



Immunosuppressants – clinical applications

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Summary

Immunosuppressants are used to control severe manifestations of allergic, autoimmune and transplant-related diseases. Some drugs have a diffuse effect on the immune system while others have specific targets. Drugs with diffuse effects are more likely to cause damaging adverse effects, but the effectiveness of the more specific drugs may be reduced if their action can be bypassed by alternative metabolic pathways. Treatment protocols therefore frequently use drug combinations to minimise adverse effects and to prevent resistance to treatment. Although protocols are essential to allow scientific evaluation, the clinician must be prepared to tailor treatment based on the ongoing assessment of drug effects, disease activity and the robustness of the individual patient.

Key words: calcineurin inhibitors, corticosteroids, transplantation.

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Introduction

Many of the currently available immunosuppressants were developed for use in oncology or transplantation. As this treatment is potentially life-saving desperate measures can be justified. However, there are now over 80 autoimmune diseases and several common allergic conditions in which immunosuppressants could play a role although they may not be life-saving.

Some immunosuppressants act through immunodepletion of effector cells, while others are predominantly immunomodulatory, affecting the activity of cells, usually through cytokine inhibition. Immunosuppressants can be categorised as glucocorticoids, small molecules or proteins.¹

Glucocorticoids

Corticosteroids are the mainstay of most immunosuppressive regimens in both the induction and maintenance phases. In high intravenous pulse doses (methylprednisolone 250–1000 mg

daily for 1–3 days) they are directly lymphocytotoxic. In smaller doses, they are immunosuppressive and anti-inflammatory by limiting cytokine production. The required dose and duration of treatment therefore tends to be disease specific.

Some diseases, for example asthma, respond to a short course which can be abruptly stopped, but most rheumatic diseases require the dose to be very slowly tapered over months, especially when single figure milligram doses of prednisone are reached. Abrupt cessation runs the risk not only of relapse of disease, but also hypoadrenocorticism. (Adrenal suppression can be confirmed by a one-hour synthetic ACTH stimulation test if there is clinical concern.) In the withdrawal phase, non-specific polyarthralgias and myalgias are common, but generally respond to a small dose increment followed by a renewed, slower taper.

Second-line drugs, usually antiproliferative drugs such as azathioprine, mycophenolate or methotrexate, may have a steroid-sparing effect in the maintenance phase of treatment. However, they also have their own toxicities.

Patients prescribed corticosteroids should be told to expect the common early adverse effects, such as sweateness, hoarse voice, loss of diurnal sleep patterns, and appetite stimulation. Rarely, more serious acute psychiatric disturbances are seen such as agitation, aggression or psychosis. Long-term, and less reversible, adverse effects include Cushingoid appearance, proximal myopathy, hypertension, hyperlipidaemia, diabetes, cataract formation, peptic ulceration, osteopenia and aseptic necrosis of bone.

Small molecules (Table 1)

The small molecule immunosuppressants include calcineurin inhibitors, such as cyclosporin, and antiproliferative drugs, such as sirolimus.

Calcineurin inhibitors

Since the 1980s, calcineurin inhibitors have been the main contributors to the success of solid organ transplantation, especially kidneys. By blocking interleukin-2 synthesis, they prevent activation of T-lymphocytes and are therefore useful in disorders of cell-mediated immunity. Calcineurin inhibitors have a proven role in the prevention of acute cellular rejection of transplanted organs, in psoriasis and in nephrotic syndrome.

