months and for patient status at 12 months in an open-label, multicenter study involving liver transplant recipients.¹⁰⁷ Participants also received steroids with or without azathioprine. At 12 months, 85 percent of cyclosporine, modified-treated patients and 86 percent of tacrolimus-treated patients survived with a functioning graft ($p=NS$). The cyclosporine, modified arm (six percent) had significantly fewer hepatitis C-positive patients die or lose their graft by 12 months when compared to the

tacrolimus arm (16 percent, $p \leq 0.03$). No difference was seen between the groups in recurrence of hepatitis C virus. At 12 months, median serum creatinine concentration was 106 $\mu\text{mol/L}$ in both treatment groups. At 12 months, more tacrolimus-treated patients who were nondiabetic at baseline received antihyperglycemic therapy (13 percent versus five percent, $p \leq 0.01$), and more tacrolimus-treated patients who were diabetic at baseline required anti-diabetic treatment (70 percent versus 49 percent, $p = 0.02$). Treatment for de novo or pre-existing hypertension or hyperlipidemia was similar in both groups.

A multicenter, randomized, open-label study compared tacrolimus ($n = 301$) and cyclosporine, modified ($n = 305$) in a total of 606 patients undergoing first orthotopic liver transplantation.¹⁰⁸ Patients in both treatment groups received combined treatment with a standard immunosuppressant regimen. The primary endpoint was the combined frequency of death, retransplantation, or treatment failure. Ninety-six percent of those randomized received the study treatment. An intention-to-treat analysis revealed the primary outcome was reached in 21 percent ($n = 62$) of patients in the tacrolimus arm versus 32 percent ($n = 99$) of patients in the cyclosporine, modified arm (relative risk 0.63, $p = 0.001$). Death occurred in 50 (17 percent) tacrolimus patients versus 72 (24 percent) cyclosporine, modified patients; retransplantations were necessary in 11 (four percent) versus 31 (ten percent); and treatment failure for immunological reasons occurred in six (two percent) versus 12 (four percent) patients, respectively. Sepsis and multi-organ failure were the main causes of death in both trial groups. No differences were seen between the two groups in the rate of renal dysfunction or the need for antihypertensive therapy; however, more tacrolimus-treated patients developed diabetes mellitus.

everolimus (Zortress) with reduced exposure tacrolimus versus standard exposure tacrolimus

A 24-month, multinational, open-label, randomized trial was conducted in liver transplant patients starting 30 days post-transplant.¹⁰⁹ A total of 1,147 patients ages 18 to 70 years old were enrolled into the run-in period of this trial. During the first 30 days after transplant and prior to randomization, patients received tacrolimus and corticosteroids, with or without mycophenolate mofetil. At 30 days post-transplant, a total of 719 patients who were eligible according to study inclusion/exclusion criteria, were randomized into one of three treatment groups (i) everolimus initiation with tacrolimus elimination (TAC Elimination) (ii) everolimus initiation with reduced-exposure tacrolimus (EVR+reduced TAC) or (iii) standard-exposure tacrolimus (TAC Control). The TAC Elimination group was discontinued prematurely due to higher incidence of acute rejection. All patients received corticosteroids during the trial. For the primary endpoint of treated biopsy-proven acute rejection, graft loss, or death at 12 months post-transplant, EVR+reduced TAC was non-inferior to TAC Control (6.7 percent versus 9.7 percent, $p < 0.001$). The secondary endpoint of change in renal function from randomization to month 12 post-transplant was superior with EVR+reduced TAC versus TAC Control ($p < 0.001$). However, drug discontinuation for adverse events occurred in 25.7 percent of EVR+reduced TAC versus 14.1 percent of TAC Control patients.

Renal Transplant

azathioprine (Imuran) versus cyclosporine

The long-term effects of azathioprine were compared to cyclosporine in live-donor kidney transplantation patients in a randomized study.¹¹⁰ Adult primary renal transplant recipients aged between 18 and 60 years with one haplotype HLA mismatch who had been transplanted before 1988 were included. Four hundred seventy-five participants received a primary immunosuppressive protocol

consisting of both steroid and azathioprine (n=300) or cyclosporine (n=175). Study endpoints included patient and graft survival rates, condition at last follow-up, rejection (acute and chronic), and graft function (serum creatinine and creatinine clearance). There was no significant difference between the groups in overall frequency of acute rejection episodes. The azathioprine-treated patients had graft survival rates of 69 percent versus 58 percent at five years, and 52 percent versus 36 percent at ten years compared to cyclosporine treatment. However, at 20 years, graft survival rates had declined to 26 percent in the azathioprine arm and 24 percent in the cyclosporine arm. No significant differences were seen between the two groups regarding post-transplant malignancies, diabetes mellitus, hepatic impairment, or serious bacterial infections.

Recipients (n=112) of haploidentical live-related donor kidney transplants were randomly assigned prior to transplantation to receive azathioprine (n=54) or cyclosporine (n=58) combined with prednisone.¹¹¹ Patients were followed for three to six years (mean 50 ± eight months). Thirteen azathioprine-treated patients (24 percent) and six cyclosporine-treated patients (ten percent) were switched to the alternate immunotherapy (p≥0.05). No significant differences were seen between the groups in patient survival, graft survival, or overall frequency of acute rejection during the follow-up period. However, the number of patients who had two or more rejection episodes was higher among the azathioprine-treated patients (p≤0.04). The mean serum creatinine concentrations were significantly higher in the cyclosporine arm at one, 12, and 24 months after transplantation.

azathioprine (Imuran) versus mycophenolate mofetil (CellCept)

After cadaveric renal transplant, patients were randomized to receive tacrolimus in combination with either azathioprine (n=59) or mycophenolate mofetil 1 gram per day (n=59) or 2 grams per day (n=58) and followed for one year post-transplant.¹¹² Participants were evaluated for the incidence of biopsy-confirmed acute rejection, patient and graft survival, and adverse events. The tacrolimus dose and trough concentrations were similar between treatment groups at all time points. By six months post-transplant, the mean dose of mycophenolate mofetil decreased in the 2 gram group to 1.5 grams, primarily due to gastrointestinal-related adverse effects. The incidence of biopsy-confirmed acute rejection at one year was 32.2 percent in the azathioprine group, 32.2 percent in the mycophenolate mofetil 1 gram group, and 8.6 percent in the mycophenolate mofetil 2 grams group (p≤0.01). There was no difference among the three groups in the use of antilymphocyte antibodies for the treatment of rejection. The incidence of most adverse events was similar across treatment groups and comparable with previous reports. No differences were seen across the three treatment groups in the incidence of malignancies or opportunistic infections.

