tension, peripheral oedema, asthenia, hyperkalaemia, and tachycardia. Nephrotoxicity has been reported.

Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should generally be avoided for the same reason. Thrombophlebitis may be avoided by infusion into a vein with a rapid blood flow. To identify those at risk of anaphylaxis, patients should be tested for skin sensitivity before infusion. If there is a locally positive skin reaction, alternative therapy should be considered although hypersensitivity reactions may still occur in patients whose skin test is negative. If there is a systemic reaction, further doses of antilymphocyte immunoglobulins should not be given. Facilities for management of anaphylaxis (see p.1205) should be available during treatment, and the patient should be observed continuously.

Effects on the kidneys. Acute renal failure has been reported after the use of antilymphocyte immunoglobulins.[1,2] Prolonged anuria requiring haemodialysis has occurred.[2]

1. Levine JM, *et al.* Antithymocyte globulin-induced acute renal failure. *Am J Kidney Dis* 1999; **34:** 1155.
2. Barakat RK, *et al.* Prolonged renal failure secondary to antithymocyte globulin treatment in severe aplastic anemia. *Ann Pharmacother* 2007; **41:** 895–8.

Uses and Administration

Antilymphocyte immunoglobulins are antibodies, raised in *animals*, which act against lymphocytes, and in particular against T-cells, to produce suppression of cell-mediated immunity.

They may be added to existing immunosuppressant regimens to treat acute rejection episodes in patients who have undergone organ or tissue transplantation. Alternatively, they may be given prophylactically as part of a combination immunosuppressant regimen with several other agents. For discussion of the role of antilymphocyte immunoglobulins in transplantation, see p.1810 *et seq*.

Antilymphocyte immunoglobulins are also used in the treatment of aplastic anaemia (p.1042) in patients unsuitable for bone marrow transplantation, and have been tried in other immunological disorders. They are under investigation for the treatment of myelodysplastic syndromes (p.654).

Different antilymphocyte preparations may vary in their activity, as may different lots of the same preparation. However, daily doses in **transplantation** have usually ranged from 10 to 30 mg/kg of *equine* immunoglobulin, or 1 to 2.5 mg/kg of *rabbit* immunoglobulin. For **aplastic anaemia**, doses of *equine* immunoglobulin range from 10 to 20 mg/kg daily; regimens vary in different countries.

For children's doses, see Administration in Children, below.

Doses of antilymphocyte immunoglobulin are given as a slow intravenous infusion diluted in sodium chloride 0.9%, or other suitable diluent. It has been recommended that the final dilution should contain no more than 1 mg/mL of immunoglobulin and be given over 4 hours or more, via an in-line filter.

Administration in children. Although data in children are limited, licensed product information in the USA states that doses of *equine* immunoglobulin for transplantation in children have ranged from 5 to 25 mg/kg daily. The dose for *rabbit* immunoglobulin is not thought to differ from that for adults, namely 1.5 mg/kg daily, based on limited European studies and US compassionate use.

Organ and tissue transplantation. Antilymphocyte immunoglobulin derived from *rabbits* was found to be more effective than the *equine* product in treating acute rejection and preventing recurrent rejection in adult kidney transplantation (p.1813); patient and graft survival rates and the incidence of infection did not differ significantly.[1] Although unlicensed for induction therapy in the USA, some consider rabbit antilymphocyte immunoglobulin to be safe and effective for such use in adult renal transplantation.[2,3] Rabbit immunoglobulin induction is also considered safe and effective[4,5] in paediatric renal transplant recipients. The incidence of acute rejection was lower in rabbit immunoglobulin recipients than in those given the equine product; however, rates of Epstein-Barr virus (EBV) infection were higher with the rabbit product. Patient and graft survival rates, incidence of chronic rejection, EBV lymphoma, or other infection did not differ significantly between the 2 groups.

In adult renal transplant recipients considered to be at high risk for acute rejection or delayed graft function, induction with rabbit antilymphocyte immunoglobulin reduced the incidence and severity of acute rejection (but not the incidence of delayed graft function) compared with basiliximab induction. Patients receiving antilymphocyte immunoglobulin had a greater incidence of infection but a lower incidence of CMV disease; patient and graft survival were similar in the 2 groups.[7]

Induction therapy with antilymphocyte immunoglobulins has also been shown to be beneficial in other solid organ transplants, with lower rates of rejection reported in liver (p.1815), pancreas (p.1816), kidney-pancreas, heart (p.1812), and heart-lung transplantation. Use in lung transplantation remains controversial due to a higher incidence of CMV infection.[8] Induction protocols differ between institutions.

In haematopoietic stem cell transplant recipients (p.1811), those given rabbit antilymphocyte immunoglobulin prior to a matched unrelated donor (MUD) transplant had comparable outcomes to those given matched related donor (MRD) transplants but no antilymphocyte immunoglobulin; the authors supposed that the use of antilymphocyte immunoglobulin caused MUD recipients to behave clinically like MRD recipients.[9] A review of the use of antilymphocyte immunoglobulins in haematopoietic stem cell transplantation concluded that it significantly reduces the severity and incidence of acute graft-versus-host disease (GVHD) and chronic GVHD. This protective effect is dependent on the dose, the timing of infusion, and the brand used. However, antilymphocyte immunoglobulin induction therapy delays immune reconstitution and there is an increased risk of infection; the use of an antilymphocyte immunoglobulin is a risk factor for EBV reactivation.[10]

1. Gaber AO, *et al.* Results of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. *Transplantation* 1998; **66:** 29–37.
2. Hardinger KL. Rabbit antithymocyte globulin induction therapy in adult renal transplantation. *Pharmacotherapy* 2006; **26:** 1771–83.
3. Wong W, *et al.* Comparison of two dosages of thymoglobulin used as a short-course for induction in kidney transplantation. *Transpl Int* 2006; **19:** 629–35.
4. Ault BH, *et al.* Short-term outcomes of Thymoglobulin induction in pediatric renal transplant recipients. *Pediatr Nephrol* 2002; **17:** 815–18.
5. Hastings MC, *et al.* Five years' experience with thymoglobulin induction in a pediatric renal transplant population. *Pediatr Transplant* 2006; **10:** 805–10.
6. Khositseth S, *et al.* Thymoglobulin versus ATGAM induction therapy in pediatric kidney transplant recipients: a single-center report. *Transplantation* 2005; **79:** 958–63.
7. Brennan DC, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355:** 1967–77.
8. Beiras-Fernandez A, *et al.* Induction of immunosuppression with polyclonal antithymocyte globulins: an overview. *Exp Clin Transplant* 2003; **1:** 79–84.
9. Duggan P, *et al.* Unrelated donor BMT recipients given pretransplant low-dose antithymocyte globulin have outcomes equivalent to matched sibling BMT: a matched pair analysis. *Bone Marrow Transplant* 2002; **30:** 681–6.
10. Bacigalupo A. Antithymocyte globulin for prevention of graft-versus-host disease. *Curr Opin Hematol* 2005; **12:** 457–62.