Table 1

Small molecule immunosuppressant drugs in current use

Class of drug	Generic name	Potential clinical uses	Drug monitoring	Main adverse effects
Immunophilin-binding drugs				
Calcineurin inhibitors	cyclosporin	organ transplants, nephrotic syndrome, psoriasis, atopic eczema, rheumatoid arthritis	TDM(C_0 or C_2), creatinine, potassium, magnesium, glucose, lipids	nephrotoxicity, hypertension, tremor, hirsutism, gum hypertrophy, diabetes, haemolytic uraemic syndrome
	tacrolimus	organ transplants	TDM(C_0), creatinine, potassium, magnesium, glucose, lipids	as for cyclosporin but more tremor, diabetes, less hypertension and fewer cosmetic effects
Mammalian target of rapamycin (mTOR) inhibitors	sirolimus everolimus	organ transplants	TDM(C_0), lipids, FBC, UA	delayed wound healing, mouth ulcers, acne, pancytopenia, hyperlipidaemia, interstitial pneumonitis, peripheral oedema, proteinuria
Inhibitors of nucleotide synthesis				
Purine synthesis inhibitors	mycophenolate mofetil mycophenolic acid	organ transplants, vasculitides, SLE	TDM not widely used, FBC	diarrhoea, dyspepsia, neutropenia, anaemia, viral infections
	azathioprine	organ transplants, rheumatoid arthritis, SLE, inflammatory bowel disease	FBC, LFTs	neutropenia, macrocytosis, liver dysfunction, skin cancers, interaction with allopurinol
Pyrimidine synthesis inhibitor	leflunomide	rheumatoid arthritis, organ transplants	FBC, LFTs	diarrhoea, nausea, rash, alopecia, hepatitis, pancytopenia
Antimetabolites				
Dihydrofolate reductase inhibitor	methotrexate	rheumatoid arthritis (may be used in parallel with TNF inhibitors or leflunomide), psoriasis, psoriatic arthritis, inflammatory bowel disease	FBC, LFTs	anaemia, neutropenia, nausea, hepatitis, pulmonary fibrosis
Alkylating drugs				
Prodrug of phosphoramidate mustard	cyclophosphamide	systemic vasculitides, especially Wegener's granulomatosis, SLE, membranous glomerulonephritis	FBC, MSU, UA	neutropenia, anaemia, alopecia, haemorrhagic cystitis, sepsis, infertility, bladder cancer
TDM	therapeutic drug monitoring C_0 = trough concentration C_2 = concentration 2 hours after a dose		TNF	tumour necrosis factor
			MSU	midstream urine for microscopy and culture
FBC	full blood count			
UA	urinalysis			
SLE	systemic lupus erythematosus			
LFTs	liver function tests			

They have been used in many other autoimmune conditions but have a diminishing role in rheumatoid arthritis. While they are good at maintaining autoimmune diseases in remission, withdrawal often leads to relapse.

In solid organ transplantation, combinations of calcineurin inhibitors, mycophenolate mofetil and prednisone give better results than monotherapy. Ironically, calcineurin inhibitors are nephrotoxic and may contribute to long-term renal failure, both in transplanted organs and normal kidneys. They also aggravate hypertension and hyperlipidaemia thereby inducing an unfavourable cardiovascular profile. There is also an increased risk of diabetes.

Mycophenolate mofetil

Since it was introduced into Australia in 1996 mycophenolate mofetil has largely replaced azathioprine in organ transplantation. One advantage over azathioprine is that allopurinol can be used for gout prophylaxis without the need to reduce the dose of mycophenolate. Possibly because of its anti-B cell properties² mycophenolate seems particularly effective in severe forms of systemic lupus erythematosus. It is also gaining favour as a steroid-sparing drug in the maintenance phase of a number of immune disorders, particularly the vasculitides.³

The main adverse effects are haematological and gastrointestinal. On higher doses a third of patients will develop diarrhoea. An enteric-coated formulation of mycophenolate has been developed to try and reduce gastrointestinal adverse effects. Therapeutic drug monitoring is available but not widely used.

Sirolimus and everolimus

These potent antiproliferative drugs have gained acceptance in renal transplantation as a strategy to minimise the use of calcineurin inhibitors in low immunological risk patients.⁴ They have a decreased likelihood of causing hypertension and glucose intolerance. Although these drugs are associated with less nephrotoxicity than calcineurin antagonists, they potentiate the renal toxicity of cyclosporin and regular monitoring of renal function is recommended. Sirolimus and everolimus are generally avoided perioperatively because they can severely delay wound healing. They are potent inhibitors of intimal hyperplasia in arteries, and sirolimus-eluting intra-arterial stents are now used to reduce re-stenosis rates. However, they can increase serum cholesterol and lipids. The balance of the harm and benefit of continued treatment should be re-evaluated in patients who develop severe refractory hyperlipidaemia. Therapeutic drug monitoring is essential because of the risk of toxicity such as anaemia, leucopenia and thrombocytopenia.