Antirejection activity and adverse events of mycophenolate mofetil were compared to azathioprine both with cyclosporine, modified and steroids (phase A) in recipients of cadaveric kidney transplants over six months in a multicenter, prospective, randomized, parallel-group trial.¹¹³ Participants were then followed for an additional 15 months without steroids (phase B). The primary endpoint, occurrence of acute rejection episodes, was analyzed by intent-to-treat. One hundred sixty-eight patients per group entered phase A. Clinical rejections were seen in 56 patients (34 percent) assigned to mycophenolate mofetil and 58 patients (35 percent) assigned to azathioprine (p=0.44). Eighty-eight patients in the mycophenolate mofetil group and 89 in the azathioprine group entered phase B. Clinical rejections were seen in 14 patients (16 percent) taking mycophenolate mofetil and 11 patients (12 percent) taking azathioprine (p=0.71).

azathioprine (Imuran) versus sirolimus (Rapamune)

A prospective, multicenter, randomized, double-blind trial compared azathioprine to sirolimus added to cyclosporine and prednisone.¹¹⁴ Recipients (n=719) of HLA-mismatched cadaveric or living-donor renal allografts who displayed initial graft function were randomly assigned to sirolimus 2 mg daily (n=284) or 5 mg daily (n=274) or azathioprine (n=161). At six and 12 months, the primary composite endpoint of efficacy failure, occurrence of biopsy-confirmed acute rejection episodes, graft loss, or death and various secondary endpoints that characterize these episodes were compared using an intention-to-treat analysis. The two sirolimus groups had a lower rate of efficacy failure at six months (2 mg: 18.7 percent, p=0.002; 5 mg: 16.8 percent, p≤0.001) compared to azathioprine (32.3 percent). In addition, the frequency of biopsy-confirmed acute rejection episodes was lower in the sirolimus groups (2 mg: 16.9 percent, p=0.002; 5 mg: 12 percent, p≤0.001) compared to azathioprine (29.8 percent). Survival was similar in all groups for grafts and patients at 12 months. Rates of infection and malignancies were similar among the groups.

cyclosporine versus sirolimus (Rapamune)

The efficacy and tolerability of a calcineurin inhibitor-free regimen was compared in a prospective, randomized trial.¹¹⁵ One hundred forty-five renal transplant recipients were given either sirolimus (n=71) or cyclosporine (n=74) along with polyclonal antilymphocyte antibodies, mycophenolate mofetil, and steroids for six months. Estimated glomerular filtration rates, the primary endpoint, were not statistically different at 12 months between the two groups. In addition, patient and graft survival, delayed and slow graft function, incidence of biopsy-proven rejection, and rates of steroid withdrawal were not statistically different between the groups at 12 months. Overall study drop-out rates were 28 percent with sirolimus and 14.9 percent with cyclosporine. In patients who remained on treatment according to protocol at 12 months, estimated glomerular filtration rates were significantly higher with sirolimus (69 ± 19 versus 60 ± 14 mL/min, p=0.01). Sirolimus-treated patients had more adverse events such as wound complications, mouth ulcers, diarrhea, hypokalemia, bronchopneumonia, and proteinuria >0.5 g/24 hours compared to cyclosporine-treated patients (38.8 percent versus 5.6 percent, p≤0.001). Additionally, sirolimus-treated patients experienced significantly fewer cytomegalovirus (CMV) infections compared to cyclosporine-treated patients (six percent versus 23 percent, p≤0.01).

A six-month, randomized, open-label, multicenter prospective study was conducted to evaluate the effects of sirolimus (n=33) versus cyclosporine (n=36) each in combination with antithymocyte globulin induction, mycophenolate mofetil, and steroids in recipients of kidney transplant.¹¹⁶ More sirolimus-treated patients withdrew because of delayed graft function and surgical complications (16 versus six, p≤0.01). In addition, delayed graft function tended to be more frequent among sirolimus recipients (45.4 percent versus 30.6 percent, p=0.22), but graft survival was similar (87.5 percent versus 97 percent, p=0.19). At six months, there were no significant differences in biopsy-proven acute rejection or calculated creatinine clearance.

A randomized, prospective trial of 61 adult primary kidney transplant recipients compared sirolimus with cyclosporine.¹¹⁷ Each patient received induction therapy with 20 mg basiliximab (Simulect®) on days zero and four, and maintenance therapy with mycophenolate mofetil 1 gram twice daily and steroids. Sirolimus doses were titrated to maintain 24-hour trough concentrations of 10 to 12 ng/mL for six months and 5 to 10 ng/mL thereafter. Cyclosporine therapy was titrated to maintain 12-hour trough concentrations of 200 to 250 ng/mL. Participants were followed for a mean duration of 18.1

months (range, 12 to 26 months). No differences were seen between the treatment groups in percentages of one year patient survival, graft survival, or biopsy-confirmed acute rejection rates. At six and 12 months, respectively, sirolimus-treated patients showed significantly better mean serum creatinine concentrations (1.29 and 1.32 mg/dL, respectively) and calculated creatinine clearances (77.8 and 81.1 mL/min, respectively) than cyclosporine-treated patients (1.74 and 1.78 mg/dL, and 64.1 and 61.1 mL/min, respectively, $p=0.008$ and $p=0.004$). Significantly higher one-year trough concentrations of mycophenolic acid were seen in the sirolimus-treated recipients (4.16 ng/mL versus 1.93 ng/mL, $p=0.001$).

Sirolimus ($n=41$) was compared to cyclosporine ($n=42$) in first cadaveric renal allograft recipients in 11 European centers.¹¹⁸ Each agent was titrated to appropriate blood concentrations and combined with corticosteroids and azathioprine. Results showed similar graft survival (98 percent sirolimus versus 90 percent cyclosporine), patient survival (100 percent versus 98 percent), and incidence of biopsy-confirmed acute rejection (41 percent versus 38 percent) at 12 months. At three and four months, serum creatinine was significantly lower with sirolimus ($p\leq 0.05$), and serum uric acid and magnesium were normal. Sirolimus-treated patients experienced laboratory abnormalities including hypertriglyceridemia (51 percent versus 12 percent), hypercholesterolemia (44 percent versus 14 percent), thrombocytopenia (37 percent versus zero percent), leukopenia (39 percent versus 14 percent), and, of lesser importance, increased liver enzymes and hypokalemia more often. When the sirolimus target serum trough concentrations were lowered from 30 to 15 ng/mL two months after transplantation, these abnormalities improved. The occurrence of CMV was comparable (14 percent versus 12 percent); however, pneumonia incidence (17 percent versus two percent, $p=0.03$) was higher with sirolimus. The difference in incidences of herpes simplex was in favor of the sirolimus group (24 percent versus ten percent, $p=0.08$) but was not statistically significant. The sirolimus-treated patients experienced no gingival hyperplasia, rare tremor, less frequent hypertension (17 percent versus 33 percent), and no malignancies. Two malignancies were observed with cyclosporine.

