2 Pharmacology of transplantation

Ian AC Rowe[1,2] *and James M Neuberger*[2]

[1]University of Birmingham, Birmingham, UK
[2]Queen Elizabeth Hospital, Birmingham, UK

Over the last three decades, there have been major developments in the drugs available for optimal management of the allograft recipient. Regimens for immunosuppression will vary for different organs and within different transplant units. Suggested regimens are described in the organ-specific chapters. Here, the pharmacology of the currently available immunosuppressive agents, and some agents in various stages of development, are discussed. Transplant recipients are often treated with many other drugs, including antiviral, antifungal, and antibacterial drugs used as prophylaxis or as treatment for various infections. Other drug classes commonly administered to transplant recipients include antihypertensives, lipid-lowering drugs, and a variety of medications used to prevent or treat post-transplant osteopenia. These latter drug categories fall out of the scope of this chapter and are covered in other chapters.

It is axiomatic that all drugs are potentially toxic but some have a beneficial effect and those benefits must be balanced against side effects. Most of the therapeutic agents used for immunosuppression are relatively non-specific in their action on the immune system. Side effects of these agents can be considered either as drug or as class specific (such as calcineurin inhibitor [CNI]-related nephrotoxicity) or integral to immunosuppression (such as increased susceptibility to infection and some cancers).

Primer on Transplantation, 3rd edition.
Edited by Donald Hricik.

Drug metabolism in organ failure

Disease of some organs, notably the liver and kidney, may affect both the pharmacokinetics (the relationship between the dose of a drug and changes in concentration over time) and the pharmacodynamics (the relationship between the drug concentration in the blood and the clinical response). The term 'pharmacokinetics' encompasses a number of pharmacologic phenomena including bioavailability, absorption, volume of distribution, clearance, and drug elimination. Each of these parameters may be abnormal in the presence of liver or kidney disease. It is therefore important for the clinician to have some understanding of the potential problems that may arise when prescribing drugs for patients with organ dysfunction. In this chapter, it is not possible to give any more than a superficial account of some of the factors that are of potential importance so the clinician will need to seek specific information in individual cases.

Liver disease

Although the standard liver tests are often referred to as 'liver function tests,' this is a misnomer because the analytes do not accurately reflect liver function nor are they always specific to the liver. Several tests of liver function have been developed and validated (such as the aminopyrine or caffeine clearance tests) but these are rarely used in clinical practice, will reflect only some aspects of liver function, and may not give any useful information about appropriate prescription of drugs in patients with liver impair-

ment. The best, but still not robust, guide to drug handling is probably the serum albumin.

The presence of liver disease may alter the response to drugs by one or more of several different mechanisms.

Absorption
Absorption of some drugs, especially those that are fat soluble, may be affected by the relative lack of excreted bile, or by the co-administration of agents (e.g., cholestyramine) that reduce absorption.

First-pass effect
Cirrhosis itself and intrahepatic stents (e.g., transjugular intrahepatic portosystemic shunts) may be associated with intrahepatic shunting of blood flow. In the presence of such shunts, drugs that are subject to significant first-pass metabolism will exhibit a significantly different profile which may make the patient more susceptible to the drug's effects.

Clearance
Hepatic drug clearance is related to both blood flow and extraction. Blood flow to the liver from the portal vein and hepatic artery may be abnormal in some liver diseases and post-transplantation situations, thus affecting drug clearance

Metabolism
Drug metabolism is potentially affected by liver disease. Distinction must be made between hepatocellular disease (e.g., alcoholic liver disease, viral hepatitis, or acute allograft rejection) and biliary disease (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, or chronic allograft rejection). Most drugs undergo metabolism within the hepatocyte and so will be affected by a variety of factors, including the patient's age, total hepatic mass, and the constituent drug-metabolizing enzymes. The activity of these enzymes may be affected by many factors including concomitant administration of other drugs that may act either as enzyme inducers or inhibitors, or that may compete for metabolic pathways. Drugs may be metabolized to the active agent and/or may be detoxified. Activities of the cytochromes (the major drug metabolizing enzymes) tend to vary during the first 6 months after liver transplantation

Distribution
The presence of ascites and peripheral edema may alter the volume of distribution of a drug. The concentrations of proteins that bind drugs and changes in acid–base balance are affected in liver disease. All of these factors may affect the drug pharmacokinetics and pharmacodynamics, e.g., drugs that are highly protein bound (such as prednisolone and phenytoin) may be more active in patients with low protein concentrations. Understanding the extent of protein binding is important because, for any total plasma concentration of drug, the amount of free (and therefore therapeutically effective) drug will vary with the protein concentration.

Excretion
For drugs that are excreted in the bile, biliary outflow obstruction (whether at the level of the cholangiocyte or the bile duct) may affect elimination, leading to retention of the parent drug and/or its metabolites. Some metabolites may themselves have a therapeutic effect and may or may not be measured in standard assays. For drugs that undergo enterohepatic recirculation, alterations in bile excretion may influence the drug's effects.

End-organ sensitivity
Liver disease may affect end-organ sensitivity, e.g., patients with advanced liver disease may be more likely to develop renal failure when given non-steroidal anti-inflammatory drugs. Those with advanced liver disease are more prone to cerebral depression and encephalopathy when given opiates for analgesia. In some cases, the presence of liver disease itself may be a risk factor for drug toxicity, e.g., methotrexate tends to be more hepatotoxic in the presence of steatosis and steatohepatitis. Of interest, viral infection may affect drug metabolism. It is now clear that tacrolimus levels will be affected when there is evidence of hepatitis C viral replication. The mechanism is not clear but the dose of CNI may need to be altered when the virus reactivates.

Drug hepatotoxicity

Drug hepatotoxicity can be categorized as either type I or II. Type I is predictable and dose related and the classic example is acetaminophen toxicity. When the normal detoxification mechanisms are overwhelmed

by the amount of drug to be metabolized, there is retention of a toxic intermediate that binds to cellular macromolecules and causes liver cell necrosis. The level at which toxicity occurs depends on many factors such as the amount of glutathione present (reduced in those with significant liver disease or malnutrition) and the rate at which the toxic metabolites are generated. The latter rate is increased in patients receiving concomitant enzyme inducers (e.g., phenobarbital or alcohol) and decreased when there is concomitant enzyme inhibition (e.g., by cimetidine).

Type II drug toxicity is unpredictable and may be due to idiosyncrasies in drug metabolism (type IIa) or the involvement of immune mechanisms (type IIb). In some transplant recipients, the patient may acquire the idiosyncratic drug responses of the donor, as has been well documented for peanut allergy. It must be stressed that there are no specific tests for adverse drug reactions and the diagnosis is one of exclusion.

Virtually every pattern of hepatic disease can be mimicked by drugs and some drugs may be associated with more than one type of liver damage, e.g., estrogens can be associated with cholestasis, peliosis, vascular thrombosis, adenoma, and even hepatocellular cancer. Azathioprine can be associated with focal nodular hyperplasia and/or hepatitis. If an adverse drug reaction is suspected, the drug should be withdrawn.

Kidney disease

As with liver disease, the presence and extent of kidney damage or reduced kidney function may affect the pharmacology of drugs by a number of mechanisms.

Metabolism

The kidney can metabolize some drugs, but this is rarely of clinical importance. In patients with impaired kidney function, alterations in drug pharmacokinetics and pharmacodynamics may occur as the result of altered acid–base homeostasis and/or with changes in the volume of distribution and concentrations of some drug-binding proteins (e.g., albumin).

