Immunosuppressive Medications 154

Donald Berry and Brian Feingold

Abstract

Immunosuppression following pediatric thoracic transplantation is typically centered on the use of calcineurin inhibitors, either cyclosporine or tacrolimus. While there is general agreement on the use of immunosuppressive medications for induction therapy, maintenance immunosuppression, and treatment of acute rejection, there is center-to-center variability with respect to target trough levels, changes in targets over time following transplantation, and selection and use of adjunctive immunosuppressive agents. In this chapter, the medications and therapies used to care for pediatric heart and lung transplant recipients are reviewed and discussed.

Keywords

Alemtuzumab • Antithymocyte globulin • Azathioprine • Basiliximab • Bortezomib • Calcineurin inhibitor • Corticosteroids • Cyclosporine • Everolimus • Heart transplantation • Intravenous immunoglobulin (IVIG) • Lung transplantation • Methylprednisolone • mTOR • Mycophenolic acid • Mycophenolate mofetil • Tacrolimus • Pediatric • Prednisone • Rituximab • Sirolimus

D. Berry (✉)
Clinical Pharmacy Specialist, Cardiac Intensive Care, Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA
e-mail: donald.berry@chp.edu

B. Feingold
Heart Failure and Cardiac Transplantation, Children's Hospital of Pittsburgh of UPMC, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA
e-mail: Brian.Feingold@chp.edu

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Introduction

Various immunosuppressive medication regimens exist for patients after thoracic organ transplantation. Essentially, all have in common the use of a calcineurin inhibitor (i.e., cyclosporine, tacrolimus) as the primary immunosuppressant. Most regimens in children also utilize an adjunctive immunosuppressant agent, such as mycophenolate mofetil, azathioprine, or sirolimus. Corticosteroids are also commonly used after thoracic organ transplantation, with a dual role as a chronic immunosuppressant in many recipients but also as a treatment for acute rejection. Other therapies, such as pooled gamma globulin (IVIG) or other targeted antibody preparations, proteasome inhibitors, and plasmapheresis, play specialized roles in the management of the thoracic organ recipient.

In this chapter, the medications and therapies used to care for pediatric heart and lung transplant recipients are reviewed. Agents are discussed by class, rather than by timing of introduction to the posttransplant care regimen; however, details about typical use and relative differences in use according to common clinical scenarios are discussed. This chapter is not intended to be a comprehensive guide to transplant-related immunosuppressive medications, but rather a clinically relevant discussion of drugs, principles of usage, doses, drug interactions, and side effects. Also, because the pediatric thoracic organ experience is much smaller than experience in adults and because thoracic organ transplantation is less common than renal and liver transplantation, much of the evidence for how these medications are used is derived from outside of the pediatric and thoracic organ recipient populations.

Calcineurin Inhibitors

The success of modern-day solid organ transplantation stems directly from the introduction of the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus [1, 2]. Whereas prior to the use of CNIs, the standard end points of clinical trials in organ transplantation were 1-year recipient and allograft survival, in the current era median heart transplant recipient survival is between 12 and 18 years [3]. These drugs are the cornerstone of nearly all posttransplant immunosuppressive regimens; the exception being late posttransplant regimens in which the toxicities of chronic CNI exposure, mainly renal insufficiency, are thought to pose a greater risk than acute allograft rejection. In these instances, low-dose CNI regimens or complete CNI-withdrawal regimens may be implemented [4–6].

CNIs block intracellular T-lymphocyte signaling, resulting in decreased T-lymphocyte activation [7]. It is important to note that in any one patient, either cyclosporine *or* tacrolimus is used, never both. Since late posttransplant graft survival rates are equivalent, the decision on whether to use one or the other is usually driven by transplant center preference. Occasionally, patients are switched from cyclosporine to tacrolimus because of its association with lower rates of hypertension and hyperlipidemia [8]. Cyclosporine is also associated with gingival hyperplasia, hirsutism, and coarsening of facial features, effects not seen with tacrolimus. Patients may be switched from tacrolimus to cyclosporine because of side effects such as posttransplant diabetes or neurological symptoms which are probably more common with tacrolimus [9].

CNIs are initiated early after transplantation, usually hours to days following transplant surgery, though the use of intravenous formulations is uncommon because of the high risk of acute renal failure. Dosing is monitored and adjusted according to trough blood plasma levels obtained at the end of the dosing interval (i.e., just before the next scheduled dose is taken). Targeted plasma levels are highest early after transplantation and are decreased over time, in the absence of acute rejection and in accordance with institutional protocol. Late posttransplant drug levels are often 30–40 % of the early posttransplant targets.

Cyclosporine

Dosing

If cyclosporine therapy is initially begun with IV dosing, 3–5 mg/kg/day is given either as a continuous infusion over 24 h or in two divided doses. The dose should be adjusted based on serum levels, and enteral dosing should be initiated as soon as feasible. Note that the oral dosage for cyclosporine is approximately three times the IV dosage.

For oral initiation of cyclosporine, 10–15 mg/kg daily divided in two daily doses is often used. Again, dosing should be based on serum levels. Oral dosage forms are available as both modified and non-modified formulations, which cannot be used interchangeably. The modified cyclosporine has increased bioavailability over the non-modified form. If the dosage forms are changed, close monitoring of cyclosporine levels must be performed. Liquid formulations have dosage form and brand specific administration directions (diluents, mixing, glass containers only), so the manufacturers recommendations should be reviewed and followed.

Pharmacokinetics

Cyclosporine is incompletely and erratically absorbed when given orally and undergoes a large first-pass metabolism. The bioavailability of Sandimmune® capsules and the oral solution (non-modified) is approximately 28 % in children. Currently, almost all children receive microemulsion (modified) formulations, such as Neoral® capsules and oral solution, which have a bioavailability averaging 43 % in children, ranging from 30 % to 68 %. Cyclosporine is extensively metabolized in the liver by CYP3A4 enzymes. Clearance is affected by age, with pediatric patients clearing cyclosporine more rapidly than adults. The half-life of cyclosporine is 7–19 h in children and 19–40 h in adults. Metabolites are excreted primarily through the bile into feces [10].