In a study, patients ($n=448$) were randomly assigned before transplant to receive sirolimus and tacrolimus (SRL+TAC) or sirolimus and cyclosporine (SRL+CsA), each with corticosteroids.¹¹⁹ Both treatments demonstrated equivalent efficacy of the composite endpoint at 12 months with efficacy failure rates of 21.9 versus 23.2 percent (SRL+TAC versus SRL+CsA, respectively, $p=0.737$). Biopsy-confirmed acute rejection rate (13.8 versus 17.4 percent) and graft survival rate (89.7 versus 90.2 percent) were similar. In evaluable patients, renal function was not superior in SRL+TAC versus SRL+CsA (54.5 versus 52.6 mL/min, $p=0.466$). At 12 months, there were no significant differences in rates of death, discontinuation because of adverse events, hypercholesterolemia, hyperlipemia, or proteinuria. Diarrhea and herpes simplex infections occurred significantly more often in SRL+TAC patients. Hypertension, cardiomegaly, increased creatinine, overdose (primarily calcineurin inhibitor toxicity), acne, urinary tract disorders, lymphocele, and ovarian cysts occurred significantly more often in SRL+CsA patients.

A prospective, open-label, multicenter randomized study evaluated the conversion of 192 patients from a cyclosporine-based regimen to a sirolimus-based regimen three months after transplantation.¹²⁰ All patients were also given mycophenolate mofetil and oral steroids, which were planned to be discontinued after eight months. The primary endpoint, creatinine clearance week 52, was significantly better in the sirolimus group (68.9 versus 64.4 mL/min, $p=0.017$). However, patient and graft survival were not statistically different. The incidence of acute rejection episodes, mainly occurring after withdrawal of steroids, was not statistically higher in the sirolimus group (17 versus

eight percent, $p=0.071$). Significantly more patients in the sirolimus group reported aphthous, diarrhea, acne, and high triglyceride concentrations.

A multicenter, prospective trial included 193 kidney recipients randomized at week 12 to switch from cyclosporine to sirolimus or to continue cyclosporine.¹²¹ All patients received mycophenolate mofetil. Quantified assessment of interstitial fibrosis by a program of color segmentation was performed at one year in 121 patients. At one year, renal function was significantly improved in the conversion group. Biopsy results, however, showed no between-group difference in percentage of interstitial fibrosis.

An open-label, parallel-group, comparative trial randomized 487 patients 2:1 to sirolimus or cyclosporine.¹²² All patients received basiliximab induction as well as maintenance mycophenolate mofetil and corticosteroids along with either sirolimus or cyclosporine. Within six months of the start of the trial, an imbalance in the incidence of acute rejection was noted. The data monitoring committee noted the sirolimus trough levels were below the target range in 39 percent of patients two weeks after transplantation. A protocol amendment increased the loading dose of sirolimus. However, the imbalance in acute rejection rates continued despite the protocol amendment and at one year the study was terminated due to the increased BCAR rate in the sirolimus group.

cyclosporine versus tacrolimus (Prograf)

Two hundred patients were randomized in a 2:1 fashion to receive tacrolimus ($n=134$) or cyclosporine ($n=66$) along with thymoglobulin induction, an antimetabolite, and prednisone.¹²³ At one year, efficacy was similar between the groups. The rate of acute rejection was four percent in the tacrolimus group and six percent in the cyclosporine group. The rate of patient survival was 99 percent in the tacrolimus group and 100 percent in the cyclosporine group, and the rate of graft survival was 95 percent in the tacrolimus group and 100 percent in the cyclosporine group. Serum creatinine concentrations were lower in the tacrolimus group compared with the cyclosporine group (1.3 ± 0.3 versus 1.6 ± 0.7 mg/dL, $p=0.03$). The incidences of CMV infection, anti-hypertensive requirement, and post-transplant diabetes mellitus were similar; however, two patients in the tacrolimus arm developed malignancy.

A multicenter, randomized trial comparing the 12-month efficacy and safety of tacrolimus-based to cyclosporine-based immunosuppressive regimens in the prevention of renal allograft rejection enrolled 448 renal transplant recipients assigned to receive triple-drug therapy consisting of tacrolimus ($n=303$) or cyclosporine ($n=145$), each in combination with azathioprine and low-dose corticosteroids.¹²⁴ Results showed that tacrolimus therapy was associated with a significant reduction in the frequency of both acute rejection (tacrolimus 25.9 percent versus cyclosporine 45.7 percent; $p \leq 0.001$) and corticosteroid-resistant rejection (11.3 percent versus 21.6 percent; $p=0.001$) at 12 months. No significant differences were seen between the groups in one-year patient survival (tacrolimus, 93 percent versus cyclosporine, 96.5 percent; $p=0.14$) and graft survival rates (82.5 percent versus 86.2 percent; $p=0.38$). The safety profiles of the tacrolimus- and cyclosporine-based regimens were similar. The tacrolimus treatment group reported higher incidences of elevated serum creatinine, tremor, diarrhea, hyperglycemia, diabetes mellitus, and angina pectoris; however, the cyclosporine treatment group reported higher incidences of acne, arrhythmia, gingival hyperplasia, and hirsutism.

In a randomized, open-label study, 412 patients receiving cadaveric kidney transplants were randomized to tacrolimus ($n=205$) or cyclosporine ($n=207$) and followed for one year.¹²⁵ Assessments were done for patient and graft survival and the incidence of acute rejection. One-year patient survival rates were 95.6 percent for tacrolimus and 96.6 percent for cyclosporine ($p=0.576$), and one-year graft survival rates were 91.2 percent for tacrolimus and 87.9 percent for cyclosporine ($p=0.289$). The

incidence of biopsy-confirmed acute rejection was significantly reduced in the tacrolimus group compared with the cyclosporine group (30.7 percent versus 46.4 percent, $p=0.001$). Both treatment groups reported impaired renal function, gastrointestinal disorders, and neurological complications; however, tremor and paresthesia were more frequently reported in the tacrolimus group. The incidence of post-transplant diabetes mellitus was 19.9 percent in the tacrolimus group and four percent in the cyclosporine group ($p\leq 0.001$).

