Modern immunosuppression

Balaji Mahendran
Rodrigo S Figueiredo
Colin Wilson

Abstract

Organ transplantation provides both life-saving and life-enhancing function for patients suffering from end-stage organ failure. Transplantation has only been possible due to the advances in immunosuppression. The viability of a transplanted organ depends on modulation of the human immune system to avoid rejection in response to foreign antigens. Modern immunosuppression consists of multi-modal therapy (chemical drugs and biological agents) acting on different parts of the immune response. Three phases of immunosuppression can be recognized: induction, maintenance and withdrawal. All patients must continue to take at least some immunosuppression to prevent rejection. Developments in immunosuppressant regimens have dramatically improved transplant success rates and experience over the years has helped to understand the side-effects and long-term complications of immunosuppression. Research continues to identify both novel compounds and ways of optimizing the use of current drugs.

Keywords Antibodies; drugs; rejection; transplantation

Introduction

The advent of solid organ transplantation, almost 60 years ago, heralded a new era for patients suffering from end-stage organ failure. The first successful life-extending organ transplant was a kidney transplant performed in 1954 in Boston. Prior to this all vascularized organ transplants had been rejected by the recipient's immune system. The key success here was identifying identical twin brothers and hence that rejection would not be an issue.

Early years

By the end of the 1960s 6-mercaptopurine (6-MP) and corticosteroids had permitted organ transplantation between non-identical patients. Although 6-MP was initially developed for the treatment of leukaemia, its benefits were soon translated into solid organ transplantation. Sir Roy Calne pioneered the use of its derivative azathioprine in kidney and liver transplantation in Cambridge, UK. In an initial series of canine experiments he had found that graft survival was significantly prolonged when combined with corticosteroids. Implementation of a similar protocol in humans moved transplantation from an experimental science into widespread clinical use.

The quantum leap forward was the development in the late 1970s of ciclosporin. Its introduction not only significantly improved the outcomes of kidney transplantation but also heart, lung and liver transplants, transforming them from high risk, high mortality surgical endeavours into accepted and even 'gold standard' treatments.

Immunology of transplant rejection

It was Peter Medawar in 1944 who first showed that graft rejection is a 'host versus graft' response: but it has only been in the last four decades that the 'nuts and bolts' of this response have become apparent and a basic understanding of transplant immunobiology is essential to understanding the rationale of modern immunosuppression.

The rejection reaction can be broadly divided into two phases: sensitization and the effector response. In both phases the T-cell plays the key role (Figure 1).

The recognition of foreign antigens by recipient T-cells leads to a cascade of intracellular signals (signal 1), resulting in the synthesis of proteins including cytokines such as interleukin-2 (IL-2). During the Antigen Presenting Cell (APC)/T-cell interaction other ligands bind, some facilitating adhesion between cells (ICAM-1 with LFA-1) and others providing a second proliferative signal (signal 2). IL-2 and other cytokines provide the final proliferative signal (signal 3) to T-cells. Modulatory ligands are also present on the surface of T-cells, which may inhibit the immune response. One such example is CTLA4, which binds to the CD80/CD86 ligands on APCs to block co-stimulation, thus regulating the immune response (*vide infra* Belatacept).

Classes of immunosuppressants

General considerations

Immunosuppression is generally classified as having a temporal relationship to graft implantation and broken down into three phases: induction, maintenance and withdrawal. During the induction phase a bolus of steroids (methylprednisolone) is given prior to releasing the vascular clamps and reperfusion of the allograft. Often this is combined with a biological antibody agent (ATG, Basiliximab, Campath) to condition the recipient T-cell population.

After graft implantation there is a maintenance phase and most organ transplant recipients will receive triple therapy combining a calcineurin inhibitor, anti-proliferative (azathioprine or MMF) and corticosteroids. In the withdrawal phase, the dose of all agents is gradually reduced as the risk of acute rejection recedes; however, in only a small minority of cases can immunosuppression be withdrawn completely.