Excretion

Impaired kidney function may be associated with reduced excretion of either active or inactive drug or metabolites. These may be pharmacologically significant or give misleading values in some therapeutic drug assays.

Sensitivity

The effects of some drugs may be increased in patients with impaired kidney function, even if metabolism is not affected.

Thus, the significance of impaired kidney function on the pharmacology of drugs will vary according to the extent and type of renal damage, the extent to which the drug is excreted by the kidney, and the therapeutic index (a marker of the ratio of safety to toxicity). The dose or the frequency of dosing for many drugs must be modified in patients with impaired kidney function.

The degree of renal impairment is best assessed by some estimate of glomerular filtration rate (GFR) because serum urea and creatinine concentrations are affected by non-renal factors such as the bulk of muscle mass or the presence of blood in the bowel. Most drug-dosing guidelines are based on the use of timed creatinine clearances to estimate the GFR. However, timed collections are notoriously inaccurate or incomplete. For this reason, many clinicians prefer surrogate estimations using calculations such as the Cockcroft–Gault or MDRD (modification of diet in renal disease) formulae. Neither is ideal nor a very accurate measure of renal function, but they are usually adequate for clinical use. Mild renal impairment is defined as a GFR between 20 and 50 mL/min, moderate impairment as between 10 and 20 mL/min, and severe impairment as <10 mL/min.

Pregnancy

As transplantation has become an established and successful treatment, pregnancy has become an option for more and more female transplant recipients. Many of the commonly used immunosuppressive agents may have adverse effects on the fetus and these effects are summarized for each drug class discussed below. In general, an assessment of drug safety during pregnancy can be made using data from animal models of teratogenicity and mutogenicity before experience is gained in humans.

The US Food and Drug Administration (FDA) introduced a classification of fetal risks due to drugs in 1979 (Table 2.1) based on a similar system introduced in Sweden a year earlier. This classification schema

Table 2.1 The USFDA pregnancy categories of medication-associated risk to the fetus

Pregnancy category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester (or subsequent trimesters) of pregnancy
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or animal studies, that have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

does not include any risks conferred by drugs entering breast milk, a phenomenon that is relevant to some of the commonly used immunosuppressants (e.g., cyclosporine, tacrolimus, and mycophenolate mofetil).

Individual immunosuppressive agents

Available immunosuppressants can be classified according to their pharmacologic mechanism of action. It should be noted that the licensed indications will vary over time and between different countries. There is often good evidence for use of drugs 'off-label' or outside their licensed indications.

Key points 2.1 Pharmacological methods of immunosuppression

Depletion of lymphocytes
- Polyclonal antibodies: ALG, thymoglobulin
- Monoclonal antibodies: OKT3

Inhibition of lymphocyte activation
- Antibodies:
  - IL2R antibodies: basiliximab, daclizumab
  - Anti CD80/86 antibodies: belatacept
- Corticosteroids
- Immunophilin–binding drugs
  - Calcineurin inhibitors: cyclosporine and tacrolimus
  - TOR Inhibitors: sirolimus

Inhibition of new nucleotide synthesis
- Purine synthesis inhibitors (IMPDH): mycophenolate
- Pyrimidine synthesis inhibitors (DHODH): leflunomide

Antimetabolites: azathioprine, cyclophosphamide

Inhibitors of lymphocyte trafficking and interaction
- Inhibitor of trafficking: FTY720
- Inhibitors of interactions:
- Antibodies to ICAM–1

ALG, anti-lymphocyte globulin; TOR, target of rapamycin; IMPDH, inosine monophosphate dehydrogenase; DHODH, IL-2R: interleukin-2 receptor; ICAM, intercellular adhesion molecule.

Drugs that cause lymphocyte depletion

These agents are used primarily in induction regimens or in desensitization protocols. Use of these agents for induction therapy varies worldwide, but generally there has been increasing use in the USA for the past decade.

Polyclonal antibodies

Rabbit antithymocyte globulin (Thymoglobulin)

Licensed indication Treatment of acute renal allograft rejection in conjunction with concomitant

immunosuppression. The drug is frequently used off-label for induction therapy.

Pharmacodynamics Thymoglobulin is a purified, pasteurized, rabbit IgG antibody preparation, obtained by repeated immunization of rabbits with human thymocytes. The exact mechanism of action is unknown but possible in vivo actions include clearance of activated T lymphocytes and modulation of T-lymphocyte homing, activation, and cytotoxic properties. The preparation includes antibodies against many T-cell antigens including the T-cell receptor, CD2, CD3, CD5, and CD8. In vitro concentrations of >0.1 μg/mL inhibit lymphocyte proliferation. Thymoglobulin has not been shown to be effective in the treatment of humoral (antibody-mediated) rejection.

Pharmacodynamics Thymoglobulin should be administered at a dose of 1.5 mg/kg body weight over a period of 4 hours (6 h for the first dose). The half-life is 2–3 days. Approximately 70% of patients will develop anti-rabbit antibodies though the effect of these is uncertain. In patients who are re-treated with Thymoglobulin measurement of lymphocyte subsets is sometimes recommended to ensure that T-lymphocyte depletion is achieved.

Adverse effects Anaphylactic reactions have been reported rarely. A substantial minority of patients will experience mild infusion reactions (fever, chills), although these may be reduced by premedication with acetaminophen, antihistamine, and/or glucocorticoid. Prolonged use may be associated with profound immunosuppression and an increased risk of opportunistic infections and/or post-transplant lymphoproliferative disease (PTLD)

Pregnancy and lactation Animal reproductive studies have not been performed with thymoglobulin and this drug should be used only if clearly needed.

Monoclonal antibodies

Rituximab

Indications Rituximab is licensed for treatment of patients with follicular lymphoma and PTLD. However, it is also being used off-label to reduce anti-donor antibody titers in highly sensitized renal transplant candidates and occasionally in combination with other modalities (e.g., plasmapheresis) for the treatment of humoral rejection mediated by anti-HLA antibodies or by ABO incompatibility.

Pharmacodynamics Rituximab is a chimeric mouse/human IgG (human IgG1 constant regions and murine light chain and heavy chain variable regions) monoclonal antibody (mAb) directed against CD20. It binds specifically to the transmembrane antigen CD20 located on pre-B and mature B lymphocytes. The antigen does not internalize upon antibody binding and does not circulate in plasma. The Fab domain of the rituximab binds to the CD20 antigen, allowing the Fc domain to recruit immune-mediated effector functions, including complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), resulting in lysis of the cell. Binding of rituximab to CD20 has also been shown to cause apoptosis.

Pharmacokinetics Rituximab is given as an intravenous infusion and should be given in 5% glucose or 0.9% sodium chloride, diluted to 1–4 mg/mL. Serum levels and the half-life are proportional to the dose administered. There are no data on the effects of renal or hepatic dysfunction on the drug's metabolism.

Adverse effects Infusion reactions are common, with up to 10% of patients experiencing systemic symptoms on the first infusion in patients with rheumatoid arthritis, and higher rates in patients being treated for lymphoma. Rituximab may provoke a severe cytokine release syndrome characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, chills, rigors, urticaria, and angioedema. In patients who develop this syndrome the infusion should be stopped immediately and appropriate treatment instituted. The syndrome is usually reversible although fatalities have been rarely reported. Patients receiving treatment should be closely monitored and antihypertensive medication withheld for 12 h before treatment. These reactions may be significantly reduced by predose administration of intravenous glucocorticoids. Caution is advised when used in patients with a history of cardiovascular disease because of the increased risk of dysrhythmia, angina, and heart failure.