Cyclosporine-treated patients who had an elevated serum creatinine (SCr) at least three months post-renal transplantation ($n=186$) were randomized in a 2:1 fashion to switch to tacrolimus or continue cyclosporine.¹²⁶ On baseline biopsy, 90 percent of patients had chronic allograft nephropathy, and baseline median SCr was 2.5 mg/dL in both treatment groups. For patients with graft function at month 24, SCr had decreased to 2.3 mg/dL in the tacrolimus-treated patients and increased to 2.6 mg/dL in the cyclosporine-treated patients ($p=0.01$). During the follow-up, acute rejection occurred in 4.8 percent of tacrolimus-treated patients and five percent of cyclosporine-treated patients. The two groups were comparable for two-year allograft survival (tacrolimus 69 percent, cyclosporine 67 percent; $p=0.7$). Tacrolimus-treated patients experienced lower cholesterol and low-density lipoprotein concentrations along with fewer new-onset infections. In addition, cardiac conditions developed in fewer tacrolimus-treated patients compared to cyclosporine-treated patients (5.6 percent versus 24.3 percent; $p=0.004$). The two groups did not differ in glucose concentrations, incidences of new-onset diabetes, or new-onset hyperglycemia.

cyclosporine, modified (Gengraf/Neoral) versus tacrolimus (Prograf)

A two-year follow-up to the European Tacrolimus versus Cyclosporine A Microemulsion Renal Transplantation Study was conducted to research the long-term clinical outcomes in terms of the rate of acute rejection, graft and patient survival, and graft function between tacrolimus and cyclosporine.¹²⁷ The European Tacrolimus versus Cyclosporine A Microemulsion Renal Transplantation Study was a randomized, comparative, six-month trial of tacrolimus and cyclosporine each in combination with azathioprine and steroids. The intent-to-treat population (ITT) consisted of 286 patients in the tacrolimus arm and 271 in the cyclosporine, modified arm. Tacrolimus whole blood concentration targets were 10 to 20 and 5 to 15 ng/mL, and cyclosporine whole blood concentration targets were 100 to 400 and 100 to 200 ng/mL during months zero to three and four to six, respectively. No specific calcineurin inhibitor target concentrations were required during the investigator-driven follow-up after termination of the main study. Follow-up data were collected at two years post-transplantation from 237 (82.9 percent of the ITT population) patients who received tacrolimus and 222 (81.9 percent of the ITT population) patients who received cyclosporine, modified. Mortality (two percent versus 3.3 percent; $p\leq 0.05$ in Kaplan-Meier analysis) was lower, but rate of graft loss (9.3 percent versus 11.2 percent; $p=0.12$ in Kaplan-Meier analysis) was not significantly different after two years with tacrolimus versus cyclosporine, modified. During months zero to six, tacrolimus-treated patients had a lower rate of biopsy-proven acute rejection compared to cyclosporine, modified-treated patients. (19.6 percent versus 37.3 percent; $p\leq 0.0001$); however, this was not significantly different during months seven to 12 and 13 to 24 (1.7 percent and 0.8 percent with tacrolimus and 4.7 percent and 0.9 percent with cyclosporine, modified, respectively). During the 24 months of follow-up, more cyclosporine, modified patients had a composite endpoint consisting of graft loss, patient death, and biopsy-proven acute rejection when compared to the tacrolimus patients (42.8 percent versus 25.9 percent; $p\leq 0.001$). Two-year post-transplant renal function, measured by SCr concentrations, was better in tacrolimus-based compared with cyclosporine, modified-based

immunosuppression (136.9 versus 161.6 micromole/L; $p \leq 0.01$). At two years, more patients in the tacrolimus arm received calcineurin inhibitor monotherapy, and fewer tacrolimus patients remained on a triple immunosuppressive regimen. Tacrolimus-treated patients had lower cholesterol and triglyceride concentrations (despite less use of cholesterol-lowering drugs) than cyclosporine, modified-treated patients. No difference in requirement for antidiabetic medication was noted.

Cyclosporine modified was compared to tacrolimus in a multicenter, randomized, six-month open-label study involving 560 patients.¹²⁸ Patients were given azathioprine and corticosteroids in addition to either tacrolimus ($n=287$) at an initial oral daily dose of 0.3 mg/kg or cyclosporine, modified ($n=273$) at an initial oral daily dose of 8 to 10 mg/kg. The proportion of patients with biopsy-proven acute rejection and the time to the event was the primary endpoint. Tacrolimus-treated patients had a lower rate of biopsy-confirmed acute rejection when compared to cyclosporine, modified (56 patients [19.6 percent] versus 101 [37.3 percent]; $p \leq 0.0001$). Tacrolimus-treated patients also had a lower incidence of biopsy-confirmed corticosteroid-resistant rejection when compared to cyclosporine, modified (27 [9.4 percent] versus 57 [21 percent]; $p \leq 0.0001$). Crossover between therapies secondary to biopsy-proven rejection was necessary in one (0.3 percent) tacrolimus-treated patient and 27 (ten percent) cyclosporine, modified-treated patients ($p \leq 0.0001$). The two treatment groups had similar rates of patient and graft survival and similar renal function. In addition, the overall rates of adverse events were similar in the two groups. However, hypertension and hypercholesterolemia were more common in the cyclosporine, modified-treated patients, and tremor and hypomagnesaemia were more frequent in the tacrolimus-treated patients.

