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Review Article

Immunosuppressive drugs in renal transplantation

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ABSTRACT

A kidney transplant, sometimes known as a renal transplant, is the treatment of choice for kidney failure at end stage renal disease (ESRD). The renal transplant surgery is followed by a lifetime course of immunosuppressive agents, divided into initial induction phase and later maintenance phase. It is seen that the risk of acute rejection is maximum in the initial months after transplantation (induction phase) and then reduces later (maintenance phase). In induction phase there is use of high-intensity immunosuppression immediately after transplantation, when the risk of rejection is maximum and then the dose reduced for long- term therapy. The main challenge in the renal transplantation community is long- term transplant survival. Long-term graft loss is mainly due to acute and chronic graft rejection, and also due to complications of immunosuppressive therapy. Currently, there is triple therapy as conventional immunosuppressive protocol: a calcineurin inhibitor, an antimetabolite agent, and a corticosteroid. The main aim of development of new immunosuppressive agents is not only improvement of short- term outcomes but also to increase the long- term graft survival by less nephrotoxicity, and minimal side-effects.

Keywords: Immunosuppressive agents, Kidney transplant, Induction therapy, Maintenance therapy

INTRODUCTION

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease (ESKD). Worldwide, tens of thousands of kidney transplants have been performed, and >220,000 patients are living with a functioning kidney transplant in the United States today. The first successful kidney transplant was performed in Boston in 1954 between identical twins without the need of immunosuppression. The introduction of immunosuppressive therapies such as azathioprine and prednisone in the 1960s established kidney transplantation across non-identical individuals (allografts). However, the results with properly matched familial donors remained significantly superior to those with organs from deceased donors. During the 1970s and 1980s, the success rate at the 1-year mark for deceased-donor allografts rose progressively after the introduction of calcineurin inhibitors. Currently, 1-year survival rates for living-donor and deceased-donor allografts are 98% and 93%, respectively, in the United States. However, long-term survival has not improved as much over time, and average allograft survival times are 14 and 10 years for living-donor and deceased-donor grafts, respectively.[1]

Age-related mortality rates after transplantation are highest in the first year due to the surgical risks: 2% for ages 18–34 years, 3% for ages 35–49 years, and 6.8% for ages ≥50–60 years.[1] Advances in transplant procedures and the introduction of immunosuppressive therapies have resulted in improvements in both post-transplant graft and patient survival.[2] Kidney transplant recipients (KTRs) have benefitted from improved one-year survival rates (>90%);[3] however, despite these improvements and longer life expectancies, the focus of long-term patient management has shifted towards managing the adverse effects of immunosuppression, recurrence of the primary kidney disease, malignancy, and chronic diseases

including diabetes, hypertension, dyslipidaemia, obesity, and cardiovascular disease. It is therefore important to focus on improving long-term transplant and patient outcomes by optimizing post-transplant care, as well as immunosuppressive regimens.[4] The mainstay of post-transplant immunosuppression consists of triple therapy with a calcineurin inhibitor (CNI) (tacrolimus or cyclosporine), plus an antiproliferative/antimetabolite agent (mycophenolate mofetil [MMF]/mycophenolate sodium [MPS], azathioprine [AZA], sirolimus, everolimus), and corticosteroids (prednisone). The introduction of new immunosuppressive agents has expanded therapy options, but has also made the long-term clinical management of kidney transplant recipients increasingly complex, with clinical practice (immunosuppressive protocols) differing between transplant centers in different countries.[1] It is important for clinicians to be familiar with all management options in order to determine the most effective combination of agents to treat individual patients.

The central issue in organ transplantation remains suppression of allograft rejection. Thus, development of immunosuppressive drugs is the key to successful allograft function. Immunosuppressive agents are used for induction (intense immunosuppression in the initial days after transplantation), maintenance, and reversal of established rejection.

IMMUNOLOGY OF REJECTION

Both T cell-mediated and antibody-mediated effector mechanisms can play roles in kidney transplant rejection.

