Immunosuppressive agents in organ transplantation

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This article reviews current and future immunosuppressive strategies in organ transplantion. Recently introduced drugs are lowering the rates of acute rejection and allowing more individualized management of transplanted patients.

In the absence of immunosuppression, the intact recipient immune system invariably rejects transplanted organs. T lymphocytes are critical in this rejection response. The main stimulus of acute rejection is the presence of alloantigens on the surface of donor cells. 'Allo' means proteins which are genetically distinct from the donor; most are encoded by the major histocompatibility complex (MHC) on chromosome 6.

Presentation of donor alloantigens to the T lymphocyte activates intracellular signalling pathways which stimulate T cell division and secretion of cytokines (*Figure 1*). Activated lymphocytes and their secreted cytokines then induce graft damage by three major mechanisms:

1. Direct cell lysis by cytotoxic T lymphocytes
2. Delayed type hypersensitivity reactions involving macrophages

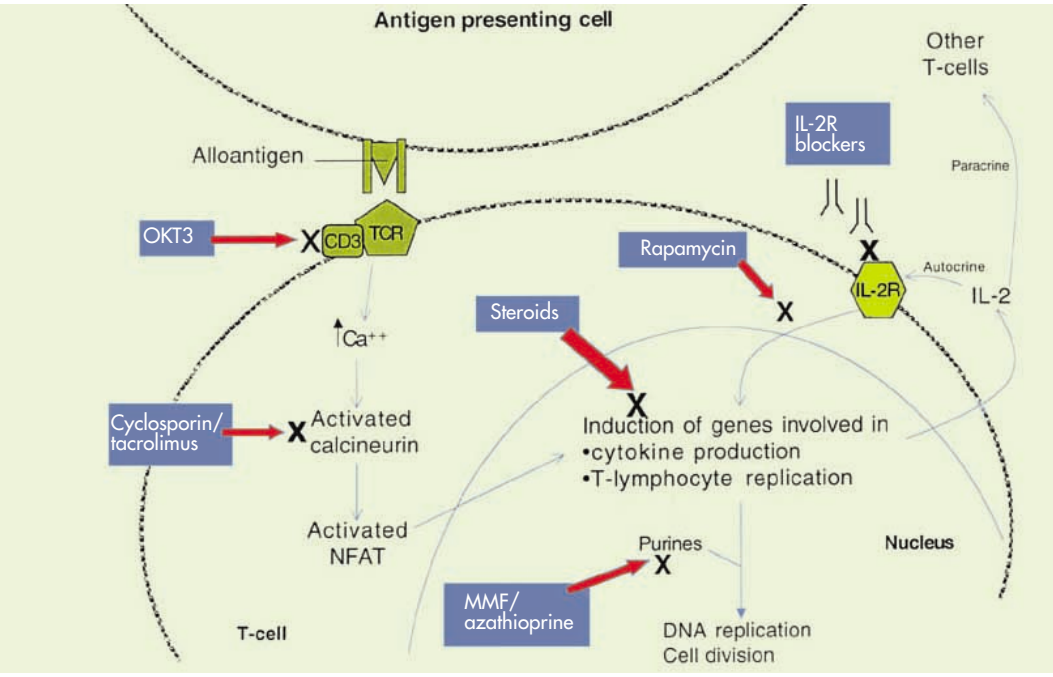

Figure 1. T lymphocyte activation and targets of immunosuppresive agents. Recognition of alloantigen by the T cell receptor (TCR) complex leads to an increase in cytosolic calcium (Ca++) which activates the calcineurin enzyme. Subsequent activation of nuclear factor of activated T cells (NFAT) allows its translocation into the nucleus where it induces genes involved in cytokine (including interleukin-2 (IL-2)) production and T cell activation. IL-2 acts in an autocrine fashion to further activate the T cell and acts in a paracrine fashion on other lymphocytes. Cyclosporin and tacrolimus inhibit calcineurin activation; steroids have multiple effects including inhibition of cytokine gene transcription. Rapamycin blocks the cell response to IL-2 while mycophenolate mofetil (MMF) and azathioprine inhibit purine synthesis and hence lymphocyte replication. OKT3 and anti-IL-2 receptor monoclonal antibodies act by binding to specialized lymphocyte surface receptors.

