Pharmacology of Immunosuppressive Medications in Solid Organ Transplantation

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THE CLINICAL AND ECONOMIC POTENTIAL OF CYCLOSPORINE DRUG INTERACTIONS

Substantial progress has been made in the past 3 decades in solid organ transplantation. The discovery of potent immunosuppressive agents capable of sustaining graft function with relatively minimal toxicity has paved the way to allow more patients to receive not only a solid organ transplant, but also more types of organs, and now even tissues, to be transplanted. As a result, solid organ transplant is a viable treatment option for many types of end-organ disease, including chronic kidney disease (CKD), liver failure, chronic heart failure, type I diabetes mellitus, chronic lung disease, and diseases that affect the small bowel.

Currently available immunosuppressive agents target T-lymphocyte activity, the primary mediator of rejection in solid organ transplantation. T-lymphocyte activity is greatest immediately after the transplant procedure when the T lymphocytes first become exposed to the foreign antigens. As a result, the degree of immunosuppression is greatest within the first months after transplantation. Immunosuppression in solid organ transplant becomes a delicate balance to maintain organ function and prevent acute rejection, while preventing the development of toxicity. The most common toxicity associated with all immunosuppressive medications is infectious complications. Thus, the risk of infections is also related to the degree of immunosuppression. As time lapses after the transplant, the risk of rejection decreases but is

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not eliminated completely. Therefore, the degree, and thus drug doses, of immunosuppression decreases but cannot be discontinued completely.

There are several strategies for managing immunosuppression after solid organ transplant. In general, all protocols involve combining several immunosuppressing agents that target different areas of T-lymphocyte activity to render the cells ineffective to mount a response to the foreign antigen. Many protocols will include induction therapy in an attempt to further suppress the immune system at the time of transplant, when the risk of rejection is greatest. Induction therapy involves administering a potent immunosuppressant, usually an antibody that targets specific markers on the T lymphocyte, to block T-lymphocyte recognition or activity against the foreign antigens. Patients then receive maintenance immunosuppression, generally a combination of drugs, for the life of the transplanted organ. In the event of an acute rejection episode, more potent immunosuppression is administered to stop the T-lymphocyte attack. High doses of steroids block T-lymphocyte recognition and decrease infiltration at the transplanted graft, whereas lymphocytic antibodies destroy activated T lymphocytes to reverse the rejection process.

The following discussion will describe the mechanism of action and relevant pharmacologic aspects associated with the immunosuppressants used in solid organ transplantation. Because maintenance immunosuppression is continued for the life of the transplanted organ, these drugs will be discussed first, followed by the antibody preparations that are used for induction therapy and treatment of rejection.

CALCINEURIN INHIBITORS

Calcineurin inhibitors are the foundation of most immunosuppressive regimens in solid organ transplantation. There are 2 calcineurin inhibitors currently available: cyclosporine and tacrolimus. The introduction of cyclosporine in the early 1980s brought with it a significant reduction in acute cellular rejection and severe infections, thereby dramatically improving graft and patient survival.[1] Today, tacrolimus is the most widely used calcineurin inhibitor for all solid organ transplants.[2]

Cyclosporine

Cyclosporine exerts its immunosuppressive effects by binding to cyclophilin, a cytoplasmic immunophilin. The resulting cyclosporine-cyclophilin complex inhibits the activity of calcineurin, a phosphatase responsible for activating the nuclear factor of activated T lymphocytes (NF-AT). NF-AT is the primary trigger responsible for initiating the transcription of cytokines responsible for the activity of T lymphocytes. One such cytokine is interleukin (IL)-2, which acts as a potent growth factor that promotes activation and proliferation of T lymphocytes.

There are 2 forms of cyclosporine currently available in the United States: cyclosporine, USP (Sandimmune®) and cyclosporine, USP [MODIFIED] (Neoral®). Cyclosporine, USP exhibits highly variable absorption because it is dependent on bile for absorption from the gastrointestinal (GI) tract. Absorption can range from 5% to 60%, and peak concentrations are reached within 2 to 6 hours. The variations in absorption are seen between patients and also within a single patient with consecutive doses. These fluctuations lead to difficulty with dosing and maintaining adequate levels to prevent acute rejection. The microemulsion formulation of cyclosporine, USP [MODIFIED] allows the product to emulsify readily in the GI fluids, which makes the product less dependent on bile for absorption and more easily absorbed. The result is a more predictable absorption of 60% with peak concentrations being reached within 1.5 to 2 hours. Cyclosporine absorption is decreased in African American patients compared with Caucasians, regardless of the formulation.[3]

Table 1
Adverse reactions associated with maintenance immunosuppressants

	CSA	TAC	Steroids	MMF	AZA	SIR	EVL
Alopecia		X			X		
Anemia				X[a]	X[a]	X	X
Diarrhea, nausea		X		X	X	X	X
GI bleeding			X				
Gingival hyperplasia	X						
Hirsutism	X						
Hyperglycemia	X	X	X				
Hyperkalemia, hypomagnesemia	X	X					
Hyperlipidemia	X	X	X			X	X
Hypertension	X	X	X				
Hyperuricemia	X	X					
Insomnia	X	X	X				
Leukocytosis			X				
Leukopenia				X[a]	X[a]	X[a]	X[a]
Mood changes			X				
Nephrotoxicity	X[a]	X[a]				X	X
Neurotoxicity (tremors, headache)	X[a]	X[a]					
Thrombocytopenia				X[a]	X[a]	X	X
Weight gain			X				
Proteinuria						X	X

Abbreviations: AZA, Azathioprine; CSA, cyclosporine; EVL, everolimus; MMF, mycophenolate mofetil; SIR, sirolimus; TAC, tacrolimus.
[a] Indicates dose-limiting adverse effect.

Once absorbed, 90% of cyclosporine is bound to plasma lipoproteins and widely distributed into tissues and body fluids. The volume of distribution can range from 3 to 5 L/kg. Cyclosporine is metabolized in the liver by cytochrome P450 (CYP) 3A4 enzymes and acts as a substrate for *p*-glycoprotein (PGP) in the GI tract and the liver. Similar to the differences in absorption, elimination half-life also differs between the 2 cyclosporine products. Cyclosporine, USP has an average half-life of 19 hours, but can range from 10 to 27 hours because of enterohepatic recycling of the drug via bile. Cyclosporine, USP [MODIFIED], however, has a more predictable half-life that averages 8 hours and ranges from 5 to 18 hours.

