An Overview of Immunosuppression in Solid Organ Transplantation

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Abstract

Significant advancements in solid organ transplantation immunosuppressive medications and regimens have resulted in improved outcomes over the years. A multidrug approach involving medications with different mechanisms of action is commonly used. Induction therapy can involve the use of antibody agents or higher doses of medications used for maintenance therapy. A calcineurin inhibitor, an antiproliferative agent, and a corticosteroid commonly serve as the initial triple medication regimen. Due to the potential for nephrotoxicity with the use of calcineurin inhibitors and chronic conditions with the prolonged use of corticosteroids, various withdrawal strategies are used in practice. Antimicrobial agents are prescribed to provide prophylaxis against certain viral, fungal, and bacterial infections. Other concomitant medications in the regimens for patients who have undergone transplantation vary depending on patient-specific factors and conditions.

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Introduction

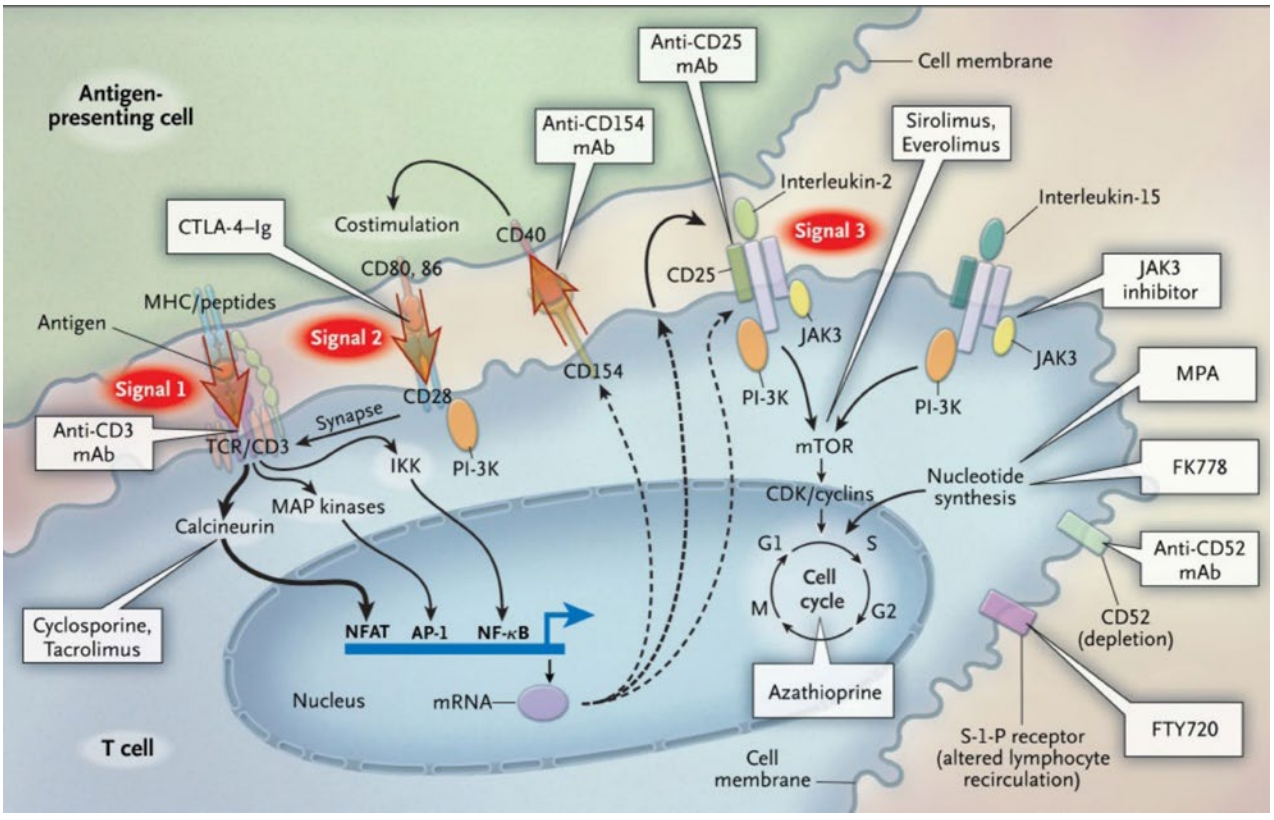
Outcomes in solid organ transplantation have improved greatly since the first organs were transplanted. In the early days of solid organ transplantation, survival was limited to a few weeks, typically without meaningful functional recovery. Significant progress occurred with the discovery and use of immunosuppressive agents. Early immunosuppressive protocols included the use of azathioprine and corticosteroids. A dramatic advancement occurred with the addition of calcineurin inhibitors to the immunosuppressive regimen for recipients of solid organ transplants, resulting in long-term survival and meaningful functional recovery.