A prospective, randomized trial compared the effect of cyclosporine, modified to tacrolimus on the development of renal allograft fibrosis, defined as chronic allograft nephropathy (CAN).¹²⁹ One hundred two patients undergoing renal transplantation were given either cyclosporine, modified (15 mg/kg per day adjusted to whole-blood trough concentrations of 200 to 300 ng/mL) or tacrolimus (0.2 mg/kg per day adjusted to whole-blood trough concentrations of 8 to 15 ng/mL) in conjunction with steroids and azathioprine. The two drugs were compared using concentrations of interstitial fibrosis in relation to observed efficacy and toxicity profiles. No difference was seen between the groups in demographic characteristics, incidence of acute rejection (cyclosporine, modified 36 percent versus tacrolimus 35 percent), or steroid-resistant rejection (both ten percent). The cyclosporine, modified-treated patients had a significant increase in allograft interstitial fibrosis. There was a higher incidence of insulin resistance in the tacrolimus group; however, this did not reach statistical significance. Cyclosporine was associated with a significant increase in total cholesterol and low-density lipoprotein concentrations, which persisted throughout the study period ($p=0.03$ and $p=0.021$, respectively).

everolimus (Zortress) and mycophenolate mofetil (CellCept)

In a randomized, multicenter, multinational, 12-month, double-blind, double-dummy, open-label, phase 3 trial in de novo renal allograft recipients ($n=588$), everolimus 1.5 mg or 3 mg daily was compared with mycophenolate mofetil 2 grams daily.¹³⁰ Patients also received cyclosporine and corticosteroids as part of a triple immunosuppressive regimen. At 12 months, there were no statistically significant differences between everolimus 1.5 mg, everolimus 3 mg, and mycophenolate mofetil in the incidence of biopsy-proven acute rejection (23.2, 19.7, and 24 percent, respectively), graft loss (4.6, 10.6, and 9.2 percent), or death (5.2, 4, and 2.6 percent). Everolimus 1.5 mg and mycophenolate mofetil were equally well tolerated. Both were better tolerated than everolimus 3 mg.

The incidence of CMV infection was significantly lower in patients receiving everolimus 1.5 mg or 3 mg than in those receiving mycophenolate mofetil (5.2, 7.6, and 19.4 percent, respectively; $p=0.001$).

A 36-month, randomized, parallel-group study compared everolimus 1.5 mg and 3 mg daily with mycophenolate mofetil 2 grams daily in de novo renal-transplant recipients ($n=583$).¹³¹ Patients also received full-dose cyclosporine and corticosteroids after randomization. For at least their first year, patients received study medication according to a double-blinded, double-dummy design before concerns over nephrotoxicity led to an amended open-label design with reduced cyclosporine troughs. Incidences of primary efficacy failure at 36 months (biopsy-proven acute rejection, graft loss, death, or loss to follow-up) were 33.7, 34, and 31.1 percent for everolimus 1.5 mg, everolimus 3 mg/day, and mycophenolate mofetil, respectively ($p=0.810$). Antibody-treated acute rejection at 36 months was significantly lower with everolimus 1.5 mg than mycophenolate mofetil (9.8 versus 18.4 percent, $p=0.014$). Discontinuation for adverse events, including death and graft loss, was more frequent with everolimus compared to the mycophenolate mofetil arm.

everolimus (Zortress) and mycophenolate sodium (Myfortic)

In a 24-month, open-label study, 833 de novo renal transplant recipients were randomized to everolimus 1.5 mg or 3 mg daily with reduced-exposure cyclosporine or mycophenolate 1.44 grams daily plus standard-exposure cyclosporine.¹³² Patients received basiliximab (Simulect) with or without corticosteroids. The primary endpoint was composite efficacy failure (treated biopsy-proven acute rejection, graft loss, death, or loss to follow-up) and the main safety endpoint was renal function at month 12 (last observation carried forward). Month 12 efficacy failure rates were non-inferior in the everolimus 1.5 mg and 3 mg versus mycophenolate groups (25.3, 21.9, and 24.2 percent, respectively). Mean eGFR at month 12 was non-inferior in the everolimus groups versus the mycophenolate group. The overall incidence of adverse events was comparable between groups.

mycophenolate sodium (Myfortic) and mycophenolate mofetil (CellCept)

Mycophenolate sodium (720 mg twice daily) was compared to mycophenolate mofetil (1,000 mg twice daily) combined with cyclosporine, modified and corticosteroids in 423 de novo kidney transplant patients in a 12-month, double-blind study.¹³³ At six months, mycophenolate sodium proved to be equivalent to mycophenolate mofetil in efficacy failure, defined by biopsy-proven acute rejection, graft loss, death, or loss to follow up (25.8 percent versus 26.2 percent [95% CI, -8.7 to 8]). At 12 months, the incidence of efficacy failure was 26.3 percent for mycophenolate sodium and 28.1 percent for mycophenolate mofetil, and the incidence of biopsy-proven acute rejection was 22.5 percent for mycophenolate sodium and 24.3 percent for mycophenolate mofetil. The rate of severe acute rejection was 2.1 percent with mycophenolate sodium and 9.8 percent with mycophenolate mofetil among those with biopsy-proven acute rejection ($p=NS$). The incidence of adverse events was similar between the groups. Within 12 months, 15 percent of mycophenolate sodium and 19.5 percent of mycophenolate mofetil patients required a dose change due to GI adverse events ($p=NS$).

In a single-center, open-label, randomized trial, mycophenolate mofetil (group A, $n=75$) was compared to enteric-coated mycophenolate sodium (group B, $n=75$) in primary renal transplant recipients receiving combined thymoglobulin/daclizumab induction along with reduced tacrolimus dosing and elimination of corticosteroids one week postoperatively.¹³⁴ The primary endpoint was the incidence rate of acute rejection during the first 12 months post-transplant. Secondary aims were to compare graft and patient survival, renal function, drug dosing and monitoring, gastrointestinal adverse effects,

and other adverse events at 12 months of follow-up. Patient/graft survival in groups A and B were 100 percent/96 percent versus 99/96 percent, respectively ($p=NS$). At 12 months, three versus nine percent in group A and group B, respectively, experienced biopsy-proven acute rejection ($p=NS$). Incidence of new onset diabetes mellitus, infections requiring hospitalization, and GI adverse effects appeared equivalent.

mycophenolate mofetil (CellCept) versus sirolimus (Rapamune)

The impact on graft survival and long-term graft function in renal transplant recipients using maintenance therapy consisting of either mycophenolate mofetil or sirolimus, each without prednisone, was compared.¹³⁵ Induction therapy was given on days zero, one and two post-transplant. Patients were then prospectively randomized to two maintenance immunosuppressive regimens with tacrolimus plus mycophenolate mofetil ($n=45$) or tacrolimus plus sirolimus ($n=37$). During the three-year follow-up, there was one kidney loss in the mycophenolate mofetil group versus six losses in the sirolimus group ($p=0.04$). Glomerular filtration rates at different time-points post-transplant were better, and the slope of glomerular filtration rate decline per month was flatter in the mycophenolate mofetil arm compared to the sirolimus arm.