Induction antibody agents

Antibody immunosuppression: antibodies can by polyclonal or monoclonal. Polyclonal antibodies are directed against multiple

Balaji Mahendran *is a Specialist Registrar in General Surgery based in the Peninsula Deanery, UK. Conflicts of interest: none declared.*

Rodrigo S Figueiredo ***PhD*** *is a Consultant Hepatobiliary and Transplant Surgeon at Newcastle University and the Institute of Transplant Surgery, Freeman Hospital, Newcastle upon Tyne, UK. Conflicts of interest: none declared.*

Colin Wilson ***PhD*** *is a Professor of Hepatobiliary and Transplant Surgery at Newcastle University and the Institute of Transplant Surgery, Freeman Hospital, Newcastle upon Tyne, UK. Conflicts of Interest: Mr Wilson has received travel grants from Novartis, Roche and Astellas.*

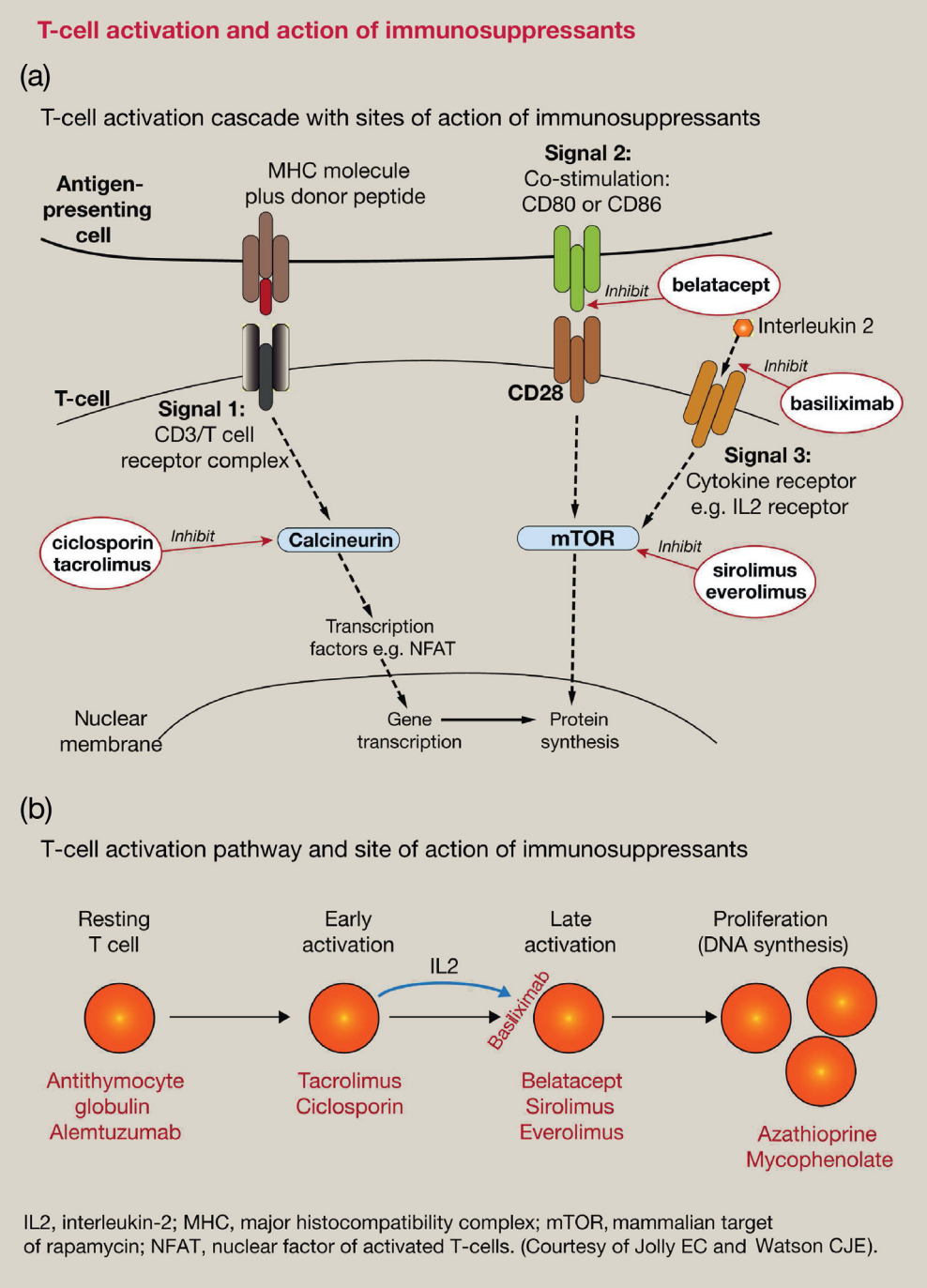

Figure 1

epitopes of antigens on human lymphocytes (such as anti-thymocyte globulin – ATG), whereas monoclonal antibodies have monovalent affinity (i.e. they bind to the same epitope). Antibodies are mainly used as induction agents, however they can be used in cases of severe rejection as 'rescue' therapy.

Anti-thymocyte globulin: there are many different varieties of ATG, but they all follow the same principles. Human lymphocytes are injected into a mammalian host (rabbit, horse) and the resulting antibodies generated are then purified from the animal's serum. This means that no two batches are the same and the patient experience in consequence is very variable. However a profound reduction in circulating T-cells is always apparent, through a combination of complement-dependent and antibody-dependent cytotoxicity. This massive cell lysis can lead to a cytokine release syndrome or 'storm' with systemic effects such as fever, pruritus, hypotension, flushing and occasionally severe bronchospasm. The severity of the reaction is dependent not only on the number of circulating lymphocytes prior to administration but also the 'batch efficacy'. ATG has been shown

to prevent acute graft rejection in kidney transplants (relative risk 0.65), even in the absence of a concurrent immunosuppressive agent.[1]