Cyclophosphamide

Cyclophosphamide is a cytotoxic drug. It is the drug of choice for Wegener's granulomatosis, but is also used in other vasculitides such as microscopic polyangiitis and systemic lupus

erythematosus.⁵ Monthly intravenous pulses are as effective as daily oral use in systemic lupus erythematosus, but allow a reduced total dosage. Cyclophosphamide is also used to induce sustained remission in relapsing nephrotic syndrome. Marrow suppression with neutropenia is common after six weeks of treatment and continuing more than six months runs the risk of gonadal suppression and infertility in both sexes.

Methotrexate

This antimetabolite is used in some autoimmune diseases including psoriasis, psoriatic arthritis, rheumatoid arthritis and Crohn's disease. As a disease-modifying antirheumatic drug, its use in combination with tumour necrosis factor inhibitors (such as infliximab or etanercept) or leflunomide has been shown to markedly improve symptoms in rheumatoid arthritis.⁶

Proteins (Table 2)

Polyclonal antilymphocyte (antithymocyte) antibodies have been used in Australia since the 1960s. More recently, hybridoma technology has produced a plethora of monoclonal antibodies against molecules expressed by human immune effector cells.

T-lymphocyte depleting antibodies such as muromonab-CD3 have been widely used to prevent or treat acute rejection of organ transplants. The main drawback is a 'cytokine storm' reaction to the first dose, which can cause life-threatening pulmonary oedema.

Basiliximab and daclizumab are monoclonal antibodies against the interleukin-2 receptor (CD25). They are used as induction drugs in transplantation as they significantly reduce the acute rejection rate, with little or no increase in morbidity. They are not yet significantly used in autoimmune diseases.

The anti-B cell antibody (anti-CD20), rituximab, is licensed for use against B-cell lymphomata, but there are now published anecdotal reports of its effectiveness in 29 different autoimmune diseases.⁷ Randomised controlled trials are proceeding in systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis and in renal transplantation of highly sensitised recipients.

A new monoclonal antibody, alemtuzumab, is directed against a surface molecule (CD54), which is widely distributed on lymphocytes, macrophages and dendritic cells, thereby causing severe and long-lasting depletion of these cell lines. As a result, the risk of serious infection is increased. The use of this antibody is cautiously making the transition from immunoprophylaxis in transplant recipients to a wider use in immune diseases.⁸

Two monoclonal antibodies against tumour necrosis factor, infliximab and adalimumab, and etanercept which prevents tumour necrosis factor binding to its receptor, are licensed for use in rheumatoid arthritis. They are also being used in ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease.⁹ Infusion reactions are common.