Basic Immunology

Knowledge of basic immunology is key to understanding the rationale for commonly used immunosuppressive regimens.[1] T-cell activation and proliferation is described by the 3-signal model (**Figure**).[1] An antigen-presenting cell binds to the T-cell receptor and triggers the T cell at signal 1. Costimulator molecules and ligands bind at signal 2. The activation of both signals 1 and 2 are needed to result in the expression of interleukin-2 (IL-2) and other factors. At signal 3, stimulation of the IL-2 receptor on the T-cell surface triggers T-cell proliferation.

A general understanding of the 3-signal model is essential because immunosuppressive medications act on specific targets within the model.[1] The mechanisms of action of the available immunosuppressive medications include blocking the production and release of cytokines from activated T cells; downregulating and inhibiting T-cell surface receptors; inhibiting T-cell proliferation; and causing T-cell depletion (Figure).[1] Cyclosporine and tacrolimus inhibit calcineurin. The monoclonal antibody basiliximab binds and inhibits the IL-2 receptor. Azathioprine acts as an antimetabolite to prevent T-cell proliferation. Mycophenolate mofetil (MMF) and mycophenolic acid (MPA) inhibit purine synthesis, which prevents proliferation of T and B cells. Sirolimus and evero-

■ **Figure.** Individual Immunosuppressive Drugs and Sites of Action in the 3-Signal Model[1]



Anti-CD154 antibody has been withdrawn from clinical trials but remains of interest. FTY720 engagement of S-1-P receptors triggers and internalizes the receptors and alters lymphocyte recirculation, causing lymphopenia. Antagonists of chemokine receptors (not shown) are also being developed in preclinical models.
AP-1 indicates activating protein 1; CD, cluster of differentiation; CDK, cyclin-dependent kinase; CTLA-4–Ig, cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; G1, gap 1; G2, gap 2; IKK, inhibitor of nuclear factor κB kinase; JAK3, Janus kinase 3; M, mitosis; mAb, monoclonal antibody; MAP, mitogen-activated protein; MPA, mycophenolic acid; mRNA, messenger ribonucleic acid; mTOR, molecular target of rapamycin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; PI-3K, phosphoinositide-3-kinase; S, synthesis; S-1-P, sphingosine-1-phosphate; TCR, T-cell receptor.

limus inhibit cytokine-stimulated T-cell proliferation. Belatacept binds to cluster of differentiation 80 (CD80) and cluster of differentiation 86 (CD86) receptors on the antigen-presenting cells, which prevents binding to cluster of differentiation 28 (CD28) on the T cell. Alemtuzumab binds to cluster of differentiation 52 (CD52), which is present on the surface of T and B cells. Multiple medications with different sites of action are used for immunosuppression (Table).[2-14] This multidrug approach allows for lower doses of each medication, and hence less toxicity compared with using higher doses of a single agent.[15] The goals of immunosuppression are to prevent graft rejection, improve graft and patient survival, reduce complications, minimize medication adverse effects, improve overall patient quality of life, and minimize the number of immunosuppressants that the patient receives for the duration of their life.[15]

Antibody Therapy

The 3 phases of immunosuppression are induction, maintenance, and treatment of rejection. Induction involves the use of high-intensity immunosuppression immediately after transplant, when the risk of rejection is highest. Oftentimes, the word induction signifies the use of antibody therapy, although induction can also refer to the use of higher doses of the medications typically used for maintenance therapy.[16] Antibody induction is considered when there is a need to delay the introduction of the calcineurin inhibitors or decrease the need for steroid use.[15,16] Induction with antibody therapy is not

Table. Immunosuppressive Medications and Their Mechanisms of Action and Adverse Effects[2-14]

