Scleroderma

The term scleroderma has been used for both systemic sclerosis, an uncommon multisystem disease characterised by collagen proliferation and fibrosis throughout the body, and for localised fibrotic changes of the skin (morphea) which rarely progresses to involve other organs. In systemic sclerosis, Raynaud's syndrome secondary to vascular involvement usually precedes skin changes; oedema is followed by thickening and tightening of the skin of hands and face, and sometimes limbs and trunk, before progressing to atrophy and contractures. Cutaneous changes may be limited or take a more aggressive diffuse form. Decreased gastrointestinal motility, dysphagia and gastro-oesophageal reflux, arthritis, muscle weakness, and cardiac involvement may occur. Among the most serious potential symptoms, which may result in death, are pulmonary disease and renal failure with malignant hypertension.[1-7]

Many treatments have been tried for localised scleroderma.[4,5] Symptomatic therapies include emollients and topical and systemic antipruritics. Topical, intralesional, and systemic corticosteroids may be useful, especially in early inflammatory stages. Other treatments include topical and systemic vitamin D analogues, topical tacrolimus, and imiquimod cream. Oral therapies used include ciclosporin, colchicine, hydroxychloroquine, interferon gamma, penicillamine, phenytoin, and methotrexate. Phototherapy with UV light, with or without psoralens, has also been reported to be of benefit.

There is a paucity of adequately controlled studies for systemic scleroderma; no treatment has been clearly shown to affect the progression of the disease, and much management is essentially symptomatic. Immunosuppressants are probably appropriate in the early oedematous stages of diffuse scleroderma.[1,6,8] Antilymphocyte immunoglobulins have been tried as an induction therapy in early stages of the disease.[8] Ciclosporin has been found to be beneficial, both for skin and visceral manifestations, but its use has been limited by nephrotoxicity and hypertension.[1,3,8-10] Tacrolimus has also been tried, though again adverse effects limit its benefit.[8-10] Mycophenolate mofetil has been tried after antilymphocyte immunoglobulins with reports of significant skin improvement.[10] Cyclophosphamide with or without corticosteroids has been shown to improve skin thickening, stabilise pulmonary function, and increase survival, especially in early disease, in a number of studies.[7] Other novel immunosuppressive strategies include bone marrow ablation followed by peripheral blood stem cell transplantation (see Haematopoietic Stem Cell Transplantation, p.1811),[1,3,5,8] photopheresis with a psoralen, and the induction of oral tolerance with native bovine type I collagen.[8] Rituximab is under investigation.[10]

Penicillamine has been widely used as an antifibrotic drug, but with variable effects; usual doses proved to be no more effective than lower doses,[1,8,11] and it is considered by some to be no more effective than placebo.[5] Interferons alfa and gamma have produced variable results;[5,8] the latter is under investigation for pulmonary fibrosis.[3] Some other drugs have been investigated for their antifibrotic properties, including halofuginone, minocycline and relaxin.[8,11] There is some evidence that oxidative stress is involved in the pathogenesis of scleroderma, so antoxidants like probucol may also be useful.[8] Other drugs that have been investigated include potassium aminobenzoate, and thymopentin.

Many patients will require therapy for organ-specific symptoms.

- *Skin* flexibility may be maintained by emollients,[12] and systemic antihistamines can relieve itching, an early feature of diffuse cutaneous scleroderma.[8] Methotrexate has been used with some benefit.[1,3,5,7,8,11]
- Most progress has been made in the management of *vascular* symptoms. ACE inhibitors are considered to be the standard treatment for patients with renal ischaemia,[3,5,6,13] although some 30% of patients will still eventually require renal replacement therapy.[8] For patients who develop pulmonary arterial hypertension the prostaglandins epoprostenol, iloprost, or treprostinil may be given intravenously;[1,3,5,6,8] some have also been investigated subcutaneously[6] or by inhalation.[3,5,6] Sildenafil or bosentan are also used.[3,5-7] There is some evidence that epoprostenol and bosentan may be associated with improved survival as well as symptomatic improvement.[3] Novel therapies for pulmonary arterial hypertension include ambrisentan[7] and sitaxentan.[6,7]