OKT3 is a murine monoclonal antibody directed against the CD3 cluster present on all lymphocytes and which has a similar side-effect profile. Case reports of severe anaphylaxis have reduced it.

Both ATG and OKT3, which cause profound and long-lasting changes in lymphocyte populations, have been associated with the development of opportunistic infections with uncertain effects on post-transplant lymphoproliferative disorders[1] (PTLD, see below; Figure 2).

Interleukin 2 receptor blockers: basiliximab and daclizumab (now withdrawn from the market due to economic reasons) are humanized monoclonal antibodies directed against the alpha subunit of the CD25 antigen present on activated T-cells. These antibodies bind and competitively inhibit the proliferative response of T-cells to IL-2, rather than causing cell lysis (c.f. ATG). Studies in kidney transplantation have shown a reduction in acute rejection (relative risk 0.72) when added to conventional therapy, with a reduction in early malignancy (relative risk 0.36).[2] There was a decrease in opportunistic infections when compared to ATG usage (relative risk 0.68).[2]

Alemtuzumab (Campath 1H): alemtuzumab targets the CD52 antigen, present on most mature nucleated bone marrow −derived cells. Like ATG the administration of Campath 1H can be associated with a cell lysis syndrome and its use is associated with a profound and prolonged depletion of both B and T cells (which take years to return to pre-administration levels).

Campath use has been associated with the development of autoimmune disease, commonly autoimmune thyroid disease and thrombocytopenia. Administration is usually intravenous but is better tolerated by the subcutaneous route which avoids a cytokine release syndrome. The 'Campath, Calcineurin inhibitor reduction and Chronic allograft nephropathy' (3C) trial published in 2013 has shown a 58% reduction in biopsy proven acute rejection (BPAR) when compared to basiliximab at 6 months, without any differences in severe infections or mortality.[3] However there have been numerous reports of this graft survival benefit disappearing after 1 year, with mixed results after this initial period. These results have led to most centres in the UK using alemtuzumab as a second-line induction agent in high-risk patients.