Early posttransplant, heart transplant recipient serum levels are often targeted around 300 ng/mL. After 4–6 months this may be decreased to 250 ng/mL and weaned thereafter to a target of 50–100 ng/mL years after transplantation in the setting of a benign rejection history. Lung and heart-lung transplant recipients are often maintained at target levels that are 50 ng/mL higher than heart transplant recipients.

Drug-Drug Interactions

Cyclosporine is involved in many drug interactions. Perhaps most significant is the interaction with "azole" antifungals that inhibit metabolism of cyclosporine, requiring a dose reduction of at least 50 % with fluconazole and 75 % with voriconazole. Grapefruit juice may also increase cyclosporine blood concentrations and should be avoided. Other commonly used drugs that can increase cyclosporine concentrations include acyclovir, aminoglycosides, amphotericin B, erythromycin, metoclopramide, ketoconazole, diltiazem, verapamil, methylprednisolone, lovastatin, simvastatin, and cimetidine. St. John's Wort should also be avoided as it may significantly decrease cyclosporine concentrations. Phenytoin, phenobarbital, carbamazepine, rifampin, trimethoprim, and nafcillin decrease cyclosporine concentration by increasing hepatic metabolism. There is an increased risk of hyperkalemia when potassium-sparing diuretics are used concomitantly. Nonsteroidal antiinflammatory drugs (NSAIDs) increase the risk of nephrotoxicity when administered with cyclosporine, and sirolimus used in combination with cyclosporine has been associated with hemolytic uremic syndrome. Digoxin may undergo reduced clearance when used with cyclosporine and should be monitored closely. Lovastatin, simvastatin, and atorvastatin should be avoided due to reduced metabolism when used with cyclosporine. Pravastatin or rosuvastatin may be used in low doses with close monitoring.

Adverse Effects

The principal adverse reactions to cyclosporine therapy include renal dysfunction, hypertension, hyperkalemia, tremor, hyperlipidemia, and gingival hyperplasia. Nephrotoxicity occurs in the majority of patients on long-term therapy.

Hypertension, tachycardia, flushing, headaches, seizure, tremor, paresthesias, and insomnia may occur. Patients may also develop, hypomagnesemia, hyperuricemia, abdominal discomfort, nausea, diarrhea, hepatotoxicity, and hirsutism. Blood/serum drug concentration (trough), renal and hepatic function, serum electrolytes, lipid profile, blood pressure, and heart rate should be monitored periodically while the patient is taking cyclosporine. As with all potent immunosuppressants, opportunistic infections and posttransplant lymphoproliferative disorders may occur.

Tacrolimus

Dosing

Nearly all patients are maintained on twice daily tacrolimus. The starting oral dose is 0.1–0.2 mg/kg/day in divided doses every 12 h. An extended release formulation, which is not approved by the US FDA, has been evaluated in a few small studies in liver and kidney transplant recipients. In these limited assessments, no increase in rejection events has been reported [11, 12]. One potential benefit of this formulation would be enhanced adherence.

Initially, if oral intake is not tolerated, an IV continuous infusion of 0.02–0.05 mg/kg/day may be used in children [13]. When switching to oral therapy, it is important to remember the oral dose should be 3–4 times the IV dose. However, since IV use may lead to decreased urine output after cardiopulmonary bypass, IV tacrolimus is rarely used. More commonly, induction therapy with T-cell-depleting antibodies is used, allowing for delayed introduction of tacrolimus orally.

Pharmacokinetics

The oral bioavailability of tacrolimus has a large range of 5–67 %, with an average of 30 %. Administration with food reduces absorption by an average of 33 %. Tacrolimus is hepatically metabolized by CYP3A4 enzymes. Plasma protein binding ranges from 75 % to 99 %. Tacrolimus has an average half-life of 8.7 h, ranging from 4 to 40 h. Pediatric patients clear the drug twice as rapidly as adults and require higher doses on a milligram per kilogram basis to achieve similar blood concentrations. Tacrolimus is primarily eliminated in bile, with less than 1 % excreted as unchanged drug in urine [10].

Early posttransplant, heart transplant recipients are often targeted around 10–12 ng/mL. After 4–6 months this may be decreased to 8 ng/mL and weaned thereafter to a target of 5–7 ng/mL years after transplantation in the setting of a benign rejection history. Lung and heart-lung transplant recipients are often maintained at target levels that are 2–3 ng/mL higher than heart transplant recipients.

Drug-Drug Interactions

Diltiazem, verapamil, nifedipine, fluconazole, itraconazole, ketoconazole, cimetidine, clarithromycin, erythromycin, methylprednisolone, protease inhibitors, and oral clotrimazole increase tacrolimus serum concentrations. Drugs that decrease tacrolimus serum concentrations include antacids, cholestyramine, sodium polystyrene sulfonate, carbamazepine, phenobarbital, primidone, phenytoin, rifabutin, rifampin, and St. John's Wort. NSAIDS, nephrotoxic antibiotics, and amphotericin B may cause additive nephrotoxicity when administered with tacrolimus. Tacrolimus should not be used in combination with cyclosporine.

Adverse Effects

Common adverse effects from tacrolimus therapy are neurotoxicity (tremor, headache, paresthesias), hyperglycemia (more common when used with corticosteroids), and hypomagnesemia. Patients may also experience GI symptoms such as diarrhea, nausea, vomiting, and constipation or less common neurological symptoms of insomnia, dizziness and seizures. Other potential side effects include hypertension, QT interval prolongation, hyperkalemia, alopecia, pruritus, and rash. Serious adverse effects of tacrolimus that can be seen are opportunistic infections, posttransplant lymphoproliferative disorder, and diabetes mellitus.