  Treatment of Raynaud's syndrome (see under Vasospastic Arterial Disorders, p.1188) unresponsive to nonpharmacological therapy involves the use of calcium-channel blockers such as nifedipine or diltiazem.[1,3,12] Topical nitrates have been used, and intravenous epoprostenol or iloprost are used in acute attacks.[1,3,6,8] Oral iloprost has been tried with variable results.[6] Bosentan can prevent the development of new digital ulcers but may not speed the healing of existing ones.[3] Calcitonin gene-related peptide is being investigated as an alternative to iloprost.[1] Because elevated levels of serotonin have been found in patients with Raynaud's phenomenon, SSRIs and ketanserin have been used.[1] Atorvastatin[6] and sildenafil[13] have been reported to be helpful. Dietary supplementation with antoxidant vitamins, fish oils, and evening primrose oil has been of anecdotal benefit.[1,8,14] Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome.[6,14]

  Cardiac involvement may be underdiagnosed;[8] ACE inhibitors or digoxin may be used.[1]
- *Lung* fibrosis is usually treated with cyclophosphamide,[1,3,5,8,15] with or without a corticosteroid such as prednisolone. There is no evidence for corticosteroids alone in lung scleroderma, and high dose may precipitate scleroderma renal crisis, leading to irreversible renal failure.[7] As mentioned above, interferon gamma is under investigation.
- In patients with *gastrointestinal* disease, proton pump inhibitors such as omeprazole, sometimes with prokinetic drugs, are extremely effective for oesophageal involvement, and broad spectrum antibacterials are helpful for small bowel bacterial overgrowth.[1,8]

NSAIDs and corticosteroids must be used with care in scleroderma because of the risk of exacerbating renal and other problems.[1,8]

1. Leighton C. Drug treatment of scleroderma. *Drugs* 2001; **61:** 419–27.
2. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med* 2004; **140:** 37–50.
3. Charles C, *et al.* Systemic sclerosis: hypothesis-driven treatment strategies. *Lancet* 2006; **367:** 1683–91.
4. Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol* 2006; **18:** 606–13.
5. Chung L, *et al.* Systemic and localized scleroderma. *Clin Dermatol* 2006; **24:** 374–92.
6. Kowal-Bielecka O. Targeting vascular disease in systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2006; **6:** 401–7.
7. van Laar JM, *et al.* Scleroderma lung: pathogenesis, evaluation and current therapy. *Drugs* 2007; **67:** 985–96.
8. Denton CP, Black CM. Scleroderma and related disorders: therapeutic aspects. *Baillieres Best Pract Res Clin Rheumatol* 2000; **14:** 17–35.
9. Morton SJ, Powell RJ. Cyclosporin and tacrolimus: their use in a routine clinical setting for scleroderma. *Rheumatology (Oxford)* 2000; **39:** 865–9.
10. Lafyatis R. Targeting fibrosis in systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2006; **6:** 395–400.
11. Matucci-Cerinic M, *et al.* Clinical trials in systemic sclerosis: lessons learned and outcomes. *Arthritis Res Ther* 2007; **9** (suppl 2): S7. Also available at: http://arthritis-research.com/content/pdf/ar2191.pdf (accessed 15/04/08)
12. Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. *Best Pract Res Clin Rheumatol* 2004; **18:** 429–62.
13. Moore SC, Hermes DeSantis ER. Treatment of complications associated with systemic sclerosis. *Am J Health-Syst Pharm* 2008; **65:** 315–21.
14. Gaby AR. Natural remedies for scleroderma. *Altern Med Rev* 2006; **11:** 188–95.
15. Tashkin DP, *et al.* Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; **354:** 2655–66.

Skin and connective tissue disorders

Immunosuppressants are used in various skin and connective tissue disorders, including Behçet's syndrome (p.1499), eczema (p.1579), pemphigus and pemphigoid (p.1582), polymyositis (p.1510), psoriasis (p.1583), SLE (p.1513), and the various vasculitic syndromes (p.1515). See also Scleroderma, above.

Abetimus Sodium *(USAN, rINNM)*

Abetimus sódico; Abétimus Sodique; LJP-394; Natrii Abetimusum.

Натрий Абетимус

CAS — 169147-32-4.
ATC — L04AA22.
ATC Vet — QL04AA22.

Profile

Abetimus sodium is an immunomodulator that arrests the production of antibodies to double-stranded DNA. It is under investigation for the treatment of lupus nephritis in patients with SLE.

◊ References.