Table 2

Protein-based immunosuppressant drugs in current use

Drug	Potential clinical uses	Adverse effects
Lymphocyte depleting antibodies		
Polyclonal antithymocyte globulin	prevention and treatment of allograft rejection treatment of moderate to severe aplastic anaemia	cytokine-release syndrome (fever, chills, hypotension), thrombocytopenia, leucopenia, serum sickness
Muromonab-CD3	prevention and treatment of allograft rejection in transplant patients	severe cytokine-release syndrome, pulmonary oedema, acute renal failure, gut upset, neurological disturbances
Alemtuzumab	treatment of B-cell chronic lymphocytic leukaemia, immunoprophylaxis for renal transplants, GVHD, multiple sclerosis, rheumatoid arthritis	mild cytokine-release syndrome, neutropenia, anaemia, pancytopenia, immune thrombocytopenia, thyroid disease
Rituximab	treatment of B-cell non-Hodgkin's lymphoma antibody-mediated transplant rejection, SLE, vasculitis	infusion reactions, hypersensitivity reactions (uncommon)
Non-depleting antibodies and fusion proteins		
Basiliximab Daclizumab	prevention of allograft rejection in transplant patients	hypersensitivity reactions (uncommon)
Belatacept (LEA29Y)	prevention and treatment of allograft rejection in transplant patients	clinical trials still in progress
Tumour necrosis factor inhibitors		
Etanercept	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis	injection site and infusion reactions, heart failure, opportunistic infections including fungi and tuberculosis, lymphoproliferative disease, demyelinating disease – reactivation of multiple sclerosis, SLE-like illness
Infliximab Adalimumab	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease	
Pooled immunoglobulin		
Intravenous immunoglobulin	Kawasaki disease, CIDP, multiple sclerosis, Guillain-Barré, ITP, bone marrow transplants, myeloma, chronic lymphocytic leukaemia with hypogammaglobulinaemia, transplant rejection	rash, headache, abdominal pain, haemolysis (especially in patients with blood groups A, AB), thromboses, liver dysfunction, aseptic meningitis, acute renal failure
GVHD	graft versus host disease	
SLE	systemic lupus erythematosus	
CIDP	chronic inflammatory demyelinating polyneuropathy	
ITP	idiopathic thrombocytopenic purpura	

Pooled intravenous immunoglobulin was introduced to restore immunocompetence to patients with congenital acquired immune deficiency syndrome. Paradoxically, the discovery of its ability to inhibit the production and binding of auto- and allo-antibodies means that it is now more widely used as an immunomodulatory drug in the treatment of debilitating autoimmune diseases and antibody-mediated allograft rejection.¹⁰ The fact that immunoglobulin also

provides passive immunity means that it is regarded as having a low risk of infectious complications compared to other immunosuppressants. Consequently, it has been used in many conditions without good supportive evidence of efficacy, so the Australian National Blood Authority guidelines now restrict its use.¹¹ Nevertheless, it is likely that immunoglobulin use will continue to rise as knowledge about its mechanisms of action accumulates.

Using immunosuppressants – strategies and protocols

Treatment protocols are designed to:

- (a) remove/suppress the predominant immune effectors and/or
- (b) resolve acute inflammation
- (c) prevent relapse.

To achieve (a) and (b), high doses are often used initially ('induction phase'). To achieve (c), lower doses of safer drugs are often chosen for the longer term ('maintenance phase').

Withdrawal of therapy is usually only considered after achieving clinical and laboratory evidence of sustained remission. Drugs are withdrawn gradually, one at a time and in the case of corticosteroids only after a long taper.

Empiricism vs controlled trials

Many protocols have evolved empirically from an understanding of the putative immune mechanisms operating in a particular disease. Sometimes the protocols were derived from what had been seen to work in conditions with apparently similar immunopathology. Randomised controlled trials of immunosuppressive protocols are available in the more common conditions such as rheumatoid arthritis or organ transplantation, but as new drugs emerge, the combinations for comparison become bewildering. Today's 'gold standard' treatment can be very quickly outdated, perhaps even before it has been optimised. Tailoring of immunotherapy to the individual is desirable, but this approach makes protocol comparisons difficult.

Similarly, the disease being treated may be so pleomorphic that finding like populations to compare in trials becomes very difficult. For example, lupus nephritis has five distinct histological subtypes, each with their own prognosis.

Choosing immunosuppressive regimens

In order to make sound judgements when choosing a treatment protocol the clinician has to consider the clinical trial evidence and then decide:

- Is the aim to pre-empt an anticipated immune response (for example, after organ transplantation) or to suppress an established immune-mediated inflammation (for example, acute glomerulonephritis)?
- In the case of an immune disease, how much immunosuppression will be required and for how long (that is, an assessment of disease activity)? Consider:
 - the natural history of the untreated disease
 - is the disease multiphasic (for example, polyarteritis nodosa) or 'single shot' (for example, microscopic polyangiitis)
 - the extent and severity of the disease in this particular patient

- is the affected organ beyond recovery
- the likelihood of relapse
- the ability to monitor disease parameters long term

■ Is this patient likely to withstand the treatment I will recommend (host fitness parameters)? Consider:

- age (older patients are easier to immunosuppress but have a greater risk of infection)
- sepsis risk
- cancer risk
- cardiovascular/diabetes risk
- presence of comorbidities
- patient compliance and availability for follow-up.