Pregnancy and lactation No data are available in pregnant or lactating women treated with rituximab. However, the immunoglobulin IgG is known to cross the placenta and also enter breast milk, such that systemic effects in the fetus and newborn are to be anticipated.

OKT3

Licensed indications Treatment of acute renal, cardiac, or hepatic allograft rejection refractory to conventional therapy (or where conventional therapy is contraindicated).

Pharmacodynamics OKT3 is a murine monoclonal IgG2 antibody to CD3. CD3 is present on the surface of all human T lymphocytes and is involved in T-lymphocyte activation through its association with the T-cell receptor (together forming the T-cell receptor complex). OKT3 reverses allograft rejection by blocking the function of all T cells and in vitro studies have shown that generation and function of effector T cells are blocked.

Pharmacokinetics No detailed pharmacokinetic information is available. The recommended dose is 5 mg/day as a single intravenous bolus dose for 10–14 days. The drug-containing solution should be drawn up through a sterile, low-protein-binding, 0.2–0.22 µm filter before rapid intravenous bolus injection.

Adverse effects The major side effects are a consequence of cytokine release. The cytokine release syndrome described above for rituximab occurs in most patients treated with OKT3 and may be severe. Pulmonary edema occasionally occurs in euvolemic patients but is more common in those with pre-existing volume overload. All patients should be assessed clinically for signs of volume overload and, if necessary, treated with diuretics or hemofiltration to assure euvolemia before treatment with this drug. The cytokine release syndrome may be prevented or palliated by pre-treatment with glucocorticoids (e.g. hydrocortisone sodium succinate). Hypersensitivity reactions including anaphylaxis have also been described, albeit less frequently than cytokine release syndrome. The two syndromes may be difficult to tell apart.

Neuropsychiatric events including headache (most commonly), seizures, encephalopathy, cerebral edema and herniation, and aseptic meningitis have been reported. Patients with pre-existing neurological disease appear to be at greatest risk. Although headache, seizures, and mild encephalopathy may resolve with continued treatment, fatalities have been reported in those developing cerebral edema, with or without herniation. All patients should be monitored for a period of 24 h after each injection for neurological signs and, if signs of cerebral edema are seen, treatment should be discontinued. Patients treated with OKT3, particularly at high cumulative doses, are at increased risk of infectious complications especially with the human herpes viruses (herpes simplex virus [HSV], cytomegalovirus [CMV], and Epstein–Barr virus [EBV]) and also EBV-mediated post-transplant lymphoproliferative disorders.

Pregnancy and lactation OKT3 is contraindicated in pregnant women, and those who are breastfeeding.

Key points 2.2 Cytokine release syndrome

Characterized by:
- Severe dyspnea, bronchospasm, and hypoxia
- Chills and rigors
- Urticaria and angioedema

Initial treatment:
- Stop treatment
- Oxygen
- Volume expansion
- Intravenous glucocorticoid

Prevention:
- Withhold antihypertensive medication for 12 h before treatment
- Ensure euvolemia
- Premedication with intravenous glucocorticoid

Alemtuzumab (Campath-1H)

Indications Alemtuzumab is licensed for the treatment of chronic lymphocytic leukemia (CLL) in patients who have had a poor response to conventional therapy. It has been used off-label as part of induction therapy, especially in protocols that putatively promote tolerance or immune hyporesponsiveness.

Initial studies, in a variety of organ grafts, show that its use is safe and effective and may allow for reduced exposure to maintenance immunosuppressive drugs. It should not be used in those with chronic hepatitis C viral infection.

Pharmacodynamics This is a genetically engineered humanized IgG1 κ monoclonal antibody directed against CD52. CD52 is a highly expressed, non-modulating antigen which is present on the surface of essentially all B and T lymphocytes, monocytes, thymocytes. and macrophages. The antibody mediates cell lysis through CDC and ADCC. CD52 is found on only a minority of granulocytes (<5%) but not on erythrocytes, platelets, hemopoietic stem cells. or progenitor cells, thus sparing these cell lines from depletion. Administration results in profound depletion of lymphocytes and monocytes. The composition of the reconstituted pool may not resemble that of the original pool of cells.

Pharmacokinetics The available data are from patients receiving treatment for CLL who have been treated with repetitive doses for a much longer period (12 weeks) than is used in transplantation. In transplant recipients, the usual dose is 0.3 mg/kg per day for the first 3–4 postoperative days, but some centers use a single perioperative dose The antibody should be infused in 100 mL 5% glucose or 0.9% sodium chloride over 2 h through a low-protein-binding 5 µm filter. Alemtuzumab is largely distributed in the extracellular fluid and plasma compartments and, because CD52-positive cells are depleted, there is decreased receptor associated clearance and a fall in systemic clearance over time.

Adverse effects The cytokine release syndrome may occur with alemtuzumab and it is recommended that all patients receive pre-treatment with glucocorticoids. Transient hypotension may also occur and antihypertensive medication should be withheld for at least 12 h before administration. Profound lymphocyte depletion inevitably occurs and may be prolonged. During this time patients are at risk for opportunistic infections and all patients should receive appropriate prophylaxis for *Pneumocystis jiroveci* pneumonia and herpes viruses. Hematological monitoring is essential because myelosuppression is common, but monitoring of CD52 is not required.

Pregnancy and lactation Alemtuzumab is contraindicated in pregnant and breast-feeding women due to the potential for the antibody to cross the placenta or into breast milk. The manufacturer advises men and women to use effective contraception during treatment and for 6 months thereafter.

Drugs that inhibit lymphocyte activation

These agents prevent immunological activation through blockade of key signals involved in lymphocyte activation. They include anti-CD25 (the interleukin-2 [IL-2] receptor) antibodies, corticosteroids, the calcineurin inhibitors, and agents that inhibit essential co-stimulatory molecules including CD80/86 and CTLA4.

Basiliximab and daclizumab

Indication Both basiliximab and daclizumab are licensed for the prophylaxis of acute rejection in renal allograft recipients who are also to be treated with cyclosporine and corticosteroids. Their use may allow reduced doses or delayed introduction of CNIs and so may be beneficial in those with delayed graft function and may reduce the risk of late CNI-associated renal failure. Although discussed below, it should be noted that daclizumab was recently removed from the market.

Pharmacodynamics Basiliximab is a murine/human chimeric monoclonal IgG1 antibody directed against the α chain of the IL-2 receptor (CD25) which is expressed on the surface of activated T lymphocytes. The antibody binds with high specificity and affinity to the IL-2 receptor (IL-2R) thus preventing IL-2 binding and cellular proliferation. Complete blocking of the IL-2R is maintained until serum basiliximab levels fall below 0.2 µg/mL (in practice between 4 and 6 weeks). CD25 expression returns and reaches pre-treatment values after an additional 1–2 weeks. Daclizumab is a recombinant humanized IgG1 anti-tac antibody that also acts as an IL-2R antagonist. It also binds to the α or tac subunits of the IL-2R. Daclizumab saturates the IL-2R for approximately 90 days. Antibodies against daclizumab have been detected in 9% of those treated but have no clinical significance.

Pharmacokinetics Basiliximab reaches peak concentrations of 7.1 ± 5.2 µg/mL after intravenous infusion. The terminal half-life is 7.2 ± 3.2 days. Distribution of the drug is not significantly affected by body weight

or gender. Basiliximab should be given as a slow intravenous injection or by slow intravenous infusion over 2 h. For adults, the dose is 20 mg before and at 4 days after transplantation. Patients weighing less than 35 kg should receive 10 mg.