Adverse effects of cyclosporine include both metabolic and cosmetic effects (see **Table 1**). The dose-limiting toxicities of cyclosporine are nephrotoxicity and neurotoxicity. Nephrotoxicity is caused by vasoconstriction of the afferent arteriole, leading to a decrease in renal vascular tone.[4] Nephrotoxicity manifests as an increase in serum creatinine concentrations and, in some cases, increases in serum potassium and decreases in serum magnesium concentrations. The renal effects are related to the dose of cyclosporine and can be reversed within the first 6 months after transplant by lowering the dose of cyclosporine in many cases.[5] However, the effects of chronic cyclosporine use on the kidney after 6 months after transplant compromise long-term

renal function in all organs and contribute to chronic allograft nephropathy (CAN) in kidney transplant recipients.[5] Nephrotoxicity of cyclosporine can be reduced by delaying administration after transplantation by using induction therapy with an IL-2 receptor antagonist or antilymphocyte globulin. Other strategies to reduce the risk of nephrotoxicity include diligent monitoring of cyclosporine concentrations, maintaining adequate hydration, and avoiding other nephrotoxic agents, such as amphotericin B, aminoglycosides, and nonsteroidal antiinflammatory agents.

Neurologic effects of cyclosporine can manifest as mild symptoms, such as tremors, headaches, insomnia, and peripheral neuropathy, but can be as severe as seizures. Neurologic toxicities are reported in 10% to 28% of patients receiving cyclosporine.[6] Similar to nephrotoxicity, the neurologic effects are related to the dose of cyclosporine and can be limited or reversed by lowering cyclosporine concentrations.

Other metabolic side effects of cyclosporine include hypertension, hyperlipidemia, and new-onset diabetes mellitus after transplant. Regimens that combine cyclosporine with steroids are associated with a higher incidence of hypertension, hyperlipidemia, and diabetes.[7,8] Hypertension is reported in as many as 80% of patients.[9] The primary mechanism by which cyclosporine causes hypertension is due to vasoconstriction of the afferent arteriole, which is accompanied by sodium and water retention.[10] The magnitude by which blood pressure increases is dependent on the dose of cyclosporine. Overall, blood pressure increases an average of 7 mm Hg in patients receiving cyclosporine, but ranges from 5 mm Hg in patients receiving low doses to 11 mm Hg in patients receiving high doses.[11] Diagnosis and treatment of hypertension are similar to those in the nontransplant population. Dihydropyridine calcium channel blockers (ie, nifedipine, amlodipine) were once considered to be the first-line drugs of choice because of their vasodilatory effects on the renal vasculature, which directly counterbalanced the effects of cyclosporine. More recent studies, however, failed to demonstrate any benefit of the calcium channel blockers over other antihypertensive agents, namely angiotensin-converting enzyme inhibitors.[12] Generally, 2 to 3 antihypertensives are necessary to adequately control blood pressure in transplant recipients.[13] Similarly, hyperlipidemia occurs in 60% to 70% of patients receiving cyclosporine.[14] The lipid profile has been correlated with cyclosporine levels.[15] Hyperlipidemia is often treated with 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors ("statins") to lower total cholesterol. Cyclosporine can cause hyperglycemia through its direct toxic effect on the islet cells of the pancreas, which decreases insulin production. However, the effects of cyclosporine on blood sugars are less pronounced than tacrolimus.[16]

Cosmetic side effects of cyclosporine can decrease the quality of life for transplant recipients. The most commonly reported cosmetic side effects associated with cyclosporine include gingival hyperplasia, acne, and hirsutism. Gingival hyperplasia is reported in 13% to 85% of transplant patients.[17] Acne is reported most commonly in adolescents, but is also common in adults.[18] Gingival hyperplasia and acne are best managed by good oral and skin hygiene, respectively. Hirsutism affects nearly 70% of patients taking cyclosporine and can be dose-related.[18]

Drug-drug interactions are common with cyclosporine because CYP 3A4 is a common pathway for many drug interactions. The most common medications known to alter cyclosporine metabolism are found in **Table 2**. The magnitude of drug interactions with cyclosporine can be profound, depending on the affinity of the co-administered drug. For example, diltiazem and erythromycin, inhibitors of CYP 3A4, can increase cyclosporine concentrations up to 82%.[19] Rifampin, on the other hand, is a potent inducer of CYP 3A4, and can decrease cyclosporine concentrations

Table 2
Common drug interactions reported with immunosuppressive agents

Cyclosporine, Tacrolimus, Sirolimus, Everolimus		Mycophenolate Mofetil, Mycophenolic Acid		Azathioprine
Increase	**Decrease**	**Increase**	**Decrease**	**Increase**
Cimetidine	Antacids (tacrolimus only)	Acyclovir	Antacids	Allopurinol
Clarithromycin	Carbamazepine	Ganciclovir	Cholestyramine	Febuxostat
Diltiazem	Cholestyramine		Cyclosporine	
Erythromycin	Phenobarbital			
Fluconazole	Phenytoin			
Grapefruit juice	Rifampin			
Itraconazole				
Ketoconazole				
Levofloxacin				
Nefazodone				
Nicardipine				
Protease inhibitors				
Voriconazole				

by 50%.[20] When possible, it is best to avoid administering drugs known to alter CYP 3A4 metabolism, although the drug interaction can easily be managed by carefully monitoring cyclosporine concentrations. Cyclosporine is also a weak inhibitor of CYP 3A4 and can alter the metabolism of weaker substrates for the enzyme, such as the case for statins, the antihyperlipidemic medications. Cyclosporine can increase statin concentrations and toxicities, such as myopathies. When statins are indicated for hyperlipidemia in patients receiving cyclosporine, the drugs should be started at the lowest dose possible and titrated slowly for effect, while carefully monitoring for toxicities associated with the statin. Simvastatin is altered to the greatest extent and should be avoided with cyclosporine.

