Long-term management of patients taking immunosuppressive drugs

***Denise C Hsu**, Immunology Registrar, Department of Immunology, Concord Repatriation General Hospital, Sydney; and **Constance H Katelaris**, Professor, Clinical Immunology and Allergy, University of Western Sydney*

Summary

The number of patients taking immunosuppressive drugs for the management of autoimmune inflammatory conditions is increasing. The general practitioner needs to be active in preventing, monitoring and managing the adverse effects of these drugs even long after the treatment has ceased. Monitoring is required because immunosuppressive drugs increase the risks of infection, malignancy, cardiovascular disease and bone marrow suppression. Some drugs have additional risks which require specific monitoring. Vigilance is needed as adverse effects may have atypical clinical presentations.

Key words: calcineurin inhibitors, corticosteroids, methotrexate.

(Aust Prescr 2009;32:68–71)

Introduction

General practitioners are increasingly likely to encounter patients who are taking immunosuppressive drugs for disease control in a variety of autoimmune inflammatory conditions. These include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and systemic vasculitis. The drugs are also used in transplantation. Although these drugs are usually started by specialists, general practitioners need to be aware of the long-term adverse effects so that there is no delay in detecting problems.

General risks of immunosuppressive drugs

Drugs which suppress the immune system are inevitably associated with increased risk of infection and malignancy. Many of these drugs also impact adversely on patients' cardiovascular risk.

Infections

Patients may be infected by common community-acquired and opportunistic organisms. The risk of infection increases with the degree of immunosuppression. Infections with *Pneumocystis jirovecii*, nocardia, aspergillus, cryptococcus and reactivation of varicella zoster, herpes simplex, cytomegalovirus, hepatitis B and C as well as tuberculosis are not uncommon in patients who are profoundly immunosuppressed.

Patients often present with atypical symptoms and disseminated disease. All patients taking immunosuppressants should have a thermometer at home and should seek urgent medical assessment if they develop a temperature over 38°C.

Annual influenza vaccination, and pneumococcal vaccination at baseline and one-time revaccination after five years, is recommended by the American College of Rheumatology. Patients with significant immunosuppression should not receive live vaccines. In those exposed to chickenpox or shingles, administration of herpes zoster immunoglobulin is an option.[1]

Malignancy

The risk of cancer, especially cutaneous and haematological malignancies, is increased. Patients taking immunosuppressive drugs should have at least yearly skin checks by their general practitioners, and be up to date with the normal recommended cancer screening programs such as faecal occult blood for those over 50, cervical smears and mammography.

Many autoimmune diseases are associated with an increased risk of malignancy. Dermatomyositis and polymyositis are associated with adenocarcinomas, while rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome are associated with lymphoid malignancy.

Marrow suppression and cytopenia

Bone marrow suppression is a common dose-limiting toxicity for most immunosuppressive drugs, apart from hydroxychloroquine and the glucocorticoids. The recommendations for monitoring are largely based on expert consensus and often differ slightly.[1,2] Table 1 has a suggested frequency of monitoring for patients who have been stable on maintenance doses of immunosuppressive drugs. Patients with white cell counts less than 3.5 x 10^6/L, neutrophils less than 2 x 10^6/L and platelets less than 150 x 10^6/L should have repeat testing within seven days and the specialist should be alerted if the results are low. Immunosuppressive drugs should be suspended if there is significant neutropenia (less than 1.5 x 10^6/L) and the specialist should be contacted immediately.

Table 1

Suggested frequency of monitoring during treatment with immunosuppressive drugs

	Full blood count	Electrolytes, urea, creatinine and fasting glucose	Liver function tests	Calcium magnesium phosphate	Fasting lipids	Eye review	Urinalysis
Corticosteroids	3 monthly	3 monthly	3 monthly	NR	6 monthly	If symptomatic	NR
Hydroxychloroquine	12 monthly	12 monthly	12 monthly	NR	12 monthly	12 monthly	NR
Azathioprine	1–3 monthly	1–3 monthly	1–3 monthly	NR	6 monthly	NR	NR
Cyclosporin/ tacrolimus	1–3 monthly	1–3 monthly	1–3 monthly	1–3 monthly	6 monthly	NR	NR
Leflunomide	1–3 monthly	1–3 monthly	1–3 monthly	NR	12 monthly	NR	NR
Methotrexate	1–3 monthly	1–3 monthly	1–3 monthly	NR	12 monthly	NR	NR
Mycophenolate	1–3 monthly	1–3 monthly	1–3 monthly	NR	12 monthly	NR	NR
Cyclophosphamide	Fortnightly to monthly	Monthly	Monthly	NR	12 monthly	NR	6 monthly

NR Not routinely recommended

Cardiovascular risk

The commonest cause of long-term morbidity and mortality in patients with autoimmune disease is cardiovascular disease. Women less than 45 years old with systemic lupus erythematosus are 50 times more likely, and patients with rheumatoid arthritis are twice as likely, to have a myocardial infarct in the next 8–10 years when compared with healthy age- and sex-matched controls. This increase in risk is attributed to the chronic inflammatory state as well as the hyperglycaemic and hyperlipidaemic adverse effects of immunosuppressive drugs such as glucocorticoids, cyclosporin and tacrolimus.