Drug	Mechanism of Action	Adverse Effects
Antithymocyte globulin	Blocks T-cell membrane proteins	• Cytokine-release syndrome • Thrombocytopenia, leukopenia • Headache, dizziness • Abdominal pain, diarrhea, nausea • Dyspnea • Hypertension, peripheral edema • Hyperkalemia
Alemtuzumab	Monoclonal antibody directed against the CD52 cell surface antigen	• Anemia, neutropenia, thrombocytopenia • Infusion reactions • Infections (cytomegalovirus, *Pneumocystis jiroveci* pneumonia, herpes virus) • Diarrhea, nausea, vomiting • Insomnia
Basiliximab	Chimeric monoclonal antibody against CD25	• Comparable to placebo • Constipation, nausea, abdominal pain, vomiting, diarrhea, dyspepsia
Cyclosporine	Binds to cyclophilin and forms complex that inhibits calcineurin	• Nephrotoxicity • Hypertension • Hyperlipidemia • Neurotoxicity • Post transplant diabetes • Hyperkalemia • Hypomagnesemia • Hirsutism • Gingival hyperplasia
Tacrolimus	Binds to FKBP12 and forms complex that inhibits calcineurin	• Similar to cyclosporine except o Fewer carvdiovascular issues o Fewer cosmetic problems such as hirsutism and gingival hyperplasia o More post transplant diabetes o More neurotoxicity than cyclosporine
Azathioprine	Inhibits protein synthesis	• Anemia, neutropenia, thrombocytopenia • Hepatotoxicity • Pancreatitis
Mycophenolate	Inhibits inosine monophosphate dehydrogenase	• Diarrhea, nausea, vomiting • Leukopenia, thrombocytopenia, anemia
Sirolimus and everolimus	Binds and forms complex with FKBP12 complex that inhibits mTOR	• Hypertension • Peripheral edema • Hyperlipidemia • Anemia, thrombocytopenia • Headache • Proteinuria • Delayed wound healing • Interstitial lung disease • Mouth ulcers
Belatacept	Selective T-cell costimulation blocker binds to CD80 and CD86 receptors on the antigen-presenting cell and prevents them from binding to CD28 on the T lymphocyte	• Hypertension • Peripheral edema • Hyperkalemia, hypokalemia • Constipation, diarrhea, nausea, vomiting • Headache • Cough, fever • Post transplant lymphoproliferative disease • Progressive multifocal leukoencephalopathy • Tuberculosis
Corticosteroids	Block T-cell–derived and antigen-presenting cell–derived cytokine expression	• Hyperglycemia • Hypertension • Hyperlipidemia • Increased risk of gastric ulcers • Risk of fungal and bacterial infections • Osteoporosis • Suppression of HPA axis • Psychosis

CD25 indicates cluster of differentiation 25; CD28, cluster of differentiation 28; CD52, cluster of differentiation 52; CD80, cluster of differentiation 80; CD86, cluster of differentiation 86; FKBP12, FK506-binding protein 12; HPA, hypothalamic-pituitary-adrenal; mTOR, mammalian target of rapamycin.

universal for all solid organ transplants. According to the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients (SRTR) Annual Data Report, in 2010 and 2011, antibody induction therapy in solid organ transplantation ranged from lowest use in liver transplant recipients (31.1%) to highest use in pancreas recipients (90.4%).[17,18] This wide range shows the variation in the use of antibody induction among the different organs and transplant centers. The potential benefits of lower incidence of acute rejection episodes must be weighed against the increased risk of developing infections and additional medication cost.

Antibody therapy includes T-cell-depleting and non-depleting agents. The depleting antibodies can further be divided into polyclonal and monoclonal agents. The polyclonal antithymocyte antibodies are rabbit antithymocyte globulin (rATG) and horse antithymocyte globulin (hATG). Alemtuzumab is a humanized monoclonal anti-CD52 antibody. The T-cell-depleting agents can also be used for the treamtent of rejection.[2,19,20]

Antithymocyte Globulin

Antithymocyte globulins (ATGs) are immunoglobulin G (IgG) from horses or rabbits immunized with human thymocytes. ATG blocks T-cell membrane proteins (clusters of differentiation 2, 3, 4, 8, 11a, 18, 25, 44, 45, human leukocyte antigen [HLA]-D related-DR, HLA class I heavy chains, and beta-2 microglobulin) which inactivate and deplete T cells and modulate homing and cytotoxic activities.[2,21,22] rATG and hATG are approved by the FDA for renal transplant acute rejection.[2,3] hATG is also indicated to prevent renal transplant rejection.[3] rATG is dosed at 1.5 mg/kg and hATG is dosed at 10 to 30 mg/kg.[2,3] However, dosing is often individualized based on patient-specific and center-specific protocols.[3] Initially, administration of rATG should be into a high-flow vein over the course of 6 hours to minimize phlebitis and thrombosis; subsequent infusions can be infused over the course of 4 hours.[2,3] ATG can be administered peripherally when heparin 1000 units and hydrocortisone 20 mg are added to the infusion.[23] rATG is administered daily for 7 to 14 days for the treatment of rejection.[2] rATG is often used as an induction agent, although it is not approved by the FDA for this indication.[1] Per the product labeling, hATG is administered daily for 14 days, and additionally every other day for up to 21 doses for the treatment or prevention of rejection.[3] rATG is preferred over hATG because of increased potency and tolerability. In addition, rATG is superior to hATG in reversing and preventing rejection.[24] When ATG is initially administered, antibodies bind to the T-cell receptor, causing T-cell activation; eventually, the T cells are destroyed. Cytokine-release syndrome produces symptoms such as fever, chills, hypotension, and pulmonary edema, and is most pronounced with the first dose. Acetaminophen, diphenhydramine, and a corticosteroid are administered prior to the ATG infusion to prevent the symptoms of cytokine release syndrome; however, cytokine release syndrome may occur despite administration of premedications.