Though blood tacrolimus concentrations should guide dosage adjustments, liver enzymes, blood urea nitrogen (BUN), serum creatinine, glucose, potassium, magnesium, phosphorus, complete blood cell count (CBC) with differential, blood pressure, neurological status, and electrocardiography should be monitored regularly to detect adverse effects of tacrolimus therapy.

Corticosteroids

Corticosteroids (steroids) exert their immunosuppressive effect by interrupting multiple steps in immune system activation, inhibiting antigen presentation, cytokine production, and lymphocyte proliferation [14]. Because of these broad immunosuppressive effects, steroids play a significant and multifaceted role in the management of thoracic transplant recipients. Perioperatively, a high dose of intravenous (IV) methylprednisolone (15–20 mg/kg) is typically used prior to allograft reperfusion, with continued dosing in the immediate postoperative phase. After heart transplantation, some centers choose to wean off completely within a few days (steroid avoidance), while others maintain patients on steroids for varying durations, ranging from 6 to 12 months (steroid withdrawal) to indefinitely. Data from the few randomized prospective studies of chronic steroid use among adult renal transplant recipients suggest that both steroid avoidance and withdrawal protocols are associated with increased rejection [15, 16], and most immunosuppressive regimens in adult heart transplantation include chronic, low-dose steroids in combination with a CNI and an adjunctive agent (e.g., MMF or sirolimus) [17]. The data are less clear following pediatric heart transplantation, and steroid avoidance and withdrawal protocols are more common than among adult recipients. Of note, because the requirements for immunosuppression are greater after lung or heart-lung transplantation, most of these patients are maintained on chronic steroids (triple-drug immunosuppression) indefinitely.

Steroids also serve a role as the first-line response to significant acute rejection episodes. In this setting, bolus intravenous dosing for 3–5 days is common, though oral prednisone or prednisolone may sometimes be substituted, dependent on the clinical situation. Patients with severe, recurrent, or refractory rejection events are also commonly placed onto chronic steroids as part of their maintenance regimen.

Methylprednisolone and Prednisolone/Prednisone

Dosing

Perioperatively, a 15–20 mg/kg dose of methylprednisolone IV is given. Then a gradual tapering dose beginning with 2 mg/kg/day may be given as a premedication to antilymphocyte antibodies.

High-dose intravenous (IV) methylprednisolone is the standard for episodes of acute rejection; typical dosing is 10 mg/kg once daily for 3 days or more. Some transplantation centers use moderate-dose oral prednisone for less severe episodes of acute rejection (e.g., 2 mg/kg for 5 days, sometimes followed by a taper).

Those centers that use long-term maintenance therapy typically use prednisone in doses of 0.5–1 mg/kg/day, with a maximum daily dose of 40–60 mg, given orally in single daily doses for the first 2 weeks after transplantation. Subsequently, the prednisone is weaned to long-term maintenance doses of 0.05–0.15 mg/kg/day. Some centers continue low-dose prednisone indefinitely, whereas others wean to discontinuation in the first few months if the rejection history is benign. Increasing evidence suggests that complete steroid avoidance beyond the intraoperative period is possible in many children, especially infants [18].

Pharmacokinetics

The peak effect is dependent on the route of administration of the corticosteroid. Onset of action after IV injection is almost immediate, while peak effect occurs within 1–2 h after oral

administration. The duration of activity of an oral dose is 30–36 h. Corticosteroids are metabolized in the liver by several CYP-450 enzymes. The half-life is 3–3.5 h, and elimination is via the kidneys [10].

Drug-Drug Interactions

Corticosteroid clearance will be increased if given with phenytoin, phenobarbital, or rifampin. Potassium-depleting diuretics such as furosemide enhance potassium depletion caused by corticosteroids. While glucose levels may be increased by corticosteroids, persistent diabetes mellitus may develop when corticosteroids are used in combination with cyclosporine or tacrolimus. Finally, tacrolimus levels may be increased by IV bolus doses of methylprednisolone.

Side Effects

Acute adrenal insufficiency may occur with abrupt withdrawal after long-term use, so withdrawal or discontinuation of corticosteroids should be done gradually.

Corticosteroids can have adverse effects on the endocrine and metabolic systems including Cushing's syndrome, pituitary-adrenal axis suppression, growth retardation, glucose intolerance, hypokalemia, alkalosis, weight gain, hyperlipidemia, and salt and water retention. Edema and hypertension may develop. Blood pressure, weight, height, serum electrolytes, and glucose should be monitored regularly. Other adverse effects include acne, skin atrophy, impaired wound healing, hirsutism, transient leukocytosis, muscle weakness, osteoporosis, and fractures. Patients should be monitored for onset of vertigo, seizures, psychoses, pseudotumor cerebri, cataracts, glaucoma, or peptic ulcer. Oral dosage forms may cause nausea or vomiting.

Antimetabolites

Medications in this class inhibit DNA synthesis by blocking the production of adenine and guanine (purines) and thereby preventing proliferation of both T- and B-lymphocytes [19]. In the 1960s, azathioprine (AZA) was used alone, and later in combination with corticosteroids, for immunosuppression after renal transplantation [20, 21]. After the introduction of CNIs, maintenance immunosuppression commonly consisted of cyclosporine/tacrolimus, azathioprine, and corticosteroids. Mycophenolate mofetil (MMF) replaced azathioprine in the mid-to-late 1990s after studies in renal transplantation showed enhanced patient and allograft survival with decreased allograft rejection [22, 23]. In a randomized, blinded study of MMF vs. AZA in adult heart transplant recipients, MMF showed improved 1-year survival and decreased treated rejection events, with a small increase in opportunistic infections [24]. In contrast to sirolimus, which also may be used as an adjunctive immunosuppressive medication, MMF lacks nephrotoxicity and does not alter the lipid profile. Its main side effects are gastrointestinal (diarrhea, abdominal pain, anorexia) and hematologic (leukopenia, anemia). The availability of an enteric-coated formulation of the active agent, mycophenolic acid (Myfortic®), can ameliorate the gastrointestinal side effects for some patients.