T cell-mediated rejection is caused by recipient T-lymphocytes that respond to donor HLA antigens expressed on the organ. CD4+ lymphocytes respond to class-II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of the immune system. CD8+ cytotoxic lymphocytes respond primarily to class-I (HLA-A, -B) antigens and mature into cytotoxic effector cells that cause organ damage through direct contact and lysis of donor target cells. Full T-cell activation requires not only T-cell receptor binding to the alloantigens presented by self or donor HLA molecules (known as indirect and direct presentation, respectively), but also engagement of costimulatory molecules such as CD28 on T-cells and CD80 and CD86 ligands on antigen-presenting cells (Figure 1).[5] Signalling through both of these pathways induces activation of the kinase activity of calcineurin, which, in turn, activates transcription factors leading to upregulation of multiple genes, including interleukin (IL)-2 and interferon-γ. IL-2 signals through the target of rapamycin (TOR) to induce cell proliferation in an autocrine fashion. There is evidence that non-HLA antigens can also play a role in renal transplant rejection episodes. Recipients who receive a kidney from an HLA-identical sibling can still have rejection episodes and require maintenance immunosuppression, whereas true identical twin transplants require no immunosuppression. There are documented non-HLA antigens, such as an endothelial-specific antigen system with limited polymorphism and a tubular antigen, which can act as targets of humoral or cellular rejection responses, respectively.

Antibody-mediated rejection is caused by circulating antibodies against donor antigens. After transplantation, donor-derived antigens are delivered to the recipient's draining lymph nodes and activate an alloimmune response. A subset of CD4+ T cells called follicular helper T cells (Tfh) are activated and promote differentiation of B-cells into antibody-secreting plasma cells. Plasma cells produce donor-targeting antibodies against HLA and non-HLA antigens, which can deposit in allograft kidney and cause injury via complement-dependent and independent mechanisms. C4d deposition in peritubular capillaries and glomerular basement membrane is a footprint of complement activation and is one of the diagnostic criteria of antibody-mediated rejection, together with the presence of circulating donor-specific antibody.

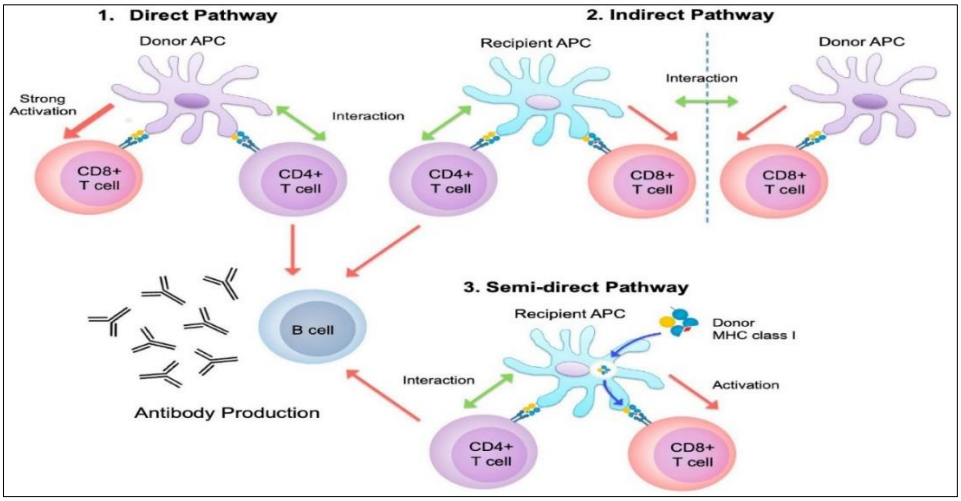

Figure 1: Recognition pathways for major histocompatibility complex (MHC) antigens.

IMMUNOSUPPRESSIVE DRUGS

Immunosuppression can be achieved by depleting lymphocytes, diverting lymphocyte traffic, or blocking lymphocyte response pathways. Immunosuppressive drugs have three effects: the therapeutic effect (suppressing rejection), undesired consequences of immunodeficiency (infection or cancer), and nonimmune toxicity to other tissues. Immunodeficiency leads to characteristic infections and cancers, such as post-transplantation lymphoproliferative disease, which are related more to the intensity of immunosuppression than to the specific agent used.[6]

New immunosuppressive protocols underscored this point by evoking a new infectious complication, BK-related polyomavirus nephropathy.[7] This syndrome of tubular injury by a virus that is usually innocuous emerged only with the recent introduction of powerful drug combinations and now contributes to renal injury and graft loss.

Fortunately, the newer immunosuppressive agents have resulted in a lower incidence of both infection and cancer than might have been expected, perhaps because preventing rejection reduces the need for powerful agents to reverse it. List of drugs used in induction and maintenance therapy is given in Table 1.

Nonimmune toxicity is agent-specific and is often related to the mechanism that is used, because each agent or class of drugs targets molecules with physiologic roles in nonimmune tissues. For example, nephrotoxicity of calcineurin inhibitors may reflect a role of calcineurin within the renal vasculature.

Table 1: Classification of immunosuppressive therapies used in renal transplantation.