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3. Antibody-mediated effects.

Thus, acute rejection of a transplanted kidney is characterized histologically by an infiltrate of immune cells, particularly lymphocytes, into the renal parenchyma; antibody-mediated vessel damage may also occur. With improvements in immunosuppression, rates of acute rejection and corresponding graft losses from acute rejection continue to decrease. The incidence of acute rejection in the first 6 months after renal transplant has fallen in the USA from 52% in 1988 to 24% in 1996 (Cecka, 1997).

The principal cause of late graft loss is chronic rejection. Clinically this is characterized by progressive, usually irreversible loss of function; histologically by atrophy of functional units, fibrosis and atherosclerosis. Changes in immunosuppressive protocols have been less successful in reducing rates of chronic than acute rejection. This may reflect that fact that although alloantigen/T lymphocyte interactions are important in the pathogenesis of chronic rejection, other 'alloantigen independent' factors such as ischaemic injury, drug side-effects and hypertension are implicated.

Because the T lymphocyte is critical in the rejection response, it is the primary target of immunosuppressive strategies. Various steps in its activation can be targeted, as shown in *Figure 1*. Many immunosuppressants, however, have additional effects on other immune cells, e.g. B lymphocytes and mononuclear phagocytes. Currently used agents can be broadly classified as anti-T cell antibodies, which target receptors on the cell surface, calcineurin inhibitors, steroids or inhibitors of purine and therefore DNA and RNA synthesis.

It is important to note that although major improvements in immunosuppression have been accomplished, non-specific immunosuppression (with its attendant risk of infection and neoplasia) and drug side-effects such as glucose intolerance and hyperlipidaemia are common complications.

IMMUNOSUPPRESSION IMMEDIATELY POST-TRANSPLANT

Because the risk of rejection is greatest in the early post-transplant period, maximum immunosuppression is given at this time and progressively decreased in the weeks thereafter. Protocols for initial immunosuppression vary between transplant centres, particularly with regard to the use of antibody treatments (see below). Most regimens simply incorporate high-dose steroids, high-dose cyclosporin/tacrolimus and azathioprine/mycophenolate mofetil (MMF).

Anti-T cell antibody preparations

Muromonab CD3/anti-thymocyte globulin: Muromonab CD3 (OKT3) and anti-thymocyte globulin/anti-lymphocyte globulin (ATG/ALG) are powerful, non-specific immunosuppressants with approximately equivalent efficacy. Their mechanisms of action and side-effects have been reviewed here before (MacGregor and Bradley, 1995) and are summarized in *Table 1*. There are two situations in which they are sometimes prescribed as additional initial immunosuppression (usually for the first 7–14 days post-transplant):

1. To patients considered to be at higher risk of acute rejection: children and those previously sensitized by transplantation, pregnancy or blood transfusion
2. In delayed renal allograft function from ischaemic acute tubular necrosis; this allows safe administration of low dose cyclosporin/tacrolimus. The renal vasoconstrictive effects of full dose cyclosporin/tacrolimus in this

TABLE 1.
Anti-T cell antibody preparations used immediately post-transplant as additional immunosuppression

Drug	Mechanism of action	Specific adverse effects	Drug interactions	Comment
ATG/ALG*	Polyclonal antibodies bind to several types of lymphocyte receptors causing cell lysis or clearance from the circulation	Reactions to foreign proteins: fever, chills, arthralgia, serum sickness type illness. 'Contaminating' antiplatelet and antileucocyte antibodies may cause thrombocytopenia and leucopenia	Azathioprine potentiates any leucopenia/thrombocytopenia so reduce dosage during course	Also used in treatment of severe or steroid resistant acute rejection
OKT3*	Monoclonal antibody binds to CD3 complex (part of T cell receptor): cells are lysed or cleared from the circulation	Cytokine release syndrome (can be life-threatening): fever, chills, pulmonary oedema, aseptic meningitis and encephalitis	Reduce cyclosporin or azathioprine during course to prevent excess immunosuppression	As above; repeat courses may be less effective because of recipient production of anti-mouse antibodies. Premedication with steroids + antihistamines and avoidance of fluid overload prevent severe reactions
Daclizumab/basiliximab	Humanized monoclonal antibody targets activated CD4+ T cells by binding to their IL-2 receptors; 'downstream' effects less clear	None reported to date?	None reported to date?	Humanizing the antibody minimizes allergic reactions and greatly prolongs serum half-life (20 days)