Daclizumab given at a dose of 1 mg/kg and the peak concentration after the first dose is 21 µg/mL. A concentration of 0.5–0.9 µg/mL is required to saturate the IL-2R and a dose of 5–10 µg/mL is required to inhibit its biological activity. The recommended dosing regimen of five 1 mg/kg doses, with the first dose given in the 24 h before surgery, is sufficient to saturate the IL-2R for more than 90 days. The terminal elimination half-life is approximately 480 h and is equivalent to that reported for human IgG. Elimination is increased with increasing body weight, hence the need for dosing based on body weight.

Adverse effects In trials of both basiliximab and daclizumab used in combination with cyclosporine and corticosteroids there were no additional adverse effects reported.

Pregnancy and lactation There are some animal data that suggest increased prenatal loss with daclizumab treatment but there are no other data and use of basiliximab and daclizumab is not recommended in pregnancy. The manufacturers advise that women of child-bearing age should use effective contraception during treatment and for 4 months thereafter.

Belatacept

Previously known under the investigational term LEA29Yl, belatacept blocks co-stimulation by binding to CD80 and CD86 on the surface of antigen-presenting cells (APCs). This interaction inhibits T-cell activation and promotes anergy and apoptosis (Figure 2.1). The agent is a human fusion protein combining the extracellular portion of CTLA4 (cytotoxic lymphocyte associated antigen-4) with the Fc portion of human IgG1. It has been shown to be of benefit in the treatment of some autoimmune diseases including rheumatoid arthritis and psoriasis. Studies in renal allograft recipients suggest a possible benefit when used in combination with other immunosuppressive agents. The doses used are not fully established: during the early weeks after transplantation, higher doses are given (10 mg/kg) than later in the post-transplant course (5 mg/kg) as a 30-min infusion every 4–8 weeks. Side effects are few.

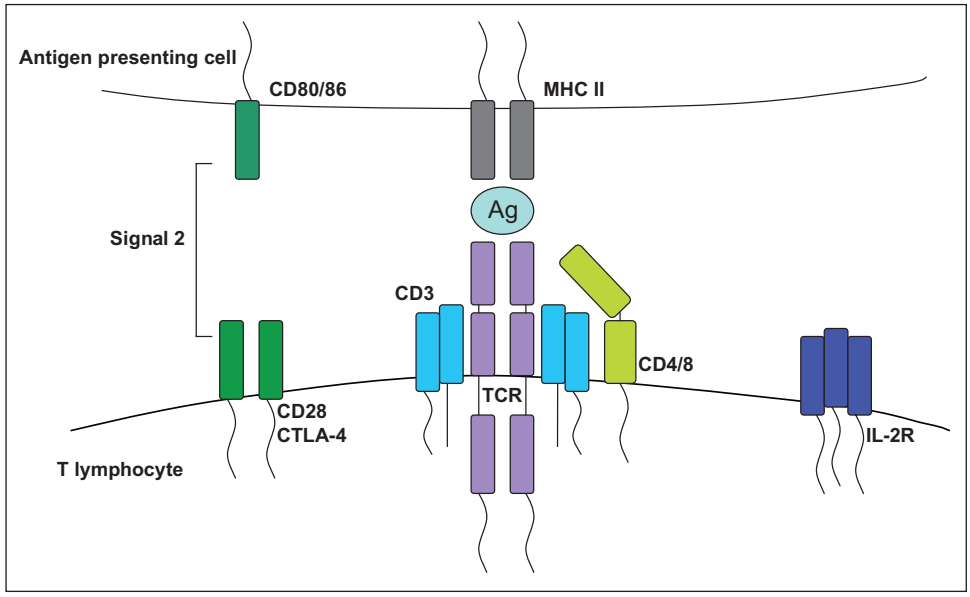

Figure 2.1 T-cell activation requires antigen (Ag) presentation in the context of major histocompatibility complex (MHC) of antigen-presenting cells (APCs) to CD3 T-cell receptor (TCR) complex. A second co-stimulatory signal (signal 2) is also required.

Glucocorticoids

Indication Prophylaxis and treatment of acute rejection following solid organ transplantation.

Pharmacodynamics Glucocorticoids are potent anti-inflammatory and immunosuppressive agents. They enter the cell by diffusion and then bind to high-affinity cytoplasmic glucocorticoid receptors. The glucocorticoid receptor steroid complex enters the nucleus where it binds to the glucocorticoid response element. The glucocorticoid receptor steroid complex may also bind to other regulatory elements, inhibiting their binding to DNA. Both actions lead to alterations in the transcription of genes involved in the immune and inflammatory responses. The most important effects on lymphocytes are mediated through a decrease in expression of the transcription factors nuclear factor (NF)-κB and activator protein-1. Functionally this leads to a decrease in the production of T-cell cytokines that are required to augment the responses of macrophages and lymphocytes. The anti-inflammatory effects are mediated largely through inhibition of phospholipase A_2 by lipocortin, thereby reducing synthesis of prostaglandins and other related compounds. Finally, glucocorticoids cause a decrease in the numbers of circulating lymphocytes by stimulating the migration of T cells from the intravascular compartment to lymphoid tissue.

Pharmacokinetics Hydrocortisone or methylprednisolone is frequently given intravenously in the first few days after transplantation. Prednisolone, given orally, is well absorbed from the gastrointestinal tract. It is widely used for maintenance immunosuppression in European centers. In the USA, prednisone (the metabolic precursor of prednisolone) is the more popular maintenance agent. Peak plasma concentrations of prednisolone are seen within 1–2 h. Absorption (but not overall bioavailability) is affected by food. The effective half-life of prednisolone is 2–4 h and elimination is in the urine after metabolism in the liver. In general, all corticosteroids are extensively bound to plasma proteins, although prednisolone is bound to a lesser extent than hydrocortisone.

Adverse effects The adverse effects of steroids are well recognized (Table 2.2) and often the physical effects are troubling for the patient. The risk of osteoporosis is great and bone density in all patients receiving long-term steroids should be measured and treatment with calcium supplementation or bisphosphonates considered in those patients at greatest risk.

Table 2.2 Adverse effects of corticosteroids

System	Adverse effect
Cardiovascular	Sodium retention Fluid retention Potassium depletion Hypertension
Endocrine	Carbohydrate intolerance and diabetes mellitus Cushingoid facies Growth retardation Menstrual irregularities
Ophthalmic	Cataract Glaucoma
Musculoskeletal	Osteoporosis and increased fracture risk Aseptic necrosis of femoral head Myopathy Muscle weakness
Dermatologic	Increased bruising Skin thinning Acne
Neurologic	Altered mood Headaches
Gastrointestinal	Peptic ulceration Pancreatitis

Pregnancy and lactation There is no evidence that treatment with glucocorticoids increases the risk of congenital malformations. However, prolonged treatment may increase the risk of intrauterine growth retardation. Although most glucocorticoids are inactivated on crossing the placenta, hypoadrenalism in the neonate is theoretically a risk, though rarely clinically important. Mothers with pre-eclampsia should be closely monitored. Only a small proportion of glucocorticoids is excreted in small amounts into breast milk. Doses up to 40 mg of prednisolone are unlikely to cause significant systemic effects in the infant and the benefits of breastfeeding are likely to