Preparations

Ph. Eur.: Anti-T Lymphocyte Immunoglobulin for Human Use, Animal.

Proprietary Preparations (details are given in Part 3)
Arg.: Apasmil†; Linfoglobulina; Timoglobulina; ***Austral.:*** Atgam; ***Austria:*** Thymoglobuline; ***Belg.:*** ATG; Thymoglobuline; ***Braz.:*** Lymphoglobuline†; Thymoglobuline†; ***Canad.:*** Atgam; Thymoglobulin; ***Chile:*** Linfoglobulina; Timoglobulina; ***Cz.:*** ATG; Lymphoglobuline†; Thymoglobuline; ***Denm.:*** Thymoglobuline; ***Fin.:*** Thymoglobuline; ***Fr.:*** Lymphoglobuline; Thymoglobuline; ***Ger.:*** Lymphoglobulin; Tecelac†; Thymoglobulin; ***Gr.:*** Lymphoglobuline; Thymoglobuline; ***Hong Kong:*** ATG; Atgam; Lymphoglobuline†; Thymoglobuline; ***India:*** Thymoglobulin; ***Israel:*** ATG; Lymphoglobuline; Thymoglobuline; ***Ital.:*** Lymphoglobuline; Thymoglobuline; ***Malaysia:*** Atgam; Lymphoglobuline†; Thymoglobuline; ***Mex.:*** Atgam; Tecelac; ***Neth.:*** ATG; Lymphoglobuline; Thymoglobuline; ***NZ:*** Atgam; ***Pol.:*** ATG; Lymphoglobuline; Tecelac; Thymoglobuline; ***Port.:*** Timoglobulina; ***Rus.:*** Atgam (Атгам); ***S.Afr.:*** Atgam; Lymphoglobuline; Thymoglobuline; ***Singapore:*** ATG†; Atgam; Lymphoglobuline†; Thymoglobuline; ***Spain:*** Atege; Atgam†; Linfoglobulina; Timoglobulina; ***Swed.:*** ATG; Thymoglobuline; ***Switz.:*** ATG; Atgam†; Lymphoglobuline; Thymoglobuline; ***Thai.:*** ATG; Lymphoglobuline†; Thymoglobuline†; ***Turk.:*** Lymphoglobuline; Thymoglobuline; ***UK:*** Thymoglobuline; ***USA:*** Atgam; ***Venez.:*** Atgam; Linfoglobulina†.

Azathioprine *(BAN, USAN, rINN)*

Atsatiopriini; Azathioprin; Azathioprinum; Azatioprin; Azatioprina; Azatioprinas; Azatiopryna; BW-57322; NSC-39084. 6-(1-Methyl-4-nitroimidazol-5-ylthio)purine.

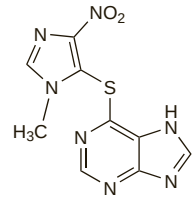
Азатиоприн

$C_9H_7N_7O_2S$ = 277.3.

CAS — 446-86-6.

ATC — L04AX01.

ATC Vet — QL04AX01.



NOTE. The abbreviation AZT, which has sometimes been used for azathioprine, has also been used to denote the antiviral zidovudine.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Azathioprine). A pale yellow powder. Practically insoluble in water and in alcohol; soluble in dilute solutions of alkali hydroxides; sparingly soluble in dilute mineral acids. Protect from light.
USP 31 (Azathioprine). A pale yellow, odourless powder. Insoluble in water; very slightly soluble in alcohol and in chloroform; sparingly soluble in dilute mineral acids; soluble in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Adverse Effects

Dose-related bone-marrow depression is common with use of azathioprine; this may be manifested as leucopenia or, less often, thrombocytopenia or anaemia, and rarely, as agranulocytosis, pancytopenia, or aplastic anaemia. Myelosuppression is generally reversible, and may occasionally be delayed. Macrocytic, including megaloblastic, anaemia has occurred. Patients with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) may be at increased risk of myelotoxicity. Azathioprine has also been associated with the development of liver damage; it has been suggested that cholestatic symptoms may be due to the mercaptopurine moiety. Rarely, delayed and potentially fatal veno-occlusive liver disease has occurred.

Other adverse effects associated with azathioprine include gastrointestinal disturbances, reversible alopecia, and symptoms including rashes, muscle and joint pains, fever, rigors, pneumonitis, pancreatitis, tachycardia, renal dysfunction, and hypotension, some or all of which may represent hypersensitivity reactions. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely.

Solutions for injection are irritant.

◊ References.

1. Lawson DH, *et al.* Adverse effects of azathioprine. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 161–71.

Carcinogenicity. Immunosuppression, including that with azathioprine, may be associated with an increased risk of certain neoplasms such as lymphomas and skin cancers in transplant recipients,[1] in patients with inflammatory bowel disease,[2,3] and in patients with rheumatoid arthritis.[4-6] Partly because of lower doses of immunosuppressants used in inflammatory bowel disease, the risk of lymphoma in these patients appears to be less than that associated with transplant recipients;[7] this risk appears to be far outweighed by the benefits of immunosuppressant therapy in inflammatory bowel disease. Rheumatic diseases may themselves be associated with an increased risk of malignancy that is independent of treatment, but one study[5] concluded that there is a further risk related to the duration of exposure to immunosuppressive drugs, including azathioprine. A recent systematic review[8] of the use of azathioprine for multiple sclerosis concluded that, when the balance between the benefits and harms were considered, azathioprine was a reasonable alternative to interferon beta in patients who frequently relapse and require corticosteroids. Other evidence in the literature suggested that the long-term risk of malignancy may be related to use for longer than 10 years and a cumulative dose above 600 g and the reviewers recommended that this dose should not be exceeded.

Skin cancer may be a particular risk in immunosuppressed patients with a history of high sun exposure.[7] A synergistic clastogenic effect has been noted with azathioprine and long-wave ultraviolet light.

1. Kinlen LJ, *et al.* Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 1979; **2:** 1461–6.
2. Kandiel A, *et al.* Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54:** 1121–5.
3. Kwon JH, Farrell RJ. The risk of lymphoma in the treatment of inflammatory bowel disease with immunosuppressive agents. *Crit Rev Oncol Hematol* 2005; **56:** 169–78.