Frequent monitoring of vital signs is important during the administration of ATG. The frequency of vital sign monitoring is institution-specific. A commonly used vital sign monitoring scheme is every 15 minutes for the first hour or 2, every 30 minutes for the next hour or 2, and then every hour for the remainder of the infusion. Doses are adjusted based on platelet and white blood cell counts. The Table describes common adverse effects associated with each immunosuppressive medication.[2-14]

Alemtuzumab

Alemtuzumab is a humanized, rat IgG1k monoclonal antibody directed against the CD52 cell surface antigen. It is approved for B-cell chronic lymphocytic leukemia.[4] Although not FDA-approved for use in solid organ transplants, alemtuzumab has been administered in this population. Studies and case reports have described alemtuzumab use for induction and the treatment of rejection in solid organ transplants.[19,20,25,26] Transplant recipients who received alemtuzumab induction had rates of rejection similar to those given rATG and a lower incidence of rejection than patients given basiliximab.[25] The recommended dose of alemtuzumab is 30 mg administered subcutaneously or intravenously over 2 hours.[27-32] As of September 2012, alemtuzumab is only available through a special distribution program. When alemtuzumab is administered, vital signs should be monitored every 15 to 30 minutes until the infusion is complete. Complete blood counts (CBCs), which include platelet levels, should be monitored weekly during alemtuzumab therapy.

Basiliximab

Basiliximab is a non-depleting, chimeric (human/murine) monoclonal antibody directed against the IL-2 receptor cluster of differentiation 25 (CD25).[5] It inhibits T-cell proliferation and differentiation, but does not cause T-cell depletion. Basiliximab is approved for

prophylaxis of acute rejection in renal transplant recipients. Adverse effects and hypersensitivity reactions are uncommon. In placebo-controlled studies, adverse effects were similar in the basiliximab and placebo groups.[33,34] No premedications or special monitoring during the infusion are required.[5] Basiliximab 20 mg should be administered via central or peripheral line over the course of 20 to 30 minutes on the day of surgery and 4 days after transplant.[5]

There is no clear consensus on which induction regimen is best. The choice of whether to use antibody induction therapy and which agents to use depends on each transplant center's experience.

Maintenance Immunosuppression

The maintenance medications for immunosupression are calcineurin inhibitors, antiproliferative/antimetabolites, corticosteroids, mammalian target of rapamycin (mTOR) inhibitors, and T-cell costimulation blockers. A combination of these medications is initiated at the time of surgery. Transplant recipients are maintained on one or a combination of agents for the remainder of their life.[1,15]

The immunosuppressive regimens vary between transplant centers. According to the most recent SRTR registry data, the triple regimen of tacrolimus, MMF/MPA, and prednisone is the most common maintenance regimen at discharge, with use ranging from 59.5% to 75% of kidney, liver, lung, heart, heart-lung, kidney-pancreas, and pancreas-after-kidney transplants.[35]

Calcineurin Inhibitors

The calcineurin inhibitors are the cornerstone of immunosuppression. Transplant recipients generally remain on calcineurin inhibitors for the remainder of their lifetime even if all other immunosuppressives are withdrawn.[1,15] Cyclosporine is produced as a metabolite by the fungus species *Beauveria nivea* and works by binding to cyclophilin.[6,7] It is available as a capsule, solution, or injection. The first cyclosporine product developed was the standard, oil-based formulation with an unpredictable, erratic bioavailability of 10% to 89%.[6,7] Later, a microemulsion formulation was developed with more predictable bioavailability (mean of 30%) and resulted in improved clinical outcomes.[36-38] Due to the difference in bioavailability, the standard and microemulsion formulations should not be interchanged. Cyclosporine is approved for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants in conjunction with corticosteroids.[6,7] Cyclosporine dosing ranges from 4 to 12 mg/kg/day orally divided into 2 equal doses.[6,7] Doses are adjusted based on drug levels. Goal trough concentrations are 100 to 300 ng/mL.[39] However, 2-hour peak concentrations (C_2) have been shown to provide a more accurate representation of the area under the curve (AUC) compared with trough concentration monitoring. Clinical outcomes are associated with AUC.[40] Maintaining the C_2 within the therapeutic range is associated with a reduced incidence and severity of acute rejection.[41] However, difficulty in obtaining the C_2 at the appropriate time is an issue. Consensus guidelines suggest a 15-minute window around the 2-hour time point when the level can be drawn with a 10% margin of error.[41] Goal C_2 concentrations range from 600 to 2000 ng/mL.[41,42] Studies have evaluated the benefits of C_2 monitoring, but practical disadvantages must be considered, as well as the insufficient evidence comparing trough versus C_2 monitoring.[43]