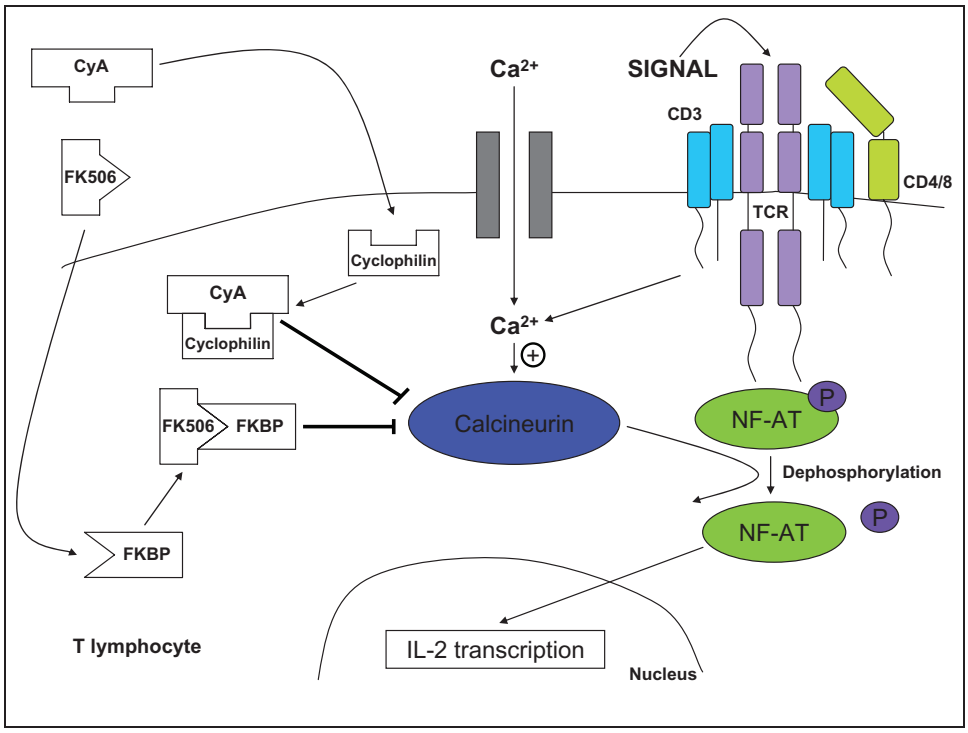

Figure 2.2 Mechanism of action of calcineurin inhibitors. Cyclosporine (CyA) binds to its immunophilin, cyclophilin, forming a complex that blocks the phosphatase activity of calcineurin. Tacrolimus (FK506) binds to the FK506-binding protein (FKBP) and this complex binds to and blocks the activity of calcineurin. The effect of blocking calcineurin is to prevent passage of nuclear factor of activated T cells (NF-AT) into the nucleus, thus preventing transcription of the interleukin-2 (IL-2) gene.

outweigh the theoretical risk to the infant at higher doses.

Immunophilin-binding drugs

Calcineurin inhibitors (Figure 2.2)

The two CNIs used in transplantation are cyclosporine and tacrolimus. Their mode of action is similar but not identical and is described in detail below. Drug interactions may affect levels or toxicity. Metabolism of both CNIs is mediated through the cytochrome P450 system (CYP3A4) and so levels may be affected by enzyme inducers and inhibitors (Table 2.3). With both drugs, therapeutic drug monitoring is required but the correlation between levels and efficacy and toxicity is relatively weak. The side effects of the two CNIs are broadly similar (Table 2.4) but do differ, e.g., hirsutism and gum hypertrophy are seen more frequently with cyclosporine whereas neurological disturbance and diabetes mellitus are more common in patients receiving tacrolimus.

Cyclosporine

Licensed indications Prophylaxis of transplant rejection in liver, renal, heart, combined heart–lung, lung, and pancreas allograft recipients.

Pharmacodynamics Cyclosporine is a small fungal cyclic polypeptide consisting of 11 amino acids and binding to cyclophilin in the cytosol. The cyclosporine–cyclophilin complex binds to calcineurin together with calmodulin and calcium, inhibiting the phosphatase activity of calcineurin. This results in the inhibition of dephosphorylation and translocation of

Table 2.3 Calcineurin inhibitor drug interactions

Effect of interaction	Drug
Increased CNI level (CYP 3A4 inhibitors)	Azole antifungals (ketoconazole, itraconazole, fluconazole) Protease inhibitors Cimetidine Clarithromycin Cyclosporine Diltiazem Erythromycin Grapefruit juice Metoclopramide Nicardipine Verapamil
Decreased CNI level (CYP3A4 inducers)	Carbamazepine Phenytoin Phenobarbital Rifampicin St John's wort
Increased nephrotoxicity	Aminoglycosides Colchicine Fibrates NSAIDs
Hyperkalemia	ACE inhibitors A2RBs
Gum hyperplasia (with cyclosporine)	Nifedipine
Myopathy (with cyclosporine)	HMG-CoA reductase inhibitors

Note: combination of these agents (such as cyclosporine and sirolimus) will interact with each other.
CYP3A4, cytochrome P450 3A4; CNI: calcineurin inhibitor; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin-converting enzyme; A2RB: angiotensin 2 receptor blockers; HMG-CoA: 3 hydroxy-3-methylglutaryl CoA.

the cytoplasmic unit of NF-AT (nuclear factor of activated T cells) and thus inhibits gene transcription of proteins such as IL-2 and interferon-γ. Inhibition of IL-2 blocks the formation of cytotoxic T cells and suppresses both T-cell activation and T-helper cell-dependent proliferation of B cells.

Table 2.4 Adverse effects of the calcineurin inhibitors (CNIs)

System	Adverse effects
Renal	Renal failure Hyperuricemia and gout Hyperkalemia Hypermagnesemia
Cardiovascular	Hypertension
Endocrine	Glucose intolerance and diabetes mellitus
Neurological	Headaches Migraine Tremor
Other	Hirsutism Gum hypertrophy

Note that some adverse effects are more common with one CNI than another.

Pharmacokinetics There are several preparations of cyclosporine currently available. The original preparation (Sandimmune) has been replaced largely by a microemulsion formulation (Neoral). Neoral is a preconcentrate formulation of cyclosporine which undergoes microemulsification in the presence of water, in the form of either a beverage or gastrointestinal fluid. This reduces intrapatient variability with a more consistent absorption profile and less effect from concomitant ingestion of food. Pharmacokinetic studies of Neoral indicate a greater correlation between trough concentrations and total drug exposure (as measured by area under the curve or AUC) than Sandimmune. Neoral therefore has greater predictability and consistency of cyclosporine exposure. In addition, there are now several generic formulations of cyclosporine available worldwide. It should be stressed that each formulation has a different pharmacologic profile and so they are not interchangeable. If a patient is switched from one formulation to another, levels and side effects should be closely monitored.

Cyclosporine is largely distributed outside the blood volume. In plasma approximately 90% is

bound to plasma proteins, mostly lipoproteins. There is extensive biotransformation to approximately 15 metabolites and although no single major metabolic pathway has been identified there is significant cytochrome P450 3A4 (CYP3A4) activity. Excretion is largely in bile. There is significant variation in terminal half-life depending on the target population, varying from 6 h in healthy individuals to 20 h in patients with severe hepatic dysfunction.

Traditionally, therapeutic dose monitoring was done using trough levels, with the guide levels of 150–250 ng/mL (whole blood levels measured by radioimmunoassay) for the first 3 months and then target levels of 100–150 ng/mL. As the maximal effect on calcineurin inhibition correlates with the time of peak blood concentration, there has been a move to focus drug monitoring on the 2-hour post-dose level (C2 monitoring, rather than C0 monitoring). Studies have suggested a better outcome using C2 monitoring in the first 3 months after transplantation. Target levels at 2 h lie between 0.8 and 1.2 µg/mL in the first 3 months and 0.7–0.9 µg/mL thereafter.