Administering cyclosporine with food decreases the amount and extent of cyclosporine absorption. When taken within 30 minutes of a high-fat meal (45 g fat), cyclosporine absorption decreases significantly, with peak concentrations approximately one-third of the concentrations reached when taken on an empty stomach.[21] It is important that the timing of cyclosporine administration be consistent with regards to meals to maintain stable cyclosporine concentrations. Grapefruit juice is a potent inhibitor of CYP 3A4 and increases cyclosporine concentrations by up to 55%, because of furocoumarins, such as quercetin, naringin, and bergamottin.[22]

Starting doses of cyclosporine range from 8 to 18 mg/kg per day, administered every 12 hours. In general, 3-drug regimens use lower starting doses, whereas 2-drug regimens use higher starting doses. Cyclosporine can be administered intravenously (IV) at one-third of the oral dose. The IV dose can be administered intermittently every 12 hours as a slow infusion over 4 to 6 hours or the total daily dose can be administered continuously over 24 hours. Typical IV doses of cyclosporine range from 2 to 5 mg/kg per day. Higher cyclosporine doses, 2- to 4-times adult doses, ranging from 14 to 18 mg/kg per day, are required for children to account for increased metabolism of the drug. It is imperative that cyclosporine concentrations are monitored to minimize the risk of toxicity and over-immunosuppression. The target cyclosporine concentration is dependent on the assay used, the type of transplant, concomitant immunosuppression, the time after transplant, and the transplant center. High-performance liquid chromatography (HPLC) is the preferred assay for cyclosporine

because it measures only the parent compound. Target concentrations range from 100 to 300 ng/mL. Radioimmunoassay (RIA) measures both the parent compound and metabolites, resulting in target ranges approximately 20% to 25% higher than HPLC for cyclosporine levels. Peak concentration, known as C_2 monitoring, has been shown to correlate better with rejection within the first year after transplant. The suggested therapeutic range for C_2 concentrations varies based on the time after transplant: 1500 to 2000 ng/mL for the first 6 months and 700 to 900 ng/mL during months 6 to 12.[23]

Tacrolimus

Tacrolimus (Prograf®) binds to a cytoplasmic protein called FK-binding protein-12 (FKBP12). The tacrolimus-FKBP12 inhibits calineurin, similar to the cyclosporine-cyclophilin complex. The net result is the same effect as cyclosporine: inhibition of NF-AT activation of cytokine transcription, namely IL-2. Thus, tacrolimus and cyclosporine produce identical effects to disrupt the immune system and, therefore, should not be used simultaneously in the immunosuppressive regimen.

Absorption of tacrolimus is more consistent than cyclosporine, but averages only 30%. Peak concentrations are generally reached within 1 to 3 hours. Once absorbed, 99% of tacrolimus is bound to plasma proteins. The volume of distribution of tacrolimus is low, ranging from 0.8 to 1.9 L/kg. The half-life of tacrolimus ranges from 8 to 12 hours.

Akin to cyclosporine, tacrolimus has the dose-limiting side effects of nephrotoxicity and neurotoxicity (see **Table 1**). Tacrolimus also causes vasoconstriction of the afferent arteriole of the kidney, leading to the nephrotoxicity. Nephrotoxicity associated with tacrolimus also manifests with increases in serum creatinine concentrations. However, the effects of tacrolimus on the kidney result in more pronounced effects on electrolytes, namely hyperkalemia and hypomagnesemia. Similar to cyclosporine, early nephrotoxic effects can be reversed or prevented by reducing or delaying the dose of tacrolimus, but late effects are generally irreversible and can contribute to long-term renal dysfunction in all organs and CAN in kidney transplant recipients. Nephrotoxicity can be minimized by monitoring tacrolimus concentrations, maintaining adequate hydration, and avoiding administering other nephrotoxic agents.

Neurotoxicity associated with tacrolimus manifests in a similar manner to cyclosporine, ranging from tremors, insomnia, headaches, and peripheral neuropathy, to more serious seizure complications. Although the neurologic effects of tacrolimus are reported with similar frequency to cyclosporine (5–30%), the effects appear to be more pronounced and major neurologic complications are reported more frequently with tacrolimus.[6,24] Several studies also note improvement in neurologic complications after tacrolimus is switched to cyclosporine.[24,25]

The metabolic side effects of tacrolimus are similar to those of cyclosporine, but differ in incidence. Hypertension and hyperlipidemia are reported less frequently with tacrolimus-based regimens compared with cyclosporine-based regimens.[20,26] In one study, conversion from cyclosporine to tacrolimus resulted in reduction or resolution of hypertension in 59.1% of patients and hyperlipidemia in 63.5% of patients.[27] In contrast, tacrolimus appears to be associated with a higher incidence of diabetes after transplant than cyclosporine by decreasing insulin production through its direct nephrotoxic effects on the islet cells of the pancreas.[16] Treatment of diabetes after transplant involves oral hypoglycemic agents, such as sulfonylureas or insulin-sensitizing agents, or insulin, when oral agents do not provide adequate control. Decreasing tacrolimus levels does not appear to have any benefit in lowering blood glucose levels or reversing diabetes after transplant.[28] Tacrolimus is not associated

with the same cosmetic side effects as cyclosporine. In fact, studies have demonstrated improvement or reversal of cosmetic side effects, including gingival hyperplasia and hirsutism.[27,29,30] However, tacrolimus can cause alopecia.[20]

Because tacrolimus is metabolized by CYP 3A4, drug-drug interactions are the same as those seen with cyclosporine (see **Table 2**), with similar magnitude. As with cyclosporine, co-administration of drugs known to interfere with tacrolimus metabolism should be avoided when possible, or tacrolimus concentrations should be carefully monitored. Tacrolimus is also a weak inhibitor of CYP 3A4 and can increase serum concentrations of weaker substates, such as the stains, but not to the same degree as cyclosporine. One drug interaction that is unique to tacrolimus occurs with concomitant administration of medications that contain positive cations, such as calcium-, magnesium- and aluminum-containing antacids, sodium bicarbonate, and magnesium oxide. These medications bind to tacrolimus in the GI tract and decrease overall tacrolimus absorption.[31] This interaction can be easily managed by separating the dosing time of the antacids from tacrolimus by at least 2 hours. The same interaction does not occur with cyclosporine.