Drug type	Drug class (drug name)
Induction agents	**Depleting antibodies (against T-cells, B-cells, or both)** Polyclonal antibodies: horse or rabbit antithymocyte globulin Mouse monoclonal anti-CD3 antibody (muromonab-CD3) Humanized monoclonal anti-CD52 antibody (alemtuzumab) B-cell depleting monoclonal anti-CD20 antibody (rituximab)
	Non- depleting antibodies and fusion proteins Humanized or chimeric monoclonal anti-CD25 antibody (daclizumab, basiliximab) Fusion protein with natural binding properties: CTLA-4–Ig Intravenous immune globulin
Maintenance agents	**Glucocorticoids and small-molecule drugs** **Immunophilin-binding drugs** - Calcineurin inhibitors, cyclophilin-binding drugs: cyclosporine, and FKBP12-binding drugs: tacrolimus, modified release tacrolimus Target-of-rapamycin inhibitors: sirolimus, everolimus
	Inhibitors of nucleotide synthesis Purine synthesis (IMPDH) inhibitors: mycophenolate mofetil, enteric-coated mycophenolic acid, mizoribine, pyrimidine synthesis (DHODH) inhibitors, leflunomide
	Antimetabolites: azathioprine
	Sphingosine-1-phosphate–receptor antagonists

INDUCTION THERAPY

Induction therapy is given to most kidney transplant recipients at the time of transplant to reduce the risk of early acute rejection and to minimize or eliminate the use of either steroids or calcineurin inhibitors and their associated toxicities. Induction therapy consists of antibodies that could be monoclonal or polyclonal and depleting or nondepleting.

Depleting agents

Depleting protein immunosuppressive agents are antibodies that destroy T-cells, B-cells, or both. T-cell depletion is often accompanied by the release of cytokines, which produces severe systemic symptoms, especially after the first dose. The use of depleting antibodies reduces early rejection but increases the risks of infection and post-transplantation lymphoproliferative disease and can be followed by late rejection as the immune system recovers. Recovery from immune depletion takes months to years and may never be complete in older adults. The depletion of antibody-producing cells is better tolerated than T-cell depletion, because it is not usually accompanied by cytokine release and immunoglobulin levels are usually maintained. However, depletion of antibody-producing cells is incomplete because many plasma cells are resistant to the available antibodies that target B-cells, such as anti-CD20 antibody.

Antithymocyte (antilymphocyte) globulins

Polyclonal antithymocyte antibodies are obtained by injecting animals, usually horses, with human lymphoid cells such as B-cell lymphoblasts, peripheral T-cell lymphocytes or thymus lymphocytes, and then harvesting and processing the immune sera to obtain purified globulin. Examples of polyclonal antilymphocyte

globulins are 'Atgam', 'Minnesota anti-lymphocyte globulin', 'ATG Fresenius' and 'ALG Institut Merieux'.

The polyclonal antithymocyte globulins are useful as prophylactic or induction immunosuppressant to prevent or delay first rejection, or to protect a newly transplanted kidney from the combined nephrotoxic effects of preservation injury and cyclosporine.[8] They are also used to treat rejection crises, especially those resistant to high dose glucocorticoid therapy.

The major mechanisms of action are complement-mediated lysis of lymphocytes, uptake of lymphocytes by the reticuloendothelial system, or masking of lymphocyte cell surface receptors. These preparations are usually infused for over 4 hours through an inline filter into a central venous catheter or arteriovenous fistula to minimise systemic reactions and the occurrence of phlebitis and local thrombosis. Potential adverse effects include fever, chills, thrombocytopenia, leucopenia, haemolysis, respiratory distress, rash, serum sickness, and rarely anaphylaxis. Many of these reactions can be prevented or relieved by increased doses of glucocorticoids and the administration of paracetamol (acetaminophen)and diphenhydramine.

Monoclonal antithymocyte globulin

Muromonab CD3 (OKT3) is a murine monoclonal antibody of the Ig2a class to the CD3 portion of the T-cell receptor. This immunoglobulin blocks T-cell function and does not react with other haematopoietic cells or tissues. It is administered as an intravenous bolus, usually in a dose of 5 mg/day for 10 to 14 days. The effect can be monitored by an assay of CD3 antigen on circulating T-cells. Within minutes of administration, circulating CD3-expressing cells are decreased. They usually become undetectable and remain so until termination of treatment with muromonab CD3, unless the patient develops neutralising antibodies. These neutralising antibodies develop in up to 50% of treated patients and can render retreatment with muromonab CD3 unsuccessful.

