Managing immunosuppression in medical patients

Immunosuppressive drugs are increasingly widely used. Safe use requires knowledge of the side-effect profile, contraindications and precautions before starting, and the monitoring regimen, and patients should be fully informed of the risks and benefits before starting.

In the past, corticosteroids were the main immunosuppressive therapy. There is now an increasingly wide array of other immunosuppressive drugs, and doctors are far more likely both to encounter medical patients on long-term immunosuppression, and also to be asked to start this therapy for their patients, with indications including transplant immunosuppression, autoimmune diseases, vasculitis and a wide range of chronic inflammatory disorders of uncertain aetiology (e.g. psoriasis, inflammatory bowel disease or multiple sclerosis). At all times there is a balance between the benefits of these often potent therapies and the risk of toxicity, both short- and long-term. This review introduces the key issues in starting treatment or assessing a patient on immunosuppression. It will only cover the commonly used drugs, and will not cover chemotherapy regimens.

Figure 1. Key points when starting immunosuppression.

1. Baseline assessment. This may include:
   - Status of disease to be treated, e.g. colonoscopy to assess severity of Crohn's colitis or magnetic resonance imaging scan to assess multiple sclerosis
   - Baseline monitoring, e.g. full blood count or liver function tests, to ensure normal at baseline
   - Screen for group at risk of toxicity, e.g. thiopurine methyl transferase status before starting azathioprine
2. Exclude active infection
3. Contraindications to treatment. Ensure no specific exclusions such as allergy, previous failure using the drug, or potential for pregnancy in drugs with teratogenic potential (e.g. methotrexate)
4. Discuss treatment with patient. This must include:
   - Benefits of therapy with patient (e.g. time to treatment response, duration of therapy and likely treatment outcomes)
   - Risks of therapy covering both common, and rare but serious toxicity
   - Agree and document monitoring schedule
5. Consider need for vaccinations before treatment
6. Provide written information for patient

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Which therapy?

The selection of an immunosuppressive therapy should be determined principally by the evidence for benefit in clinical trials. There is generally a first-line therapy for most conditions, but there may be many second- or third-choice therapies. Where possible, therapies with the lowest risk of toxicity should be used initially. Examples include poorly absorbed or topical corticosteroids with high first-pass metabolism (see below) or topical tacrolimus gel for skin disorders such as pyoderma gangrenosum. *Figure 1* lists specific points to cover before starting a therapy and *Table 1* lists commonly used drugs.

Why not just use corticosteroids?

Although familiar to many doctors, there should be no complacency in the use of long-term corticosteroids. They are often effective in the short-term (3–4 months), but with time these drugs have increasing toxicity (*Table 2*). In addition loss of effect is a common phenomenon caused by loss of lymphocyte responsiveness to corticosteroids (Creed and Probert, 2007). Infection risk is often greater on long-term corticosteroids than on other maintenance immunosuppressive drugs (Lacaille et al, 2008). Because corticosteroids used continuously for as little as 3 weeks can cause adrenal suppression, they must be tapered down slowly. If possible patients needing long-term therapy should be converted to alternative long-term immunosuppressive drugs. Azathioprine is the most widely used, but is slow acting, so should be introduced early, allowing at least 2–3 months before complete corticosteroid withdrawal.

Minimizing corticosteroid toxicity

Consider use of topical corticosteroids wherever possible, (inhaled, eye, ear or nasal preparations, skin creams or ointments, intradermal or intra-articular injections, enemas or controlled ileal release). Some preparations (e.g. fluticasone dipropionate or budesonide; Bar-Meir et al, 1998) have high first-pass metabolism in the liver, and so systemic levels and adrenal suppression are less. Previously uninfected patients on corticosteroids exposed to chicken pox are at risk of disseminated infection, and should be given varicella-zoster immunoglobulin (Centers for Disease Control and Prevention, 2006) (ideally

within 4 days, but at most 10 days after exposure). Likewise measles-exposed patients can be given prophylaxis with normal immunoglobulin. Patients should always carry a steroid treatment card.

Corticosteroids and bones

Oral corticosteroids cause an increased risk of fracture, and although the risk is greater with higher doses, there is still a risk at low doses. Dose and duration should be minimized. In addition, lifestyle advice such as exercise, good nutrition, smoking cessation and adequate calcium intake should be encouraged (e.g. calcium and vitamin D tablets). Consider bisphosphonates for all high risk patients on corticosteroids (age >65 years, prior fragility fracture). When steroid treatment is required for >3 months, or in high-risk patients (e.g. low body mass index, active disease), dual energy X-ray absorptiometry (DEXA) scanning is advised, with bisphosphonates recommended for patients with a T-score <-1.5 (Royal College of Physicians, 2002).