4. Silman AJ, *et al.* Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. *Ann Rheum Dis* 1988; **47:** 988–92.
5. Asten P, *et al.* Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999; **26:** 1705–14.
6. Patel P, *et al.* Azathioprine induced Hodgkin lymphoma: a case report and review of literature. *Am J Clin Oncol* 2005; **28:** 427–8.
7. Boyle J, *et al.* Cancer, warts, and sunshine in renal transplant patients: a case-control study. *Lancet* 1984; **i:** 702–5.
8. Casetta I, *et al.* Azathioprine for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).

Effects on the blood. Neutropenia in patients receiving mercaptopurine has been reported to correlate negatively with the concentration of the metabolite tioguanine nucleotide in erythrocytes,[1] and it has been suggested that measurement of metabolite concentrations in erythrocytes,[2] or activity of the enzyme thiopurine methyltransferase (TPMT),[3-6] permits prediction of those individuals likely to experience severe bone-marrow toxicity with mercaptopurine and the related drugs tioguanine and azathioprine. However, not all studies have found such correlations,[7] and effects on the bone marrow with this class of drugs are probably multifactorial;[8,9] low activity of other enzymes such as lymphocyte 5-nucleotidase,[10] and other factors, may contribute to toxicity. A review[9] of studies investigating TPMT activity in patients with Crohn's disease concluded that measurement of TPMT activity on starting azathioprine has a role in identifying those at risk of severe myelosuppression. Lower TPMT activities correlate with low neutrophil counts in the initial 4 months of thiopurine therapy; identification of the heterozygote might allow for safer management (see Therapeutic Drug Monitoring, below). However, in those patients established on therapy, TPMT did not predict clinical response or toxicity. Pure red cell aplasia occurs rarely with use of azathioprine; reported cases have all been in renal transplant recipients. In one such case,[11] reduction of the dose and use of erythropoietin was ineffective; however, the patient recovered within weeks of stopping azathioprine.

1. Lennard L, *et al.* Childhood leukaemia: a relationship between intracellular 6-mercaptopurine metabolites and neutropenia. *Br J Clin Pharmacol* 1983; **16:** 359–63.
2. Maddocks JL, *et al.* Azathioprine and severe bone marrow depression. *Lancet* 1986; **i:** 156.
3. Schütz E, *et al.* Azathioprine-induced myelosuppression in thiopurine methyltransferase deficient heart transplant recipient. *Lancet* 1993; **341:** 436.
4. Lennard L, *et al.* Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993; **69:** 577–9.
5. Jackson AP, *et al.* Thiopurine methyltransferase levels should be measured before commencing patients on azathioprine. *Br J Dermatol* 1997; **136:** 133–4.
6. Black AJ, *et al.* Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. *Ann Intern Med* 1998; **129:** 716–18.
7. Boulieu R, *et al.* Intracellular thiopurine nucleotides and azathioprine myelotoxicity in organ transplant patients. *Br J Clin Pharmacol* 1997; **43:** 116–18.
8. Soria-Royer C, *et al.* Thiopurine-methyl-transferase activity to assess azathioprine myelotoxicity in renal transplant recipients. *Lancet* 1993; **341:** 1593–4.
9. Lennard L. TPMT in the treatment of Crohn's disease with azathioprine. *Gut* 2002; **51:** 143–6.
10. Kerstens PJSM, *et al.* 5-Nucleotidase and azathioprine-related bone-marrow toxicity. *Lancet* 1993; **342:** 1245–6.
11. Agrawal A, *et al.* Azathioprine-induced pure red cell aplasia: case report and review. *Transplant Proc* 2004; **36:** 2689–91.

Effects on the liver. A review[1] of drug-related hepatotoxicity noted that azathioprine has been associated with hepatocanalicular cholestasis, in which the interference with bile flow is combined with hepatocyte damage, and with several hepatic vascular disorders, including focal sinusoidal dilatation, peliosis, and veno-occlusive disease. A later review[2] grouped reported cases into three syndromes: hypersensitivity, idiosyncratic cholestatic reaction, and presumed endothelial cell injury, with the imidazole and 6-mercaptopurine components of azathioprine playing different roles in pathogenesis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Romagnuolo J, *et al.* Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. *Can J Gastroenterol* 1998; **12:** 479–83.

Hypersensitivity. In 2 of 5 renal transplant recipients with acute allergic reactions associated with azathioprine, the symptoms (interstitial nephritis) were initially mistaken for acute rejection episodes.[1] In another report,[2] shock, fever, and acute renal insufficiency in a patient led to an initial mistaken diagnosis of sepsis, and it was recommended that a hypersensitivity reaction be considered as a cause if any of these symptoms occurred within 4 weeks of azathioprine ingestion. Other reported features of hypersensitivity include malaise, gastrointestinal disturbances, myalgia, arthralgia, fever, headache and raised liver enzymes.[3,4] Skin lesions have been reported, with maculopapular erythema occurring most frequently; purpura, urticaria, and erythema nodosum-like lesions have also been described.[4,5] Skin biopsies often showed features of leucocytoclastic vasculitis.[4] Stevens-Johnson syndrome has also been reported.[5] In some cases, skin patch testing for azathioprine was negative;[3,5] a drug-induced lymphocyte stimulation test (which evaluates the antigen specific reactivity of lymphocytes by measuring the proliferation of peripheral blood lymphocytes exposed to the suspected drug) has been proposed as a sensitive and reliable test for azathioprine hypersensitivity.[5]

1. Parnham AP, *et al.* Acute allergic reactions associated with azathioprine. *Lancet* 1996; **348:** 542–3.
2. Fields CL, *et al.* Hypersensitivity reaction to azathioprine. *South Med J* 1998; **91:** 471–4.
3. Hinrichs R, *et al.* Azathioprine hypersensitivity in a patient with peripheral demyelinating polyneuropathy. *Br J Dermatol* 2003; **148:** 1076–7.
4. Sinico RA, *et al.* Azathioprine hypersensitivity: report of two cases and review of the literature. *J Nephrol* 2003; **16:** 272–6.
5. Mori H, *et al.* Drug eruption caused by azathioprine: value of using the drug-induced lymphocytes stimulation test for diagnosis. *J Dermatol* 2004; **31:** 731–6.

Precautions

Regular monitoring of blood counts is required. Patients with renal or hepatic impairment require more frequent monitoring of blood counts and may need reduced doses; liver function tests should be performed in hepatic impairment. Consideration should be given to testing patients for thiopurine methyltransferase (TPMT) activity. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason. Azathioprine should generally be avoided in pregnancy (see below).