Muromonab-CD3 has been effectively used as part of induction immunosuppressive therapy, as first treatment for rejection crisis, and as 'rescue' treatment for acute rejection unresponsive to high dose glucocorticoids and/or polyclonal antithymocyte globulin.[9]

The administration of muromonab CD3 is nearly always accompanied by a cytokine release syndrome characterised by (with decreasing frequency) fever, dyspnoea, nausea, vomiting, chest pain, diarrhoea, tremor, wheezing, headache, tachycardia, chills and hypertension. This usually occurs within 2 days of the first dose. The severity of the cytokine release syndrome can be reduced by the administration of intravenous methylprednisolone, diphenhydramine, and paracetamol prior to the first dose of muromonab CD3, and by a cooling blanket and intravenous hydrocortisone 30 minutes post-injection. One of the most serious side effects, pulmonary oedema, can be prevented by weight reduction to ≤3% above the minimum weight reported in the week prior to muromonab CD3 administration and the demonstration of no pre-existing pulmonary oedema or pleural effusion on chest radiograph taken within 24 hours preinjection.

Alemtuzumab (Campath 1H) is a recombinant DNA-derived humanized monoclonal antibody directed against the cell surface glycoprotein CD52 and induces a profound, rapid and effective depletion of peripheral and central lymphoid cells. Its use may facilitate minimization of maintenance immunosuppressive protocols. The haematological, infective and lymphoma risks are similar to other depletion-inducing agents.

Rituximab is a monoclonal anti-CD20 antibody, targeted against the CD20-antigen on B lymphocytes. In transplantation it is used to suppress antibody formation, such as to treat acute humoral rejection, to treat recurrent post-transplantation focal and segmental glomerulosclerosis, or to treat post-transplantation lymphoproliferative diseases (PTLD).

Non-depleting agents

Nondepleting protein drugs are monoclonal antibodies or fusion proteins that reduce responsiveness without compromising lymphocyte populations. They typically target a semi redundant mechanism such as CD25, which explains their limited efficacy but the absence of immunodeficiency complications.

These drugs have low non-immune toxicity because they target proteins that are expressed only in immune cells and trigger little release of cytokines.

Humanized anti-CD25 monoclonal antibodies are Basiliximab (Simulect) and Daclizumab (Zenapax). These antibodies are targeted against the alpha chain of the IL-2 receptor and the IL-2 mediated responses are blocked. They are designed to prevent, but not to treat the acute rejection. These antibodies complement the effect of calcineurin inhibitors and have no significant side effects.

Other monoclonal antibodies

Efalizumab (Raptiva) is a humanized CD11a-specific IgG1, targeted against lymphocyte-associated function-1 (LFA-1) molecule. Alefacept (Amevive) is a humanized LFA-3-IgG1 fusion protein that binds to CD2 in the T-lymphocyte and interferes with T-cell activation. Janus kinase and protein kinase inhibitors are a family of cytoplasmic tyrosine kinases involved in cell surface signaling.

Bortezomib (Velcade) is a proteosomal inhibitor and suppresses the T-cell function, it may be used for the prevention and treatment of antibody-mediated and cell-

mediated rejection and reduces the level of donor-specific antibodies.

Intravenous immune globulins (IVIG) are pooled human gamma globulin preparations which inhibit anti-HLA antibodies and produce long-term suppression of anti-HLA reactive T-cells and B-cells. They are used in transplantation to reduce high levels of preformed anti HLA antibodies in sensitized patients, to treat acute humoral rejection and to treat certain post-transplantation viral infection.

MAINTENANCE THERAPY

The most frequently used combination is an antimetabolite, usually azathioprine/mycophenolic acid, a calcineurin inhibitor (CNI), usually tacrolimus/cyclosporine, and, with or without early steroid withdrawal. More recently, the U.S. Food and Drug Administration (FDA) approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term CNI toxicity. The mTOR inhibitors sirolimus and everolimus are infrequently used as first-line maintenance immunosuppression.

Antimetabolites

Azathioprine is an imidazolyl derivative of mercaptopurine that acts as an antimetabolite and reduces lymphocyte proliferation by inhibiting DNA and RNA synthesis. It is very well absorbed from the gastrointestinal tract with a peak plasma concentration achieved within about 2 hours of oral administration.[10] Azathioprine is available as 25 and 50 mg tablets and as 50 and 100mg powder for reconstitution administration for intravenous. The drug is administered as a single daily oral dose or as the same dose in an intravenous infusion, usually over 30 to 60 minutes. The usual initial dose is 3 to 5 mg/kg at the time of transplantation. This is rapidly tapered within the first week to a maintenance dose of 1 to 3 mg/kg depending on the peripheral white blood cell (WBC) count. Azathioprine is used for induction and maintenance immunosuppression, usually with glucocorticoids and often with cyclosporine.