Patients should be encouraged to cease smoking and have regular monitoring of weight, blood pressure, fasting lipids and glucose. Although there are no evidence-based cardiovascular guidelines specifically for patients on immunosuppressive drugs, efforts to achieve risk factor reduction should be more rigorous than for the general population. The threshold for further cardiac investigation should be low in the presence of symptoms, even if they are atypical.

Specific long-term toxicities requiring monitoring

In addition to their general effects on the immune system, immunosuppressant therapies have drug interactions (see box) and adverse effects. Monitoring aims to detect these problems early.

Glucocorticoids

Corticosteroids are commonly used immunosuppressive drugs. They have potential adverse effects on multiple organs. Their toxicity is related to both the average dose and the cumulative duration of use. General practitioners need to be especially alert as many adverse effects are asymptomatic, but treatable with early diagnosis and intervention. Weight control and dietary advice at the outset of long-term treatment may assist in preventing weight gain and diabetes. Patients should also be screened for diabetes periodically.

Some important interactions with immunosuppressive drugs

Azathioprine	and	allopurinol
Calcineurin inhibitors	and	azole antifungals colchicine diltiazem erythromycin phenytoin atorvastatin, simvastatin
Methotrexate	and	non-steroidal anti-inflammatory drugs trimethoprim (and sulfamethoxazole)

Bone protection

Glucocorticoids alter bone metabolism. They reduce bone formation and increase resorption leading to substantial decreases in bone mineral density, especially in the first few months of use, and to increased fracture rates. Baseline bone mineral density should be measured if corticosteroid therapy is likely to be required for more than three months. Bone-protective therapy should be commenced at the time of starting corticosteroids in high-risk individuals, for example those aged 65 years or over, those with prior fragility fracture and those who are osteopenic.[3] There is evidence for the use of adequate doses of calcium and vitamin D with bisphosphonates for the prevention or reduction of steroid-induced bone loss and fracture.[4]

Patients need encouragement to remain active and to take regular weight-bearing exercise. They should also have their bone mineral density checked every 1–2 years.

Cardiovascular risk

A large cohort study has shown that even after adjustment for known covariates, the relative risk for cardiovascular events in patients receiving high-dose glucocorticoids was 2.56.[5] The risks of individual outcomes such as death, heart failure, myocardial infarction, stroke and transient ischaemic attacks are all significantly higher for those prescribed high-dose glucocorticoids. Tight control of cardiovascular risk factors is therefore essential for those taking corticosteroids.

Eyes

Glucocorticoids cause cataract formation and can increase intraocular pressure. Currently, there is no recommendation for regular ophthalmological review, however enquiry about eye symptoms and yearly optometry review with measurement of intraocular pressure is prudent.

Hydroxychloroquine

This antimalarial drug has immunomodulatory properties and is used in a variety of autoimmune diseases. It is relatively well tolerated at the commonly used dosages of 200–400 mg/day. Retinopathy has been well documented with doses greater than 6.5 mg/kg/day (a dose rarely used today). Hydroxychloroquine is contraindicated in patients with pre-existing maculopathy. Guidelines regarding the need for regular ophthalmological reviews vary. The American Academy of Ophthalmology recommends ophthalmological examination within the first year of treatment. If a patient is in the low-risk category (no liver disease, no retinal disease and age less than 60), no further ophthalmological testing is needed for the next five years. Patients at high risk require annual examinations.[6] The usual practice in Australia is annual ophthalmological review.

Leflunomide

Elevation of liver enzymes is a common toxicity of leflunomide. Three-fold elevations occur in up to 10% of patients, but these are generally reversible with dose reduction or discontinuation of the drug. Liver function tests should be done at regular intervals.

Blood pressure monitoring is required as a small percentage of patients become hypertensive. The risk is increased with concomitant use of non-steroidal anti-inflammatory drugs.

Methotrexate

Methotrexate is usually taken orally once a week on a nominated day, in combination with folic acid to reduce toxicity. The general practitioner needs to take special care as toxicity from methotrexate can occur during long-term use, with up to 30% of patients treated for more than five years discontinuing due to unacceptable toxicity in some series.

An interaction with non-steroidal anti-inflammatory drugs can increase toxicity, but this is less likely to occur with low doses of methotrexate. Penicillins and sulfonamides reduce the excretion of methotrexate. As trimethoprim also increases the risk of toxicity, the combination of trimethoprim and sulfamethoxazole should generally be avoided in patients taking methotrexate.

Myelosuppression

Myelosuppression is the major dose-limiting adverse effect of methotrexate. It is particularly likely in the elderly and patients with renal impairment or concomitant administration of antifolate drugs such as cotrimoxazole and phenytoin. A full blood count every 1–3 months is advisable.