For a recommendation that the cumulative dose of azathioprine should not exceed 600 g in patients with multiple sclerosis, see under Carcinogenicity, above.

Breast feeding. Low concentrations of mercaptopurine have been found in human colostrum and breast milk of patients taking azathioprine.[1] Breast feeding by these patients has not been recommended because of the potential risk of immunosuppression in the infant.[1-3] However, there are reports[1,2] of 3 breast-fed infants, whose mothers had been taking doses of 75 or 100 mg of azathioprine daily, in whom no evidence of immunosuppression was found. All 3 had normal blood counts, no increase in infections, and above average growth rate. In one case, the levels of mercaptopurine were determined at 2 days and after 2 weeks of breast feeding,[1] and in the other 2 cases, no levels were determined.[2] In a third report, 31 breast-milk samples were collected from 10 breast-feeding women (taking from 75 to 150 mg azathioprine daily);[3] low concentrations of mercaptopurine were only detected in one case. The neonates were followed for up to 28 days, and showed no signs of immunosuppression, nor were mercaptopurine and tioguanine nucleotides detectable in their red blood cells. The authors concluded that breast feeding should not be withheld in infants of mothers receiving azathioprine. However, they cautioned that there were no data on the effect of thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, below) on metabolite concentrations in breast milk, and expressed concern as to whether a TPMT-deficient infant, unable to inactivate mercaptopurine absorbed into the breast milk, will be exposed to significant blood levels of the drug. In a study of 4 mothers and their infants,[4] all of whom had the wild-type TPMT genotype (with normal TPMT activity), infant exposure to azathioprine through breast milk was undetectable. The authors also cautioned that mothers taking higher doses or those with decreased TPMT activity might transfer more drug to the infant. It has been noted[5] that many breast-fed infants would have already been exposed to potentially much higher concentrations of mercaptopurine *in utero*.

1. Coulam CB, *et al.* Breast-feeding after renal transplantation. *Transplant Proc* 1982; **14:** 605–9.
2. Grekas DM, *et al.* Immunosuppressive therapy and breast-feeding after renal transplantation. *Nephron* 1984; **37:** 68.
3. Sau A, *et al.* Azathioprine and breastfeeding—is it safe? *Br J Obstet Gynaecol* 2007; **114:** 498–501.
4. Gardiner SJ, *et al.* Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. *Br J Clin Pharmacol* 2006; **62:** 453–6.
5. Moretti ME, *et al.* Breast-feeding during maternal use of azathioprine. *Ann Pharmacother* 2006; **40:** 2269–72.

Pregnancy. Azathioprine and/or its metabolites have been found in low concentrations in fetal blood after maternal use of azathioprine.[1] Azathioprine is teratogenic in *animals*, and congenital abnormalities, chromosomal aberrations,[2] fetal growth retardation,[3,4] low birth-weight, and spontaneous abortion have been reported in the offspring of pregnant women taking azathioprine. Neonatal leucopenia and thrombocytopenia have also been reported after maternal exposure.[5] Cohort studies have found an increased risk of congenital abnormalities, perinatal mortality, and preterm births after maternal or paternal exposure to azathioprine.[6,7] However, adverse birth outcomes may be related to the underlying disease rather than use of azathioprine or mercaptopurine,[8] and some consider its use in inactive inflammatory bowel disease to be safe;[9] however, there is suggestion that those with active disease, especially Crohn's disease, may have a higher incidence of spontaneous abortion, premature births, or still-births.[9] Given the nature of the severe chronic conditions for which azathioprine is generally used, stopping therapy in patients who become pregnant may not be necessary or desirable, but it seems prudent to avoid its use where possible during pregnancy.

1. de Boer NKH, *et al.* Azathioprine use during pregnancy: unexpected intrauterine exposure to metabolites. *Am J Gastroenterol* 2006; **101:** 1390–2.
2. The Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. *Br J Obstet Gynaecol* 1980; **87:** 839–45.
3. Pirson Y, *et al.* Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; **313:** 328.
4. Hou S. Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; **313:** 328.
5. Davison JM, *et al.* Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. *Br J Obstet Gynaecol* 1985; **92:** 233–9.
6. Nørgård B, *et al.* Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. *Aliment Pharmacol Ther* 2003; **17:** 827–34.
7. Nørgård B, *et al.* The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. *Aliment Pharmacol Ther* 2004; **19:** 679–85.
8. Langagergaard V, *et al.* Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: a Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007; **25:** 73–81.
9. Alstead EM, *et al.* Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology* 1990; **99:** 443–6.

Interactions

The effects of azathioprine are enhanced by allopurinol and the dose of azathioprine should be reduced to one-third to one-quarter of the usual dose when allopurinol is given. A further dose reduction or alternative therapy should be considered in those patients with low or absent thiopurine methyltransferase (TPMT) activity.

◊ In addition to being affected by allopurinol, azathioprine may itself affect other drugs including the following:

- competitive neuromuscular blockers (antagonism, see under Immunosuppressants on p.1904)
- vaccines (reduced response or generalised infection, see p.2202)
- warfarin (inhibition, see Immunosuppressants p.1431).

Gastrointestinal drugs. For mention of *5-aminosalicylates* inhibiting the metabolism of thiopurines such as azathioprine, and increasing their toxicity, see Mercaptopurine, p.744.

Mercaptopurine. The Institute for Safe Medication Practices in the USA reported a case in which a patient with a history of Crohn's disease was prescribed azathioprine and mercaptopurine by separate practitioners. The patient developed profound myelosuppression, severe sepsis, and died. Many drug information software programs were found to not warn of this possible therapeutic duplication.[1]

1. Institute for Safe Medication Practices. Duplication with azathioprine and mercaptopurine (issued 29 June, 2006). Available at: http://www.ismp.org/Newsletters/acutecare/articles/20060629_3.asp?ptr=y (accessed 15/01/08)

Pharmacokinetics

Azathioprine is well absorbed from the gastrointestinal tract when given orally. After oral or intravenous doses it disappears rapidly from the circulation and is extensively metabolised to mercaptopurine (which is then further metabolised—see p.744). Both azathioprine and mercaptopurine are about 30% bound to plasma proteins. About 10% of a dose of azathioprine is reported to be split between the sulfur and the purine ring to give 1-methyl-4-nitro-5-thioimidazole. The proportion of different metabolites is reported to vary between patients. Metabolites and small amounts of unchanged azathioprine and mercaptopurine are eliminated in the urine. Azathioprine is distributed into breast milk in low concentrations.