1. Alarcón-Segovia D, *et al.* LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2003; **48:** 442–54.
2. Wallace DJ, Tumlin JA. LJP 394 (abetimus sodium, Riquent) in the management of systemic lupus erythematosus. *Lupus* 2004; **13:** 323–7.
3. Cardiel MH. Abetimus sodium: a new therapy for delaying the time to, and reducing the incidence of, renal flare and/or major systemic lupus erythematosus flares in patients with systemic lupus erythematosus who have a history of renal disease. *Expert Opin Invest Drugs* 2005; **14:** 77–88.
4. Furie R. Abetimus sodium (Riquent) for the prevention of nephritic flares in patients with systemic lupus erythematosus. *Rheum Dis Clin North Am* 2006; **32:** 149–56.
5. Mosca M, *et al.* LJP-394 (abetimus sodium) in the treatment of systemic lupus erythematosus. *Expert Opin Pharmacother* 2007; **8:** 873–9.

Antilymphocyte Immunoglobulins

Inmunoglobulinas antilinfocitarias.

Иммуноглобулины Антилимфоцитарные

ATC — L04AA03 (antilymphocyte immunoglobulin, horse); L04AA04 (antilymphocyte immunoglobulin, rabbit).
ATC Vet — QL04AA03 (antilymphocyte immunoglobulin, horse); QL04AA04 (antithymocyte immunoglobulin, rabbit).

Description. Antilymphocyte immunoglobulins are polyclonal antibodies to human lymphocytes produced by the purification of sera from appropriately immunised animals. The term antilymphocyte immunoglobulin (ALG; lymphocyte immune globulin) implies a product raised against all lymphocyte subsets. The term antithymocyte immunoglobulin (antithymocyte gammaglobulin; antithymocyte globulin; ATG) implies specificity for T-cells (thymus lymphocytes or thymocytes). However, in practice the nomenclature does not seem to be used consistently, and both terms tend to be used for antibodies raised against T-cells. Nomenclature normally includes an indication of the animal source of the immunoglobulin e.g. antithymocyte immunoglobulin (horse), or antithymocyte immunoglobulin (rabbit).
In addition to the purified immunoglobulins the native sera (antilymphocyte serum and antithymocyte serum, sometimes referred to as lymphocytic antiserum and thymitic antiserum) have also been used as immunosuppressants.

Pharmacopoeias. *Eur.* (see p.vii) includes an anti-T lymphocyte immunoglobulin.

Ph. Eur. 6.2 (Anti-T Lymphocyte Immunoglobulin for Human Use, Animal; Immunoglobulinum Anti-T Lymphocytorum ex Animale ad Usum Humanum). A liquid or freeze-dried preparation containing immunoglobulins, obtained from serum or plasma of animals, mainly rabbits or horses, immunised with human lymphocytic antigens. It has the property of diminishing the number and function of immunocompetent cells, in particular T-lymphocytes. It contains principally immunoglobulin G, and may contain antibodies against other lymphocyte subpopulations and against other cells. It is intended for intravenous administration, after dilution with a suitable diluent where applicable. Protect from light.

Adverse Effects and Precautions

Common adverse reactions to antilymphocyte immunoglobulins include fever, chills, and skin reactions including rash, pruritus, and urticaria, which may be manifestations of hypersensitivity. Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. To minimise fever and chills, the first dose can be infused over at least 6 hours. Dyspnoea, hypotension, chest, back or flank pain may indicate anaphylaxis, which can occur in up to 1% of patients. Fever, pruritus, rashes, myalgia, and arthralgia may represent serum sickness, especially in patients with aplastic anaemia. Use with other immunosuppressants may reduce the incidence or severity of hypersensitivity but increase the risk of acquired systemic infections, such as CMV or herpes simplex. Enhanced immunosuppression may also increase the incidence of post-transplant lymphoproliferative disease or other malignancies.

Leucopenia and thrombocytopenia are also common. Although usually transient, dosage adjustment may be necessary if they become severe or prolonged, and if unremitting, they may warrant stopping therapy. Other adverse effects include dizziness, malaise, headache, abdominal pain, gastrointestinal disturbances, hyper-

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.

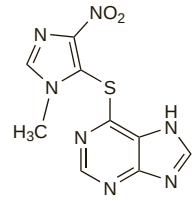
Азатиоприн

$C_9H_7N_7O_2S$ = 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.