*As potent, non-specific immunosuppressants, OKT3/ATG increase the risk of invasive cytomegalovirus infection and neoplasia. ATG/ALG= anti-thymocyte globulin/anti-lymphocyte globulin, IL-2= interleukin-2

setting could prolong the period of acute tubular necrosis and complicate management.

Use of these powerful drugs remains controversial. Although they decrease the incidence of very early acute rejection episodes, this may not translate into improved long-term renal allograft survival (Katznelson and Cecka, 1997). Both preparations are costly and have significant side-effects. The availability of more potent orally active agents such as MMF is decreasing the need for OKT3 and ATG as initial immunosuppression.

Humanized/chimeric anti-IL-2 receptor monoclonal antibodies: An exciting development has been the introduction of humanized/chimeric anti-IL-2 receptor monoclonal antibodies (mAbs) into clinical transplantation (*Table 1*). Unlike OKT3 and ATG, these have the potential for more specific immunosuppression because the IL-2 receptor is only expressed on activated T cells. Humanization of the antibody avoids the problem of recipient generation of anti-mouse antibodies (a problem with repeat courses of OKT3), thus prolonging antibody half-life and efficacy.

Randomized, double-blind trials involving renal allograft recipients on conventional cyclosporin plus steroid therapy (also azathioprine in the daclizumab trial) showed one-third reduction in acute rejection rates with daclizumab (Vincenti et al, 1998) or basiliximab (Nashan et al, 1997) compared to placebo. In the former trial, for example, the 6-month acute rejection rate was reduced from 35% to 22% of patients with IL-2 receptor blockade. These preparations have been well tolerated with minimal toxic effects reported to date. Long-term studies of anti-IL-2 receptor mAbs are not yet available; further work is needed to determine their role in organ transplantation.

MAINTENANCE IMMUNOSUPPRESSION

Maintenance therapy usually consists of three classes of drugs: a calcineurin inhibitor (cyclosporin or tacrolimus), an antiproliferative agent (azathioprine or MMF) and glucocorticoids (*Table 2*). This should allow adequate immunosuppression without using toxic doses of any one agent. To some extent, total immunosuppression is adjusted according to the perceived risk of rejection: a 65-year-old recipient of a 'fully matched' (in terms of MHC antigens) kidney transplant will receive less immunosuppression than a 25-year-old recipient of a less well matched graft.

The wider choice of potent immunosuppressive drugs also allows greater flexibility in minimizing side-effects for the individual patient. Tacrolimus might be preferred to cyclosporin in a patient where cosmetic side-effects are of great concern but not in a patient at high risk of post-transplant diabetes mellitus (see below). Precise titration of drug therapy to maintain the optimum balance between over- and under-immunosuppression remains difficult; techniques for prospective monitoring of the recipient's immune response have not yet been clinically validated.

Calcineurin inhibitors

Cyclosporin: Cyclosporin functions as a partial inhibitor of calcineurin, thereby reducing the synthesis of several critical T cell activation factors, including IL-2 (*Figure 1*). Acute rejection rates and 1-year graft outcomes have fallen significantly since the introduction of cyclosporin but its effects on long-term outcomes have been less impressive. Important side-effects include nephrotoxicity, hyperlipidaemia, glucose intolerance and cosmetic defects. In renal transplantation, nephrotoxicity is troublesome as it may be difficult to clinically distinguish from acute rejection; cyclosporin may also contribute to long-term graft dysfunction and loss (see below).

With the standard preparation of cyclosporin, bioavailability can vary greatly from patient to patient; poor absorption is a risk factor for adverse short and long-term outcome (Kahan et al, 1996). Monitoring trough blood cyclosporin levels is therefore essential for appropriate dosing. Cyclosporin is metabolized via the p450 system: clinicians should be aware that a wide variety of drugs which alter this enzyme system may affect cyclosporin levels (*Table 2*).