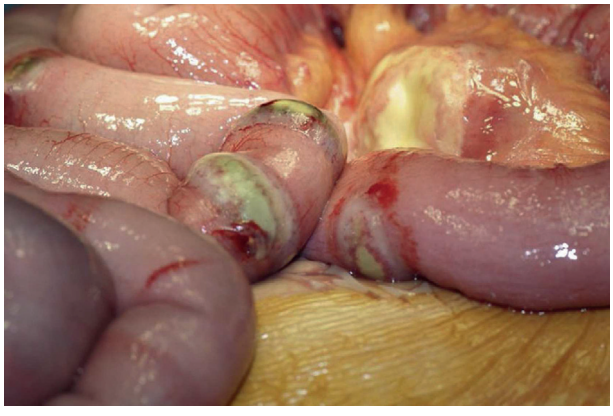

Figure 2 Post-transplant lymphoproliferative disease affecting the GI tract. Lymphoproliferative disease affects around 2% of transplant recipients. Many are B-cell lymphomas and are treated by chemotherapy regimens including the B-cell depleting monoclonal antibody rituximab. This figure shows the appearance of the small bowel at laparotomy one week after rituximab therapy, with necrotic tumour masses in the mesentery and wall of the bowel, some of which had perforated.

Rituximab: is directed against the CD20 antigen, present on most mature B-cells, causing B-cell depletion. Its initial use was in the treatment of B-cell lymphomas, but more recently it has been used as part of antibody-removal protocols where ABO blood group antibodies or antibodies to donor HLA antigens would otherwise preclude transplantation. It has also been used in the treatment of antibody-mediated rejection. Rituximab has been linked with an increased risk of infectious complications following renal transplantation and a recent trial of induction therapy with rituximab was stopped due to an excess of acute rejection in the rituximab arm.[4]

Belatacept: this is the newest monoclonal antibody in transplantation and uniquely can be given as maintenance, as well as induction therapy. It blocks co-stimulation at the CD80 ligand by containing the CTLA-4 extracellular domain. Subcutaneous maintenance doses can be given at monthly intervals, thus reducing the requirement for daily oral medication. Its role is yet to be determined but may be useful in adolescents (who don't like acne and hirsutism associated with taking steroid tablets), small bowel transplants or other patients with impaired gut function (diabetics). Side effects are generally mild, although there have been reports of PTLD in patients who were Epstein −Barr virus (EBV) naïve at the time of transplant.[5]

Maintenance agents

Calcineurin inhibitors: act by binding to cytoplasmic immunophilins to form complexes that inhibit calcineurin, blocking protein transcription in response to Il-2 and preventing cellular proliferation (Figure 1). The most commonly used calcineurin inhibitors (CNI) are ciclosporin and tacrolimus. Multiple generic formulations are now available for both drugs and the junior surgeon should ensure that the correct formulation is prescribed for their patient.

CNIs have a number of dose-dependent adverse side effects, perhaps the most significant being nephrotoxicity (Table 1). Other toxicities more common in ciclosporin than tacrolimus include hypertension, hyperlipidaemia, hirsutism and gingival hypertrophy. Alopecia, neurotoxicity and new onset diabetes after transplantation (NODAT) are more common with tacrolimus.

Mammalian target of rapamycin (mTOR) inhibitors: include sirolimus (rapamycin) and everolimus (Figure 1). This class of immunosuppressants act by binding to and inhibiting mTOR, thereby inhibiting cytokine receptor signal transduction arresting the cell cycle in the G1-S phase. This effect is not limited to lymphocytes and its anti-proliferative effects have been

Side effect profiles of common immunosuppressants

Agent	Potency	Nephrotoxicity	Neurotoxicity	Diabetes	Hyperlipidaemia	GI disturbance	Hirsutism/ hypertrichosis	Hepatotoxicity	Marrow suppression
Prednisolone	+	−	−	++	+	+	++	−	−
Azathioprine	+	−	−	−	−	−	−	+	+
Mycophenolate	++	−	−	−	−	++	−	−	+
Belatacept	++	−	−	−	−	−	−	−	−
Sirolimus & Everolimus	+++	−	−	+	++	+	−	+	+
Ciclosporin	+++	++	+	+	±	−	++	±	−
Tacrolimus	++++	++	++	++	+	−	−	±	−

Key: − no effect; + mild (or low incidence) toxicity/potency; ++++ extreme toxicity or potency.