Pregnancy and lactation Cyclosporine is not teratogenic in animals. Epidemiological studies in humans have not identified teratogenicity, although there may be an associated increase in pre-term delivery. Offspring exposed to cyclosporine should be actively followed for evidence of drug toxicity. Cyclosporine is excreted in breast milk and mothers receiving treatment should not breastfeed because detrimental effects on the newborn cannot be excluded.

Tacrolimus

Licensed indications Prophylaxis of transplant rejection in liver, kidney, and heart allograft recipients.

Pharmacodynamics Tacrolimus accumulates in the cellular cytoplasm by binding to a cytosolic protein called FKBP12. The FKBP12–tacrolimus complex specifically and competitively binds to calcineurin, leading to a calcium-dependent inhibition of T-cell transduction pathways through suppression of synthesis of cytokines including IL-2. The formation of cytotoxic T cells is inhibited. T-cell activation and T-helper cell-dependent proliferation of B cells are suppressed.

Pharmacokinetics Tacrolimus is well absorbed throughout the gastrointestinal tract and intravenous administration is rarely required. After oral administration peak blood levels are seen within 1–3 h. Studies in patients after liver transplantation have shown that steady-state concentrations are reached within 3 days in most patients. The rate and extent of absorption are maximal under fasting conditions. The presence of food in the gastrointestinal tract reduces the rate and extent of absorption and bioavailability is reduced most following administration after a high fat meal. In practice, patients should be advised to take the medication on an empty stomach either 1 h before or 2–3 h after, a meal.

In whole blood tacrolimus is highly bound to erythrocytes resulting in a whole blood to plasma ratio of 20:1. In plasma, more than 98% of the drug is bound to plasma proteins, mainly albumin and α_1-acid glycoprotein. Tacrolimus is widely metabolized in the liver by CYP3A4. There is also considerable metabolism in the intestinal wall. Several metabolites have been identified and only one of these has been shown in vitro to have immunosuppressive activity similar to tacrolimus. The others have either weak or no immunosuppressive activity. In the circulation, only one of the inactive metabolites is present at low concentrations. Excretion is in bile. In studies with ^{14}C-labelled tacrolimus, less than 1% of unchanged tacrolimus can be identified in urine and feces, indicating that tacrolimus is almost completely metabolized before elimination.

The starting dose is 0.1 mg/kg per day in two divided doses. A strong correlation exists between drug exposure (as measured by the AUC) and whole blood trough levels, and most units aim for target trough whole blood levels of 10–15 ng/mL in the first 3 months and between 5 and 10 ng/mL thereafter. The half-life is long and variable in healthy individuals but is significantly shorter in transplant recipients (43 h vs 12–16 h). Increased clearance rates in transplant recipients contribute to the decreased half-life.

More recently, a modified-release formulation with an extended oral absorption profile has been developed for use as a single daily dose. Although the pharmacokinetics of the two preparations are broadly similar, there are some differences, so that close monitoring is recommended for the first few weeks if

patients are switched from the twice-daily to the single-daily dosing regimen.

Pregnancy and lactation Tacrolimus is able to cross the placenta but the limited data available do not show an increased risk of adverse effects in the course and outcome of pregnancy in comparison with other immunosuppressive agents. Due to the need for treatment, tacrolimus can be considered in pregnant women when no safer alternative is available and where the benefit of treatment outweighs the risk to the fetus. There is a risk of premature delivery and the newborn is at risk of transient hyperkalemia after birth. The newborn should also be monitored for potential complications including effects on the kidney. Tacrolimus is excreted in breast milk and women should not breastfeed because detrimental effects on the newborn cannot be excluded.

Adverse effects Compared with cyclosporine, use of tacrolimus is associated with an increased risk of post-transplant diabetes mellitus. In children, cardiac hypertrophy has been reported.

Drugs that inhibit lymphocyte proliferation

Target of rapamycin inhibitors (sirolimus and everolimus)

Licensed indications Sirolimus is used in patients receiving a kidney transplant and everolimus is used in patents receiving either a kidney or heart transplant as prophylaxis of organ rejection in those with low-to-moderate immunological risk when receiving a renal transplant. It is recommended that sirolimus be used initially in combination with cyclosporine and corticosteroids, but may be continued as maintenance therapy with corticosteroids alone only if cyclosporine can be progressively withdrawn. Everolimus may be used for prophylaxis of organ rejection in kidney and heart transplantation

Pharmacodynamics Sirolimus and everolimus inhibit proliferation of both T and B lymphocytes by blocking calcium-dependent and calcium-independent intracellular signal transduction (Figure 2.3). Target of rapamycin (TOR) inhibitors bind to FKBP12 but, rather than inhibiting the calcineurin pathway, the TOR inhibitor–FKBP12 complex interacts with mTOR, a protein kinase that is integral to signal transduction. Inhibition of mTOR blocks synthesis of proteins required for cell cycle progression. As the drugs inhibit both T and B cells, antibody-mediated immunity is also affected. The TOR inhibitors also inhibit growth-factor-stimulated cell cycle progression of vascular smooth muscle cells at the G1 stage, and so may be of benefit in reducing the transplant vasculopathy seen in ischemic/reperfusion injury and chronic rejection.

Pharmacokinetics Both sirolimus and everolimus are rapidly, although relatively poorly, absorbed from the gut (oral bioavailability about 15%). Absorption is mediated via the counter-transporter activity of P-glycoprotein. Absorption is affected by concomitant ingestion of food and the patient should be advised to take the medicine consistently with or without food. Sirolimus is metabolized extensively through the CYP3A4 in the liver. There are seven major metabolites, none of which has significant immunosuppressive activity. Everolimus is broadly similar but has a shorter half-life. The half-life is long in healthy individuals (about 60 h for sirolimus and 28 h for everolimus) and longer in those with liver disease. Thus, steady state is reached in 6 days for sirolimus and 4 days for everolimus. Excretion is largely in the bile and little drug is excreted by the kidneys. Patients with liver disease may have impaired metabolism.

The recommended dose regimen for sirolimus is a loading dose of 6 mg followed by 2 mg daily, with the dose adjusted to maintain trough whole blood levels between 4 and 15 ng/mL. Higher trough levels are required in those on monotherapy. The drug should be taken consistently, at the same time of day, either with or without food. Sirolimus may be used in combination with cyclosporine (4 h after taking cyclosporine) and with corticosteroids. As cyclosporine is an inhibitor of CYP3A4, lower doses of sirolimus may be required by those taking both agents. For everolimus, the initial daily dose is 1.3–3.0 mg/day with target trough levels of 3–8 ng/ml.