Azathioprine

Dosing

Azathioprine dosage must be carefully individualized according to patient response. The usual initial dose is 2–5 mg/kg/dose once daily given IV or orally, with maintenance dose range of 1–2 mg/kg/day. The dosage of azathioprine must be adjusted for renal dysfunction and should be reduced if significant bone marrow suppression develops.

Pharmacokinetics

Azathioprine is a prodrug that undergoes extensive hepatic metabolism to 6-mercaptopurine (6-MP), the active metabolite. 6-MP has a bioavailability of 50 % and is 30 % protein bound. The half-life of AZA is 12 min and of 6-MP is 0.7–3 h. In anuric patients, the half-life of 6-MP increases to 50 h. Metabolites and

a small amount of unchanged AZA are eliminated eventually in the urine [10].

Drug-Drug Interactions

Concomitant azathioprine therapy with angiotensin-converting enzyme (ACE) inhibitors such as captopril and enalapril may induce severe anemia and leukopenia and should be avoided. Xanthine oxidase is important in the conversion of 6-MP to its inactive metabolites. Because allopurinol inhibits this enzyme, dosage reduction of AZA to 25–33 % of the normal dose is necessary when this drug combination cannot be avoided. Olsalazine, mesalamine, and sulfasalazine may inhibit thiopurine methyltransferase (TPMT) metabolism of 6-MP, increasing the risk of myelosuppression by AZA; therefore, careful monitoring is required. Decreased anticoagulant effectiveness by warfarin may be seen with AZA use.

Adverse Effects

Azathioprine can cause bone marrow suppression, leukopenia, macrocytic anemia, and thrombocytopenia. Hematological effects are dose-related and usually respond to dosage reduction. During severe toxicity, the white blood cell (WBC) count and hemoglobin levels drop first, followed by a decreasing platelet count. Gastrointestinal adverse effects such as nausea, vomiting, anorexia, and diarrhea may occur in patients who are receiving large doses of AZA. These GI effects may be avoided by giving AZA in divided doses and/or with meals. As with all immunosuppressants, there is an increased risk of infection. Fungal, protozoal, viral, and uncommon bacterial infections may occur, with the highest risk during significant leukopenia. If infection occurs, the dosage of AZA (and other immunosuppressive agents) should be reduced as much as possible and appropriate antiinfective therapy instituted. Hepatotoxicity may occur as well as hepatic sinusoidal obstruction syndrome.

CBC with differential, platelet count, creatinine, total bilirubin, alkaline phosphatase, and liver function should be monitored in all patients taking azathioprine.

Mycophenolate Mofetil (Cellcept®)/ Mycophenolic Acid (Myfortic®)

Dosing

The initial oral or IV dose of mycophenolate mofetil (MMF) in children is 600 mg/m^2/dose twice daily, with a maximum initial dose of 2 g/day. An alternative dosing of 30–45 mg/kg/day divided every 12 h can be used. However, some pediatric patients require every 8 h dosing because of rapid clearance. Gastrointestinal side effects are common and may be reduced if dosing is started lower (i.e., 20 mg/kg/day divided every 12 h) and dosing is gradually increased to target dose and/or levels.

If mycophenolic acid (MPA) delayed release tablets are used, the initial maximum target dose is 1,080 mg given twice daily. It is important to note that mycophenolate mofetil and mycophenolic acid delayed release tablets cannot be used interchangeably. Mycophenolate mofetil doses as high as 3–3.5 g/day were used in clinical trials, but with no greater efficacy than lower doses, and side effects were more common.

Pharmacokinetics

MMF has rapid and extensive absorption, and the bioavailability is 81–94 %. Mycophenolate mofetil is metabolized to MPA after oral or intravenous administration, and MPA, in turn, is glucuronidated to the inactive MPA glucuronide (MPAG). The half-life of MPA is approximately 18 h. Most of the drug (87 %) is excreted in the urine as MPAG [18].

Use of therapeutic drug monitoring remains controversial. Many centers choose to dose based on weight and utilize a fixed-dose regimen. Because fairly good associations of MPA concentration and its pharmacologic effects have been demonstrated, monitoring of trough MPA levels may be utilized though target levels have not been well established.

Drug-Drug Interactions

Magnesium supplements or antacids containing aluminum or magnesium hydroxide decrease the absorption of mycophenolate unless separated by 2 h or more. Cholestyramine decreases plasma MPA concentrations via binding mycophenolate metabolites in the intestines and should be avoided.

Acyclovir/valacyclovir and ganciclovir/valganciclovir compete with MPAG for tubular secretion, possibly resulting in increased concentrations of the antiviral agents and increasing the risk of toxicities.

Probenecid inhibits tubular secretion MPA and MPAG resulting in increased concentrations of both. Rifampin, on the other hand, significantly reduces MPA blood concentrations requiring increased mycophenolate dosage if used together.

Adverse Effects

Common adverse effects are gastrointestinal and include diarrhea or constipation, nausea, and vomiting. A delayed release tablet (Myfortic®) was designed to reduce adverse GI events by slowly delivering drug to the small intestines and may be helpful in patients intolerant to standard release formulations. Heart transplant patients may also experience hypertension, edema, hypercholesterolemia, hyperglycemia, hypokalemia, anxiety, insomnia, headache, elevated BUN and creatinine, fever, and pain. Serious hematological abnormalities may occur including leukopenia, anemia, and thrombocytopenia. CBC with differential and platelet count should be monitored. As with other immunosuppressive agents, there is an increased risk of infection with mycophenolate therapy.