Tacrolimus is a macrolide antibiotic derived from *Streptomyces tsukubaensis* which binds to FK506-binding protein 12 (FKBP12) to form a complex that inhibits calcineurin.[8] Inhibition occurs with greater potency compared with cyclosporine. Tacrolimus absorption is not affected by the presence of bile and it occurs in the duodenum and jejunum, providing an advantage for use in patients with cholestasis or biliary issues.[16] Tacrolimus is approved by the FDA for organ rejection prophylaxis in liver, kidney, and heart transplants.[8] It is available as capsules or an intravenous (IV) formulation. Initial dosing is 0.075 to 0.2 mg/kg/day orally divided into 2 equal doses depending on the type of transplant.[8] Tacrolimus absorption is best when taken on an empty stomach, since food decreases bioavailability. In 2013, a modified-release tacrolimus product became available, allowing for once-daily dosing.[44] Goal tacrolimus trough concentrations vary depending on the type of organ transplant, time since transplant, concomitant immunosuppression, and other factors (eg, active infection, adverse effects). For maintenance immunosuppression in adult transplant recipients, tacrolimus trough concentrations can range from 5 to 15 ng/mL.[8] The IV formulation should be avoided because its castor oil derivatives are associated with neurotoxicity, nephrotoxicity, and anaphylaxis.[8] Tacrolimus can safely be administered sublingually with good absorption in patients unable to use the oral route. Several studies have been published describing the successful use of sublingual administration in different transplant populations and they have

shown equivalent or better absorption than oral administration.[45-47]

There is a difference in dosing when switching from the IV to the oral form of both of the calcineurin inhibitors, cyclosporine and tacrolimus. The oral dose of cyclosporine is approximately 3 times the IV dose, and the oral dose of tacrolimus is approximately 3 to 5 times the IV dose; therefore, the dose should be increased when converting from the IV to oral form.[6,8] Other important considerations include the administration of the solution formulations of cyclosporine. The non-modified cyclosporine solution may be diluted with milk, chocolate milk, or orange juice in a glass container.[6] The modified cyclosporine solution may be diluted with orange or apple juice that is at room temperature in a glass container.[7]

Adverse effects are more likely to occur if drug concentrations are above the goal range, but can also be idiosyncratic and occur when concentrations are within the goal range.[6-8] Acute and chronic nephrotoxicity is a common side effect of calcineurin inhibitor therapy; it can range from mild elevations in serum creatinine and blood urea nitrogen values and be responsive to dose reductions, or to more progressive cases causing histological or structural changes evident on kidney biopsy.[7,8] Electrolyte abnormalities include hypomagnesemia and hyperkalemia.[7,8] Neurotoxicity can range from tremors and headaches to seizures, delirium, and coma.[7,8] Posterior reversible encephalopathy syndrome (PRES) occurs in a small percentage of patients receiving calcineurin inhibitors.[7,8] The clinical presentation includes mental changes, headache, focal neurological deficits, and/or visual disturbances with diagnosis confirmed by radiological procedures.[7,8] PRES may occur with or without supratherapeutic levels of calcineurin inhibitors.[48] Post transplant diabetes or hyperglycemia caused by the calcineurin inhibitor may be reversible or require treatment with insulin.[8] Tacrolimus adverse effects are similar to cyclosporine. However, tacrolimus has a lower incidence of hyperlipidemia, hypertension, and cosmetic problems such as hirsutism and gingival hyperplasia, but is more likely than cyclosporine to induce post transplant diabetes and neurotoxicity.[7,8]

Both calcineurin inhibitors are metabolized by the cytochrome P450 (CYP) 3A4 enzyme system, and several important drug interactions exist.[7,8] Calcineurin inhibitor concentrations are increased with concomitant administration of calcium channel blockers (eg, diltiazem), triazole antifungals (eg, ketoconazole, itraconazole, voriconazole), macrolide antibiotics (eg, erythromycin), prokinetic agents (eg, metoclopramide), and other medications such as amiodarone, cimetidine, omeprazole, and protease inhibitors.[7,8] Decreased calcineurin inhibitor concentrations occur with anticonvulsants (eg, carbamazepine, phenytoin, and phenobarbital), rifampin, and St. John's wort.[7,8] Cyclosporine and tacrolimus can also result in increased renal toxicity with concomitant use of aminoglycoside, amphotericin B, diuretics, and nonsteroidal anti-inflammatory drugs.[7,8] Rhabdomyolysis can occur with concurrent use of statins.[7] Absorption is increased by metoclopramide.[7] Due to the CYP3A4 interaction, patients should be educated to avoid grapefruit and grapefruit juice.[7,8]