The major toxic effects of the drug are leucopenia, thrombocytopenia and gastrointestinal problems including nausea, vomiting, pancreatitis, and hepatitis. Periodic measurements of WBC and platelet counts, pancreatic enzymes and liver function studies are necessary for the timely detection of azathioprine toxicity. Alopecia is a troublesome side effect that is often transient and may improve without reducing the dose. Allopurinol, a xanthine oxidase inhibitor, significantly increases hematologic toxicity and immunosuppression and, when given concomitantly with azathioprine, the dose of azathioprine must be reduced by 66 to 75%.

Azathioprine is a prodrug that must first be activated to form thioguanine nucleotides. Thiopurine S-methyltransferase (TPMT) inactivates azathioprine. Patients with two non-functional TPMT alleles experience life-threatening myelosuppression when treated with azathioprine, and those who carry one non-functional TPMT allele may also have significant side effects; therefore, the FDA recommends TPMT genotyping or phenotyping before starting treatment with azathioprine. Azathioprine, which inhibits synthesis of DNA and RNA and thereby inhibits T-cell proliferation, was the keystone of immunosuppressive therapy in kidney transplant recipients until the 1990s but has been replaced by more effective agents. Mycophenolate mofetil and mycophenolate sodium, both of which are metabolized to mycophenolic acid, are now used in place of azathioprine based on superior efficacy. Mycophenolic acid has a similar mode of action as azathioprine and is associated with a mild degree of gastrointestinal toxicity but less bone marrow suppression.

MMF (CellCept) and enteric-coated MPA (Myfortic) have gastro-intestinal adverse effects more frequently, such as diarrhoea (30%), varying degrees of nausea, bloating, dyspepsia, vomiting (20%), frank esophagitis, gastritis. Most of these symptoms respond to the reduction of drug dosage. The gastro-intestinal effect of Myfortic is not statistically significantly different from CellCept. Haematological side effect like leucopenia, anaemia or thrombocytopenia may require dose adjustment. The incidence of lymphoproliferative disorders and infections are similar to other immunosuppressive drugs, and rare cases of progressive multifocal leukoencephalopathy (PML) have been described. Nephrotoxicity, neurotoxicity and hepatotoxicity have not been reported with MMF.[11]

Glucocorticoids

The primary mechanism of action of glucocorticoids, usually prednisone or prednisolone, is probably prevention of IL-1 and IL-6 production by macrophages. The drug is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring within 1 to 3 hours. Prednisone is metabolised in the liver to prednisolone. Much like cyclosporine, plasma concentrations can be influenced by drugs which induce or inhibit hepatic metabolism. After induction immunosuppression with high intravenous doses, either prednisone or prednisolone is usually given as a single oral daily dose. Glucocorticoids usually methyl prednisolone may be given in relatively high doses 250- 500 mg and the dose is tapered to 20 mg within a week as part of induction immunosuppressive therapy, or to ameliorate the cytokine release syndrome associated with muromonab CD3, and to treat rejection crises. Lower doses 5-10 mg per day are administered as part of maintenance immunosuppressive regimens in patients whose renal function is stable after 6 months or a year of transplantation along with azathioprine and/ or cyclosporine or FK-506. Some transplant units have in fact successfully withdrawn glucocorticoids from both induction and maintenance immunosuppression protocols.[12]

High doses of glucocorticoids may result in Cushing's syndrome, metabolic bone disease, cataracts, peptic ulcer, hyperlipidaemia and poor wound healing. Prophylactic therapy against peptic ulcer disease is administered when patients receive high doses of glucocorticoids.

Calcineurin inhibitors

Cyclosporine

Cyclosporine is a cyclic polypeptide consisting of 11 amino acids, most of which are hydrophobic. The drug is mainly active against T-helper cells, where it prevents the production of lymphokines, especially IL-2. Cyclosporine is available in 25 mg and 100 mg capsules, as an oral solution containing cyclosporine 100 mg/ml, and as a concentrate for injection containing 50 mg/ml. It is usually administered orally as a single daily dose of 5 to 15 mg/kg and then tapered to a maintenance dose of about 5 mg/kg, depending somewhat on suspected nephrotoxicity and plasma concentrations. Some transplant units prefer twice-daily oral dosing. When oral administration is not possible, one-third the calculated oral dose is given as an intravenous infusion over 2 to 24 hours. Children may require higher or more frequent doses than adults to maintain therapeutic concentrations. Absorption of cyclosporine from the gastrointestinal tract is incomplete and variable. A peak plasma concentration is usually reached 2 to 6 hours after a single oral dose, and the half-life is 10 to 27 hours.[13] It is primarily metabolised in the liver through the cytochrome P450-III system. Thus, drugs that induce this system will increase the metabolism of cyclosporine, lower its plasma concentration, and result in under-immunosuppression. Conversely, drugs that inhibit these hepatic enzymes can result in high cyclosporine concentrations and toxicity. Nephrotoxic synergy has been reported with a variety of drugs. Table 2 lists generally accepted drug interactions.