A one-year, randomized, multicenter clinical trial was conducted comparing the combination of sirolimus ($n=185$) or mycophenolate mofetil ($n=176$) with tacrolimus and corticosteroids in kidney transplant patients.¹³⁶ The primary endpoint of the study was the incidence of biopsy-confirmed acute rejection at six months. Patient and graft survival, renal function, study drug dosing and discontinuations were evaluated at one year, and results showed no differences in patient or graft survival. However, patients without delayed graft function receiving mycophenolate mofetil had significantly better graft survival (99 percent versus 93 percent, $p=0.01$), and those receiving a transplant from a live donor had a trend towards better graft survival with mycophenolate mofetil (98 percent versus 91 percent, $p=0.07$). The sirolimus-treated group had a higher incidence of study drug discontinuations (26.5 percent versus 14.8 percent, $p=0.006$). The mycophenolate mofetil-treated patients had better mean serum creatinine concentrations (1.3 mg/dL versus 1.5 mg/dL, $p=0.03$) and a trend towards higher calculated creatinine clearance (58.4 mL/min versus 54.3 mL/min, $p=0.06$). More sirolimus-treated patients experienced serum creatinine concentrations greater than 2 mg/dL (20.4 percent versus 11 percent, $p=0.02$).

One hundred kidney transplant recipients receiving tacrolimus-based immunosuppressive regimens were randomized into equal groups and given mycophenolate mofetil 2 grams per day or sirolimus at a loading dose of 150 mg followed by 5 mg daily until day seven and 2 mg daily thereafter.¹³⁷ No differences were observed in incidences of the composite primary endpoint, biopsy-confirmed acute rejection, graft loss, and death. In addition, no differences were seen between the groups in biopsy-confirmed acute rejection or one-year patient, graft, or death-censored graft survival. However, patients treated with sirolimus had a higher mean creatinine (1.6 ± 0.5 mg/dL versus 1.4 ± 0.3 mg/dL, $p=0.007$), incidence of proteinuria (52 percent versus 10.7 percent, $p=0.041$), mean urinary protein concentrations (0.3 ± 0.5 g/L versus 0.1 ± 0.2 g/L, $p=0.012$), mean cholesterol (217 mg/dL versus 190 mg/dL, $p=0.03$), and percentage of premature drop outs (26 percent versus eight percent, $p=0.031$) when compared to the mycophenolate mofetil-treated patients.

In addition to tacrolimus, 325 participants were given sirolimus 2 mg daily, 325 participants were given sirolimus 0.5 mg daily, and 327 participants were given mycophenolate mofetil 1 gram daily.¹³⁸ Initially, the tacrolimus dose was 0.2 mg/kg daily, and the sirolimus loading dose was 6 or 1.5 mg followed by a

daily dose of 2 or 0.5 mg. All groups received identical steroid doses. The sirolimus 2 mg group had a lower incidence (15.7 percent) of biopsy-proven acute rejection compared with the sirolimus 0.5 mg (25.2 percent, $p=0.003$) group and the mycophenolate mofetil (22.3 percent, $p=0.036$) group. Six-month graft survival was 91 percent for the sirolimus 2 mg arm, 92.6 percent for the sirolimus 0.5 mg arm, and 92.4 percent for the mycophenolate mofetil arm. The respective values for patient survival were 98.1 percent, 97.8 percent, and 97.9 percent. Study drop-out rates due to adverse events were as follows: 34 patients (10.5 percent) in the sirolimus 2 mg group, 19 patients (5.8 percent) in the sirolimus 0.5 mg group, and 16 patients (4.9 percent) in the mycophenolate mofetil group. More patients in the sirolimus 2 mg group experienced hyperlipidemia compared with the sirolimus 0.5 mg and the mycophenolate mofetil group (24 percent, 19.4 percent, and 11 percent, respectively).

sirolimus (Rapamune) versus tacrolimus (Prograf)

A prospective, randomized trial compared the safety and efficacy of sirolimus (target concentration 12 to 18 ng/dL in the first month) to tacrolimus (target concentration 12 to 15 ng/mL in the first month) each combined with mycophenolate mofetil 750 mg twice daily, prednisone tapered to 10 mg per day by three months and immunosuppressant induction with thymoglobulin.¹³⁹ Preliminary results at four months in 85 patients showed acute rejection rate of 7.5 percent in the tacrolimus group compared to 6.7 percent in the sirolimus group. Eight sirolimus patients withdrew from the study, most commonly due to wound complications. At one month, renal function appeared to be better in the sirolimus group; however, this had not reached statistical significance.

tacrolimus extended-release (ER) versus tacrolimus (Prograf)

A randomized, open-label, multicenter, trial compared tacrolimus ER to tacrolimus over 12 months in patients with a kidney transplant.¹⁴⁰ All patients received basiliximab induction and concomitant treatment with MMF and corticosteroids. Patients 17 to 77 years of age were randomized to receive tacrolimus ER ($n=214$) 0.15 mg/kg/day or tacrolimus ($n=212$) 0.1 mg/kg/day. The primary efficacy outcome was the percentage of patients who developed biopsy-proven acute rejection (BPAR), graft failure, death, and/or were lost to follow-up at 12 months. In the tacrolimus ER group 30 (14 percent) patients experienced the combined outcome compared to 32 (15.2 percent) in the tacrolimus group with treatment difference of -1.1 percent (95 percent confidence interval (CI) (-7.8 percent to 5.6 percent). Premature discontinuation from treatment at the end of one year occurred in 14 percent of tacrolimus ER patients and 16 percent of tacrolimus patients, primarily due to adverse reactions.

A randomized, double-blind, multicenter, trial of identical trial design with the exception of no basiliximab induction compared tacrolimus ER to tacrolimus over 12 months in patients receiving a kidney transplant. All patients received concomitant treatment with MMF and corticosteroids without antibody induction.¹⁴¹ Patients 18 to 65 years of age were randomized to receive tacrolimus ER ($n=331$) or tacrolimus ($n=336$) at a pre-operative dose of 0.1 mg/kg/day and a post-operative dose of 0.2 mg/kg/day. After post-operative day one, the doses were altered to achieve comparable mean tacrolimus trough concentrations between tacrolimus ER and tacrolimus. Higher total mean daily doses of tacrolimus ER were required than tacrolimus dose, on average by 25 percent. The primary efficacy outcome was the percentage of patients who developed biopsy-proven acute rejection (BPAR), graft failure, death, and/or lost to follow-up at 12 months. In the tacrolimus ER group 93 (28 percent) patients experienced the outcome compared to 78 (23 percent) in the tacrolimus group with treatment difference of 4.9 percent (95 percent CI (-1.7 percent to 11.5 percent). Premature

discontinuation from treatment at the end of one year occurred in 24 percent of tacrolimus ER patients and 19 percent of tacrolimus patients, primarily due to adverse reactions.