Thiopurine drugs

Azathioprine is converted non-enzymatically to 6-mercaptopurine (2.07 mg azathioprine is equivalent to 1 mg 6-mercaptopurine). Apart from the dose, the drugs are otherwise very similar in effect. A genetic polymorphism in the key metabolizing enzyme (TPMT), as shown in *Figure 2*, means that 11% of the population have intermediate and 0.3% have low TPMT activity, resulting in greatly increased risk of bone marrow toxic-

Table 1. Commonly used immunosuppressive drugs

	Dose range (consult specific disease guidelines)	Onset of action	Potency	Initial tests	Initial monitoring	Maintenance monitoring	Drug level monitoring	Toxicity (frequent or severe only)	Notes
Azathioprine 6-mercaptopurine	Oral 1–3 mg/kg daily Oral 0.5–2 mg/kg daily	2–3 months	+	FBC, LFT, TPMT level	FBC weekly for 4 weeks	FBC, LFT every 2–3 months	No	Bone marrow suppression, infection, hypersensitivity reaction, nausea and vomiting, cholestasis, pancreatitis	
Methotrexate	Subcutaneous or intramuscular 15–25 mg once a week. Oral 2.5–20 mg once a week	2–3 months	+	CXR FBC LFT U+E	FBC, U+E, LFT weekly for 4 weeks or until stable dose	FBC, U+E, LFT every 2–3 months	No	Bone marrow suppression, liver cirrhosis, infection, interstitial pneumonitis (especially in rheumatoid arthritis)	Teratogenic
Ciclosporin	Oral micoemulsion 2–6 mg/kg in two divided doses (can be given iv by 24-hour infusion)	<1 week	++	FBC, U+E, magnesium, cholesterol	U+E and blood pressure every 2 weeks for 3 months	U+E, blood pressure, FBC monthly	Target pre-dose levels 100–250 ng/ml	Nephrotoxicity, hypertension, infection, headache, tremor, hirsutism and gingival hyperplasia, (ciclosporin)	Hepatic p450 metabolism results in many drug interactions
Tacrolimus	Oral 150–300 μg/kg in two divided doses (can be given iv by 24-hour infusion)	<1 week	++				Target pre-dose levels 10–20 ng/ml	hypomagnesaemia, impaired glucose tolerance, neuropathy	
Anti-TNF drugs (etanercept, infliximab, adalimumab)	Various	2–4 weeks	++	CXR, tuberculin test, FBC, LFT, U+E		FBC, U+E, LFT every 2 months	No	Infection, hypersensitivity, heart failure, blood disorders, lupus-like reaction	Opportunistic infection including tuberculosis reactivation
Leflunomide	10–20 mg oral daily	2–3 months	+	FBC, LFT	FBC + LFT 2-weekly for 6 months	FBC + LFT, blood pressure every 8 weeks	No	Hepatotoxicity, bone marrow suppression, diarrhoea and nausea, hypertension	In case of toxicity, cholestyramine or activated charcoal aids elimination
Mycophenolate mofetil	Oral 1–1.5 g twice a day	2–3 months	+	FBC, LFT	FBC weekly for 4 weeks, then fortnightly for 2 months	FBC monthly	No	Nausea, diarrhoea, leucopaenia	Teratogenic

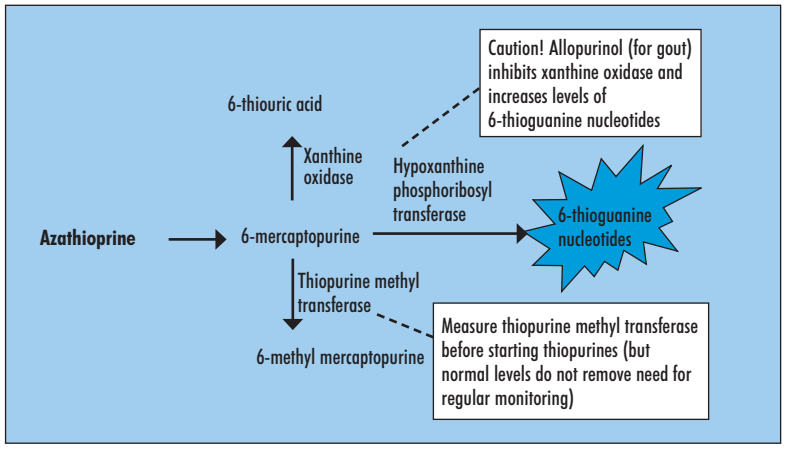
CXR = chest X-ray; FBC = full blood count; IV = intravenous; LFT = liver function test; TNF = tumour necrosis factor; TPMT = thiopurine methyl transferase; U+E = urea and electrolytes.