Proliferation Signal Inhibitors (Mammalian Target of Rapamycin (mTOR) Inhibitors)

Until recently, sirolimus was the only proliferation signal inhibitor approved for systemic use in the USA. Both sirolimus and everolimus bind FKBP12, the same target as tacrolimus, but do not inhibit calcineurin. Rather, the complex binds target of rapamycin and prevents cell cycle activation, thereby preventing lymphocyte proliferation. Sirolimus, also known as rapamycin, is most commonly used as an adjunctive immunosuppressive agent. However, in some patients in whom CNI have been fully withdrawn for toxicities, sirolimus may be supplemented by MMF and/or steroids for immunosuppression. Sirolimus use in solid organ transplantation has been limited by its side effect profile, primarily the additive nephrotoxicity which may occur when used in combination with either cyclosporine or tacrolimus [25]. Sirolimus use is also associated with impaired wound healing, limiting its utility early after transplantation for fear of sternal wound dehiscence [26]. While animal and limited human data suggest that sirolimus and everolimus slow the progression of coronary allograft vasculopathy (i.e., chronic rejection) [27, 28], further research is needed before superiority over MMF in this domain can be established.

Sirolimus

Dosing

The usual dosing for children begins with an oral loading dose of 3 mg/m^2 on day 1, followed by 1 mg/m^2/day administered daily or as twice daily dosing. In one study of sirolimus dosing in pediatric heart transplants, an average dose of 0.25 mg/kg/day (or 7 mg/m^2/day) was required to maintain target sirolimus levels of 5–15 mcg/mL [29]. Adults $\geq$40 kg can be loaded with 6 mg orally for 1 day and then given a maintenance dose of 2 mg/day. Doses should be taken consistently either with or without food. Subsequent dosing is adjusted to maintain sirolimus trough levels between 3 and 7 ng/mL. Higher target sirolimus levels may be used if there is a clinical indication to maintain CNI levels very low because of side effects or toxicities. Data from clinical trials suggest that creatinine levels will be higher when cyclosporine is used with sirolimus than when used with mycophenolate mofetil or

azathioprine, necessitating careful monitoring of renal function. Since sirolimus can impair wound healing, it should probably be avoided until surgical sites are healed.

Pharmacokinetics

Sirolimus is absorbed rapidly and reaches a peak concentration within 1–3 h for the oral solution and 1–6 h for tablets. Bioavailability is approximately 14–18 %, with extensive distribution to red blood cells and tissues. Sirolimus is hepatically metabolized by the CYP3A4 enzyme. The half-life averages 14 h in children and 62 h in adults. The majority (91 %) of sirolimus is eliminated in the feces [10].

Drug-Drug Interactions

Concurrent therapy with sirolimus and cyclosporine can result in increased sirolimus toxicity manifested by anemia, leukopenia, thrombocytopenia, hypokalemia, and diarrhea. Administration of sirolimus 4 h after the cyclosporine dose reduces this effect. Tacrolimus levels are reduced when combined with sirolimus therapy, and adverse effects of both drugs can occur. Care should be used when these drugs are used in combination.

Sirolimus is metabolized by CYP3A4. Inhibitors of CYP3A4 (calcium channel blockers, azole antifungal agents, macrolide antibiotics, and protease inhibitors) can increase sirolimus concentrations.

CYP3A4 inducers (rifampin, phenobarbital, carbamazepine, fosphenytoin, and phenytoin) decrease serum concentrations of sirolimus. Grapefruit juice may reduce the metabolism of sirolimus and should be avoided during therapy with sirolimus.

Adverse Effects

Some of the more common adverse effects of sirolimus therapy include hypertension, peripheral edema, fever, headaches, pain, acne, rash, impaired wound healing, nausea, diarrhea, constipation, abdominal pain, increased serum creatinine, and arthralgias. The more serious complications involve hematologic abnormalities including anemia, neutropenia, and thrombocytopenia. Hyperlipidemia is common and may include severe hypercholesterolemia and hypertriglyceridemia. Hepatotoxicity and interstitial pneumonia are also reported.

Whole blood sirolimus trough concentration, serum cholesterol and triglycerides, serum creatinine, CBC with differential, platelet count, blood pressure, liver function, and healing of surgical wounds should be monitored.

Everolimus

Doses

There is limited dosing information for everolimus in pediatric transplantation. In renal transplants, children $\geq$1-year-old and adolescents have been given initial doses of 0.8 mg/m^2/dose twice daily with a maximum single dose of 1.5 mg, targeting a serum concentration of 3–6 ng/ml. In a study looking at renal function benefits of switching from a CNI to everolimus in pediatric heart transplants, an average initial dose of 0.07 mg/kg/day divided twice daily was used, with an average maintenance dose of 0.15 mg/kg/day needed to achieve the target trough level of 5–8 ng/mL [30].

Adult initial dosing of everolimus is 0.75 mg give twice daily, with adjustments every 4–5 days if needed based on target serum concentrations.

Pharmacokinetics

Oral absorption of everolimus is rapid, with a bioavailability of 30 % and reaching a peak concentration at 1–2 h. It is hepatically metabolized by CYP3A4, with a half-life of approximately 30 h, and is eliminated primarily in feces (80 %).

Drug-Drug Interactions

Everolimus is metabolized by CYP3A4. Inhibitors of CYP3A4 (calcium channel blockers, azole antifungal agents, macrolide antibiotics, and protease inhibitors) can increase everolimus concentrations.

CYP3A4 inducers (rifampin, phenobarbital, carbamazepine, fosphenytoin, and phenytoin) decrease serum concentrations of everolimus.

Grapefruit juice may reduce the metabolism of everolimus and St. John's Wort may increase metabolism of everolimus. Both should be avoided during therapy with everolimus. Cyclosporine doses and target levels should be reduced when given in combination with everolimus.

Adverse Effects

Some of the more common adverse effects of everolimus therapy include hypercholesterolemia and hypertriglyceridemia, hypertension, peripheral edema, fever, acne, rash, impaired wound healing, nausea, diarrhea, constipation, abdominal pain, increased serum creatinine, cough, and upper respiratory infections. The more serious complications involve hematologic abnormalities including anemia, neutropenia, and thrombosis; hepatotoxicity; pneumonitis; infectious diseases; and malignancies.