A microemulsion formulation of cyclosporin with improved bioavailability and less variable pharmacokinetics is replacing the standard preparation. The trough level of cyclosporin microemulsion correlates better with total drug exposure (as calculated by the time concentration curve). Potential advantages are more effective dose titration and a reduction in rejection rates (particularly in 'poor absorbers'). Overall, there appears to be a lower rate of acute rejection in de novo transplant recipients with the microemulsion compared to standard formulation and conversion (Shah et al, 1998). Conversion of stable patients from standard cyclosporin to cyclosporin microemulsion is a matter of centre preference as no consistent benefits of such intervention have been shown.

The contribution of long-term cyclosporin therapy to chronic renal allograft dysfunction is controversial. Although long-term deterioration in transplant or native kidney function in cyclosporin-treated patients is well documented (presumably reflecting to some extent inadequate immunosuppression) (Woolfson and Neild, 1997), many clinicians feel that chronic rejection is a more important contributor to graft loss than

chronic cyclosporin nephrotoxicity (Burke et al, 1994). In our opinion, the cyclosporin dose in most patients should aim for adequate immunosuppression rather than absolute avoidance of chronic nephrotoxicity. When the clinical and histological picture suggests that cyclosporin toxicity is the principal cause of chronic renal allograft dysfunction, judicious dose reduction is indicated.

Tacrolimus (FK506): Although tacrolimus is structurally distinct from cyclosporin, its mode of action, drug interactions and side-effects, including nephrotoxicity, are similar. Important differences from cyclosporin are better bioavailability (than the standard cyclosporin formulation) and greater potency. The risk of post-transplant diabetes mellitus is increased but cosmetic complications, hyperlipidaemia and hypertension are less common. It is often used in liver transplantation.

Two randomized, open label trials have shown a significantly lower incidence of acute rejection in tacrolimus compared to cyclosporin-treated renal allograft recipients (Mayer et al, 1997; Pirsch et al, 1997). Mayer et al (1997) found that tacrolimus reduced acute rejection at 12 months from 46% to 26%. However, both trials used standard cyclosporin rather than the microemulsion, and toxicity was greater with tacrolimus. This raises the 'dosing issue': do differences in efficacy and toxicity reflect the degree of calcineurin inhibition? If higher doses of cyclosporin were used to achieve a similar degree of calcineurin inhibition, would tacrolimus still be more effective? Another issue is the 'learning curve': as doctors become more familiar with tacrolimus, efficacy and toxicity rates may improve.

Tacrolimus has yielded impressive results in uncontrolled studies of reversal of renal and hepatic allograft rejection refractory to high dose steroid and/or antibody therapy (Woodle et al, 1996); it should be considered for such cases. In patients with severe hypertrichosis or gum enlargement from cyclosporin, switching to tacrolimus may be beneficial. Another advantage, particularly in children, is its steroid-sparing effect. Preliminary studies of tacrolimus as primary maintenance therapy in heart and lung transplants are promising; it may supercede cyclosporin in pancreas–kidney transplantion (Gruessner et al, 1996), despite its diabetogenic potential.

Antiproliferative agents

Azathioprine: Azathioprine is a purine analogue which inhibits DNA and RNA synthesis. It thereby inhibits proliferation of cells, including T and B lymphocytes. Bone marrow suppression is the most common side-effect, but azathioprine is generally well tolerated at 1–2 mg/kg. It has been widely used in clinical transplantation for 30 years but its role in maintenance therapy is being challenged by MMF. Azathioprine is inactivated by xanthine oxidase, the enzyme inhibited by allopurinol. If allopurinol therapy for recurrent gout is required (a relatively common problem in transplant patients), the dosage of azathioprine