ity. TPMT activity can now be measured before starting thiopurine therapy, and this should be done where available. If levels are intermediate, the drugs can be used in lower doses, but they should be avoided in patients with very low TPMT activity. A rise in mean corpuscular volume is common with thiopurines, and does not require any action (although this can be confused with vitamin B_{12} or folate deficiency). A fall in white cell count is almost invariable on treatment, and more significant falls are associated with a beneficial effect of the drug. Higher TPMT levels require higher doses to affect white cell count. If total white cell count falls below $3.5x10^9$/litre, dose should be reduced, and stopped temporarily if below $3.0x10^9$/litre (until levels increase when it can be reintroduced cautiously).

Table 2. Dose equivalence and toxicity of corticosteroids

Dose equivalence	Prednisolone	5 mg
	Betamethasone	750 μg
	Cortisone acetate	25 mg
	Deflazacort	6 mg
	Dexamethasone	750 μg
	Hydrocortisone	20 mg
	Methylprednisolone	4 mg
	Triamcinolone	4 mg
Side effects	Mineralocorticoid	Hypertension
		Salt and water retention
		Potassium loss
	Mental	Insomnia
		Euphoria
		Psychosis
	Skin	Acne
		Moon-face
		Striae
		Buffalo hump
		Bruising and skin thinning
	Endocrine	Adrenal suppression
		Diabetes mellitus
	Musculoskeletal	Osteoporosis
		Avascular necrosis of femoral head
		Proximal myopathy
		Growth retardation in children

Figure 2. Thiopurine metabolic pathway. 6-thioguanine nucleotides are the active metabolites of azathioprine and 6-mercaptopurine. Thiopurine methyl transferase is a genetic polymorphism, low activity of which increases active metabolites and increases the likelihood of bone marrow suppression.



Methotrexate

This drug is widely used in rheumatoid arthritis and psoriasis. It is given weekly. (Daily administration carries a high risk of toxicity.) The drug has curious pharmacokinetics and higher oral doses reduce absorption, so there is no point in exceeding an oral dose of 20 mg weekly. Some patients prefer subcutaneous injections weekly because there is less chance of nausea or diarrhoea. Methotrexate interferes with cellular utilization of folic acid and risk of toxicity can be reduced by coadministration of folic acid 1 mg daily, or 5 mg once a week. Methotrexate is teratogenic (see below).

Ciclosporin and tacrolimus

Ciclosporin and tacrolimus are calcineurin inhibitors, primarily used following organ transplant as first-line therapy to prevent organ rejection. However, they are also used for a variety of other conditions, including severe psoriasis, rheumatoid arthritis, severe inflammatory bowel disease, uveitis, nephritic syndrome and aplastic anaemia.

The main side effects of both are nephrotoxicity and hypertension. Both can cause hyperkalaemia and hypomagnesaemia, and for this reason electrolyte levels should be checked before initiating therapy. More common side effects include headache, gastrointestinal upset and tremor. Patients must avoid grapefruit juice while taking either drug.

Anti-tumour necrosis factor agents

These are licensed in the UK for the treatment of a number of inflammatory conditions, including rheumatoid arthritis, seronegative spondyloarthropathies and inflammatory bowel disease. Infliximab is a chimeric (mouse/human) monoclonal antibody, while adalimumab is fully humanized. Etanercept is a recombinant fusion protein. These drugs are reserved for refractory disease which has failed to respond to conventional therapy. They are recommended in combination with methotrexate therapy in rheumatoid arthritis, as effects are better than for monotherapy (Klareskog et al, 2004); the efficacy of all three drugs is similar (Kristensen et al, 2007).