Whole blood everolimus trough concentration, serum cholesterol and triglycerides, serum creatinine, CBC with differential, platelet count, blood pressure, liver function, and healing of surgical wounds should be monitored.

Antibody Therapies and Fusion Proteins

The medications in this section can be subdivided into lymphocyte-depleting and non-depleting agents. Depleting drugs destroy lymphocytes whereas non-depleting agents are monoclonal antibodies or fusion proteins that reduce lymphocyte responsiveness without decreasing lymphocyte numbers [19]. Most of these medications are used for induction therapy after transplantation or less commonly as rescue therapy for refractory rejection. One exception is belatacept, a recombinant fusion protein that is currently being investigated in renal and liver transplant recipients as a chronic immunosuppressive therapy in the context of CNI avoidance. While the monoclonal anti-CD20 antibody rituximab is technically a depleting antibody, its use in transplantation is in the treatment of posttransplant lymphoproliferative disorders (PTLD) and the avoidance/treatment of antibody-mediated rejection. For this reason, rituximab will not be discussed here but rather in the next section of drugs used in the management of antibody-mediated rejection.

Of note, muromonab CD3 (OKT3), a monoclonal murine anti-CD3 antibody, and daclizumab (Zenapax®), a therapeutic humanized monoclonal antibody to the alpha subunit of the IL-2 receptor on T-lymphocytes, are no longer produced and will not be discussed in this chapter.

Depleting Antibodies

The currently available T-lymphocyte-depleting agents are polyclonal antilymphocyte antibody preparations produced by immunizing horses (Atgam®) or rabbits (Thymoglobulin®) with human lymphoid cells [19]. These preparations result in profound T-lymphocyte depletion by way of complement-dependent opsonization and cell lysis [17] and are used for induction therapy in the perioperative phase and for treatment of steroid-resistant rejection in both heart and lung transplant recipients. In practice, these potent agents often allow for a 2–4-day CNI-free window immediately after transplantation to enable recovery of renal function, which sometimes may be depressed from a peri-transplant low cardiac output state combined with the insult of cardiopulmonary bypass. Also, because of the manner by which these preparations are made, there may be antibodies which bind platelets and/or erythrocytes, resulting in thrombocytopenia and/or anemia. Also, allergic reactions up to and including anaphylaxis can occur particularly with first use due to marked cytokine release with cell lysis [31]. In addition to these side effects, when multiple courses are used (e.g., for treatment of refractory rejection after previous use as induction therapy), serum sickness may occur [32].

Equine Antithymocyte Globulin (Atgam®)

Dosing

An intradermal skin test for sensitivity is recommended before administration of the initial Atgam® dose.

For cardiac allograft rejection prevention, 15 mg/kg/day for 7 days is one of several different protocols used. The initial dose should be administered within 24 h of transplantation. For treatment of rejection 10–15 mg/kg/day for 7–14 days has been used. Atgam® is currently less frequently used than Thymoglobulin®.

Premedications of acetaminophen (10 mg/kg, orally), diphenhydramine (1 mg/kg, IV), and methylprednisolone (1–2 mg/kg, IV) should be given 30 min before each dose, and each dose should be administered over at least 4 h. With administration times greater than 6 h, acetaminophen and diphenhydramine should be repeated. Atgam® should be administered through a central line to reduce phlebitis.

Pharmacokinetics

Atgam® binds to circulating lymphocytes, granulocytes, platelets, and bone marrow cells. The plasma half-life is 1.5–12 days, with only 1 % of a dose excreted in urine.

Drug-Drug Interactions

Though live virus vaccines are typically contraindicated after pediatric thoracic organ transplantation, avoidance of the use of live vaccines in the first 6 months after Atgam® therapy is recommended as the desired immune response may be reduced and increased risk of infection with the live vaccinal organism may develop.

Adverse Effects

The most common adverse effects are infusion-related reactions, such as fever, shivering, headache, and rash. This can be minimized using the premedications mentioned above. The patient may also experience diarrhea, nausea, vomiting, abnormal BUN/Cr, or dyspnea. Leukopenia and thrombocytopenia may be severe, as well as hemolysis. Anaphylaxis (symptoms can include hypotension, respiratory distress, chest pain, rash, and tachycardia) may occur at any time during therapy. Epinephrine and oxygen should be readily available. Serum sickness reactions or pulmonary edema may also occur. Atgam® may cause primary or reactivation of cytomegalovirus (CMV) infection.

Monitoring parameters while on Atgam® therapy include CBC with differential and platelet count, lymphocyte profile (T-cell levels), vital signs during administration, and renal function.

Rabbit Antithymocyte Globulin (Thymoglobulin®)

Dosing

Thymoglobulin® induction dosing for children varies from center to center, with many centers using 1.5 mg/kg/day IV once daily for 5 days. For treatment of severe or refractory acute rejection, a dose of 1.5 mg/kg/day once daily for 7–14 days has been used.

Premedications of acetaminophen (10 mg/kg, orally), diphenhydramine (1 mg/kg, IV), and methylprednisolone (1–2 mg/kg, IV) should be given 30 min before each dose, and each dose should be administered over at least 4 h. With administration times greater than 6 h, acetaminophen and diphenhydramine may be repeated.

Pharmacokinetics

Thymoglobulin® serum half-life after the first dose is approximately 44 h and increases with subsequent doses up to 13 days. The onset of T-cell depletion usually occurs within 1 day. Lymphopenia may persist for $\geq$1 year.

Drug-Drug Interactions

Though live virus vaccines are typically contraindicated after pediatric thoracic organ transplantation, avoidance of the use of live vaccines in the first 6 months after Thymoglobulin® therapy is recommended as the desired immune response may be reduced and increased risk of infection with the live vaccinal organism may develop.

