20. Spada M, *et al.* Randomized trial of basiliximab induction versus steroid therapy in pediatric liver allograft recipients under tacrolimus immunosuppression. *Am J Transplant* 2006; **6:** 1913–21.
21. Segovia J, *et al.* A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. *Transplantation* 2006; **81:** 1542–8.
22. Mattei MF, *et al.* Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. *J Heart Lung Transplant* 2007; **26:** 693–9.
23. Hachem RR, *et al.* A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant* 2005; **24:** 1320–6.
24. Borro JM, *et al.* Comparative study of basiliximab treatment in lung transplantation. *Transplant Proc* 2005; **37:** 3996–8.
25. Funke VAM, *et al.* Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. *Bone Marrow Transplant* 2006; **37:** 961–5.

Skin disorders. There are a few case reports of successful treatment with basiliximab in psoriasis[1-4] (p.1583), chronic atopic dermatitis[5] (see Eczema, p.1579), lichen planus,[6] and epidermolysis bullosa acquisita[7] (p.1579).

1. Salim A, *et al.* Successful treatment of severe generalized pustular psoriasis with basiliximab (interleukin-2 receptor blocker). *Br J Dermatol* 2000; **143:** 1121–2.
2. Mrowietz U, *et al.* Treatment of severe psoriasis with anti-CD25 monoclonal antibodies. *Arch Dermatol* 2000; **136:** 675–6.
3. Owen CM, Harrison PV. Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. *Clin Exp Dermatol* 2000; **25:** 195–7.
4. Bell HK, Parslew RAG. Use of basiliximab as a cyclosporin-sparing agent in palmoplantar pustular psoriasis with myalgia as an adverse effect. *Br J Dermatol* 2002; **147:** 606–7.
5. Kägi MK, Heyer G. Efficacy of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in a patient with severe chronic atopic dermatitis. *Br J Dermatol* 2001; **145:** 350–1.
6. Rebora A, *et al.* Basiliximab is effective for erosive lichen planus. *Arch Dermatol* 2002; **138:** 1100–1.
7. Haufs MG, Haneke E. Epidermolysis bullosa acquisita treated with basiliximab, an interleukin-2 receptor antibody. *Acta Derm Venereol (Stockh)* 2001; **81:** 72.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Simulect; ***Austral.:*** Simulect; ***Belg.:*** Simulect; ***Braz.:*** Simulect; ***Canad.:*** Simulect; ***Chile:*** Simulect; ***Cz.:*** Simulect; ***Denm.:*** Simulect; ***Fin.:*** Simulect; ***Fr.:*** Simulect; ***Ger.:*** Simulect; ***Gr.:*** Simulect; ***Hong Kong:*** Simulect; ***Hung.:*** Simulect; ***Irl.:*** Simulect; ***Israel:*** Simulect; ***Ital.:*** Simulect; ***Malaysia:*** Simulect; ***Mex.:*** Simulect; ***Neth.:*** Simulect; ***Norw.:*** Simulect; ***NZ:*** Simulect; ***Philipp.:*** Simulect; ***Pol.:*** Simulect; ***Port.:*** Simulect; ***Rus.:*** Simulect (Симулект); ***S.Afr.:*** Simulect; ***Spain:*** Simulect; ***Swed.:*** Simulect; ***Switz.:*** Simulect; ***Thai.:*** Simulect; ***Turk.:*** Simulect; ***UK:*** Simulect; ***USA:*** Simulect; ***Venez.:*** Simultec.

Belatacept *(USAN, rINN)*

Bélatacept; Belataceptum; BMS-224818; LEA-29Y.

Белатацепт

CAS — 706808-37-9.

Profile

Belatacept is a derivative of abatacept (p.14). It is a fusion protein and co-stimulation blocker that prevents T-cell activation. Belatacept is under investigation for the management of solid organ transplant rejection.

◊ References.

1. Vincenti F, *et al.* Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; **353:** 770–81.

Biolimus A9

42-*O*-(2-Ethoxyethyl) rapamycin.

$C_{55}H_{87}NO_{14}$ = 986.3.