It is difficult to compare the efficacy of cyclosporine and tacrolimus. Tacrolimus has been favored for a lower incidence of acute cellular rejection and less renal toxicity compared with cyclosporine in the first 1 to 2 years following transplantation.[49-52] Some studies show a lower incidence of biopsy-proven rejection with tacrolimus during the first 6 months, but comparable outcomes with cyclosporin at 2 years in terms of graft loss, death, and biopsy-proven rejection.[53] The Efficacy Limiting Toxicity Elimination (ELITE)–Symphony study found that low-dose tacrolimus was associated with a lower rate of biopsy-proven acute rejection, a higher rate of allograft survival, and a higher mean glomerular filtration rate (GFR) compared with standard-dose cyclosporine, low-dose cyclosporine, or low-dose sirolimus.[39] On the other hand, some studies have shown comparable safety, efficacy, and cost when cyclosporine or tacrolimus is used with antibody induction, an antimetabolite, and a corticosteroid.[54,55] Other studies have shown an association between tacrolimus use and a greater incidence of adverse effects that result in drug discontinuation compared with cyclosporine.[51,52]

Antiproliferatives

The antiproliferative (also known as antimetabolite) agents azathioprine and MMF/MPA work by inhibiting purine base synthesis required for T- and B-cell proliferation.

Azathioprine, which is available as an oral formulation, is indicated for the prevention of rejection in renal transplantation.[9] Azathioprine maintenance dosing is 1 to 3 mg/kg/day orally.[9] Oral bioavailability is approximately 47%.[56] Azathioprine is a prodrug that releases 6-mercaptopurine (6-MP). 6-MP acts as a metabolite after incorporation into the cellular DNA, resulting in a reduction in T-cell proliferation. 6-MP is metabo-

lized via 2 major pathways, one of which is thiopurine S-methyltransferase (TPMT).[9] Since TPMT activity is controlled by genetic polymorphisms, genotyping and phenotyping can identify patients at higher risk of developing toxicities from azathioprine.[57]

The main adverse effects of azathioprine are hematologic and gastrointestinal.[9] Dose-dependent myelosuppression can occur, with over 50% of patients developing leukopenia.[9] Thrombocytopenia and leukopenia can be reversed by stopping the drug or decreasing the dose. For this reason, it is important to monitor CBCs weekly during the first month of treatment, twice monthly for the second and third months, and then monthly or more frequently if dosage alterations or other therapy changes are needed. Nausea and vomiting are common and can be alleviated by administration of the drug in divided doses and/or after meals. Azathioprine concentrations are increased with concomitant use of allopurinol because one of the metabolism pathways for 6-MP (needed for inactivation of azathioprine) is catalyzed by xanthine oxidase (which is inhibited by allopurinol). Additive myelosuppression occurs with angiotensin-converting enzyme inhibitor therapy, and hepatotoxicity can occur with methotrexate.[9,58] Additionally, azathioprine can inhibit warfarin's anticoagulant effects by a mechanism that is incompletely understood.[9]

Mycophenolate inhibits inosine monophosphate dehydrogenase, causing inhibition of guanine nucleotide synthesis; as a result, it inhibits T- and B-cell proliferation. MMF is indicated for prophylaxis of organ rejection in patients receiving renal, cardiac, or hepatic transplants.[10] MMF is available as capsules, tablets, a suspension, and an injection. The dose is 1 to 1.5 g twice daily and can be given orally or intravenously.[10,59] MPA is approved for organ rejection prophylaxis in patients who have undergone a kidney transplant and is dosed at 720 mg orally twice daily.[11] MPA is the delayed-release formulation of mycophenolate that was developed to improve gastrointestinal tolerability.[60] No significant differences in the rates of acute rejection, patient or graft survival, rates of malignancy, or rates of gastrointestinal disorders were observed between MMF and MPA.[61,62] The adverse effects of MMF/MPA can be categorized as gastrointestinal or hematological. Monitoring and dose adjustments for MMF/MPA is done by assessing the CBC, since drug levels are not routinely monitored. A CBC should be performed every week during the first month, twice a month for the second and third months, and then monthly during the remainder of the first year.[10] In patients developing neutropenia with an absolute neutrophil count less than 1.3×10^3/mcL or anemia, dose interruption or reduction is recommended.[10,59]

Mycophenolate concentrations are decreased with the use of antacids, iron, cholestyramine, rifamycins, and sevelamer.[10] Medications that increase concentrations of mycophenolate include acyclovir, ganciclovir, valacyclovir, and probenecid.[10] Additionally, mycophenolate can affect other drugs such as oral contraceptives, phenytoin, and theophylline.[10] Women of childbearing age should be counseled on pregnancy prevention and planning due to the risk of first trimester pregnancy loss and congenital malformations with the use of mycophenolate.[10] The mycophenolate Risk Evaluation and Mitigation Strategy (REMS) is a program mandated by the FDA to inform healthcare providers and patients about the risks of taking mycophenolate during pregnancy. The goal of this program is to prevent unplanned pregnancy in patients using mycophenolate, minimize fetal exposure and risks associated with fetal exposure, and inform patients about the serious risks associated with mycophenolate.[63] It discusses appropriate birth control options, including abstinence, methods which can be used alone (intrauterine devices, tubal sterilization, partner's vasectomy), and dual-method contraception options.