Adverse Effects

The most common adverse effects are infusion-related reactions, such as fever, shivering, and headache. This can be minimized using the premedications mentioned above. The patient may also experience diarrhea, nausea, abdominal pain, myalgia, or dyspnea. Leukopenia and thrombocytopenia may be severe. Anaphylaxis may occur at any time during therapy. Epinephrine and oxygen should be readily available. Serum sickness reactions and peripheral edema may also occur. Thymoglobulin® therapy may result in severe viral, bacterial, fungal, or protozoal infections or malignancies including posttransplant lymphoproliferative disease.

Monitoring parameters while on Thymoglobulin® therapy include CBC with differential and platelet count, lymphocyte profile (T-cell levels), vital signs during administration, and signs of infection.

Alemtuzumab (Campath(R))

Alemtuzumab targets CD52 which is expressed on mature mononuclear cells, including T- and B-lymphocytes. In addition to its role as an induction agent, alemtuzumab has been used as treatment for refractory rejection [33, 34] after renal and heart transplantation. Though limited, data on the use of alemtuzumab induction therapy after lung transplantation suggested fewer acute rejection events in the first 6 months after transplant [35].

In late 2012, alemtuzumab was withdrawn for commercial purchase in the US by the manufacturer for its FDA approved indication of treatment of B-cell chronic lymphocytic leukemia. At present it is being evaluated by the FDA and European Medicines Agency (EMEA) for approval (as brand name Lemtrada(R)) for treatment of multiple sclerosis. Its availability for off-label use in transplantation is uncertain.

Dosing

IV infusions of 30 mg/dose for one to two doses have been used in adult solid organ transplantation. Limited dosing information is available for pediatric transplantation. In renal transplants in children, an induction dose of 0.4–0.5 mg/kg/dose IV with a maximum dose of 30 mg has been used. In a case report of one 16-year-old heart transplant, the dose used was 30 mg IV on day 1 and day 4 posttransplant [34]. Pretreatment with diphenhydramine, acetaminophen, and corticosteroids should be considered to prevent or ameliorate infusion-related reactions.

Pharmacokinetics

Alemtuzumab clearance decreases with repeated dosing because of loss of CD52 receptors in the periphery. The elimination half-life is initially 11 h and increases to 6 days after repeat doses [36].

Drug-Drug Interactions

Administration of live vaccines should be avoided in immunosuppressive therapy with alemtuzumab.

Adverse Effects

Alemtuzumab can cause serious hematological toxicities, including autoimmune idiopathic thrombocytopenic purpura (ITP), bone marrow hypoplasia, and autoimmune hemolytic anemia. Single doses >30 mg or cumulative doses greater than 90 mg/week have been associated with pancytopenia.

Infusion-related adverse events are common and can include rigors, hypotension, drug-related fever, nausea, vomiting, rash, fatigue, urticaria, dyspnea, pruritus, headache, and diarrhea. Other adverse effects that can occur include peripheral edema and skeletal muscle pain. Alemtuzumab therapy may result in severe viral, bacterial, fungal, or protozoal infections, and appropriate drug prophylaxis should be considered.

Carefully monitor blood pressure and other vital signs during alemtuzumab infusions. CBC and platelets should be monitored weekly, signs and symptoms of infection should be monitored regularly, and T-lymphocyte counts should be monitored after treatment until recovery.

Non-depleting Antibodies and Fusion Proteins

The principle non-depleting induction agent that is currently available commercially is basiliximab (Simulect®). Basiliximab binds the alpha subunit of the IL-2 receptor expressed on activated T-lymphocytes [17, 37]. Belatacept (Nulojix®) is a novel agent that is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 linked to the crystallizable fragment portion of human immunoglobulin G1 [38]. Its mechanism of action is via binding of CD80 and CD86 on antigen presenting cells, thereby blocking a key co-stimulatory signal required for T-lymphocyte activation [39]. Unlike basiliximab, belatacept is not used for induction but has been shown to be effective as maintenance immunosuppression (i.e., rejection prophylaxis) in conjunction with MMF and steroids after de novo renal transplantation [40]. The obvious advantage here is the complete avoidance of CNIs and their associated toxicities. Also, in contrast to depleting antibody therapies, the non-depleting agents are associated with fewer serious adverse effects, such as cytokine release [41].

Basiliximab

Basiliximab has been described in a handful of studies in heart transplantation, which collectively suggest that when given as induction therapy with standard maintenance immunosuppression, basiliximab is well tolerated and not inferior to depleting antibody preparations in terms of acute rejection events [42–44].

Dosing

In pediatric patients weighing less than 35 kg, the recommended basiliximab regimen is two IV doses of 10 mg each. In pediatric patients weighing at least 35 kg, the recommended regimen is two IV doses of 20 mg each. The first dose is administered just before starting cardiopulmonary bypass or within 6 h of organ perfusion. The second dose should be administered 4 days after transplantation.

Pharmacokinetics

Basiliximab has a mean duration of activity of 36 days. The elimination half-life in children 1–11 years old is 9.5 days, in adolescents 12–16 years it is 9.1 days, and in adults it is 7.2 days.

Drug-Drug Interactions

Basiliximab may decrease the therapeutic effect of vaccines. There is an increased risk of vaccinal infection when live vaccines are given during and up to 3 months after basiliximab therapy.

Adverse Effects

Severe acute hypersensitivity reactions including anaphylaxis have been observed with initial doses and reexposure to basiliximab. If a severe hypersensitivity reaction occurs, therapy with basiliximab should be permanently discontinued. Basiliximab therapy results in an increased susceptibility to infection and increased risk of lymphoproliferative disorders. Adverse effects that occur with basiliximab treatment include abdominal pain, vomiting, hypertension, edema, insomnia, pain, fever, dizziness, asthenia, anemia, dysuria, dyspnea, candidiasis, cough, and CMV infections.

Belatacept

Though belatacept has shown promise as a possible CNI avoidance therapy in renal transplantation, there is no published data on the use of this agent after thoracic organ transplantation.