Therapeutic drug monitoring. Although plasma concentrations of 6-thiouric acid (the inactive product of mercaptopurine, and hence of azathioprine) can be readily measured in patients who have been receiving azathioprine, they are of little value in therapeutic drug monitoring.[1] The active moieties are the tioguanine nucleotides (6-TGN) formed intracellularly, which appear to have extremely long half-lives,[2] and mean erythrocyte concentrations of which appear to vary considerably between individuals.[2] The formation of other inactive metabolites is catalysed by thiopurine methyltransferase (TPMT) and its activity is genetically determined, with a trimodal distribution in the general population; 0.3% have low activity of TPMT, 11% have intermediate activity, and 89% have normal or high activity. Patients with low or intermediate activity appear to shift metabolism toward production of 6-TGN.

Because excess concentrations of 6-TGN have been associated with leucopenia, it has been suggested[3] that:

- patients with normal or high TPMT activity receive standard doses of azathioprine or mercaptopurine
- those with intermediate TPMT activity have reduced doses
- those with low activity not be treated with either drug

However, these recommendations remain controversial.[4] Haematological toxicity is not always explained by TPMT status, and other factors may be involved[5] (see also Effects on the Blood, above). Some consider that TPMT deficiency is not a contra-indication to thiopurine therapy; an initial dose reduction to 10 to 15% of the standard azathioprine dose has been used in TPMT-deficient patients with inflammatory bowel disease.[5] There are a proportion of patients in whom TPMT activity is very high; these patients appear to respond less well to standard doses, and higher-than-standard doses have been recommended.[6] While recommendations for pre-treatment measurement of TPMT status remain controversial,[4,5] some consider the avoidance of potentially fatal toxicity a compelling argument for TPMT assessment before thiopurine therapy is started.[6] However, TPMT units and normal ranges vary between laboratories depending on the methodology used,[6] and TPMT genotype or phenotype testing is not a surrogate for monitoring of complete blood counts.[4]

Because low concentrations of erythrocyte 6-TGN have been associated with disease relapse in lymphomas and leukaemias, a small study[7] of patients with inflammatory bowel disease attempted to define a therapeutic window of drug efficacy. Without monitoring TPMT genotype, treatment efficacy was found to correlate with erythrocyte 6-TGN levels. It was concluded that patients who remain symptomatic despite apparently therapeutic 6-TGN concentrations should be treated with adjunctive or alternative immunosuppression or surgery. However, a large study[8] did not confirm disease correlation with 6-TGN concentrations, and concluded that therapeutic drug monitoring of 6-TGN may be premature. It was noted that methodological differences, such as assay technique, existed between their study and others. As the role of routine monitoring of 6-TGN remains controversial,[4,9,10] it has been suggested that selective monitoring, such as in those with low or intermediate TPMT activity, be considered.[3] Some consider the measurement of 6-TGN useful to assess treatment compliance, or in cases of malabsorption.[4]

1. Chan GLC, *et al.* Pharmacokinetics of 6-thiouric acid and 6-mercaptopurine in renal allograft recipients after oral administration of azathioprine. *Eur J Clin Pharmacol* 1989; **36:** 265–71.
2. Chan GLC, *et al.* Azathioprine metabolism: pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in renal transplant patients. *J Clin Pharmacol* 1990; **30:** 358–63.
3. Sandborn WJ. Rational dosing of azathioprine and 6-mercaptopurine. *Gut* 2001; **48:** 591–2.
4. Lichtenstein GR. Use of laboratory testing to guide 6-mercaptopurine/azathioprine therapy. *Gastroenterology* 2004; **127:** 1558–64.
5. Teml A, *et al.* Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. *Clin Pharmacokinet* 2007; **46:** 187–208.
6. Sanderson J, *et al.* Thiopurine methyltransferase: should it be measured before commencing thiopurine drug therapy? *Ann Clin Biochem* 2004; **41:** 294–302.
7. Cuffari C, *et al.* Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. *Gut* 2001; **48:** 642–6.
8. Lowry PW, *et al.* Measurement of thiopurine methyltransferase activity and azathioprine metabolites in patients with inflammatory bowel disease. *Gut* 2001; **49:** 665–70.
9. Dubinsky MC. Monitoring of AZA/6-MP treatment in children with IBD is necessary. *Inflamm Bowel Dis* 2003; **9:** 386–8.
10. Griffiths AM. Monitoring of azathioprine/6-mercaptopurine treatment in children with IBD is not necessary. *Inflamm Bowel Dis* 2003; **9:** 389–91.

Uses and Administration

Azathioprine is an immunosuppressive antimetabolite with similar actions to those of mercaptopurine (p.744), to which it is converted in the body. Its effects may not be seen for several weeks after a dose. It is given orally, but where this is not feasible it may be given by slow intravenous injection or by infusion as azathioprine sodium. If given by infusion, the required dose should be diluted to a concentration of 0.25 to 2.5 mg/mL in sodium chloride 0.9% or glucose 5%, and infused over 30 to 60 minutes.

Azathioprine is mainly used as an immunosuppressant for the prevention of rejection in **organ and tissue transplantation** (p.1810). The dose for this purpose, given orally or intravenously, varies from 1 to 5 mg/kg daily and depends partly on the regimen used; the higher doses are used initially, adjusted according to clinical response and haematological tolerance.

Azathioprine is also used in **auto-immune diseases** or conditions that are considered to have an auto-immune component, see below. The usual dose of azathioprine, given orally or intravenously, in these conditions is in the range of 1 to 3 mg/kg daily. If no improvement is seen after 12 weeks, therapy may be stopped.

For doses in children, see Administration in Children, below.

Use of azathioprine with a corticosteroid (p.1495) may have a corticosteroid-sparing effect.

Blood counts should be carried out regularly during treatment and azathioprine withdrawn or the dosage reduced at the first indication of bone-marrow depression. Measurement of thiopurine methyltransferase (TPMT) activity may be used to identify patients at risk of haematological toxicity, although this cannot substitute for blood count monitoring.

Administration in children. UK licensed product information for azathioprine allows for the same doses in children as those used in adults (see Uses and Administration, above), both in organ and tissue transplantation and for diseases with an autoimmune component. The *BNFC* recommends that children aged 1 month to 18 years be given a maintenance dose of 1 to 3 mg/kg once daily for suppression of **transplant rejection**; alternatively, the total daily dose may be given in 2 divided doses. Although unlicensed for **severe ulcerative colitis and Crohn's disease**, the *BNFC* states that azathioprine may be given to children aged 2 to 18 years in an oral dose of 2 mg/kg (if necessary up to 3 mg/kg) once daily, reduced according to response to the lowest effective dose; alternatively, the total daily dose may be given in 2 divided doses.