Hepatotoxicity

Hepatotoxicity occurs at a frequency of 1 per 35 patient years. It is usually associated with a cumulative dose of at least 1.5 g. Alcohol is a major risk factor and should be avoided. The general practitioner should enquire regularly about the patient's alcohol intake. Coexisting hepatitis B and C also increases the risk of hepatotoxicity. The current recommendation is for 1–3 monthly monitoring of liver function. Liver biopsy is indicated if six of twelve tests are abnormal in any year (or five of nine if testing is performed at six-week instead of monthly intervals).[2]

Pulmonary toxicity

Methotrexate-induced pulmonary toxicity is an idiosyncratic reaction, occurring at a frequency of 1 per 108 patient years. Hypersensitivity pneumonitis is the most common manifestation. Evidence for screening is lacking. Patients with respiratory symptoms should have lung function testing and a chest X-ray, with specialist review for further investigations, such as a high resolution computed tomography scan, and treatment.

Azathioprine

Azathioprine can be associated with life-threatening myelosuppression and liver enzyme abnormalities. Most patients would have had their concentration of thiopurine methyltransferase measured before treatment.[7] Deficiency of this enzyme is associated with a significantly increased risk of serious adverse haematological events. While azathioprine is contraindicated in homozygous deficiency, individuals with heterozygous deficiency are likely to be prescribed a reduced dose and will need more frequent monitoring. Mild leucopenia can be managed by dose reduction. More severe cytopenia and liver function abnormality will require drug cessation, however this should be done in liaison with the patient's specialist. Myelotoxicity may be precipitated by an interaction with allopurinol, so this combination is best avoided.

Cyclophosphamide

Cyclophosphamide given in intravenous pulses is generally used for inducing remission in a variety of autoimmune

diseases as it has a better adverse effect profile than daily oral dosing. Nowadays, it is usually replaced by other drugs for maintaining remission so patients rarely take it for a long time.

While the patient is taking cyclophosphamide it is crucial to monitor for cytopenia, haemorrhagic cystitis and early signs of infections. Even after the drug is discontinued it is necessary to monitor for haematuria and check urine cytology 6–12 monthly as bladder transitional cell carcinomas can develop up to 15 years after stopping cyclophosphamide. Patients with new-onset non-glomerular haematuria or atypical urine cytology findings should be referred to a urologist for further evaluation, including cystoscopy.

Calcineurin inhibitors

The adverse effects and monitoring required for cyclosporin and tacrolimus are similar. The doses used in autoimmune disease are much lower than in transplantation so there is less toxicity, and regular monitoring of drug concentration is not mandatory. Nephrotoxicity characterised by rising urea and creatinine is a common dose-related adverse effect leading to discontinuation of the drug. Tubular dysfunction can also occur resulting in hypomagnesaemia and hyperkalaemia.

The drugs adversely impact on patients' cardiovascular risk, causing glucose intolerance and hyperglycaemia, hyperlipidaemia, hyperuricaemia and hypertension. These toxicities are usually responsive to dose reduction. Calcium channel blockers are the preferred antihypertensives as they reverse the vasoconstriction mediated by calcineurin inhibitors. Diltiazem also impairs calcineurin inhibitor metabolism, thereby allowing a lower dose to be given. If a lipid lowering drug is necessary, drugs metabolised by cytochrome P450 3A4, such as simvastatin, should be avoided as cyclosporin may increase the concentrations and thus adverse effects. A drug such as pravastatin would be a suitable alternative. Similar caution is needed if ezetimibe is prescribed for a patient taking cyclosporin and cyclosporin concentrations should be monitored.

Every 1–3 months check the patient's weight, blood pressure, full blood count, urea, electrolytes and creatinine, liver function tests, calcium magnesium and phosphate, uric acid, and fasting glucose. Check the fasting lipids every six months.

Mycophenolate

The main toxicity of mycophenolate which requires monitoring is cytopenia. As mycophenolate is renally cleared, dose adjustment is necessary in renal impairment.

Conclusion

Immunosuppressive drugs are efficacious in inducing and maintaining remission in organ threatening inflammatory diseases, but are also associated with significant adverse effects and toxicity. Health professionals involved in the patient's management need to be vigilant and proactive in preventing, monitoring and managing adverse effects. This surveillance may need to continue long after the drugs have been stopped.

References

1. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
2. Chakravarty K, McDonald H, Pullar T, Taggart A, Chalmers R, Oliver S, et al; British Society for Rheumatology, British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group; British Association of Dermatologists. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology (Oxford) 2008;47:924-5.
3. Romas E. Corticosteroid-induced osteoporosis and fractures. Aust Prescr 2008;31:45-9.
4. Bone and Tooth Society, National Osteoporosis Society, National Osteoporosis Society (Great Britain), Royal College of Physicians of London. Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: Royal College of Physicians; 2003.
5. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141:764-70.
6. American College of Rheumatology. Screening for hydroxychloroquine retinopathy. 2006. www.rheumatology.org/publications/position/hydroxyp2.asp [cited 2009 May 5]
7. TPMT testing before azathioprine therapy? Drug Ther Bull 2009;47:9-12.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

3. Immunosuppressive drugs increase the risk of cardiovascular disease.
4. Patients taking methotrexate should not drink alcohol.

See **Dental notes: Immunosuppressive drugs** page 75.