For the antiproliferative/antimetabolite agents, mycophenolate is used more frequently than azathioprine.[35] Randomized studies involving MMF and azathioprine have found that MMF reduced the incidence of acute rejection compared with azathioprine alone, and that patients in the MMF group had lower rates and longer times to first biopsy-proven rejection.[64-67]

Corticosteroids

Corticosteroids exhibit anti-inflammatory and immunosuppressive activity by blocking T-cell–derived and antigen-presenting cell-derived cytokine expression.[16] Corticosteroids are available in several formulations including tablets, liquid, and injection. Due to the potential adverse effects, the long-term use of high-dose corticosteroids is avoided by some transplant centers.[15]

mTOR Inhibitors

The mTOR inhibitors, sirolimus and everolimus, are used (1) as an alternative or replacement for calcineurin inhibitors and antiproliferatives; (2) in combination with the calcineurin inhibitors at low and high doses; or (3) with a variable dose of a calcineurin inhibitor.[68] mTOR inhibitors bind to FKBP12 and this complex inhibits

TOR and IL-2–driven T-cell proliferation. Sirolimus is available as a tablet and solution and is FDA-approved for use in renal transplant recipients.[12] Maintenance dosing of sirolimus is 2 to 5 mg daily and it is adjusted to maintain trough concentrations of 12 to 20 ng/mL.[68] Target concentrations in clinical practice, however, may be lower than those suggested in the product information depending on the specific clinical situation. Everolimus is available in a tablet formulation and is FDA-approved for low-moderate immunological risk renal transplant recipients, and liver transplant recipients no earlier than 30 days post transplant.[13] Everolimus dosing is 0.75 mg twice daily, and the dose should be adjusted to maintain a target trough level of 3 to 8 ng/mL.[13]

Both sirolimus and everolimus have black box warnings regarding an increased risk of infections and malignancies. Additionally, the black box warning for sirolimus cautions against use in liver and lung transplant recipients due to safety and efficacy issues. In liver transplant recipients receiving sirolimus, excess mortality, graft loss, and hepatic artery thrombosis have occurred, and in lung transplant recipients receiving sirolimus, cases of bronchial anastomotic dehiscence have occurred.[12] The black box warning for everolimus states that there is an increased risk of kidney thrombosis resulting in graft loss within the first 30 days post transplantation. Use of everolimus in heart transplantation should be avoided due to serious infections and increased mortality observed within the first 3 months post transplant.[13] Since delayed wound healing is a concern, it is generally recommended not to start mTOR inhibitors immediately after transplant surgery. Additionally, interstitial lung disease can occur and usually resolves with drug discontinuation.[12,13]

Like the calcineurin inhibitors, sirolimus and everolimus are metabolized by the CYP3A4 pathway; therefore, concentrations are increased by calcium channel blockers, antifungals (azoles), macrolide antibiotics, metoclopramide, cyclosporine, and others.[12,13] As with the calcineurin inhibitors, grapefruit and grapefruit juice should be avoided.[12,13] Sirolimus and everolimus should be administered the same way each time, consistently with or without food.[12,13] Special procedures should be followed when administering sirolimus oral solution. The solution should be drawn up with an amber oral syringe, placed in a glass or plastic cup with 2 ounces of water or orange juice, mixed, stirred, and consumed at once. An additional 4 ounces of water or orange juice should be placed in the same cup, mixed vigorously, and consumed in order to ensure that all the medication is administered.[12]

Belatacept

Belatacept is a selective T-cell costimulation blocker that binds to CD80 and CD86 receptors on the antigen-presenting cell, prevents binding to CD28 on the T cell, and is used with basiliximab, MMF, and corticosteroids.[14] Belatacept is approved for use in kidney transplants.[14] Belatacept has been studied in liver, islet cell, and heart transplants.[69-71] Belatacept dosing is divided into 2 phases. In the initial phase, a dose of 10 mg/kg is administered intravenously on day 1 (ie, day of transplant, prior to implantation), day 5, and at the end of weeks 2, 4, 8, and 12. The maintenance phase follows with an IV dose of 5 mg/kg at the end of week 16 and every 4 weeks thereafter.[14] Patients who are Epstein-Barr virus (EBV)-negative have a higher risk of developing post transplant lymphoproliferative disease (PTLD); therefore, belatacept should only be used in those who are EBV-positive. The belatacept REMS program informs healthcare providers and patients of the increased risk of PTLD and progressive multifocal leukoencephalopathy. Belatacept is used as an alternative to the calcineurin inhibitors. Studies comparing belatacept with cyclosporine have shown equivalent patient and graft survival, and sustained GFR improvement over 5 years; however, patients given belatacept had a higher incidence of acute rejection.[72,73]