TABLE 2.
Drugs used as maintenance immunosuppression*

Drug	Mechanism of action	Specific adverse effects	Drug interactions	Comment
Cyclosporin	Inhibits calcineurin: synthesis of IL-2 and other molecules critical for T-cell activation is inhibited	Nephrotoxicity (acute and chronic) hyperlipidaemia, hypertension, glucose intolerance, cosmetic complications	Diltiazem, verapamil, ketoconazole and erythromycin impair metabolism and increase cyclosporin levels; phenytoin, rifampicin have opposite effect. Risk of muscle toxicity with HMG-CoA reductase inhibitors is increased	Monitoring of drug levels is essential
Cyclosporin microemulsion	As above	As above	As above	As above; improved bioavailability over standard cyclosporin
Tacrolimus	Similar to cyclosporin although binds to different cytoplasmic protein	Broadly similar to cyclosporin but diabetes mellitus more common; hypertension, hyperlipidaemia and cosmetic complications less common	Similar to cyclosporin	Used as maintenance and rescue therapy in liver and kidney transplantation. May be steroid sparing
Azathioprine	Inhibits purine biosynthesis	Bone marrow suppression, pancreatitis, hepatitis	Metabolism inhibited by allopurinol: severe bone marrow suppression may result	Monitor full blood count
MMF	Inhibits de novo pathway of purine biosynthesis, relatively lymphocyte selective	Gastrointestinal upset; invasive cytomegalovirus disease more common	Tacrolimus may increase gastrointestinal toxicity of MMF and also MMF blood levels	Decreases incidence of acute rejection in kidney transplants by 50%; much more expensive than azathioprine
Glucocorticoids	Block synthesis of several cytokines including IL-2; multiple anti-inflammatory effects	Glucose intolerance, hypertension, hyperlipidemia, osteoporosis, growth suppression in children	Shared side-effects with cyclosporin increase the risk of cardiovascular disease	Cessation of steroids may be appropriate in select cases; risk of long-term deterioration in graft function, however

*Most regimens incorporate cyclosporin/tacrolimus (calcineurin inhibitor) + azathioprine/MMF (antiproliferative agent) + steroids. HMG-CoA = 3-hydroxy-3-methyl-glutaryl coenzyme A; IL-2 = interleukin-2; MMF: mycophenolate mofetil

must be greatly reduced under expert guidance to avoid life-threatening bone marrow suppression.

Mycophenolate mofetil: MMF is a reversible inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme in de novo purine synthesis. B and T lymphocytes are mainly dependent on de novo synthesis of guanosine nucleotides, so the antiproliferative effect of MMF is relatively lymphocyte specific.

Most studies of MMF have been in renal transplantation. In three recent randomized trials, MMF was compared to azathioprine or placebo in kidney transplant recipients (all received steroids and cyclosporin). A pooled analysis of these trials has shown that MMF halved the incidence of acute rejection in the first year post-transplant from 40% to 20% (Halloran et al, 1997). On the basis of these impressive results, new kidney transplant patients are now receiving MMF instead of azathioprine in many centres. Side-effects include gastrointestinal upset and diarrhoea (which may be dose limiting) and a higher incidence of tissue-invasive cytomegalovirus infection.

The reduction in acute rejection rates with MMF (acute rejection is a known risk factor for chronic rejection) and experimental evidence that this drug inhibits development of the occlusive vascular changes seen in chronic rejection suggest it may be effective in improving long-term graft survival. This remains to be clinically proven. Three-year follow-up data have failed to show a significant benefit in graft or patient survival for MMF over azathioprine (Mathew, 1998). Use of MMF in non-renal transplantation is now under study.

A multi-centre trial comparing MMF to azathioprine in cardiac transplantation showed that MMF improved survival and decreased rejection at 1 year post-transplantation, but only when patients were analysed on a treated rather than intent-to-treat basis (Kobashigawa et al, 1998). The combination of MMF and tacrolimus will probably prove very effective in preventing acute rejection (Roth et al, 1998), but the long-term effects of this combination are unknown, and it should mainly be reserved for study patients or those at high risk of graft loss from rejection.

Steroids

Despite their side-effects, glucocorticoids are still important maintenance immunosuppressive therapy in most transplant patients. The dose is progressively decreased after transplantation to a maintenance level of prednisolone 5–10 mg/day. While steroid withdrawal in stable transplant patients is tempting, caution is advised. Two prospective studies have shown that, while steroid withdrawal may have little effect on short-term renal allograft function, long-term graft outcome may be compromised (Sinclair, 1992; Ratcliffe et al, 1996). Newer regimens including MMF and/or tacrolimus may allow safer steroid withdrawal.