Infliximab is recommended for refractory Crohn's disease (Behm and Bickston 2008), and is effective in

moderately to severe ulcerative colitis refractory to conventional treatment (Lawson et al, 2006). Infliximab is given intravenously, while adalimumab and etanercept are given subcutaneously, with injection site reactions being a frequently occurring but usually minor problem (Moreland et al, 1997). Infusion reactions with infliximab are usually acute and occur in about 5% of infusions (Cheifetz et al, 2003), but the majority are anaphylactoid and can usually be managed by slowing the rate of the infusion, and administering chlorpheniramine and hydrocortisone. Delayed infusion reactions can occur up to 14 days after the infusion, presenting as myalgia, joint pains, skin rash and fever.

Biologic agents are associated with an increased risk of infection, in particular the reactivation of latent tuberculosis (Theis and Rhodes, 2008), therefore screening for tuberculosis before initiating therapy is advised. A past history of malignancy is an absolute contraindication because of the risk of reactivating latent malignancy.

Vaccination

Live vaccines should not be given to patients on high-dose corticosteroids or other immunosuppressive therapy. Killed or inactivated vaccines can be given. Ideally, vaccination should be thought about early in disease management before immunosuppressive therapy is required, although this is not always possible. Vaccines against influenza and pneumococci are recommended for patients on immunosuppressive therapy (Glück and Müller-Ladner, 2008). Human papillomavirus vaccination is not contraindicated in immunosuppressed women, but it is not yet known whether the immunogenicity of the vaccine is altered (Torne et al, 2008).

Pregnancy and conception

This is an important consideration in young people who may wish to start a family, or who may be at risk of accidental pregnancy. Patients should be counselled before treatment starts, and given written information. Methotrexate, mycophenolate mofetil and leflunomide are all teratogenic, and effective contraception must be used, for both women and men taking the drugs. They are also contraindicated during pregnancy and breastfeeding.

Data on anti-tumour necrosis factor drugs (etanercept, infliximab and adalimumab) are unclear. There are case reports of many successful pregnancy outcomes, but patients should be counselled that the level of risk is unknown and contraception is strongly advised. The drugs should only be continued during pregnancy if the drug is essential to the mother's health. Drugs which are considered relatively safe during conception and pregnancy include glucocorticoids, azathioprine and 6-mercaptopurine. Ciclosporin does not cross the placenta, and tacrolimus also appears safe, although data are more limited. No drug can ever be deemed completely safe, however, and patients must always be counselled about risks and benefits. Breastfeeding is generally not advised on these drugs, and although data for men are sparse, it is prudent to stop the drug in men 3 months before stopping contraception.

Malignancy

In general any immunosuppressive drug increases the risk of malignancy for the patient. It is likely that the degree of risk is proportional to the overall intensity and duration of immunosuppression. However, many chronic immune or inflammatory disorders carry an increased risk of malignancy themselves. Patients receiving allogeneic transplants are at significantly increased risk. Persistent Epstein–Barr or other viruses may explain the increased risk of B-cell lymphomas and squamous tumours such as cervical and skin cancer.

Conclusions

Use of immunosuppressive drugs is always a balance of risks against benefits. Simple checklists will help when assessing patients already on these drugs (*Figure 3*), and starting new therapy (*Figure 1*). Always take advice from ward pharmacists, senior colleagues and reference material before starting or continuing unfamiliar drugs. **BJHM**

Conflict of interest: Dr Hawthorne has served as a speaker, a consultant and an advisory board member for Abbott and Schering Plough Pharmaceuticals Ltd, and has received research funding from Novartis and UCB.

Figure 3. Checklist for assessing patients on immunosuppression.

Regimen Immunosuppressive therapy being taken in the correct dose, route and with appropriate indication. (May need confirmation from old hospital notes or GP records)

Side-effects Are current symptoms related to immunosuppressive therapy (e.g. fever as a result of opportunistic infection, abdominal pain caused by azathioprine-induced pancreatitis)?

Monitoring Are specific blood tests needed, e.g. trough ciclosporin levels, full blood count for azathioprine therapy, or chest radiograph for methotrexate patient with breathlessness (causes lung fibrosis rarely)?

Interactions Will any of the new therapies interact (e.g. ciclosporin and erythromycin)?

Stop therapy Can therapy be continued safely, or temporarily stopped (e.g. patient at high infection risk)?

KEY POINTS

- Discuss the risks and benefits of an immunosuppressive drug with the patient before starting therapy.
- Evaluate thoroughly before starting therapy (e.g. baseline blood tests, exclude active or latent infection (e.g. tuberculosis), discuss vaccination needs and contraception).
- Confirm monitoring needs while on drug.
- Patients on long-term immunosuppression have an increased risk of atypical infection and malignancy and this must be considered if they present with unexplained symptoms.

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