Comparable with cyclosporine, administration of tacrolimus with food decreases the absorption of tacrolimus. High-fat meals further decrease the rate and extent of tacrolimus absorption from the GI tract by up to 27%.[32] Consistent timing of tacrolimus administration related to meals is important to minimize fluctuations in tacrolimus concentrations. Grapefruit juice can also interact with tacrolimus via irreversible inhibition of CYP 3A4 enzymes.[22]

Initial starting doses of tacrolimus range from 0.1 to 0.3 mg/kg/d administered every 12 hours. Tacrolimus can also be administered IV as a continuous infusion over 24 hours. The IV doses are one-third the oral doses, with usual doses ranging from 0.05 to 0.1 mg/k/d. Trough tacrolimus concentrations correlate well with rejection and toxicity and should be closely monitored through the duration of therapy. Trough concentrations should be measured immediately before the next dose of tacrolimus is administered. Whole blood concentrations are generally monitored via RIA, which measures both parent drug and metabolites, or HPLC, which measures parent drug only; target ranges for tacrolimus will be lower for the latter assay. The target range for tacrolimus concentrations varies with the time after transplantation, the immunosuppressive regimen, and the transplant type. Generally, target ranges are 15 to 20 ng/mL within the first month after transplantation, 10 to 15 ng/mL for the next 3 months, and 5 to 12 ng/mL after month 3 after transplant.[20] Serum concentrations should be measured multiple times weekly immediately after transplant and can be monitored less frequently as organ function stabilizes and the time after transplant increases.

CORTICOSTEROIDS

Corticosteroids are the most widely used of all the immunosuppressants and have been used since the first solid organ transplants were performed. They continue to be a key part of the immunosuppressive regimen, even though they are associated with multiple side effects. The most commonly used corticosteroids in transplantation are methylprednisolone and prednisone.

Corticosteroids are nonspecific in their immunosuppressive action. They block multiple co-signaling cytokines that are responsible for interlymphocytic communications. Specifically, corticosteroids block the synthesis of IL-1, -2, -3, and -6, interferon-γ, and tumor necrosis factor α. As a result, corticosteroids interfere with cell migration, recognition, and cytotoxic effects.

Once absorbed, prednisone is converted to prednisolone, which has multiple effects in the body. Because prednisone is well absorbed from the GI tract and has

a long biological half-life, it is generally dosed once daily. High dose are divided multiple times throughout the day to improve patient tolerability.

Adverse effects are common with high doses of corticosteroids, affecting up to 10% of patients, and range from hyperglycemia, insomnia, mood changes, and increased appetite (see **Table 1**). Less common side effects are generally seen with prolonged doses and include cataracts, hirsutism, bruising, acne, sodium and water retention, hypertension, osteoporosis, and esophagitis. In children, corticosteroids are known to decrease growth and development, both physically and cognitively.[33]

Corticosteroids are metabolized by the CYP 3A4 enzyme system and, therefore, are subject to drug interactions. However, given that corticosteroids are either used in high doses or in combination with other immunosuppressives, the drug interactions prove to be clinically insignificant. Some drugs known to decrease corticosteroid exposure are the barbiturates phenytoin and rifampin.

During the perioperative period, high doses of corticosteroids, specifically methylprednisone, are generally given for most immunosuppressive regimens. Doses are quickly tapered over the first few days after transplant and switched to oral agents, namely prednisone or prednisolone. Once patients are receiving daily doses of corticosteroids, it is preferable to administer the doses between 7 AM and 8 AM to mimic natural circadian rhythms of cortisol release within the body. For most immunosuppressive regimens, prednisone doses are tapered progressively over the course of the next few weeks to months, depending on organ function. In many cases, corticosteroids may be withdrawn completely within the first 6 to 12 months. Most immunosuppressive regimens limit the long-term use of corticosteroids. Many protocols use a steroid-withdrawal protocol, whereby corticosteroids are withdrawn within the first 1 to 6 months after transplant. At a minimum, most protocols aim to reduce corticosteroids to physiologic doses (equivalent of prednisone 5 mg daily doses) within the first 3 to 6 months after transplantation. It is important to remember that corticosteroids should never be discontinued abruptly, but slowly tapered over the course of several days to months, depending on the duration of therapy, to avoid suppression of the hypothalamic-pituitary-adrenal axis.

Corticosteroids are also used as the first-line agents for the treatment of acute rejection. Generally, treatment consists of high doses of IV methylprednisolone, 500 to 1000 mg, administered over 1 to 3 days. High doses of oral prednisone (200 mg) have also been administered for treatment of acute rejection, which are quickly tapered over 5 to 7 days.

ANTIMETABOLITES

Similar to corticosteroids, antimetabolites have been used since the early days of transplantation to inhibit proliferation of lymphocytes. The “gold standard” of immunosuppressive regimens has included azathioprine, along with corticosteroids and cyclosporine. However, it is recognized more recently that the newer agents have increased efficacy over this traditional regimen. Today, newer antimetabolite agents, such as mycophenolic acid, continue to be a key part of the immunosuppressive regimen.

Mycophenolate Mofetil and Mycophenolate Sodium

Mycophenolic acid (MPA) was fist isolated from the *Penicillin glaucum* mold. Currently, there are 2 formulations of MPA available: mycophenolate mofetil (Cellcept®), which is a pro-drug of MPA, commercially available as mycophenolate sodium, an enteric-coated, delayed release formulation (Myfortic®).

MPA exerts its immunosuppressive effect by inhibiting inosine monophosphate dehydrogenase (IMPDH), an enzyme responsible for the synthesis of the nucleotide guanosine. This enzyme is only used in the de novo pathway of nucleotide synthesis. Inhibition of IMPDH results in a reduction of DNA polymerase activity, which decreases lymphocyte proliferation. It is important to note that T and B lymphocytes depend only on the de novo pathway for nucleotide synthesis and do not have a salvage pathway to produce guanosine, unlike most other cells within the body. This makes MPA very specific in its actions, targeting primarily T and B lymphocytes, which decreases its overall effects on other cells in the body, thereby decreasing side effects to a great extent.