Table 2: Drug interactions with cyclosporine.

Drugs which affect cyclosporine plasma concentration		Drugs with nephrotoxic synergy
Decreases	**Increases**	
Rifampicin, carbamazepine, phenobarbitone, phenytoin isoniazid	Diltiazem, verapamil, danazol, bromocriptine, ketoconazole, fluconazole, itraconazole, erythromycin, methylprednisolone, metoclopramide	Gentamicin, tobramycin, vancomycin, azapropazone, amphotericin-B, ketoconazole, melphalan, cotrimoxazole, cimetidine, ranitidine, diclofenac

Cyclosporine adverse effects have involved renal, hepatic, dermatological, gastrointestinal, metabolic, neurological, dental and haematological systems. Nephrotoxicity is the most common effect, and occurs in 3 clinical settings: immediately after transplantation as an additive effect on renal ischemia; 2 or 3 weeks after transplantation; and long-term with a slow decline of renal function and interstitial fibrosis. Although high plasma trough concentrations are often associated with nephrotoxicity and low values with rejection, biopsy may be necessary to exclude the latter.

Cyclosporine therapy is usually monitored with whole blood or plasma trough concentration. Because of cyclosporine binding to red blood cells and the time it takes to perform high performance liquid chromatography when compared with radioimmunoassay, most transplantation units use the latter with whole blood for this determination. Plasma concentrations range from 20 to 50% of whole blood values, and they vary with the temperature and time of separation from red blood cells.

Because of nephrotoxicity, cyclosporine administration is often delayed or initiated in a low dose until satisfactory renal function has occurred. Cyclosporine is used for induction and maintenance immunosuppression, usually in combination with glucocorticoids, with or without azathioprine.

FK-506 (Tacrolimus)

Tacrolimus (FK-506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side effect profile. It is mainly active against T-helper cells, where it prevents the production of Iymphokines, especially IL-2, by inhibiting lymphokine gene expression. It is available as an intravenous preparation and as an oral capsule formulation.

The oral bioavailability of FK-506 ranges from 5 to 67%, with a mean value of 27%.[14] In 14 patients peak plasma concentrations occurred 0.5 to 4 hours after a single oral dose, and the half-life was 3.5 to 40.5 hours. Like cyclosporine, FK-506 is primarily metabolised in the liver through the cytochrome P450 system.

FK-506 is used for induction and maintenance immunosuppression, usually in combination with glucocorticoids which are often successfully withdrawn. Protocols with FK-506 are still evolving. One example is a continuous infusion of 0.1 mg/kg/day until patients can tolerate a solid diet, then an oral dose of 0.15 mg/kg twice daily.[15]

The adverse effects are similar to those associated with cyclosporine, and include nephrotoxicity and neurotoxicity. It does not produce hirsutism or gingival hyperplasia; in contrast, it can be associated with hair loss.

De novo diabetes mellitus following transplantation more commonly occurs with tacrolimus. An extended-release formulation of tacrolimus is now available and is given once daily. Owing to its nephrotoxicity and narrow therapeutic window, the drug level of CNIs should be monitored, and drug–drug interactions should be carefully examined. Antibiotics and antifungals (e.g., erythromycin, ketoconazole, fluconazole) and non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) inhibit the activity of cytochrome P450 C3A enzyme and cause elevated levels of CNIs. On the other hand, antiepileptics, such as phenytoin and carbamazepine, increase metabolism, resulting in lower levels. Therapy is usually monitored with whole blood or plasma trough concentrations. Whole blood may be preferable to plasma because, like cyclosporine, plasma FK-506 concentrations are modified by temperature and haematocrit on separating plasma from whole blood.