Table 1

demonstrated in specific tumours where mTOR inhibitors have been licensed for use. Side effects can be problematic and include mouth ulceration, anaemia, proteinuria, thrombocytopenia and leucopenia, as well as hypercholesterolaemia and hypertriglyceridaemia (Table 1). More seriously mTOR inhibitors have also been implicated as causative agents in the development of a progressive interstitial lung disease (characterized by dyspnoea, dry cough, weight loss and fever).

It is well recognized that these agents cause wound breakdown after transplantation and can also lead to the accumulation of lymphatic fluid (lymphocoele). However, they are not nephrotoxic and a number of trials have looked at converting patients from calcineurin inhibitors to mTOR inhibitors around 3 months after transplantation to reduce the incidence of late kidney failure or 'chronic allograft dysfunction' (CAD). Another role being explored for these drugs is in the management of post-transplant malignancies, particularly patients having liver transplants for hepatocellular carcinoma.[6]

Antiproliferative agents: there are two specific agents in this group: azathioprine (AZA) and mycophenolate mofetil (MMF). Both interfere with DNA synthesis and therefore cell cycle progression. Azathioprine has more bone marrow suppressive effect than MMF as it is less lymphocyte specific. Azathioprine is converted into 6-MP in the liver, which then inhibits purine synthesis. Mycophenolate also impairs purine production but by a different mechanism of action; it acts by inhibiting inosine monophosphate (IMP) dehydrogenase, which is required to produce purine. The side effects of antiproliferative agents include nausea, diarrhoea, leucopenia and thrombocytopenia due to marrow suppression.

Corticosteroids: act by binding to cytoplasmic glucocorticoid receptors and have widespread effects on multiple body systems. From the transplant perspective they affect the production of several inflammatory mediators and multiple cytokines including IL-1, IL-2, IL-3, IL-6, TNF-α, IFN-γ, leukotrienes and prostaglandins. However, the long-term side effects of high-dose steroid usage (Cushing's syndrome) are well recognized. These include weight gain and impaired glucose tolerance, hyperlipidaemia, osteoporosis and gastrointestinal disturbance. Hip and vertebral fractures, particularly after liver and kidney transplantation where vitamin D metabolism is already disturbed, are a serious problem and have led to the development of bone protective 'steroid free' protocols.

Despite these side effects they are highly effective immunosuppressants and remain the mainstay of induction, maintenance and 'rescue' therapies in transplantation. The commonest treatment given for acute rejection in all organ transplantation is bolus methylprednisolone.

Drug interactions

Monitoring trough levels of calcineurin inhibitors and mTOR inhibitors is performed routinely throughout the post-transplant period. Both CNIs and mTOR inhibitors are metabolized through the cytochrome P450 superfamily system of liver enzymes (CYP3A4) which is responsible for the degradation of many classes of drugs, hence the potential for multiple drug interactions as indicated in Table 2. In addition, caution when co-prescribing statins is required as mTOR inhibitors and CNIs may increase statin levels through interacting with CYP3A4 metabolism and, therefore, lead to an increased risk of rhabdomyolysis.

Immunosuppression protocols

Current practice involves using multi-modal immunosuppression protocols. By using more than one immunosuppressive agent with different modes of action, one can use lower (less toxic) doses of each, thereby reducing long-term effects. Common regimes are described below.

Kidney and pancreas transplantation: the use of induction agents is almost ubiquitous in kidney transplantation. The UK National Institute of Clinical Excellence (NICE) has recommended the use of basiliximab in all standard risk kidney transplant recipients. Campath and ATG are also commonly used in highly sensitized recipients to reduce the risk of severe acute rejection. Maintenance therapy in most units is triple therapy with a calcineurin inhibitor, antiproliferative and steroids.