Administration in hepatic or renal impairment. UK licensed product information states that controlled studies have not supported the suggestion that toxicity of azathioprine might be enhanced in the presence of renal impairment. Nevertheless, doses used should be at the lower end of the normal range, and haematological response should be carefully monitored. US licensed product information also recommends low doses, while stating that relatively oliguric patients, especially those with tubular necrosis in the immediate post-cadaveric transplant period, may have delayed clearance of azathioprine and/or its metabolites.

UK licensed product information states that the metabolism of azathioprine may be impaired in patients with hepatic dysfunction; regular blood counts and liver function tests should be performed and the dosage of azathioprine reduced if hepatic or haematological toxicity occurs.

Blood disorders. Immunosuppressants such as azathioprine are occasionally tried in auto-immune haemolytic anaemia (p.1043) refractory to other treatment and may permit reduction of corticosteroid dosage. Similarly in patients with idiopathic thrombocytopenic purpura (p.1505), immunosuppressants may be tried as a last resort. Azathioprine with a corticosteroid has been tried in the rare condition of acquired haemophilia (p.1048).

Cogan's syndrome. Azathioprine has been used with corticosteroids for severe Cogan's syndrome with large-vessel vasculitis (see p.1502).

Connective tissue and muscular disorders. Azathioprine is one of many drugs tried for disease control in Behçet's syndrome[1] (p.1499) and SLE[2] (p.1513). In polymyositis (p.1510), combined therapy with azathioprine and a corticosteroid has been found to be better than a corticosteroid alone for maintenance long-term.[3] However, there is also some evidence that methotrexate may be more effective in refractory polymyositis than azathioprine.[4]

1. Yazici H, *et al.* A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990; **322:** 281–5.
2. Abu-Shakra M, Shoenfeld Y. Azathioprine therapy for patients with systemic lupus erythematosus. *Lupus* 2001; **10:** 152–3.
3. Bunch TW. Prednisone and azathioprine for polymyositis: long-term followup. *Arthritis Rheum* 1981; **24:** 45–8.
4. Joffe MM, *et al.* Drug therapy of the idiopathic inflammatory myopathies; predictors of response to prednisone, azathioprine, and methotrexate and a comparison of their efficacy. *Am J Med* 1993; **94:** 379–87.

Inflammatory bowel disease. Azathioprine, or its metabolite mercaptopurine, is used to induce remission in chronically active inflammatory bowel disease (p.1697), and to maintain remission, particularly in Crohn's disease.[1-3] They have a useful corticosteroid-sparing effect. Azathioprine may also be useful as a postoperative maintenance treatment in Crohn's disease.[4] In patients with ulcerative colitis, azathioprine may be an effective maintenance therapy for those who are refractory to or intolerant of mesalazine or sulfasalazine; it may also be useful for patients who require repeated courses of corticosteroids.[5]

Continuation of azathioprine therapy beyond 4 years has had conflicting results in terms of relapse rates and flare incidence. A randomised study in patients with Crohn's disease and in clinical remission, having been treated with azathioprine for at least 42 months, found that relapse rates were higher in those patients continued on placebo compared with those continued on azathioprine.[6] In another study of patients with corticosteroid-dependent Crohn's disease, a breakthrough of symptoms during continuous therapy was common, particularly after 48 months on azathioprine.[7] In an analysis of 1176 patients with inflammatory bowel disease, the authors concluded that stopping azathioprine therapy may be considered after 3 to 4 years in Crohn's disease patients in complete remission and without corticosteroid requirements but that continuation appears beneficial in all other Crohn's disease patients and for patients with ulcerative colitis.[8]

The onset of benefit from oral azathioprine may be delayed for several months. One study[9] reported that a more rapid response could be achieved with an intravenous loading dose but a later study failed to confirm this.[10]

1. Sandborn W, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 15/01/08).
2. Pearson DC, *et al.* Azathioprine for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998 (accessed 15/01/08).
3. Fraser AG, *et al.* The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002; **50:** 485–9.
4. Myrelid P, *et al.* Azathioprine as a postoperative prophylaxis reduces symptoms in aggressive Crohn's disease. *Scand J Gastroenterol* 2006; **41:** 1190–5.
5. Timmer A, *et al.* Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/01/08).
6. Lémann M, *et al.* A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128:** 1812–18.
7. Chebli JM, *et al.* Long-term results with azathioprine therapy in patients with corticosteroid-dependent Crohn's disease: open-label prospective study. *J Gastroenterol Hepatol* 2007; **22:** 268–74.
8. Holtmann MH, *et al.* Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. *Dig Dis Sci* 2006; **51:** 1516–24.
9. Sandborn WJ, *et al.* An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. *Gastroenterology* 1995; **109:** 1808–17.
10. Sandborn WJ, *et al.* Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease: North American Azathioprine Study Group. *Gastroenterology* 1999; **117:** 527–35.

Leprosy. For mention of the use of azathioprine as a corticosteroid-sparing agent in the management of type 1 lepra reactions, see p.176.

Liver disorders. Azathioprine has been widely used with corticosteroids to produce and maintain remission of chronic active hepatitis (p.1501); such combination therapy, which also permits a reduction in corticosteroid dosage, is generally thought to be more effective than azathioprine alone. Patients successfully maintained in remission for at least a year on azathioprine with a corticosteroid can subsequently be maintained on azathioprine (at a dose of 2 mg/kg daily) alone.[1] Results in patients with primary biliary cirrhosis (p.2408) have been more equivocal, and initial studies did not indicate much benefit from azathioprine, although a later study did seem to indicate improved survival and disease retardation.[2]

1. Johnson PJ, *et al.* Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995; **333:** 958–63.
2. Christensen E, *et al.* Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis: final results of an international trial. *Gastroenterology* 1985; **89:** 1084–91.

Lung disorders. Although corticosteroids remain the mainstay of treatment for the various forms of diffuse parenchymal lung disease (p.1502) including cryptogenic fibrosing alveolitis (CFA), there is some evidence that combined therapy with azathioprine improves survival in the latter condition,[1] and the British Thoracic Society now recommends that initial treatment of CFA should be with oral prednisolone plus azathioprine 2 to 3 mg/kg daily.[2]

1. Raghu G, *et al.* Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991; **144:** 291–6.
2. British Thoracic Society. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999; **54** (suppl 1): S1–S30. Also available at: http://www.brit-thoracic.org.uk/portals/0/Clinical%20Information/DPLD/Guidelines/Parenchymaltext.pdf (accessed 17/07/08)

Neuromuscular disorders. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corticosteroid treatment for myasthenia gravis (p.629). It may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient. Azathioprine is not usually used alone because it may be several months before any beneficial effect is seen. Some studies have also indicated modest benefit from azathioprine in patients with multiple sclerosis (p.892). It has been suggested that the benefits are too slight to justify the toxicity of the required doses, but it has also been pointed out that in terms of relapse reduction azathioprine appears as effective as newer treatments such as interferon beta. For a recommendation that the cumulative dose of azathioprine should not exceed 600 g, see under Carcinogenicity, above.