The mTOR (mammalian target of rapamycin) inhibitors

Sirolimus (Rapamune) and *everolimus (Certican)*

Sirolimus is a macrolide antibiotic compound and everolimus is a similar compound with a short half-life. They inhibit mTOR, a key regulatory kinase in the process of cell division. Both hematopoietic and non-hematopoietic cells are affected. The mTOR inhibitors do not produce acute or chronic reductions in glomerular filtration rate, unless administered with a standard dose of CNI, when it appears to have increased nephrotoxicity. Thus, the dose of CNI should be lower in combination with sirolimus. The sirolimus may be tubulotoxic and may produce hypokalaemia and hypomagnesaemia, proteinuria or nephritic syndrome, de novo or enhancing pre-existing proteinuria. Sirolimus may delay the recovery of the renal function after acute tubular necrosis. Sirolimus may replace MMF or be used in combination with MMF, but as a primary agent in less than 10% of cases, because of the side effects and the failure to show its superiority over MMF. mTOR inhibitors may increase the incidence of lymphoceles, poorly granulating wounds, particularly in obese patients, painful mouth ulcers. Hyperlipidaemia may occur in more than 50% of patients, but this elevation may be controlled by statins. A non-infectious interstitial pneumonia has been described as a bilateral lower-lobe pneumonia, or several cases of fatal pneumocystis pneumonia in patients who did not receive prophylactic Sumetrolim (trimethoprim/sulfamethoxazole). Anaemia or thrombocytopenia are more severe with MMF or azathioprine; thrombotic microangiopathy occurs more frequently when CNI are used in combination with sirolimus. The incidence of malignancy and post-transplant PTLD is small, which is why it should be used in patients with high risk to develop post-transplant malignancy, or those who have already developed malignancy.

Belatacept

Belatacept is a fusion protein composed of the Fc fragment of human IgG1 immunoglobulin and the extracellular domain of cytotoxic T-lymphocyte associated protein 4 (CTLA-4). It binds to its costimulatory ligands (CD80 and CD86) on antigen-presenting cells, interrupting their binding to CD28 on T-cells. This inhibition leads to T-cell anergy and apoptosis. Belatacept is FDA approved for kidney transplant recipients and is given monthly as an intravenous infusion. The 7-year follow-up of the Belatacept evaluation of nephroprotection and efficacy as first-line immunosuppression trial (BENEFIT) showed improved patient and graft survival for the belatacept-treated group compared to patients treated with cyclosporine, despite short-term risks of higher rates of acute rejection.

PROTOCOL DEVELOPMENT AND EMERGING ISSUES

For two decades, the options for immunosuppressive drugs were initial induction with the use of protein immunosuppressive therapy; pre adaptation maintenance therapy with three drugs — a calcineurin inhibitor, a second line of drugs (azathioprine and now mycophenolate mofetil), and glucocorticoids; and post adaptation therapy with the same combination of drugs at lower doses. Rejection was reversed with high-dose steroids or depleting antibodies. Now hundreds of potential combinations exist, and many new protocols have emerged, often including a reduced reliance on glucocorticoids and calcineurin inhibitors.[16] Developing evidence-based approaches to this confusing choice of protocols presents a challenge.

Progress in the control of early and late rejection and in managing infections such as cytomegalovirus has improved both the survival of patients and the function of grafts. For example, in kidney transplantation, the estimated glomerular filtration rate has improved and is stable in many patients, rather than slowly deteriorating, as in the past. This raises the hope that many organ transplantations that are performed today represent a permanent cure for end-stage organ failure.

But concerns temper this optimism. Outcomes are not continuing to improve, and the rate of late graft loss remains excessive. For example, in the United States each year, end-stage kidney failure develops in 4500 patients who have undergone kidney transplantation, a finding that highlights transplant failure as a major cause of end-stage renal disease.[17] Patients who have undergone liver transplantation have an excessive recurrence rate of hepatitis; coronary artery disease develops in some patients with transplanted hearts; and bronchiolitis obliterans often develops in patients with transplanted lungs. The rate of premature death with functioning allografts remains excessive, in part because of

cardiovascular and other complications of immunosuppression.

Non-immune and immunodeficiency complications of transplant immunosuppression should be reduced. The major non-immune toxic effects are nephrotoxicity, hypertension, hyperlipidaemia, diabetes mellitus, and anaemia. Five years after surgery, serious renal injury is present in 7 to 21 percent of patients who have undergone non renal transplantation, and end-stage kidney failure develops in many patients.[18] The toxic effect of calcineurin inhibitors is an important contributor to the problem of renal failure. Post-transplantation diabetes mellitus develops after three years in 24 percent of patients who have undergone renal transplantation.[19] Hyperlipidaemia and anaemia are common and undertreated. Options for reducing toxicity include choosing more selective drugs, avoiding toxic combinations, and maintaining vigilance for toxic effects.