The Elite-Symphony study, which originally reported in 2007 showed clear benefits for the use of tacrolimus as the initial

Drugs causing significant interactions with CNI and mTOR inhibitor immunosuppressants

Interaction effect	Drug class	Examples
Increase CNI and mTOR levels	Calcium channel blocker	verapamil, diltiazem, lercanidipine, nifedipine
	Antifungal agents	ketoconazole, fluconazole, itraconazole, miconazole, voriconazole
	Anti-retroviral agent	indinavir, saquinavir, fosamprenavir
	Antibiotic	erythromycin, clarithromycin, chloramphenicol, chloroquine, hydroxychloroquine, doxycycline
Decrease CNI and mTOR level	Anticonvulsant	phenytoin, carbamazepine, barbiturates
	Anti-tuberculous agent	isoniazid, rifampicin

Table 2

choice of CNI and this would be the first line therapy in most units.[7]

Most pancreas transplants are performed in conjunction with a kidney for patients with diabetic renal failure (type 1 diabetes) and induction immunosuppression with Campath or ATG is the standard. Wound complications are common in this group, when steroids are also used, and depleting antibody induction means that most patients can be maintained without corticosteroids.

Liver: the use of biological induction agents in liver transplantation has been less widespread than in kidney transplantation. However, a large multicentre randomized trial comparing different immunosuppression regimens found that the use of daclizumab induction permitted late introduction of tacrolimus, at a reduced dose. This had no effect on graft survival, but was associated with significantly less nephrotoxicity ($p = 0.012$)[8] and late kidney failure, a significant complication in liver transplantation.

The use of IL-2 inhibitors as induction agents is further backed up by a review demonstrating that the incidence of acute rejection and steroid-resistant rejection are significantly reduced following administration of daclizumab or basiliximab (p0.002 & 0.011, respectively).[9]

Maintenance therapy again is triple therapy in most units with tacrolimus the CNI of choice after the TMC study reported in the Lancet 2002.[10] The liver is the most tolerogenic organ and most reports of weaning immunosuppression completely are in liver transplantation.

Small bowel: transplantation, due to the high density of lymphocytes in Peyer's patches, remains high risk for rejection and depleting antibodies are often used at induction. Novel agents (like the TNF-α blocker infliximab) have also been trialled in this area and have shown promise. Furthermore, increasing interest in altering the microbiome of recipients has prompted some research in this area, opening new avenues of therapy.[11] MMF, with its gastrointestinal side effects, is not well tolerated and parenteral (sublingual or intravenous), and therefore tacrolimus is the cornerstone of maintenance immunosuppression.

Cardiothoracic: traditionally, cardiac transplant recipients are subjected to the most aggressive immunosuppression protocols as the heart is much less forgiving of rejection episodes. The first sign of acute rejection may be arrhythmia and death. For this reason regular endomyocardial biopsies are performed in all recipients.[12] Routine induction therapy has not been shown to provide superior immunosuppression, but may delay introduction of a CNI. It may however be used in patients at high risk of rejection or renal dysfunction.[12]

Unlike with liver or kidney there is no clear evidence base for ciclosporin or tacrolimus, and many transplant units start with ciclosporin and 'step up' to tacrolimus if there is evidence of rejection on endomyocardial biopsy. The latest guidance for cardiac transplantation suggests the early introduction of mTOR inhibitors is now recommended, especially in a CNI free regime.[12]

Lung transplant maintenance immunosuppression is typically triple therapy with a CNI, MMF and corticosteroids. A recent Cochrane review found no clear benefit or harm from the use of antibody induction agents and they are not routinely used. Interestingly there appears to be an interaction between gastro-oesophageal reflux disease and immunosuppression leading to chronic graft rejection (bronchiolitis obliterans).[13]

CNI sparing: the main indications for switching patients from a CNI to an mTOR inhibitor post-transplant are in those with biopsy-proven CNI nephrotoxicity (despite minimization of CNI dose) and in individuals who develop post-transplant malignant disease (especially skin cancer, Kaposi's sarcoma and post-transplant lymphoproliferative disease (Figure 2)) where disease remission has been observed on switching to sirolimus-based immunosuppression.[14] Although CNI minimization strategies have been shown to be successful, albeit with a modest improvement in renal function, complete CNI avoidance is challenging.