In choosing the dose and duration of immunosuppressive treatments, one must always weigh disease activity versus host fitness. For example, an elderly patient with perinuclear-ANCA positive microscopic polyangiitis, confined to the kidneys, with crescents in 10% of glomeruli, will not need as aggressive an approach as the same disease in a young patient, with 80% crescents, lung haemorrhage and mononeuritis multiplex.

Managing and monitoring patients taking immunosuppressants

Patients need to be under constant surveillance, usually by a partnership between the specialist and the general practitioner. Frequency of visits depends on perceived level of risk, but typical parameters to monitor are summarised in Table 3. Patients may need prophylaxis against the adverse effects of their treatment (Table 4).

Therapeutic drug monitoring is available now for a number of drugs, for example cyclosporin, tacrolimus, sirolimus and mycophenolate. This allows for 'concentration-controlled' regimens. Some common drugs, for example corticosteroids, still have no good measure of individual bioavailability.

Infection risk

Immunosuppression increases susceptibility to infections which can become life-threatening in a matter of hours. At first, common bacterial infections of wounds, chest or urine predominate, but after 1–2 months of therapy opportunistic infections emerge, particularly herpes viruses, pneumocystis pneumonia, fungi and atypical mycobacteria.

Vaccinations against influenza (injected) and pneumococcus are recommended in chronically immunosuppressed patients.¹² They are safe and reasonably effective when given in the stable maintenance phase. In general, live attenuated virus vaccines, such as varicella or measles, should not be given to immunosuppressed patients (or to close family contacts).

Cancer risk

In patients taking immunosuppressants, early cancers are often viral induced. They include lymphoproliferative disorders and

Table 3

Routine monitoring of patients taking immunosuppressant drugs

Monitoring of immune system	<p>Acute phase reactants (e.g. C-reactive protein, erythrocyte sedimentation rate)</p> <p>Disease-specific auto-antibodies (e.g. antineutrophil cytoplasmic antibody, anti-double-stranded DNA antibody)</p> <p>Immunoglobulin and complement concentrations</p> <p>Organ function and histology</p> <p>Neutrophil and lymphocyte counts, and T-cell subsets</p>
Monitoring of adverse effects	<p>Haemoglobin, platelets, lipids, blood glucose</p> <p>Blood pressure</p> <p>Skin cancer surveillance, rectal examination, pap smear and possibly prostate specific antigen</p> <p>Bone densitometry</p> <p>Cataract screening</p>
Therapeutic drug monitoring	<p>Meeting therapeutic targets (where known)</p> <p>Defines poor absorption</p> <p>Helps assess compliance</p>

cervical cancer. In the long term, nearly all common cancers are increased, but particularly skin cancers. After 20 years of immunoprophylaxis following renal transplant, 80% of Australian patients will have developed skin cancer.

Conclusion

Advances in our understanding of the immune aetiology of many debilitating diseases have resulted in wider use of immunosuppressant drugs in common clinical practice. The last two decades have seen the development of several useful small molecule drugs but also a profusion of monoclonal antibodies targeting the immune system. Increasingly, primary care physicians are involved in the supervision of patients taking these drugs. This task has been made easier and safer by the establishment of therapeutic targets for drug monitoring and the obligatory use of prophylactic drugs to prevent common adverse effects. Good clinical judgement, supported by laboratory investigations, is needed to differentiate the patients who are over-immunosuppressed (and therefore at risk of infections and cancer) from those experiencing relapse of their underlying disease.