OSAKA: The Optimizing immunoSuppression After Kidney transplantation with Advagraf (European name) trial was an open-label, parallel-group European trial that randomized 1,241 patients to one of four arms.¹⁴² Arm 1 patients received tacrolimus 0.2 mg/kg/day divided twice daily, Arm 2 patients received tacrolimus ER 0.2 mg/kg/day given once daily in the morning, Arm 3 patients received tacrolimus ER 0.3 mg/kg/day, and Arm 4 patients received tacrolimus ER 0.2 mg/kg/day given once daily in the morning plus basiliximab and corticosteroids only during induction. All patients in any of the four treatment arms also received mycophenolate mofetil and patients in Arms 1, 2 and 3 received corticosteroids that were tapered over time per protocol. The primary endpoint was non-inferiority for efficacy failure rates between Arm 1 and the other three treatment groups. Efficacy failure rate was defined as incidence and time to first occurrence of one of the following: graft loss (retransplantation, nephrectomy, death or dialysis ongoing at study end), biopsy-confirmed acute rejection (BCAR) or graft dysfunction at week 24. To prove noninferiority, a 12.5 percent difference in composite endpoint was determined to be within the range in which a meaningful clinical difference in efficacy between the treatment regimens becomes apparent (based on sample size and 80 percent power to detect a difference). Noninferiority of efficacy failure rates was established between Arm 1 (42.2 percent) and Arm 2 (40.6 percent), (difference -1.6 percent, 95 percent confidence interval, -12.2 percent to -9.0 percent). However, noninferiority of efficacy failure was not established between Arms 3 and 4 when compared to Arm 1. The dominant reason for efficacy failure in all arms was graft dysfunction at week 24. Adverse events were comparable across the four arms. The authors concluded that in adult, de novo kidney transplantation, the efficacy of tacrolimus ER given once daily in the morning was non inferior to tacrolimus dosed twice daily when using the same starting dose. Increasing the starting dose of tacrolimus ER to 0.3 mg/kg/day (Arm 3) did not increase efficacy. The study was funded by Astellas Pharmaceuticals.

A phase 3 randomized, open-label, comparative, noninferiority study examined 638 patients de novo kidney transplants.¹⁴³ Patients were randomized to one of three treatment arms: tacrolimus, ER once daily, tacrolimus twice daily, or cyclosporine twice daily. All patients received basiliximab induction, mycophenolate mofetil and corticosteroids. Patients were followed for four years. Four-year Kaplan-Meier estimates of patient survival were 93.2 percent, 91.2 percent, and 91.7 percent, respectively for tacrolimus ER, tacrolimus and cyclosporine arms. Graft survival was 84.7 percent, 82.7 percent and 83.9 percent in these same groups. Adjusted mean differences in renal function, as measured by the Cockcroft-Gault formula, over the four-year period were not statistically different between tacrolimus ER and tacrolimus, but there was a statistically significant difference, favoring tacrolimus ER when compared to cyclosporine ($p=0.0118$). Evidence of treatment-emergent glucose intolerance in the continuation phase was more common in the tacrolimus ER and tacrolimus groups compared to the cyclosporine group. Rates of HbA1c ≥ 6.5 percent over time were statistically significantly lower in the cyclosporine group compared to the tacrolimus-based groups (log rank test: tacrolimus versus cyclosporine, $p=0.01$, tacrolimus ER versus cyclosporine, $p=0.0006$).

Psoriasis

cyclosporine (Sandimmune) and cyclosporine, modified (Neoral)

Patients with severe, chronic, plaque-type psoriasis were randomized on a 1:1 basis to 24 weeks of cyclosporine, modified ($n=152$) or cyclosporine ($n=157$) at a starting dose of 2.5 mg/kg per day.¹⁴⁴ Dose

increases were allowed after four weeks to maintain efficacy, and for patients who achieved remission, dose decreases were allowed after 16 weeks at four-week intervals. The maximum permitted dose for each formulation was 5 mg/kg per day. Since remission rates were higher for cyclosporine, modified during the first eight weeks of treatment, it was concluded that cyclosporine, modified produced a more rapid response than cyclosporine. The number of dose reductions for safety was similar in both groups; however, there were more dose increases to maintain efficacy in the cyclosporine group than the cyclosporine, modified group. There were no differences between groups in the frequency or type of adverse events seen. The mean dose required to control disease was ten percent lower with fewer dose adjustments needed in the cyclosporine, modified group than in the cyclosporine group.

Rheumatoid Arthritis

azathioprine (Imuran) versus methotrexate

Azathioprine was compared to methotrexate in a randomized, double-blind fashion for the treatment of patients with RA in whom parenteral gold and/or D-penicillamine treatment had been ineffective.¹⁴⁵ Participants were given azathioprine (n=33) 100 mg daily or methotrexate (n=31) 7.5 mg weekly for eight weeks. After eight weeks, the dosage was increased if needed based on clinical improvement for a total intervention time of 48 weeks. Treatments were compared at 24 weeks with baseline values and showed improvements in 12 of 13 disease variables in the methotrexate group and in six of 13 in the azathioprine group. A significant overall clinical improvement, measured by disease activity score, was found in seven of 20 patients treated with azathioprine and 18 of 30 treated with methotrexate after 24 weeks of treatment. At 48 weeks, a significant overall clinical improvement was seen in six of 12 azathioprine-treated patients and 19 of 25 methotrexate-treated patients. The number of dropouts due to adverse events was significantly higher in the azathioprine group. After 48 weeks, 12 azathioprine-treated patients (36 percent) and 25 methotrexate-treated patients (81 percent) were still using the initial therapy.