Side effects Delayed wound healing arises from drug-induced inhibition of certain growth factors and tends to be more common in obese patients. Many units will delay introduction until 3 months post-transplantation. In trials of sirolimus in liver

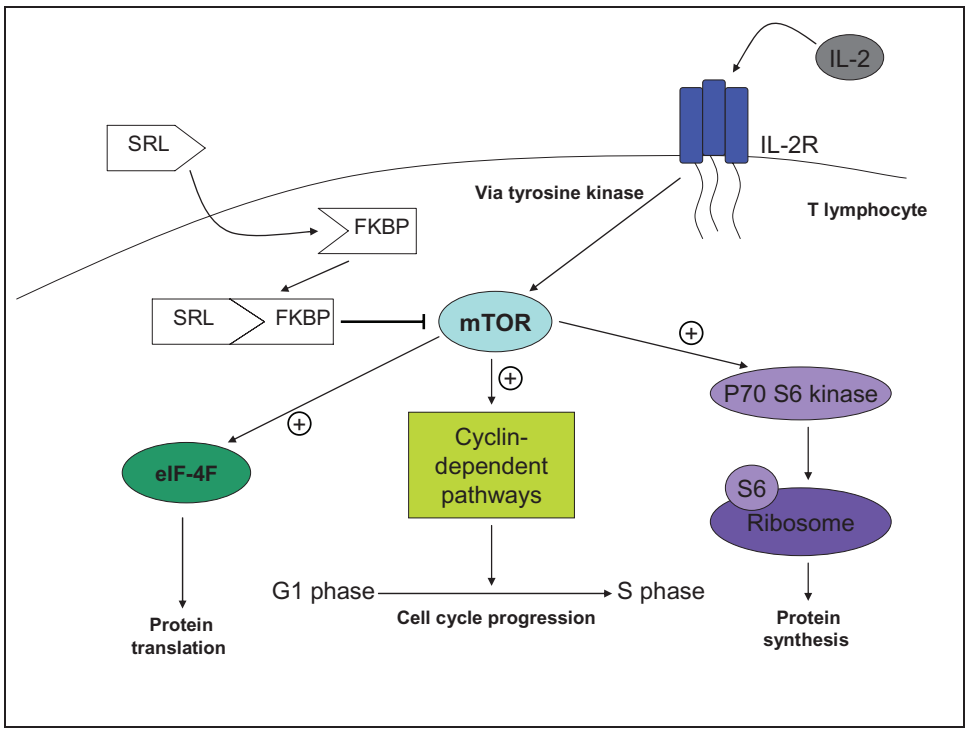

Figure 2.3 Mechanism of action of sirolimus. Sirolimus binds to the FK506-binding protein (FKBP); the complex that is formed then binds to the mammalian target of rapamycin (mTOR). This final complex inhibits pathways vital for cell cycle progression through a cyclin-dependent pathway, protein translation through eukaryotic initiation factor eIF-4F, and protein synthesis through the S6 protein kinase P70 S6 kinase. TOR1 inhibits proliferation of both T and B lymphocytes by blocking calcium-dependent and calcium-independent intracellular signal transduction. TOR1 binds to the FKBP12 but, rather than inhibiting the calcineurin pathway, the TOR1–FKBP12 complex interacts with mTOR, a protein kinase that is integral to signal transduction. Inhibition of mTOR blocks synthesis of proteins required for cell cycle progression, thus effectively blocking signal transduction. As TOR1 inhibits both T and B cells, antibody-mediated immunity is also affected. TOR1 also inhibits growth factor-stimulated cell cycle progression of vascular smooth muscle cells at the G1 stage, and so may be of benefit in reducing the transplant's vasculopathy seen in ischemic–reperfusion injury and chronic rejection.

transplantation, an increased incidence of hepatic artery thrombosis led to a 'black box' warning by the FDA for its use in this setting. New use of sirolimus has also been associated with failure to heal the tracheal anastomosis after lung transplantation. Hyperlipidemia, manifest as both hypercholesterolemia and hypertriglyceridemia, is common but often modified by co-administration of hydroxymethyl coenzyme A (HMG-CoA) reductase inhibitors and/or fibrates. Other common side effects include lymphocele, tachycardia, stomatitis, abdominal pain and diarrhea, anemia, leucopenia, thrombocytopenia, arthralgia, pneumonitis, acne, proteinuria, and urinary tract infections. Interstitial lung disease is a rare but potentially serious complication. Both drugs may exacerbate CNI-associated nephrotoxicity so renal function should be monitored regularly. Many transplant centers lower their target blood levels for the CNIs when they are used concomitantly with one of the TOR inhibitors.

Pregnancy and lactation In animal models, sirolimus has been associated with fetal toxicity manifested by increased mortality and reduced fetal weights. There are no human data from the use of sirolimus in pregnant women but it should not be used in pregnancy

unless no other therapy is available. Effective contraception should be used while taking a TOR inhibitor and for at least 12 weeks after its cessation. In rats, sirolimus is excreted in breast milk and although no human data are available mothers taking sirolimus should be advised not to breastfeed.

Inhibitors of new nucleotide synthesis

Purine synthesis inhibitors (mycophenolate derivatives)

Indications These agents are approved for prophylaxis of rejection in combination with cyclosporine or corticosteroids in patients receiving liver, kidney, or cardiac allografts. Monotherapy with mycophenolate mofetil may be associated with chronic rejection so most will use the agent in conjunction with either a CNI or corticosteroids. Although not licensed for use with tacrolimus, the two agents are frequently used together.

Pharmacodynamics Use of mycophenolate derivatives exploits the fact that lymphocytes, unlike other cells, do not have a salvage pathway for synthesis of purines. Thus, mycophenolate inhibits T- and B-cell proliferation by inhibition of new purine synthesis by potent, selective, and reversible inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH). The effect of this is to block synthesis of the guanosine nucleotide. Without its incorporation into DNA, there is a cytostatic effect on lymphocytes, inhibiting mitogen- and alloantigen-induced stimulation as well as inhibiting antibody production, adhesion to endothelial cells, and, possibly, cell recruitment.

Pharmacokinetics Two preparations of mycophenolate are available: mycophenolate mofetil and enteric-coated mycophenolate sodium. Mycophenolate mofetil is an ester of mycophenolate and undergoes rapid and extensive absorption from the gastrointestinal tract and then complete presystemic metabolism to the active metabolite. Enteric-coated mycophenolate sodium is also extensively absorbed from the gastrointestinal tract and absorption of both formulations is not affected by concomitant ingestion of food. Mycophenolate is highly protein bound in plasma and, in conditions where there is reduced protein binding (e.g. uremia, hepatic failure, hypoalbuminemia, or concomitant use of drugs with high protein binding), patients are at increased risk of mycophenolate-related adverse effects.

Mycophenolate is metabolized by glucuronyl transferase in the liver to form mycophenolate glucuronide (MPAG). The majority of MPAG is excreted in the urine although a small proportion is excreted in the bile. MPAG excreted in the bile is deconjugated by gut flora and the resulting mycophenolate is reabsorbed to create a second peak of mycophenolate in blood that can be measured 6–8 h after dosing.

Clinically there is little to choose between the two preparations, although some suggest that gastrointestinal upset is less common with the enteric-coated formulation. The usual maintenance dose for enteric-coated mycophenolate sodium is 1440 mg/day and for mycophenolate mofetil is 2 g/day, both given in two or three divided doses. Mycophenolate mofetil is available in an intravenous formulation. Therapeutic drug monitoring is available but not used commonly. Patients should be monitored for neutropenia and the dose reduced or stopped if the absolute white count falls below 1.3×10^9/L.

Pregnancy and lactation Genotoxicity studies of mycophenolate in mouse models demonstrate a potential for chromosomal aberrations. This effect is clearly related to the pharmacodynamic mechanism of action. In animal models mycophenolate is excreted in breast milk. Human data are limited. However, the FDA recently classified these agents as category D (see Table 2.2) so that many transplant centers avoid the mycophenolate derivatives during pregnancy. When deemed necessary, effective contraception should be used before, during, and for 6 weeks after therapy.

Adverse effects Significant side effects include diarrhea, upper gastrointestinal disturbances. and myelosuppression, especially leukopenia and anemia.

Pyrimidine synthesis inhibitors (leflunomide)

Leflunomide is available for use in patients with rheumatoid arthritis. The agent has been used in transplantation, not so much because of its immunosuppressive properties, but because of putative benefit in controlling BK polyoma viral infection in transplanted kidneys. The active metabolite, A77172G, has a very long half-life (1–4 weeks). In those with arthritis, the

loading dose is 100 mg daily for 3 days with a maintenance dose of 10–20 mg once daily. Side effects are few and include modest increase in blood pressure, mild gastrointestinal upset, reversible alopecia, leukopenia, and hepatitis. Stevens–Johnson syndrome may develop. Full blood count and liver function monitoring should be performed. FK778 is a synthetic malononitrilamide related to leflunomide and is currently being evaluated in allograft recipients.