Mycophenolate mofetil serves as a pro-drug that helps to overcome degradation of MPA in the acid environment of the stomach. Mycophenolate mofetil is readily absorbed from the GI tract and is rapidly converted to MPA by first-pass metabolism. Absolute bioavailability of mycophenolate mofetil is 94%, and MPA concentrations reach peak levels within 1 hour after the dose of mycophenolate mofetil is administered. The commercially available mycophenolic acid formulation is enteric-coated to protect the drug from the acidic pH in the stomach and is absorbed from the upper portion of the small intestines. The absolute bioavailability of MPA is somewhat less than mycophenolate mofetil at 72%. Once absorbed, 97% of MPA is bound to albumin in the bloodstream. The volume of distribution of MPA is approximately 4 L/kg. The drug undergoes glucuronidation in the liver to form an inactive metabolite, mycophenolic acid glucuronide (MPAG). The half-life of MPA is 18 hours.

The most common adverse effects of MPA are related to its direct antiproliferative effects on the GI tract, leading to nausea, vomiting, abdominal pain, and diarrhea (see **Table 1**). Decreasing the dose or dividing the dose over more frequent dosing intervals (ie, 3 to 4 doses daily) can decrease the GI side effects associated with MPA. High doses of MPA can suppress the bone marrow, leading to leukopenia, thrombocytopenia, and anemia. It is important to note that because MPA alters DNA synthesis through inhibition of nucleotide synthesis, MPA is teratogenic and should be avoided in patients who are pregnant. The Pregnancy Category of MPA was recently changed to Category D, indicating the risks outweigh benefits of taking the drug.

Co-administration of magnesium- or aluminum-containing antacids or cholestyramine can decrease the absorption of MPA (see **Table 2**). To avoid this drug interaction, doses should be separated by at least 2 hours from the MPA dose. Acyclovir, and presumably ganciclovir, competes with tubular secretion of MPAG, which can then be recycled back into the bloodstream, thereby increasing the immunosuppressive effects and toxicities associated with MPA. Cyclosporine can interfere with the enterohepatic recirculation of MPAG, decreasing MPA concentrations.[34] It may be necessary to administer higher doses of MPA with cyclosporine-based regimens, compared with tacrolimus. Conversely, tacrolimus-MPA–based regimens may be associated with more MPA toxicity, namely GI-related reactions.

Food can affect the time to reach peak concentrations and time to elimination of the drug. As a result, overall exposure to MPA, reflected as the area-under-the-curve (AUC), is unaltered when MPA is administered with food. Therefore, patients experiencing GI-related side effects may be told to take MPA with food to increase tolerability.

Mycophenolate mofetil is available in multiple formulations, including oral capsules and tablets, an oral suspension, and an IV formulation. Although the two are not considered to be bioequivalent, oral and IV doses can be administered at the same doses.[35] Mycophenolate sodium is only available in oral tablets. Doses of MPA are

based on the type of organ transplant. Cardiac transplantation generally requires a higher degree of immunosuppression, warranting higher starting doses of MPA. Starting doses of mycophenolate mofetil are 1500 mg twice daily for cardiac transplants and 1000 mg twice daily for all other organ transplants. Because mycophenolate sodium does not contain the mofetil ester, starting doses are smaller at 1440 mg twice daily for cardiac transplants and 720 mg twice daily for all other transplants. Plasma MPA concentrations can be measured, although the clinical utility is somewhat debatable. Monitoring AUC levels, which requires measurement of 2 to 4 sequential MPA concentrations, correlates best with rejection, but not with toxicity.[36] The reported reference range for MPA AUC levels is 30 to 60 mcg/mL/h.[37] Trough MPA concentrations do not correlate well with rejection, but are the most commonly use method to monitor MPA because of the ease of blood sampling for a single measurement.[36]

Azathioprine

Azathioprine itself is an inactive compound that must be converted to 6-mercaptopurine (6-MP) in the blood. 6-MP is metabolized by hypoxanthine-guanine phosphoribosyltransferase to active metabolites, 6-thioguanine nucleotides (TGNs). TGNs are incorporated into the nucleic acids, which block both the de novo and salvage pathways of nucleic acid synthesis. Ultimately, azathioprine disrupts DNA, RNA, and protein synthesis within the cell, thereby blocking cell proliferation.

Azathioprine is well absorbed after oral dosing and approximately 47% is converted to 6-MP after absorption. Protein binding is approximately 30% for both azathioprine and 6-MP. The volume of distribution of azathioprine is 0.8 L/kg. 6-MP is metabolized by xanthine oxidase (XO), found in the liver and GI tract, to the final end product, 6-thiouric acid, which is excreted by the kidneys. The half-life of azathioprine, the parent compound, is 3 hours, whereas the half-life of 6-MP is approximately 60 to 90 minutes. However, the active metabolites, the TGNs, have a much longer half-life, estimated to be up to 9 days.[38]

The adverse effects of azathioprine are related to the disruption of both the de novo and salvage pathways of nucleotide production. The resulting effects on DNA, RNA, and protein synthesis are evident in all cells within the body and are not limited to T and B lymphocytes. The dose-limiting toxicity is bone marrow suppression, which is related to the dose of azathioprine (see **Table 1**). Other adverse reactions reported to azathioprine result from its effects on blocking proliferation of other cells. Nausea, vomiting, and abdominal pain result from the effects of azathioprine on cells in the GI tract. Similarly, azathioprine affects hair follicles and can cause alopecia. Hepatotoxicity and pancreatitis are reported less commonly with azathioprine. The occurrence of all adverse effects is related to the dose of azathioprine and is reversible by lowering or discontinuing the drug. Because azathioprine disrupts cell proliferation of many cell lines, it is teratogenic (Pregnancy Category D) and its use should be avoided in pregnant women.

The most significant drug interaction with azathioprine occurs with drugs that inhibit the activity of XO, namely allopurinol and febuxostat (see **Table 2**). Allopurinol can increase azathioprine and 6-MP concentrations by as much as 4-fold.[39] Blocking XO shifts the metabolism of azathioprine and 6-MP to favor production of TGNs, the pharmacologically active metabolites which, in turn, increases suppression of cell proliferation. The net result is increased bone marrow suppression and pancytopenia.[39] When allopurinol or febuxostat are co-administered with azathioprine, the dose of azathioprine should be reduced by 50% to 75% to avoid toxicities. Other drug interactions with azathioprine result from administration of drugs with overlapping

bone marrow suppression or GI toxicities, such as sulfamethoxazole-trimethoprim, ganciclovir, and sirolimus.