Sixty-four patients with active RA who either had not responded to or who had intolerable adverse effects with parenteral gold and D-penicillamine were given either azathioprine 100 mg daily or methotrexate 7.5 mg weekly in a double-blind, randomized 48-week trial.¹⁴⁶ After eight weeks of therapy, the dose was increased to either azathioprine 150 mg daily or methotrexate 15 mg weekly. Clinical and laboratory assessments were done every four weeks for the first 24 weeks then every eight weeks for the remainder of the 48 week trial by the same physician. Initial radiologic scores were comparable in both groups and correlated with disease duration. An intention-to-treat analysis after 24 weeks showed significantly fewer new erosions in the methotrexate group compared to the azathioprine group (two [95 percent CI, 0.2 to 3.9] and 48 (3.5 [95 percent CI, 1.3 to 5.8])). After 24 weeks, the change in joint score was also significantly less pronounced in the methotrexate group than in the azathioprine group (difference 2.8 [95 percent CI, 0.2 to 5.2]). After 48 weeks, the change in joint score was significantly less pronounced in the methotrexate-treated patients compared to the azathioprine-treated patients as well (difference 3.9 [95 percent CI, 0.3 to 7.4]). Ten percent of the azathioprine group had reached radiologic stabilization after 48 weeks compared to 29 percent of the methotrexate group.

cyclosporine versus azathioprine (Imuran)

Patients with severe RA were randomized to receive cyclosporine (n=25) or azathioprine (n=27) for six months.¹⁴⁷ The initial mean dose of cyclosporine was 4.2 mg/kg and the initial mean dose of

azathioprine was 1.7 mg/kg. At six months, the mean dose of cyclosporine was 3.4 mg/kg and the mean dose of azathioprine was 1.9 mg/kg. Both treatment groups exhibited statistically significant improvement in standard outcome parameters compared to baseline values. However, there were no statistically significant differences in these same parameters between the two study groups. Although no one withdrew due to impaired renal function, there was a mean increase in serum creatinine associated with cyclosporine.

A prospective, randomized, double-blind, multicenter study compared cyclosporine (starting dose 5 mg/kg) to azathioprine (1.5 to 2 mg/kg) in 117 patients with RA.¹⁴⁸ Ninety-two patients completed the six-month study. Results showed mean improvement rate using the Ritchie-Index of 8.2, morning stiffness of 41.6 minutes, grip strength of 10.9 mmHg, and swollen joint count of 28.9 percent in cyclosporine-treated patients compared to 7.7, 28.4 minutes, 15.2 mmHg, and 27.9 percent, respectively in the azathioprine-treated patients. Treatment was discontinued early in 12 patients in each group. No differences in the efficacy or safety outcomes measured reached statistical significance.

cyclosporine (Sandimmune) and cyclosporine, modified (Neoral)

A 52-week, double-blind, multicenter, parallel-group study involving 51 patients with RA receiving stable conventional cyclosporine maintenance treatment was conducted.¹⁴⁹ Participants were randomized to continue conventional therapy (n=27) or to convert to cyclosporine, modified (n=24). Cyclosporine trough blood concentrations were measured before conversion and at specified intervals after conversion. Cyclosporine Area under the curve at steady-state was assessed at one week before and six weeks after randomization in 15 patients in each treatment arm. Cyclosporine doses were titrated as needed based on disease activity and clinical evaluation in both groups. The initial mean daily doses of cyclosporine were 3.5 mg/kg per day compared to 3.3 mg/kg per day in the cyclosporine, modified group and did not change significantly during the study period. The mean bioavailability was 23 percent higher in the cyclosporine group compared to the cyclosporine, modified group; however, cyclosporine, modified had a more reproducible pharmacokinetic profile. Results were similar for overall incidence and nature of adverse events and changes in vital signs and laboratory variables. There was no significant difference in efficacy between the groups, and no loss of efficacy or intolerability was seen when recipients were switched from cyclosporine to cyclosporine, modified.

SUMMARY

Currently marketed oral immunosuppressants are primarily utilized in the setting of organ transplantation. While azathioprine and cyclosporine are approved for the treatment of rheumatoid arthritis and cyclosporine is approved for the treatment of plaque psoriasis, these agents are far down the line of recommended treatment options for these disorders.

The goal of immunosuppressant therapy in a transplant patient is to prolong graft survival, minimize episodes of rejection and improve overall survival while minimizing adverse effects of the drug. The best immunosuppressant regimen for a transplant patient should be one individualized based on adverse effect profile, tolerability, type of organ transplanted, and rejection patterns.

The use of corticosteroids has historically been associated with immunosuppression. While corticosteroids are still widely utilized during induction phases of immunosuppression and to treat acute or chronic graft rejection, the goal is to minimize their utilization during long-term maintenance therapy due to the adverse effects seen with long term therapy.

Cyclosporine (Gengraf, Neoral, Sandimmune) and tacrolimus (Prograf, Hecoria, Astagraf XL) are effective calcineurin inhibitors with a well established role in the prophylaxis of organ rejection. While treatment with any formulation of cyclosporine has been found to reduce the incidence of graft rejection, the Gengraf and Neoral formulations are preferred due to their more reliable pharmacokinetic profiles, which result in greater ease of monitoring. Blood concentration of calcineurin inhibitors are routinely monitored in order to keep patients in a therapeutic range that maximizes antirejection properties while minimizing adverse effect potential. Cyclosporine has been used successfully to prevent rejection in heart, liver and renal transplantation, but tacrolimus is often used instead, especially in renal transplantation, due to the established nephrotoxic effects of cyclosporine. An extended-release tacrolimus preparation (Astagraf XL) offers a once-daily dosage in renal transplantation. Cyclosporine is still, however, a preferred agent in heart and heart/lung transplants.

In the setting of renal transplantation, current standard induction protocols followed by a maintenance regimen of a calcineurin inhibitor plus an antiproliferative agent and corticosteroids have resulted in one year graft survival rate approaching 90 percent and acute rejection rates of 20 percent or less. However, the calcineurin inhibitors, cyclosporine and tacrolimus, are associated with nephrotoxicity as well as other long-term toxicities. Recent protocols are exploring the outcomes associated with calcineurin inhibitor-free or calcineurin inhibitor-reduced exposure to determine both short and long term efficacy and safety outcomes.

Mycophenolate (CellCept, Myfortic) has replaced azathioprine (Imuran) in conventional maintenance immunosuppressant regimens because it is less likely than azathioprine to induce severe bone marrow depression. Other antiproliferatives, such as everolimus (Zortress) and sirolimus (Rapamune), are finding their niche in transplant immunosuppression and can be used to decrease the dose and, therefore, the potential for adverse effects with other drugs such as calcineurin inhibitors.

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