'Steroid sparing': in kidney transplantation the second most common cause of graft loss is death of the recipient with a functioning graft. The majority of these deaths are related to cardio- or cerebrovascular disease. Hence, minimization of steroids has become a high clinical priority.

Similar to CNI sparing protocols, the use of induction agents with tacrolimus and MMF has proven effective and facilitates the safe and earlier withdrawal of steroids. A Cochrane review into steroid avoidance and withdrawal, using these protocols, has shown that although it was associated with slightly increased rates of acute rejection, there was no effect on late graft loss.[15]

Generic complications

As well as the individual drug side-effect profiles; long-term immunosuppression is also associated with significant risks. Cardiovascular risks are, in part, related to deranged lipid profiles associated with certain drugs. However, infections and malignancy reflect the global level of immunosuppression and for highly sensitized patients needing large doses of drugs represent the most significant risk of mortality.

Malignancy: may occur in a recipient with pre-existing malignancy, as a result of transmission from the donor or *de novo* in the recipient. The rate of *de novo* malignancies in recipients is almost double that of age- and sex-matched controls.[16] As well as being more common, malignancies tend to occur at a younger age and are more advanced at the time of diagnosis. Organ transplant recipients are at particular risk of developing skin cancers, particularly epithelial skin cancers, Kaposi's sarcoma, and Merkel cell carcinoma.[17] The rate of squamous cell carcinoma (SCC) is 60–100 times higher than the general immunocompetent population.

Lymphoproliferative disorders are also significantly more common in organ transplant recipients. The rates of different types of lymphoma vary, with T-cell lymphoma, Burkitt's lymphoma and diffuse large B-cell lymphoma showing the greatest relative increase in incidence compared with the immunocompetent population. Younger patients who are EBV virus negative at the time of transplantation have the highest risk and some paediatric programs actively match organs from EBV negative donors to EBV negative recipients to reduce that risk.[18]

Infections: infections are a major source of morbidity and mortality in organ transplant recipients at all stages post-transplantation. The types and sources of infections, however, change with time. In the short term following transplantation, most common infections are nosocomial in origin, such as wound, catheter or chest infections. In the medium term, it is often activation of latent infections or opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV) and hepatitis B & C.

Pre-transplant knowledge of recipient serostatus for CMV, EBV, HBV, and HCV can help optimize post-transplant management. Patients can also be screened for latent tuberculosis (TB). Patients seronegative for measles, mumps, rubella, hepatitis A and B should be immunized prior to transplantation.

Viral infections (particularly herpes viruses) are the most common type of infection post transplantation. These range from minor self-limiting reactivation reactions through to fulminant life-threatening disease. Prevention of viral infections can be achieved by anti-viral prophylaxis and careful monitoring of immunosuppression. Most units give specific antiviral prophylaxis (valganciclovir) to CMV negative recipients if they receive CMV positive organs for a period of 100–200 days. Recipients of mTOR inhibitors also appear to be predisposed to reactivation of VZV and HSV infections.

The polyomaviruses are now emerging as significant pathogens in transplantation as well. Like herpes viruses they remain latent in human tissues long after a mild self-limiting illness, until re-activation in the immunosuppressed state. BK virus infects renal tubular cells and up to 90% of the population carry the virus. Re-activation appears to be a particular problem in renal transplantation where it can manifest as graft dysfunction and mimic acute rejection on biopsy. Diagnosis is based on finding 'decoy' cells in the urine or viral DNA in the blood with quantitative PCR. Treatment is controversial but most clinicians advocate reducing the general level of immunosuppression.

Opportunistic bacterial infections are also common. Most units have specific protocols and give prophylactic antibiotics to prevent both PCP and TB.