Initial starting doses of azathioprine are 3 to 5 mg/kg administered as a single daily dose. Therapeutic drug monitoring does not target azathioprine or 6-MP concentrations, but rather the dose-limiting toxicity of blood cell production, namely white blood cell (WBC) count. The goal for azathioprine therapy is to maintain the WBC count between 3500 and 6000 cells/mm^3. When initiating therapy, WBC count should be monitored frequently to avoid oversuppression of the bone marrow. Thus, patients are usually instructed to take azathioprine doses in the evening to allow for dose adjustments based on WBC counts.

PROLIFERATION SIGNAL INHIBITORS

The newest class of immunosuppressive agents, also known as mTOR inhibitors, targets the mammalian target of rapamycin (mTOR). These agents are often used as adjunctive therapy to reduce the dose of calcineurin inhibitors in an attempt to spare the long-term renal effects.

Sirolimus

The first Federal Drug Administration–approved agent in the class of mTOR inhibitors is sirolimus (Rapamune®), also known as rapamycin. Sirolimus is an immunosuppressive macrolide antibiotic that is structurally similar to tacrolimus. Resembling tacrolimus, sirolimus binds to FKBP12. However, the resulting sirolimus-FKBP12 complex does not inhibit calcineurin and cytokine production. Instead the complex binds to a regulatory kinase, mTOR, which inhibits the cellular response to cytokines. Specifically, sirolimus inhibits stimulation of mTOR by IL-2, IL-4, and IL-15, preventing activation of kinases that advance the cell cycle from the G_1 to the S phase. Therefore, the ultimate action of sirolimus is to inhibit cytokine-mediated progression of the cell cycle in response to IL-2, thereby inhibiting T-lymphocyte proliferation.

Sirolimus is poorly absorbed from the GI tract, with only 27% bioavailability with the tablet formulation and 15% bioavailability with the oral solution. Peak concentrations are reached within 1 to 2 hours after oral administration. After absorption, 92% of sirolimus is bound to plasma proteins. Sirolimus is widely distributed in the body because of the presence of FKBP12 in red blood cells (RBCs), resulting in a volume of distribution of 12 L/kg. Similar to tacrolimus, sirolimus is also metabolized in the liver and GI tract by the CYP 3A4 enzyme system and PGP. However, the half-life of sirolimus is much longer, approximately 62 hours. In patients with liver dysfunction, the half-life can be as long as 110 hours.[40]

Thrombocytopenia is evident within the first 2 weeks starting sirolimus therapy but improves as treatment is continued (see **Table 1**). Leukopenia and anemia may be transient.[41] Bone marrow suppression appears to be dose related as thrombocytopenia and leukopenia correlate with sirolimus concentrations above 15 ng/mL.[42] Sirolimus is associated with dyslipidemia, specifically hypercholesterolemia and hypertriglyceridemia. The mechanism may be related to an overproduction of lipoproteins or inhibition of lipoprotein lipase.[43] Cholesterol and triglyceride levels peak within the first 3 months after starting sirolimus, but decrease after 1 year of therapy. Hyperlipidemia can be managed by decreasing the dose or discontinuing sirolimus, or starting a statin or fibric acid derivative. Despite the high levels of cholesterol and triglycerides, this does not appear to be a major risk factor for cardiovascular complications within the first year of transplant.[43] Sirolimus causes proteinuria, which appears to be dose-related.[44] There are conflicting reports about the significance of the proteinuria causing kidney damage. Angiotensin converting

enzyme (ACE) inhibitors may help to control sirolimus-induced proteinuria.[44] Sirolimus inhibits smooth muscle proliferation and intimal thickening, which prolongs wound healing and can lead to wound dehiscence.[45] Mouth ulcers are reported more commonly with sirolimus oral solution, although they can occur with the tablet formulation as well, and may be the result of herpes simplex reactivation.[46] Reversible interstitial pneumonitis has been described.[40] Other adverse effects that have been reported with sirolimus include increased liver enzymes, hypertension, rash, diarrhea, acne, and arthralgias. The combination of sirolimus and a calcineurin inhibitor may have a synergistic effect on nephrotoxicity early after kidney transplant.[47]

Because of CYP 3A4 metabolism, sirolimus is prone to numerous drug interactions, comparable with cyclosporine and tacrolimus (see **Table 2**). Cyclosporine increases sirolimus concentrations; conversely, sirolimus also increases cyclosporine concentrations because of competitive inhibition of CYP 3A4 and PGP. The doses of each drug should be separated by at least 4 hours, and lower doses of each should be used to avoid toxicities of both drugs. Tacrolimus does not produce the same results.

Food decreases sirolimus absorption, particularly when administered with a high-fat meal. Total sirolimus exposure is reduced by 23% to 35% after a high-fat meal. Grapefruit juice also inhibits the metabolism of sirolimus, leading to increased concentrations.

Sirolimus is approved with a fixed-dose regimen, using a 6-mg or 15-mg loading dose, followed by 2 mg or 5 mg, respectively. However, therapeutic drug monitoring is advocated to maintain adequate immunosuppression and avoid toxicities. Sirolimus concentrations should be measured in whole blood using HPCL, which measures the parent compound only. Target levels are 10 to 15 ng/mL when used in combination with a calcineurin inhibitor, or 15 to 20 ng/mL when not used in combination with a calcineurin inhibitor. RIA, which measures both parent compound and metabolites, can also be used to measure sirolimus concentrations, but higher target levels should be used with reference ranges of 15 to 20 ng/mL and 20 to 30 ng/mL, respectively.

Everolimus

Everolimus (Zortress®) is a new immunosuppressive agent approved in the United States, although it has been available for several years in Europe. Resembling sirolimus, everolimus binds to FKBP12 to form a complex that binds to mTOR, preventing IL-2–mediated T-lymphocyte proliferation. Approximately 74% of the drug is bound to plasma proteins after oral absorption. The volume of distribution is variable in kidney transplant recipients, ranging from 107 to 342 L, likely reflecting distribution to FKBP12 receptors in RBC. Everolimus is metabolized by CYP 3A4 and PGP in the GI tract and liver. The half-life of everolimus appears to be shorter than sirolimus at 30 hours.