Ocular disorders. For mention of the use of azathioprine in various disorders characterised by ocular lesions such as scleritis or uveitis, see p.1810.

Polymyalgia rheumatica. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corti-

costeroid treatment for polymyalgia rheumatica (p.1510) and in whom withdrawal is difficult.

Psoriatic arthritis. Azathioprine may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p.13) when the arthritis is not controlled by physical therapy and NSAIDs.

Rheumatoid arthritis. Although azathioprine may be beneficial in rheumatoid arthritis (p.11) in the short-term, its toxicity is significantly more severe than other disease-modifying antirheumatic drugs (DMARDs).[1] It may, however, be useful in patients with severe disease unresponsive to other DMARDs especially in those with extra-articular manifestations such as vasculitis.[2]

1. Suarez-Almazor ME, *et al.* Azathioprine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).
2. Heurkens AHM, *et al.* Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. *Arch Intern Med* 1991; **151:** 2249–54.

Sarcoidosis. Cytotoxic immunosuppressants such as azathioprine have been tried in patients with sarcoidosis (p.1512) who do not respond to or cannot tolerate corticosteroids.

Skin disorders. Like other immunosuppressants, azathioprine has been tried in various refractory skin disorders, notably in pemphigus and pemphigoid[1,2] (see below). Other conditions in which it has been tried include atopic eczema,[3-8] nodular prurigo,[9] chronic actinic dermatitis,[3,6] pyoderma gangrenosum,[4] erythema multiforme,[4,10] pompholyx, and plaque psoriasis,[6] as well as in the skin manifestations of systemic disorders such as dermatomyositis and lupus erythematosus.[2] Guidelines for the use of azathioprine in dermatology have been developed.[1] The recommended dose for azathioprine in dermatological disorders is 1 to 3 mg/kg daily, adjusted according to response. Treatment should be withdrawn if no response is seen within 3 months. Azathioprine should not be used in dermatology patients with very low or absent thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, above), due to the danger of prolonged and severe myelosuppression (see Effects on the Blood, above). If azathioprine is given to patients with low TPMT activity, doses of 0.5 to 1 mg/kg daily should be used, with monitoring for myelosuppression. Patients with normal to high TPMT activity should be started on doses at the higher end of the range of 1 to 3 mg/kg daily; in those who do not respond, and have not experienced adverse effects, doses above this range may be considered for a trial period.

1. Anstey AV, *et al.* British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004; **151:** 1123–32. Also available at: http://www.bad.org.uk/healthcare/guidelines/Azathioprine.pdf (accessed 15/01/08)
2. Patel AA, *et al.* Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol* 2006; **55:** 369–89.
3. Younger IR, *et al.* Azathioprine in dermatology. *J Am Acad Dermatol* 1991; **25:** 281–6.
4. Tan BB, *et al.* Azathioprine in dermatology: a survey of current practice in the UK. *Br J Dermatol* 1997; **136:** 351–5.
5. Lear JT, *et al.* A retrospective review of the use of azathioprine in severe atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 47): 38.
6. Scerri L. Azathioprine in dermatological practice: an overview with special emphasis on its use in non-bullous inflammatory dermatoses. *Adv Exp Med Biol* 1999; **455:** 343–8.
7. Murphy L-A, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147:** 308–15.
8. Meggitt SJ, *et al.* Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367:** 839–46.
9. Lear JT, *et al.* Nodular prurigo responsive to azathioprine. *Br J Dermatol* 1996; **134:** 1151.
10. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p.1582). Other immunosuppressants may be added to maintain disease control and allow a reduction in corticosteroid dosage, and azathioprine is commonly used in this way in pemphigus vulgaris.[1] There is limited evidence to suggest that azathioprine may also be effective as monotherapy to induce remission in mild pemphigus.[1] Azathioprine has been used similarly in bullous pemphigoid, but there is some disagreement about its efficacy,[2] and guidelines suggest that it should only be considered if the corticosteroid cannot be reduced to an acceptable dose.[3]

1. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37. Also available at: http://www.bad.org.uk/healthcare/guidelines/Pemphigus_Vulgaris.pdf (accessed 15/01/08)
2. Walsh SRA, *et al.* Bullous pemphigoid: from bench to bedside. *Drugs* 2005; **65:** 905–26.
3. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21. Also available at: http://www.bad.org.uk/healthcare/guidelines/Bullous_Pemphigoid.pdf (accessed 15/01/08)

Vasculitic syndromes. Azathioprine has been tried in vasculitic syndromes, including giant cell arteritis (p.1503), microscopic polyangiitis (p.1510), Churg-Strauss syndrome (p.1501), Takayasu's arteritis (p.1514), and Wegener's granulomatosis (p.1515). In general it is most useful in maintenance for its corticosteroid-sparing effect. Cyclophosphamide tends to be preferred where a more aggressive regimen is required, as in some combinations for induction of remission.

Preparations

BP 2008: Azathioprine Tablets;
USP 31: Azathioprine Oral Suspension; Azathioprine Sodium for Injection; Azathioprine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Imuran; ***Austral.:*** Azahexal; Azamun; Azapin; Imuran; Thioprine; ***Austria:*** Azaallen; Azaglax; Azarek†; Glaxoprin; Imurek; ***Belg.:*** Imuran; ***Braz.:*** Aseroprin†; Imunen; Imuran; ***Canad.:*** Imuran; ***Chile:*** Azafalk†; Imuran; ***Cz.:*** Azaprine; Immunoprin; Imuran; ***Denm.:*** Imurel; ***Fin.:*** Azamun; Imuprin†; Imurel; ***Fr.:*** Imurel; ***Ger.:*** Aza-Q; Azafalk; Azathiodura; Colinsan; Imurek; Zytrim; ***Gr.:*** Imuran†; ***Hong Kong:*** Azamun†; Imuran; ***Hung.:*** Imuran; ***India:*** Azoran; Imuran; Transimune; ***Indon.:*** Imuran; ***Irl.:*** Imuger; Imuran; ***Israel:*** Azopi; Imuran; ***Malaysia:*** Imuran; ***Mex.:*** Azatrilem; Imuran; Satedon†; ***Neth.:*** Imuran; ***Norw.:*** Imurel; ***NZ:*** Azamun; Imuran; Thioprine; ***Philipp.:*** Imuran; ***Pol.:*** Imuran; ***Port.:*** Imuran; ***Rus.:*** Imuran (Имуран)†; ***S.Afr.:*** Azamun; Azapress; Imuran; Zaprine; ***Singapore:*** Imuran; ***Spain:*** Imurel; ***Swed.:*** Imurel; ***Switz.:*** Azarek; Imurek; ***Thai.:*** Imuran; ***Turk.:*** Imuran; ***UK:*** Immunoprin†; Imuran; ***USA:*** Azasan; Imuran; ***Venez.:*** Azaprin.