Summary

Modern immunosuppression relies on a cocktail of different agents prescribed in combination to minimize toxicity. Despite this, complications are common and lead to significant patient morbidity and even mortality. Further research is ongoing to tackle these issues and move towards drugs with minimal side-effect profiles; however, it remains highly likely that malignancy and infections will continue to be a problem with medications designed to reduce the body's intrinsic defences. ◆

REFERENCES

1 Hill P, Cross NB, Barnett AN, et al. Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients. *Cochrane Database Syst Rev* 2017; **1**: CD004759.
2 Webster AC, Ruster LP, McGee R, et al. Interleukin 2 receptor antagonists for renal transplant recipients. *Cochrane Database Syst Rev* 2010; **2010**: CD003897.
3 Haynes R, Baigent C, Harden P, et al. Campath, calcineurin inhibitor reduction and chronic allograft nephropathy (3C) study: background, rationale, and study protocol. *Transplant Res* 2013; **2**.
4 Barnett AN, Hadjianastassiou VG, Mamode N. Rituximab in renal transplantation. *Transpl Int* 2013; **26:** 563–75.
5 Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. *New Engl J Med* 2016; **374:** 333–43.
6 Geissler EK, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. *Am J Transplant* 2008; **8:** 2212–8.
7 Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J M* 2007; **357:** 2562–75.
8 Neuberger JM, Neuhaus P, Pirenne J, et al. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the ReSpECT study. *Am J Transplant* 2009; **9:** 327–36.
9 Goralczyk AD, Hauke N, Bari N, et al. Interleukin 2 receptor antagonists for liver transplant recipients: a systematic review and meta-analysis of controlled studies. *Hepatology* 2011; **54:** 541–54.
10 O'Grady JG, Burroughs A, Hardy P, et al. UK and Republic of Ireland Liver Transplant Study Group. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; **360:** 1119–25.
11 Dogra H, Hind J. Innovations in immunosuppresion for intestinal transplantation. *Front Nutr* 2022; **9**: 8609399.
12 Velleca A, Shullo MA, Dhital K, et al. The international society for heart and lung transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2023; **42:** e1–141.

13 Au J, Hawkins T, Venebles C, et al. Upper gastrointestinal dysmotility in heart-lung transplant recipients. *Ann Thorac Surg* 1993; **55:** 94–7.

14 Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352:** 1317–23.

15 Haller MC, Royuela A, Nagler EV, et al. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev*, 2016.

16 Manzia TM, Angelico R, Gazia C, et al. De novo malignancies after liver transplantation: the effect of immunosuppression-personal data and review of literature. *World J Gastroenterol* 2019; **25**.

17 Mittal A, Colegio OR. Skin cancers in organ transplant recipients. *Am J Transplant* 2017; **17:** 2509–30.

18 Clarke CA, Morton LM, Lynch C. Risk of lymphoma subtypes after solid organ transplantation in the United States. *Br J Cancer* 2013; **109:** 280–8.

Practice points

- Modern immunosuppression is the cornerstone of transplantation, allowing grafts to be transplanted to higher risk recipients with confidence. The development of newer agents has also improved patient concordance with therapy, with an improved side-effect profile
- The immunosuppression regime is generally divided into induction, maintenance and withdrawal. Induction agents are given intraoperatively, prior to implantation, and a triple-therapy maintenance regime is generally preferred. Their doses can be reduced eventually as the risk of rejection reduces during the withdrawal phase
- A dose of glucocorticoid (methylprednisolone) and a biological antibody agent (anti-thymocyte globulin, basiliximab or campath) are generally used as induction agents, whilst a combination of a calcineurin inhibitor (tacrolimus/cyclosporine), anti-proliferative agent (azathioprine or mycophenolate mofetil), and a steroid is used for maintenance
- The exact protocols vary according to the organ being transplanted, and there are some institutional variations as well
- The most common side effects from immunosuppression are opportunistic infections, nausea, diarrhoea, leucopenia, thrombocytopenia, and wound breakdown. Malignancies are also seen in this population, with the onset being at a younger age and more advanced at time of diagnosis
- An understanding of immunosuppression is important for all providers involved in transplant patients' care, from the preoperative stage to the long-term follow up