Adverse reactions reported with everolimus appear to be similar to sirolimus. Everolimus delays wound healing because of the antiproliferative effects on smooth muscle. Hyperlipidemia is also common with everolimus. Everolimus also causes proteinuria, which has been reported to increase the incidence of nephrotoxicity in cyclosporine-based regimens. Leukopenia, anemia, and thrombocytopenia are reported, although there are no data to compare the incidence with sirolimus. Other adverse reactions reported with everolimus include peripheral edema, constipation, hypertension, nausea, and urinary tract infections.[48]

Drug interactions with everolimus are similar to those seen with cyclosporine, tacrolimus, and sirolimus. Single dose studies indicate everolimus concentrations are increased by concomitant administration of cyclosporine, ketoconazole, erythromycin,

and verapamil, whereas rifampin decreases everolimus concentrations. Grapefruit juice also increases everolimus concentrations, whereas a high-fat meal decreases concentrations by 60%.[48]

Everolimus therapy should be initiated at 0.75 mg twice daily. Doses should be adjusted to maintain trough concentrations between 3 and 8 ng/mL.[49]

Belatacept

Belatacept (Nulojix®) is the newest immunosuppressive agent approved in the United States. Unlike the other maintenance immunosuppressants, which are oral medications, belatacept is an IV medication. Belatacept is a costimulation blocker that binds to CD80 and CD86 ligands found on antigen presenting cells (APCs). Blockade of CD80 and CD86 prevents interaction with the CD28 receptor, a critical costimulatory receptor found on T lymphocytes responsible for activation of naïve T lymphocytes after presentation of antigens via APCs.[50] Such T lymphocytes that do not receive a costimulatory signal become anergic and undergoes apoptosis.[51]

Side effects of belatacept include anemia, diarrhea, peripheral edema, hypertension, dyslipidemia, potassium abnormalities, and leukopenia. The most serious adverse effect associated with belatacept is post-transplant lymphoproliferative disorder (PTLD), seen most commonly in patients without immunity to Epstein-Barr virus (EBV).[52] Belatacept is contraindicated in patients who are EBV seronegative. Progressive multifactoral leukoencephalopathy (PML) has also been reported in clinical trials with belatacept. The starting dose of belatacept is 10 mg/kg on the day of transplantation, 4 days after transplantation, and 2, 4, 8 and 12 weeks after transplantation. Beginning 16 weeks after the transplant, maintenance doses of 5 mg/kg should be administered every 4 weeks. Basiliximab should be given as induction therapy before starting maintenance therapy with belatacept in combination with mycophenolate mofetil and prednisone. Belatacept may have a role in preserving kidney function in kidney transplant patients who are at risk for chronic allograft nephropathy.[52]

LYMPHOCYTE-DEPLETING AGENTS

Certain polyclonal and monoclonal antibodies that target T or B lymphocytes can cause lymphocyte depletion of one or both cell lines. These agents are useful for induction therapy administered before transplantation to provide a high degree of immunosuppression at the time of transplantation or as treatment for acute cellular rejection to reverse the effects of the activated immune system on the transplanted organ.

Antithymocyte Globulin

The antithymocyte globulins are polyclonal antibodies that target thymocytes (T cells). The 2 currently available preparations are ATG (ATGAM®), an equine preparation, and RATG (Thymoglobulin®), a rabbit preparation. Because the rabbit preparation is more potent than ATG and better tolerated because of lower immunogenicity, it is the primary agent used today for transplantation.[53] The products are prepared by injecting human T lymphocytes into an animal medium (horses for ATG and rabbits for RATG). The animals produce an immunologic response to the human cells, generating antibodies directed at antigens expressed on the human T lymphocytes. The antibodies are removed from the serum of the animals, purified, and pasteurized into the respective products for use in humans. The result is a polyclonal antibody product that targets a number of receptors found on lymphocytes, including CD2, CD3, CD4,

CD8, CD25, and CD45, as well as others. Upon binding to the various receptors, the drugs cause a complement-mediated cell lysis, which ultimately results in lymphocyte depletion. Damaged T lymphocytes are subsequently removed by the spleen, liver, and lungs. Because some of the target receptors are not exclusive to T lymphocytes, other cells are also affected by administration of the antithymocyte globulins, including B lymphocytes, WBC, RBC, and platelets.

Both ATG and RATG bind primarily to circulating T lymphocytes in the bloodstream and are poorly distributed into lymphoid tissue in the body. The volume of distribution for RATG is 0.12 L/kg. The terminal half-life differs for the 2 products: 5.7 days for ATG and 30 days for RATG. Antibodies can form to the animal serum after administration of these products. Antiequine antibodies form in 78% of patients receiving ATG, and antirabbit antibodies form in 68% of patients receiving RATG. The clinical significance of the respective antibodies is not well understood.

The side effects of ATG and RATG are related to the lack of specificity of the polyclonal antibodies for T lymphocytes. Pancytopenia can occur after therapy because of direct lysis of the other circulating blood cells. This often limits the number of doses and duration of therapy for these products. Other side effects are related to the immune reaction that occurs with the infusion of the antibody products that can result in anaphylaxis or severe cytokine-release syndrome, manifesting as fever, hypotension, hypertension, tachycardia, dyspnea, urticaria, and rash. Patients must be monitored closely when receiving ATG or RATG throughout the infusion. A rapid rate of infusion is associated with a higher incidence of cytokine-release syndrome and severe reactions. The infusion-related reactions can be minimized or prevented by administering acetaminophen, diphenhydramine, and corticosteroids before starting the infusion. Serum sickness can occur after administration of ATG because of the equine nature of the product; serum sickness can also occur with RATG but is rare.

The immune response to live vaccines can be altered by the administration of ATG and RATG. Live vaccines should be avoided within 2 months of receiving either product, if possible.