TREATMENT OF ACUTE REJECTION

First-line treatment for acute rejection in solid organ transplantation is generally a short course of high dose steroids: so-called 'pulse' therapy. Steroid resistant rejection is usually treated with a course of OKT3 or ATG. If there is a poor response to antibody treatment, cyclosporin treated patients may be converted to tacrolimus 'rescue' therapy; switching azathioprine to MMF may also be beneficial (Mycophenolate Mofetil Renal Refractory Rejection Study Group, 1996). At all stages, however, the benefits of further aggressive immunosuppression in salvaging allograft function must be weighed against the increased risk of serious infection or neoplasia.

TREATMENT OF CHRONIC REJECTION

Current immunosuppressive therapies have limited effectiveness in preventing the development and progression of chronic rejection. A major problem is our incomplete understanding of the pathogenesis of this process. It is hoped that newer regimens incorporating MMF, tacrolimus, daclizumab or other drugs under investigation (see below) will reduce the incidence of chronic rejection in solid organ transplantation. Control of alloantigen independent factors such as hypertension and hyperlipidaemia is important but is beyond the scope of this article.

POTENTIAL NEW AGENTS/REGIMENS

A number of agents including sirolimus and mAbs directed against critical leukocyte cell surface receptors are undergoing clinical evaluation. Equally important, however, is determining the safest and most effective combinations of the drugs already licensed. Trials of various combinations of cyclosporin microemulsion, tacrolimus, MMF and daclizumab are already underway.

Sirolimus (rapamycin) exerts its potent immunosuppressive effect by blocking the proliferative response of T and B lymphocytes to cytokines. It has mainly been used in combination with cyclosporin; phase II trials have shown that sirolimus added to cyclosporin plus steroids significantly decreases acute rejection. Sirolimus is generally well tolerated, with thrombocytopenia and hyperlipidaemia the main side-effects; it is not nephrotoxic. Phase III trials are underway.

mAbs against specific leukocyte cell surface receptors may allow more targeted immunosuppression. Agents under investigation are anti-

ICAM-1 mAbs (targeting adhesion molecule interaction) and anti-CD40L mAbs (targeting co-stimulation, the second signal needed as well as antigen recognition for full T cell activation) (Sayegh and Turka, 1998). Another agent, CTLA4Ig is a fusion protein developed to block CD28-B7-mediated Tcell co-stimulation. CTLA4Ig prolongs allograft survival in animals, including primates; it is particularly effective when combined with anti-CD40L (Kirk et al, 1997). Trials of CTLA4Ig in humans have not yet taken place.

CONCLUSION

The incidence of acute rejection and early graft failure is falling with the use of new immunosuppressive drugs. The focus is shifting toward minimizing drug-related morbidity and improving long-term outcomes. Ongoing trials will determine if combining newer agents will allow safe cessation of steroid or calcineurin inhibitor therapy and reduce the incidence of chronic rejection. The expanding choice of therapies allows greater flexibility and individualization of regimens on a patient-by-patient basis, according to the perceived risk of rejection and the risk of drug-related complications. Nevertheless, side-effects of immunosuppression remain a challenging clinical problem.

Development of new techniques to measure the potency of the anti-graft response will hopefully allow more sophisticated tailoring of immunosuppression. Specific modulation of the recipient anti-graft immune response will continue to be a major focus of transplantation research; anti-IL-2 receptor mAbs are an important step towards this. Innovations in pharmacological immunosuppression may also benefit non-transplanted patients, such as those with autoimmune disease. HM

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KEY POINTS

- Standard immunosuppression in organ transplantation consists of a calcineurin inhibitor, an anti-proliferative agent and glucocorticoids.
- Newer immunosuppressive agents show improved prevention of acute rejection and it is hoped that this will translate into better long-term graft survival.
- The expanded choice of immunosuppressive agents allows more individualized patient immunosuppression. Better techniques of immune system monitoring should allow further improvements in this regard.
- Non-specific immunosuppression and non-immune side-effects continue to be important complications of current therapies, so donor-specific immunosuppression is a major goal of transplantation research.
- Research is ongoing to identify new drug combinations with lower requirements for steroids and/or calcineurin inhibitors.