Antimetabolites

Azathioprine

Indications Azathioprine is licensed to prolong survival in combination with glucocorticoids or other immunosuppressive agents in allograft recipients including those undergoing cardiac, kidney, or liver transplantation.

Pharmacodynamics Azathioprine is an imidazole derivative of 6-mercaptopurine (6MP) (an analogue of the purines, hypoxanthine and adenine). It is rapidly broken down in vivo by thiopurine methyl transferase (TPMT) to 6MP which rapidly crosses cell membranes. Once in the intracellular space, 6MP is further broken down into a number of purine thioanalogs including the main active metabolite thioinosine monophosphate. Although the exact mechanism of action remains unclear, it seems likely that a number of pathways for synthesis of nucleic acids are inhibited, thus preventing proliferation of cells involved in the determination and amplification of the immune response.

Pharmacokinetics Azathioprine may be given orally or as an intravenous injection and is well absorbed in the upper gastrointestinal tract. It undergoes rapid metabolism to 6MP and after intravenous injection the half-life is 6–28 min. The half-life of 6MP is similarly short at 38–114 min. Elimination is as 6-thiouric uric acid through the kidney.

Adverse effects Side effects of azathioprine include leukopenia (which may be significant in about 15%), hepatotoxicity (especially veno-occlusive disease), pancreatitis, pneumonitis, and megaloblastosis. After initiation of treatment, the white blood cell count should be monitored every 2 weeks and dose reduction instituted if the white count falls. Individuals with an inherited deficiency of TPMT may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow suppression after starting treatment. Drug interactions are few but allopurinol (which competes for metabolism via xanthine oxidase) should be avoided because of the increased risk of bone marrow suppression.

Pregnancy and lactation Evidence of teratogenicity in humans is equivocal. There have been reports of preterm delivery and low birth weight following treatment with azathioprine, especially when it is given in combination with glucocorticoids. There have been extremely rare reports of physical abnormalities following treatment with azathioprine. 6MP has been shown in the breast milk of mothers who are breastfeeding, so mothers should be advised not to breastfeed.

Mizoribine

Indications Prophylaxis of acute rejection in kidney transplant recipients in combination with other immunosuppressive medication.

Pharmacodynamics The antimetabolite mizoribine is an imidazole nucleotide that blocks the purine biosynthesis pathway and thus inhibits T- and B-lymphocyte proliferation.

Pharmacokinetics Mizoribine is administered at a dose of 2 mg/kg per day.

Adverse effects Mizoribine is usually well tolerated but may cause hyperuricemia.

Cyclophosphamide

This is given orally or intravenously and, as a prodrug, requires hepatic metabolism to the active compound. A metabolite may induce a hemorrhagic cystitis.

Drugs that inhibit lymphocyte trafficking

FTY720

FTY720 is a potent agonist of the spingosine-1-phosphate receptor (SIPR). The effect of FTY720 is to sequester lymphocytes in the lymph nodes, away from

the allograft and sites of inflammation. The agent also induces apoptosis in activated lymphocytes. More recently, it has been shown that FTY720 has anti-angiogenic properties, making it a potentially valuable agent in the immunosuppression of those transplanted for hepatocellular carcinoma. In contrast to conventional immunosuppressive agents, it does not affect the activation, proliferation, or effector functions of either B or T lymphocytes. In animal models, the agent is also effective in preventing the effects of ischemia/reperfusion injury. Preliminary studies in a variety of organ allograft recipients suggest that the agent is effective in maintaining graft function, at doses of 2.5–5 mg/day. Side effects include bradycardia because of the presence of the SIPR on atrial myocytes. Unfortunately, its development in transplantation has been suspended. However, the drug was recently approved for use in multiple sclerosis and therefore could re-emerge for off-label indications in the future.

Further reading

Augustine JJ, Bodziak KA, Hricik DE. Use of sirolimus in solid organ transplantation. *Drugs* 2007;**67**:369–91.

Bowman H, Lennard TW. Immunosuppressive drugs. *Br J Hosp Med*. 1992;**48**:570–9.

Campsen J, Zimmerman MA, Trotter JF, et al. Sirolimus and liver transplantation: clinical implications for hepatocellular carcinoma. *Exp Opin Pharmacother* 2007;**8**:1275–82.

Cantarovich D, Vistoli F, Soulillou JP. Immunosuppression minimization in kidney transplantation. *Front Biosci* 2008;**13**:1413–32.

Ciancio G, Burke GW 3rd. Alemtuzumab (Campath-1H) in kidney transplantation. *Am J Transplant* 2008;**8**:15–20.

Danovitch G. Mycophenolate mofetil: a decade of clinical experience. *Transplantation* 2005;**80**:S272–4.

de Mattos AM, Olyaei AJ, Bennett WM. Pharmacology of immunosuppressive medications used in renal diseases and transplantation. *Am J Kidney Dis* 1996;**28**:631–67.

Grinyó JM, Cruzado JM. Mycophenolate mofetil and sirolimus combination in renal transplantation. *Am J Transplant* 2006;**6**:1991–9.

Gummert JF, Ikonen T, Morris RE. Newer immunosuppressive drugs: a review. *J Am Soc Nephrol* 1999;**10**:1366–80.

Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus for liver transplanted patients. *Cochrane Database Syst Rev* 2006;(4):CD005161.

Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004;**4**:583–95.

Hood KA, Zarembski DG. Mycophenolate mofetil: a unique immunosuppressive agent. *Am J Health Syst Pharm* 1997;**54**:285–94.

Kahan BD. Cyclosporine: the agent and its actions. *Transplant Proc* 1985;**17**:5S–18S.

Kapturczak MH, Meier-Kriesche HU, Kaplan B. Pharmacology of calcineurin antagonists. *Transplant Proc* 2004;**36**:25S–32S.

Kirk AD. Induction immunosuppression. *Transplantation* 2006;**8**:593–602.

MacGregor MS, Bradley JA. Overview of immunosuppressive therapy in organ transplantation. *Br J Hosp Med* 1995;**54**:276–84.

Morris PJ. Cyclosporine, FK-506 and other drugs in organ transplantation. *Curr Opin Immunol* 1991;**3**:748–51.

Mottershead M, Neuberger J. Daclizumab. *Exp Opin Biol Ther* 2007;**7**:1583–96.

Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. *Clin J Am Soc Nephrol* 2007;**2**:374–84.

Shipkova M, Armstrong VW, Oellerich M, Wieland E. Mycophenolate mofetil in organ transplantation: focus on metabolism, safety and tolerability. *Exp Opin Drug Metab Toxicol* 2005;**1**:505–26.

Taylor AL, Watson CJ, Bradley JA. Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. *Crit Rev Oncol Hematol* 2005;**56**:23–46.

UK Renal Pharmacy Group. *The Renal Drug Handbook*. Oxford: Radcliffe Medical Press, 1999.

UK Renal Pharmacy Group. *The Renal Drug Handbook*, 2nd edn. Oxford: Radcliffe Medical Press, 2004.

Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005;**331**:810.

White DJ. Cyclosporin A. Clinical pharmacology and therapeutic potential. *Drugs* 1982;**24**:322–34.

Yabu JM, Vincenti F. Novel immunosuppression: small molecules and biologics. *Semin Nephrol* 2007;**27**:479–86.