Both ATG and RATG are available as IV formulations only. The dosing of ATG is 10 to 30 mg/kg per day as a single dose. RATG is administered at doses of 1 to 1.5 mg/kg per day as a single dose. The duration of therapy depends on the indication of the product. Induction therapy generally involves 5 to 7 days of therapy, whereas treatment of acute cellular rejection requires 7 to 14 days of therapy. Premedication with acetaminophen, diphenhydramine, and corticosteroids should be administered 30 to 60 minutes before each dose of ATG or RATG. Both products should be administered via central line or high-flow vein whenever possible. RATG has been administered peripherally with the addition of hydrocortisone (20 mg) and heparin (1000 U) to reduce the risk of phlebitis and thrombosis.[54]

Alemtuzumab

Alemtuzumab (Campath-1H®) is a humanized monoclonal antibody directed against CD52, produced through recombinant DNA technology in Chinese hamster ovary cells. The CD52 target is found on several immune cells, including T and B lymphocytes, macrophages, monocytes, eosinophils, and natural killer cells. Alemtuzumab is approved for use in B-lymphocyte chronic lymphocytic leukemia (B-CLL), but is also used for solid organ transplantation. Upon binding to the CD52 receptor, alemtuzumab binds to T and B lymphocytes in the blood, bone marrow, lymphatic system, and organs, causing rapid, complete, and long-lasting lymphocyte depletion.

B lymphocytes return within a few months, but T lymphocytes do not fully recover for 1 to 3 years after alemtuzumab therapy.[55]

Although the pharmacokinetics of alemtuzumab has not been formally studied in solid organ transplantation, data from its use in B-CLL indicate that the volume of distribution is 0.18 L/kg after repeated dosing. The half-life is reported as 11 hours after the first 30-mg dose after rapid dose escalation. The same pharmacokinetic parameters may not apply to solid organ transplantation, however, as the dosing strategies are different for the 2 indications.

Adverse effects associated with alemtuzumab include severe infusion-related reactions, which manifest as rigors, hypotension, fever, dyspnea, brochospasms, and chills. Administration of acetaminophen, diphenhydramine, and corticosteroids helps to lessen, although not completely eliminate, these effects. Hematologic reactions, including neutropenia, lymphopenia, thrombocytopenia, and anemia, are reported frequently with alemtuzumab.

Alemtuzumab is most commonly administered as a single 30-mg dose in solid organ transplantation, without dose escalation, IV over 2 hours. The same dose is used for both induction therapy and for treatment of acute cellular rejection. Other dosing strategies that have been used in solid organ transplantation include 0.3 mg/kg per dose for one or more doses, and two 20-mg doses administered on the day of transplant and the first postoperative day.[56]

Acetaminophen, diphenhydramine, and corticosteroids must be administered 30 to 60 minutes before infusion. Vital signs must be closely monitored immediately after the infusion.

Muromonab-CD3

Muromonab-CD3, also known as OKT3 (Orthoclone OKT3®), was the first monoclonal antibody approved for use in the United States. OKT3 targets the CD3 receptor found exclusively on mature T lymphocytes. The antibody is a murine-derived antibody that causes complete and rapid T-lymphocyte lysis and depletion. Because of its potency and specificity for T lymphocytes, OKT3 was used extensively as induction therapy and as treatment of allograft rejection. However, OKT3 is associated with significant side effects due to the profound cytokine release, which led to fever, chills, rigors, pruritus, and alterations in blood pressure, capillary leak syndrome and pulmonary edema.[57] The effects were most pronounced with the first dose, and were best managed by prophylactic administration of acetaminophen, diphenhydramine, and corticosteroids before OKT3. With the discovery of newer antibodies that were better tolerated and resulted in equivalent or better outcomes, OKT3 eventually became the last-line treatment for resistant rejection episodes. Because use of OKT3 declined, the manufacturer discontinued the drug from the market in 2010.

NON-LYMPHOCYTE–DEPLETING ANTIBODIES

Basiliximab

Basiliximab (Simulect) is a chimeric, murine-derived, monoclonal antibody directed at CD25, expressed on activated T lymphocytes. Daclizumab (Zenapax) is a similar drug with a humanized chimeric structure in the same class, known as IL-2 receptor antagonists, but was removed from the market in 2009. Both drugs exert the same mechanism of action. Upon binding to the receptor, basiliximab competitively blocks IL-2 to prevent activation and proliferation of T lymphocytes. Basiliximab has a volume of distribution of 8 L and saturates CD25 immediately after administration. The terminal half-life of basiliximab is approximately 7 days. Liver transplant recipients may require an additional dose of basiliximab if more than 10 L of ascites is removed

after transplantation because clearance of basiliximab is increased with drainage of ascites.[58]

Few adverse reactions have been reported with the IL-2 receptor antagonists. Basiliximab is not associated infusion-related reactions, unlike the depleting antibodies. The dose of basiliximab is a fixed dose of 20 mg administered intravenously on the day of transplant and 4 days after transplant. The dose is administered as a slow infusion over 20 to 30 minutes.

INVESTIGATIONAL AGENTS FOR SOLID ORGAN TRANSPLANTATION

Bortezomib

Bortezomib is a proteosomal inhibitor currently approved for use in multiple myeloma marketed as Velcade. Bortezomib binds to the 26S proteosome responsible for degradation of regulatory molecules critical for various cellular mechanisms, including protein synthesis, cell cycle, transcription and signaling, immune response, and antigen presentation. The result is arrest of the cell cycle and subsequent apoptosis. Bortezomib appears to have a specific effect on antibody-producing plasma cells and has been used in solid organ transplantation for the treatment of antibody-mediated rejection and reduction of donor-specific antibody (DSA) levels.[59] The most commonly reported side effects of bortezomib include GI effects and thrombocytopenia. Paresthesias have been reported rarely.

Rituximab

Rituximab (Rituxan) is a humanized monoclonal antibody against the CD20 receptor found on B lymphocytes. Rituximab is currently approved for CD20-positive non-Hodgkins lymphoma, CD20-positive CLL, and rheumatoid arthritis. Upon binding to the CD20 receptor, rituximab induced complement-mediated B lymphocyte lysis. Rituximab has been used in transplantation for treatment of CD20-positive PTLD, antibody-mediated rejection, and reduction of DSA before transplantation.[60–62] Adverse reactions include infusion-related reactions resulting in urticaria, hypotension, angioedema, bronchospasm, pulmonary edema, and anaphylaxis.

SUMMARY

The multitude of immunosuppressants available for solid organ transplantation allows for many combinations of immunosuppressive therapies that can be tailored to a patient's specific lifestyle and immunosuppression needs. Newer agents currently being studied offer even more possibilities for the future to further reduce the incidence of acute rejection and prolong graft and patient survival.

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