Withdrawal and Avoidance Strategies

Tapering, withdrawal, and complete avoidance of corticosteroids have been attempted to minimize toxicities associated with their chronic use. Corticosteroid-sparing therapy has been used in patients at higher risk for developing adverse effects such as hypertension, hyperlipidemia, hyperglycemia, and osteoporosis.[74-78] Meta-analyses have indicated that these corticosteroid-sparing regimens are associated with a higher risk of acute rejection and chronic allograft nephropathy.[74-78] The benefits of early steroid withdrawal include improved cardiovascular effects and decreased adverse effects.[79-81] These benefits must be weighed against the increased rate of acute rejection that is seen when steroids are removed from the immunosuppressive regimen.[79-81]

Corticosteroid-free regimens have been evaluated primarily in low-risk patients (ie, living donor transplants, non–African Americans, nonsensitized recipients) receiving antibody induction and have shown promising results.[81-85] Further studies in this area are warranted.

Calcineurin inhibitor–sparing therapy can be used in low-risk recipients. Studies have assessed the early conver-

sion from a calcineurin inhibitor to an mTOR inhibitor. Studies involving the conversion from a calcineurin inhibitor to sirolimus have shown an improvement of GFR after calcineurin inhibitor withdrawal; however, there was an increased incidence of rejection.[86-88] Similar results have been observed with everolimus. Studies involving conversion from a calcineurin inhibitor to everolimus showed that patients given everolimus had higher GFRs but also a higher incidence of biopsy-proven rejection compared with those given a calcineurin inhibitor.[89]

The current approach to transplantation has been the use of combined immunosuppressive regimens to avoid rejection, with the consequent adverse effects from this therapy, such as opportunistic infections, cancer, and many others. Improved survival and quality of life among transplant recipients will largely depend on research guided toward enhancing tolerance with the goal of achieving an immunosuppression-free state post transplantation.[90] Immunological tolerance has been described after liver transplantation in select recipients.[91] More recently, infusion of marrow-derived autologous mesenchymal stem cells (MSCs) in living-related kidney transplant recipients resulted in a lower incidence of acute rejection, reduced opportunistic infections, and improved renal function compared with anti-IL-2 receptor antibody induction therapy.[92] Further research on the use of MSCs, xenotransplantation, and advances in regenerative medicine should achieve better outcomes in transplant recipients by enhancing tolerance while avoiding or minimizing the use of immunosuppressive therapy.

Adjunctive Therapies

Solid organ transplant recipients are susceptible to opportunistic infections. The risk of developing infections occurs in a predictable pattern post transplant.[93] Antimicrobial prophylaxis is initiated after transplant to prevent infections with pathogens such as cytomegalovirus (CMV), *Pneumocystis jirovecii*, and *Candida albicans*.[93] Antiviral prophylaxis is used to prevent CMV, herpes simplex virus, varicella-zoster virus, EBV, human herpes virus 6, and human herpes virus 7 infections.[93] Antivirals commonly used include acyclovir, valacyclovir, ganciclovir, and valganciclovir.[93] Valganciclovir or IV ganciclovir provides coverage for CMV and the other viruses.[94] While acyclovir does not provide appropriate coverage for CMV, it can be used in low-risk patients to provide herpes virus prophylaxis.[95] Nystatin or clotrimazole is used to prevent oral fungal infections.[96] Sulfamethoxazole/trimethoprim is the preferred medication for *Pneumocystis jirovecii* pneumonia prophylaxis.[97] Sulfamethoxazole/trimethoprim has an added benefit of providing coverage for *Toxoplasma gondii*, *Nocardia* species, and pathogens that cause urinary tract infections.[96,97] Alternative therapies for patients with a sulfa allergy include pentamidine, dapsone, and atovaquone.[97] Antifungals such as voriconazole or itraconazole are given to lung transplant recipients to prevent aspergillus infections.[98] Antifungal prophylaxis with fluconazole, liposomal amphotericin, caspofungin, or another agent is ordered for high-risk liver transplant recipients.[99]

Other medications added to the transplant recipient's regimen vary depending on patient-specific comorbid conditions and the type of organ transplant. Electrolyte replacements, such as magnesium supplements, can be added for patients that develop hypomagnesemia. Insulin may be added for hyperglycemia or diabetes.[8] Antihypertensive medications are added for hypertension, and a statin may be added for hyperlipidemia.[96] Osteoporosis is common after transplantation due to the use of corticosteroids, which often requires patients to take calcium, vitamin D, and bisphosphonates.[96] Azithromycin may be used for lung transplant recipients to prevent or treat bronchiolitis obliterans syndrome.[100]

Conclusion

Advances in immunosuppression have resulted in improved acute rejection rates and patient and graft survival. Combinations of medications with varying mechanisms of action are commonly used; the immunosuppressants selected are based on transplant center-specific protocols and patient-specific factors. When designing the immunosuppressive regimen, factors such as the prevention of rejection episodes, improving patient and graft surivial, minimizing medication-related adverse effects, and the risk of developing infections must be considered.

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