Cancers and infections that are induced by transplantation remain frequent, with infections now exceeding rejection in paediatric transplant recipients.[20] Choosing more selective drugs can reduce these risks. For example, anti-CD25 antibody has little effect on the risk of infection and post transplantation lymphoproliferative disease. New protocols must emphasize reducing the rates of cancer and infection rather than simply lowering the rate of rejection.

New immunosuppressive drug applications and protocols are emerging without adequate trials to establish dosing, safety, and efficacy. Examples are the regimens of induction with alemtuzumab or radical minimization of maintenance immunosuppression. Moreover, the quality of transplantation trials is suboptimal.[21] One problem is that the decline in the incidence of rejection, the end point in most trials, now limits the evaluation of new agents.[22] New composite end points could incorporate organ function and drug toxicity or emerging laboratory measurements of immune mechanisms.

Optimizing outcomes requires long-term follow-up by knowledgeable caregivers who recognize and react to changes. Allografts with deteriorating function should not be dismissed as instances of "chronic rejection"; instead, the source of injury should be diagnosed (e.g., rejection that is T-cell mediated or antibody-mediated, recurrent disease, drug toxicity, or infection). The assumption must be that new deterioration reflects new injury, not an inexorable consequence of an earlier injury. The identification of mechanisms of injury may be rewarded by the arresting of further deterioration.

Robust tests for rejection that is T-cell-mediated or antibody-mediated would change clinical management and clinical trials (e.g., microarray analysis of gene expression in biopsy specimens). Measurement of immune responses could guide transplantation management in the same way that measurement of disease activity guides other fields (e.g., the measurement of lipid levels in the management of hyperlipidaemia).

Interest in suppressing alloantibody responses is growing. Emerging evidence links alloantibody to late graft deterioration, and transplantation is increasingly offered to patients who have previously been excluded by existing alloantibody, including ABO blood-group barriers.[23] Options include the optimization of baseline immunosuppression, the administration of rituximab or intravenous immune globulin, and plasmapheresis, but new strategies are needed.

Pharmacogenomics offers possibilities for individualizing immunosuppression, an important goal with respect to toxic drugs with narrow therapeutic indexes.[24] For example, CYP3A (cytochrome P-450-3A) allele CYP3A5*1, which is associated with increased CYP3A5 levels, is present in 70 to 80 percent of blacks but in only 5 to 10 percent of whites.[25] Since CYP3A5 genotyping can be used to predict slower achievement of target tacrolimus levels and earlier rejection, it could help reduce rejection in black patients. For most patients, no practical method of achieving true tolerance to HLA-incompatible organ transplants is at hand. True tolerance is durable antigen specific unresponsiveness in an immunocompetent host that is induced by previous exposure to the antigen. The only clinical strategy that currently meets this definition is stem-cell transplantation.[26]

The stability of the adaptation usually depends on immunosuppression or damage to the immune tissues. At some point, most immunosuppressive agents are billed as tolerogenic, an assertion that is typically followed by the realization that, among at least some patients, the immunologic tolerance is not durable after withdrawal of the drug therapy and recovery from its effects. Indeed, the first report of an immunosuppressive drug was entitled "drug induced immunological tolerance." Many "tolerance trials" in fact use immunosuppression and are probably based on host–graft adaptation. Excellent immunosuppression with long-term clinical surveillance remains the best prospect for achieving the potential of transplantation to restore and maintain health.

CONCLUSION

Kidney transplant recipients need to take immunosuppressive drugs for life, except identical twins and simultaneous bone marrow–kidney transplant recipients. Immunosuppressive therapy, as currently available, suppresses all immune responses non-specifically, including those to bacteria, fungi, and even malignant tumors. In general, all clinically available drugs are more selective to primary rather than to memory immune responses. During renal transplant surgery, immune status of the recipient is kept under a strict margin that allows prevention of graft rejection as well as prevention of infections.

The actual survival benefit of transplantation compared to chronic dialysis becomes apparent within days to months following transplantation, even after risk adjustments for age, diabetes, and cardiovascular status. While the loss of kidney transplant due to acute rejection is now a rare event, most allografts eventually succumb at varying rates to a chronic process consisting of interstitial fibrosis, tubular atrophy, vasculopathy, and glomerulopathy, the pathogenesis of which in varying degrees is likely a combination of an alloimmune response, drug toxicity, and the end result of a variety of other insults. Overall, transplantation results in an improved life expectancy with a higher quality of life compared to patients whom remain on dialysis.

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