Drugs Used in the Management of Antibody-Mediated Rejection

With the exception of corticosteroids, which are somewhat broadly immunosuppressive, all of the drugs described thus far in this chapter are directed against T-lymphocyte-mediated (cellular) acute rejection. In stark contrast to this impressive armamentarium, there are very few medications that are known to be useful in the treatment of antibody-mediated rejection (AMR). Until relatively recently, AMR was poorly

understood and often not diagnosed. Though currently a topic of intense research, optimal diagnostic and management schemes remain uncertain [45]. Risk factors for AMR include the presence of alloantibodies (allosensitization) directed against the donor prior to transplantation (donor-specific antibodies, DSA) as well as the development of posttransplant, de novo DSA [46]. These antibodies fix and activate complement, resulting in tissue injury and coagulation [47].

It is not surprising that therapies employed in the treatment and prevention of AMR are focused primarily on removal and cessation of production of the offending alloantibodies. To that end there are currently three medications that are utilized in conjunction with plasmapheresis either prior to transplantation (desensitization) or for treatment of AMR: intravenous immunoglobulin (IVIG), rituximab (Rituxan®), and bortezomib (Velcade®).

There are also emerging reports in the renal and lung literature on AMR salvage therapy with eculizumab (Soliris(R)), a humanized monoclonal antibody directed against complement component C5 that blocks downstream formation of membrane attack complexes [54, 55].

Immunoglobulin (IVIG)

IVIG is a potent immunomodulator and has been widely used as an effective treatment for various autoimmune disorders [48]. It has also been used for desensitization and for treatment of AMR after solid organ transplantation. The mechanism of action has not been elucidated but has been postulated to occur as a result of anti-idiotypic antibodies in IVIG that bind to the B-lymphocyte receptor and crosslink the Fcγ receptor IIB, abolishing B-lymphocyte proliferation and resulting in B-lymphocyte apoptosis [49, 50]. IVIG may also modulate T-cell function.

Dosing

Various doses are used for desensitization and as part of a regimen for treatment of antibody-mediated rejection, ranging from 0.5 to 2.0 g/kg monthly for 4–6 months after transplantation across a positive cytotoxicity cross-match or diagnosis of antibody-mediated rejection. Because IVIG is removed by plasmapheresis, it should be given following the conclusion of planned plasmapheresis treatments.

Pharmacokinetics

Intravenous dosing of immune globulin provides immediate antibody levels. The half-life is variable at 14–40 days. Fever and infection may contribute to a shorter half-life.

Drug-Drug Interactions

The effect of live vaccines will be decreased by immune globulins. Vaccination with live organisms should be withheld for up to 6 months post-immune globulin therapy.

Adverse Effects

Acute renal dysfunction may occur with IV immune globulin administration, usually occurring within 7 days. Infusion-related reactions may occur and manifest as fever, chills, nausea, and vomiting and may be helped by decreasing the rate of infusion. Non-cardiogenic pulmonary edema, thrombotic events, and aseptic meningitis have been reported with IVIG use.

Rituximab

Rituximab (Rituxan®) is a mouse-human chimeric monoclonal antibody that binds CD20, expressed on the surface of B-lymphocytes. Use for desensitization and treatment of AMR is off-label and is based on the premise that while antibody-producing plasma cells are CD20 negative, most are relatively short-lived and require replacement from CD20 positive precursors [19]. Other mechanisms of action beyond B-cell depletion may also be important.

Dosing

Usual dosing of rituximab in children and adults is 375 mg/m^2 by slow IV infusion given

weekly for 3–4 doses. Premedication with acetaminophen and diphenhydramine may attenuate infusion reactions.

Pharmacokinetics

B-cell recovery begins in 6 months following treatment, with normal levels obtained by 12 months. The elimination half-life is variable within the range of 5–78 days.

Drug-Drug Interactions

Rituximab may decrease the therapeutic effect of vaccines. There is an increased risk of vaccinal infection when live vaccines are given during and up to 3 months after rituximab therapy.

Adverse Effects

Severe infusion reactions have occurred within 24 h of rituximab administration, with most occurring within 30–120 min of the first infusion. Progressive multifocal leukoencephalopathy (PML) and severe mucocutaneous reactions have been reported with rituximab use. There is a risk of developing serious bacterial, viral, and fungal infections up to 1 year after rituximab therapy. Other adverse effects associated with rituximab therapy include hypertension, cardiac dysrhythmias, peripheral edema, night sweats, fever, pain, pruritus, rash, diarrhea, nausea, vomiting, anemia, leukopenia, thrombocytopenia, neuropathy, arthralgia, and cough.

Bortezomib

Unlike IVIG or rituximab, bortezomib (Velcade®) is not an antibody-based therapy. It is a proteasome inhibitor that is approved for use in the USA for the treatment of multiple myeloma [51]. Though experience is limited, to date its use for desensitization and treatment of antibody-mediated rejection after heart transplantation has been described in small case series [52, 53].

Dosing

Bortezomib is given in a dose of 1.3 mg/m^2 intravenously by rapid injection as a series of four doses distributed over 2 weeks (1 cycle).

Pharmacokinetics

Bortezomib distributes widely to peripheral tissues. It is metabolized by hepatic CYP3A4 and CYP2C19 enzymes and has a half-life of 76–108 h with multiple dosing.

Drug-Drug Interactions

Azole antifungals (fluconazole, voriconazole) are CYP3A4 inhibitors and may increase the concentration of bortezomib. Clopidogrel active metabolites may be reduced due to CYP2C19 inhibition by bortezomib. St. John's Wort, ascorbic acid, and green tea may decrease the effectiveness of bortezomib and should be avoided. Rifampin, phenytoin, phenobarbital, and carbamazepine may reduce bortezomib plasma concentrations.

Adverse Effects

Reported adverse effects include peripheral neuropathy, gastrointestinal symptoms (diarrhea, nausea, emesis), leukopenia, anemia, and thrombocytopenia. Hypotension, new-onset heart failure, rash, myalgia, headache, and fever have also been reported. Whether increased infection may also be a concern for use in patients receiving other immunosuppressive agents remains to be seen.

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