TABLE 337-3 MAINTENANCE IMMUNOSUPPRESSIVE DRUGS

Agent	Pharmacology	Mechanisms	Side Effects
Glucocorticoids	Increased bioavailability with hypoalbuminemia and liver disease; prednisone/prednisolone generally used	Binds cytosolic receptors and heat shock proteins. Blocks transcription of IL-1, -2, -3, -6, TNF-α, and IFN-γ	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Cyclosporine (CsA)	Lipid-soluble polypeptide, variable absorption, microemulsion more predictable	Trimolecular complex with cyclophilin and calcineurin → block in cytokine (e.g., IL-2) production; however, stimulates TGF-β production	Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums
Tacrolimus	Macrolide, well absorbed	Trimolecular complex with FKBP-12 and calcineurin → block in cytokine (e.g., IL-2) production; may stimulate TGF-β production	Similar to CsA, but hirsutism/hyperplasia of gums unusual and diabetes more likely
Azathioprine	Mercaptopurine analogue	Hepatic metabolites inhibit purine synthesis	Marrow suppression (WBC > RBC > platelets)
Mycophenolate mofetil/sodium	Metabolized to mycophenolic acid	Inhibits purine synthesis via inosine monophosphate dehydrogenase	Diarrhea/cramps; dose-related liver and marrow suppression is uncommon
Sirolimus/everolimus	Macrolide, poor oral bioavailability	Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation	Hyperlipidemia, thrombocytopenia
Belatacept	Fusion protein, intravenous injections	Binds CD80 and CD86, prevents CD28 binding and T cell activation	Posttransplant lymphoproliferative disease

Abbreviations: FKBP-12, FK506 binding protein 12; IFN, interferon; IL, interleukin; RBC, red blood cells; TGF, transforming growth factor; TNF, tumor necrosis factor; WBC, white blood cells.

diabetes), only nephrotoxicity presents a serious management problem and is further discussed below.

Tacrolimus (previously called FK506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side effect profile; it does not, however, produce hirsutism or gingival hyperplasia. De novo diabetes mellitus is more common with tacrolimus. The drug was first used in liver transplantation and may substitute for cyclosporine entirely or as an alternative in renal patients whose rejections are poorly controlled by cyclosporine.

mTOR Inhibitors *Sirolimus* (previously called rapamycin) is another fungal macrolide but has a different mode of action; i.e., it inhibits T cell growth factor signaling pathways, preventing the response to IL-2 and other cytokines. Sirolimus can be used in conjunction with cyclosporine or tacrolimus, or with mycophenolic acid, to avoid the use of calcineurin inhibitors.

Everolimus is another mTOR inhibitor with similar mechanism of action as sirolimus but with better bioavailability.

Belatacept *Belatacept* is a fusion protein that binds costimulatory ligands (CD80 and CD86) present on antigen-presenting cells, interrupting their binding to CD28 on T cells. This inhibition leads to T cell anergy and apoptosis. *Belatacept* is FDA approved for kidney transplant recipients and is given monthly as an intravenous infusion.

CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT

Adequate hemodialysis should be performed within 48 h of surgery, and care should be taken that the serum potassium level is not markedly elevated so that intraoperative cardiac arrhythmias can be averted. The diuresis that commonly occurs postoperatively must be carefully monitored. In some instances, it may be massive, reflecting the inability of ischemic tubules to regulate sodium and water excretion; with large diureses, massive potassium losses may occur. Most chronically uremic patients have some excess of extracellular fluid, and it is useful to maintain an expanded fluid volume in the immediate postoperative period. Acute tubular necrosis (ATN) due to ischemia may cause immediate oliguria or may follow an initial short period of graft function. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Superimposition of rejection on ATN is common, and the differential diagnosis may be difficult without a graft biopsy. Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is reduced drastically. Many centers avoid starting cyclosporine for the first several days, using antilymphocyte globulin (ALG) or a monoclonal antibody along with mycophenolic acid and prednisone until renal function is established. Figure 337-2 illustrates an algorithm followed by many transplant centers for early posttransplant management of recipients at high or low risk of early renal dysfunction.

THE REJECTION EPISODE

Early diagnosis of rejection allows prompt institution of therapy to preserve renal function and prevent irreversible damage. Clinical evidence of rejection is rarely characterized by fever, swelling, and tenderness over the allograft. Rejection may present only with a rise in serum creatinine, with or without a reduction in urine volume. The focus should be on ruling out other causes of functional deterioration.

Doppler ultrasonography may be useful in ascertaining changes in the renal vasculature and in renal blood flow. Thrombosis of the renal vein occurs rarely; it may be reversible if it is caused by technical factors and intervention is prompt. Diagnostic ultrasound is the procedure of choice to rule out urinary obstruction or to confirm the presence of perirenal collections of urine, blood, or lymph. A rise in the serum creatinine level is a late marker of rejection, but it may be the only sign. Novel biomarkers are needed for early noninvasive detection of allograft rejection.

Calcineurin inhibitors (cyclosporine and tacrolimus) have an afferent arteriolar constrictor effect on the kidney and may produce permanent vascular and interstitial injury after sustained high-dose therapy. This action will lead to a deterioration in renal function difficult to distinguish from rejection without a renal biopsy. Interstitial fibrosis, isometric tubular vacuolization, and thickening of arteriolar walls are suggestive of this side effect, but not diagnostic. Hence, if no rejection is detected on the biopsy, serum creatinine may respond to a reduction in dose. However, if rejection activity is present in the biopsy, appropriate therapy is indicated. The first rejection episode is usually treated with IV administration of methylprednisolone, 500–1000 mg daily for 3 days. Failure to respond is an indication for antibody therapy, usually with antithymocyte globulin.

Evidence of antibody-mediated injury is present when endothelial injury and deposition of complement component c4d is detected by fluorescence labeling. This is usually accompanied by detection of the antibody in the recipient blood. The prognosis is poor, and aggressive use of plasmapheresis, immunoglobulin infusions, anti-CD20 monoclonal antibody (rituximab) to target B lymphocytes, bortezomib to target antibody-producing plasma cells, and eculizumab to inhibit complement is indicated.

MANAGEMENT PROBLEMS

The typical times after transplantation when the most common opportunistic infections occur are shown in Table 337-4. Prophylaxis for cytomegalovirus (CMV) and *Pneumocystis jiroveci* pneumonia is given for 6–12 months after transplantation.

The signs and symptoms of infection may be masked or distorted. Fever without obvious cause is common, and only after days or weeks may it become apparent that it has a viral or fungal origin. Bacterial infections are most common during the first month after transplantation.