Table 4

Common prophylactic treatments for patients taking immunosuppressant drugs

Infection prophylaxis	<p>'Heavy' immunosuppression may warrant prophylaxis for cytomegalovirus (valganciclovir), <i>Pneumocystis jiroveci</i> pneumonia (cotrimoxazole) and candidiasis (oral nystatin)</p> <p>Influenza and pneumococcal vaccines</p>
Anticoagulation	Immune diseases are frequently associated with thrombophilia requiring antiplatelet drugs or warfarin
Cardiovascular/diabetes risk	Corticosteroids, calcineurin inhibitors and mammalian target of rapamycin inhibitors all have adverse cardiovascular risk profiles. 'Statins' and antidiabetic drugs are often indicated.
Bone preservation	May require calcium, vitamin D and bisphosphonate supplements
Ulcer prophylaxis	Consider H ₂ antagonist or proton pump inhibitor especially with steroid use

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 115)

5. The risk of cervical cancer is increased in women taking immunosuppressant drugs.
6. Calcineurin inhibitors increase the risk of cardiovascular disease.

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Painful paediatric procedures (see page 94)

Dental procedures can be one of a child's most uncomfortable experiences if not handled correctly. They can have adverse psychological effects for the remainder of the child's life with regard to both future dental experiences, and how they relate to other healthcare professionals. Dentists need to be acutely aware of a child's feelings of vulnerability and fear of the unknown when coming to the dentist for the first time. Ideally the dentist should follow guidelines such as the standards of care of the Australasian Academy of Paediatric Dentistry.

Children should be introduced to the dental surgery in a non-threatening manner, ideally when only an examination is necessary. However, on occasion a child requires treatment after they have been in pain for some time, and the expectation of treatment is overlayed by previous experience or embellished accounts of the experiences of their friends, siblings and most importantly the attitudes portrayed by adults, particularly their parents. The concerns and procedures outlined in the medical article (page 94) are generally applicable to dental practice. Establishing rapport with the child and communicating at the appropriate developmental level leads to the use of behaviour management techniques such as 'tell, show, do', distraction and systematic desensitisation which should result in an atraumatic dental visit for the child.

Local anaesthesia has, in the past, been considered by some practitioners to be unnecessary for deciduous teeth; however it should be stressed that if a procedure is predicted to be painful anaesthesia should be provided. Topical anaesthesia should be used, with the material localised onto dry mucosa for 60 seconds, minimising the amount that the child may taste by using the end of a cotton roll. Local anaesthesia should be introduced through tight mucosa for inferior alveolar blocks and buccal infiltrations. For palatal tissues, the needle can

be inserted in the already anaesthetised buccal papilla and gently forwarded until the solution can be deposited into the palatal tissues. Care should be taken regarding dosage and toxic concentrations and practitioners should be aware of the signs of toxicity. Occasionally, referral to a specialist paediatric dentist and the use of sedation or general anaesthesia for lengthy and involved procedures may be the best approach for the long-term psychological well-being and positive health behaviour of the child.

Xerostomia: a common adverse effect of drugs and radiation (see page 97)

Xerostomia (dry mouth) is a relatively common condition and is due to salivary dysfunction. It has multiple causes, including developmental, inflammatory and neoplastic disorders. Common causes are anxiety, an adverse effect of drugs, and radiotherapy in the head and neck region. A decrease in the quantity or quality of saliva has a profound effect on the oral environment. This results in extensive and recurrent smooth surface dental decay, increased periodontal disease, significant worsening of any underlying mucosal disease and an increased likelihood of oral candidosis and difficulty with the retention of dentures. Ideally, before patients start taking drugs that can cause xerostomia or undergoing radiotherapy in the head and neck region, they should have a detailed dental check-up followed by treatment of any active disease. Topical agents can be very useful in reducing decalcification and promoting mineralisation of teeth. Dentists can advise patients on methods for the care of their teeth as well as methods to diminish the feeling of oral dryness that so profoundly affects patients' quality of life. Patients with xerostomia must have regular dental reviews and excellent oral hygiene as the removal of any teeth may result in them being unable to cope with dentures. Patients with Sjogren's syndrome also require long-term follow-up as they have a significantly higher incidence of lymphoma in their salivary glands.