Multi-ingredient: ***Ger.:*** Azamedac.

Basiliximab *(BAN, USAN, rINN)*

Basiliksimab; Basiliksimabi; Basiliximabum; chRFT5; SDZ-CHI-621. Immunoglobulin G1, anti-(human interleukin 2 receptor) (human-mouse monoclonal CHI621 γ1-chain), disulfide with human-mouse monoclonal CHI621 light chain, dimer.

Базиликсимаб
CAS — 179045-86-4.
ATC — L04AC02.
ATC Vet — QL04AC02.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with basiliximab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, sneezing, hypotension, tachycardia, cardiac failure, wheezing, dyspnoea, bronchospasm, pulmonary oedema, and respiratory failure. Capillary leak syndrome and cytokine release syndrome have been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Patients in whom other immunosuppression was prematurely stopped, after initial therapy with basiliximab, appear to be at increased risk of hypersensitivity reactions. Therapy should be permanently stopped if a severe reaction occurs.

Giving basiliximab as a bolus may cause nausea, vomiting, and local reactions, including pain.

Pharmacokinetics

Basiliximab has a terminal half-life of about 7 days in adults and about 9 days in children.

Uses and Administration

Basiliximab is a chimeric murine/human monoclonal antibody similar to daclizumab (p.1833) that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection episodes in patients undergoing renal transplantation, and is given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids; azathioprine or mycophenolate mofetil may also be added to the regimen. Doses are given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes. The recommended dose for adults is 20 mg, given within 2 hours before transplant surgery and repeated once after 4 days. (For children's doses, see Administration in Children, below). The second dose should be withheld if graft loss or a severe hypersensitivity reaction occurs.

Administration in children. Licensed product information recommends the following intravenous doses of basiliximab in children over 1 year of age, for prophylaxis of acute rejection in allogeneic renal transplantation, as part of an immunosuppressive regimen containing ciclosporin and corticosteroids:

- body-weight under 35 kg: 10 mg within 2 hours before transplantation surgery; 10 mg 4 days after surgery
- body-weight 35 kg or more: 20 mg within 2 hours before transplantation surgery; 20 mg 4 days after surgery (same as adults, see Uses and Administration, above)

Doses may be given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes.

Organ and tissue transplantation. Basiliximab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p.1813), including paediatric renal transplant recipients;[1-6] it is usually given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. A small study found that basiliximab significantly reduced the occurrence of rejection episodes in those treated with dual therapy (calcineurin inhibitor and corticosteroids) but not in those given triple therapy (including mycophenolate).[7] In a study of paediatric renal transplant recipients, addition of basiliximab to a tacrolimus-based regimen was safe, but did not result in a lower incidence of rejection episodes.[8] There is some suggestion that antilymphocyte immunoglobulins may be more effective than basiliximab in reduction of acute rejection in adult renal transplant patients,[9,10] although some consider basiliximab to offer improved clinical efficacy over antilymphocyte immunoglobulin induction in paediatric patients,[11] and others have commented[12] that graft survival at 12 months has been similar with each drug. Two reviews[13,14] concluded that the use of basiliximab in renal transplantation was safe and effective, with reduced rates of acute rejection, but no long-term benefit in terms of graft survival; basiliximab appears to allow the safe withdrawal of corticosteroids or the use of corticosteroid-free immunosuppressive regimens.

There is a short report suggesting that the use of a single dose is as effective as the standard 2-dose regimen in renal transplantation in terms of the incidence of acute rejection.[15]

Basiliximab has also been investigated in liver transplantation (p.1815). Given with dual therapy to adult patients, it was found to reduce the incidence of acute rejection episodes in the first year when compared with placebo, including patients positive for hepatitis C.[16] Basiliximab with dual therapy also reduced the incidence of acute graft rejection in small paediatric studies.[17,18] In paediatric liver transplantation, corticosteroid-free immunosuppressive regimens using basiliximab and tacrolimus have been associated with significantly lower rejection rates at 1 year than corticosteroid-based regimens.[19,20]

Basiliximab has been investigated for the prevention of rejection in heart,[21,22] lung,[23,24] and pancreatic transplantation (see p.1812). It has been reported to be effective[25] in the treatment of corticosteroid-refractory acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p.1811).

1. Nashan B, *et al.* Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet* 1997; **350:** 1193–8. Correction. *ibid.*; 1484.
2. Kahan BD, *et al.* Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. *Transplantation* 1999; **67:** 276–84.
3. Thistlethwaite JR, *et al.* Reduced acute rejection and superior 1-year renal allograft survival with basiliximab in patients with diabetes mellitus. *Transplantation* 2000; **70:** 784–90.
4. Ponticelli C, *et al.* A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001; **72:** 1261–7.
5. Swiatecka-Urban A, *et al.* Basiliximab induction improves the outcome of renal transplants in children and adolescents. *Pediatr Nephrol* 2001; **16:** 693–6.
6. Pape L, *et al.* Single centre experience with basiliximab in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; **17:** 276–80.
7. Lee BM, *et al.* Effect of basiliximab on renal allograft rejection within 1 year after transplantation. *Transplant Proc* 2006; **38:** 2025–8.
8. Grenda R, *et al.* A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant* 2006; **6:** 1666–72.
9. Heilman RL, *et al.* Acute rejection risk in kidney transplant recipients on steroid-avoidance immunosuppression receiving induction with either antithymocyte globulin or basiliximab. *Transplant Proc* 2006; **38:** 1307–13.
10. Brennan DC, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355:** 1967–77.
11. Clark G, *et al.* Improved efficacy of basiliximab over antilymphocyte globulin induction therapy in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; **17:** 1304–9.
12. Josephson MA. Rabbit antithymocyte globulin or basiliximab for induction therapy? *N Engl J Med* 2006; **355:** 2033–5.
13. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs* 2003; **63:** 2803–35.
14. Boggi U, *et al.* A benefit-risk assessment of basiliximab in renal transplantation. *Drug Safety* 2004; **27:** 91–106.
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