CAS — 851536-75-9.

Profile

Biolimus A9 is an analogue of sirolimus (p.1841). A biolimus A9-releasing stent has been developed to reduce restenosis after coronary artery stent placement.

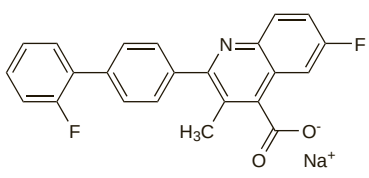
Brequinar Sodium *(USAN, rINNM)*

Brequinar sódico; Bréquinar Sodique; DuP-785; Natrii Brequinarum; NSC-368390. Sodium 6-fluoro-2-(2′-fluoro-4-biphenyl)-3-methyl-4-quinolinecarboxylate.

Натрий Брехинар

$C_{23}H_{14}F_2NO_2Na$ = 397.3.

CAS — 96187-53-0 (brequinar); 96201-88-6 (brequinar sodium).



Profile

Brequinar sodium is an inhibitor of pyrimidine metabolism with potent immunosuppressant properties that has been investigated for the prevention and treatment of rejection episodes after organ and tissue transplantation and for treating various cancers.

Ciclosporin *(BAN, rINN)*

27-400; Ciclosporina; Ciclosporina A; Ciclosporine; Ciclosporinum; Ciklosporin; Ciklosporinas; Cyclosporin; Cyclosporin A; Cyclosporine *(USAN)*; Cyklosporin; OL-27-400; Siklosporiini; Siklosporin. Cyclo{-[4-(*E*)-but-2-enyl-*N*,4-dimethyl-L-threonyl]-L-homoalanyl-(*N*-methylglycyl)-(*N*-methyl-L-leucyl)-L-valyl-(*N*-methyl-L-leucyl)-L-alanyl-D-alanyl-(*N*-methyl-L-leucyl)-(*N*-methyl-L-leucyl)-(*N*-methyl-L-valyl)-}.

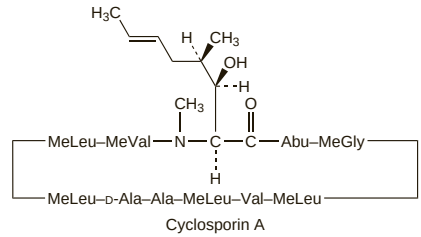
Циклоспорин

$C_{62}H_{111}N_{11}O_{12}$ = 1202.6.

CAS — 59865-13-3.

ATC — L04AD01.

ATC Vet — QL04AD01; QS01XA90.



Cyclosporin A

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Ciclosporin). A substance produced by *Beauveria nivea* (=*Tolypocladium inflatum* Gams) or obtained by any other means. A white or almost white powder; practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Cyclosporine). A white to almost white powder. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, in dichloromethane, in ether, and in methyl alcohol; slightly soluble in saturated hydrocarbons. Store in airtight containers. Protect from light.

Incompatibility. The plasticiser diethylhexyl phthalate, which is a possible carcinogen, was leached from PVC containers by ciclosporin preparations containing polyoxyl castor oil.[1] Such preparations should not be given through PVC tubing nor stored in PVC containers. Polysorbate 80, which is an excipient in other ciclosporin preparations, also leached plasticiser from PVC,[1] and similar precautions would apply to preparations so formulated. UK licensed product information further recommends that containers and stoppers be free of silicone oil and fatty substances.

For reported incompatibility between ciclosporin and mycophenolate, see Incompatibility, under Mycophenolate, p.1836.

1. Pearson SD, Trissel LA. Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components. *Am J Hosp Pharm* 1993; **50:** 1405–9.

Stability. Ciclosporin was stable over 72 hours after dilution in glucose 5% or glucose/amino-acid solutions and storage at room temperature in the dark; similar stability was seen after dilution in lipid emulsion, but dilutions in sodium chloride 0.9% were considered to be stable only for 8 hours.[1] In all cases miscibility in the diluent was poor and vigorous shaking was required after addition to produce even distribution of ciclosporin. An extemporaneously compounded paste produced from ciclosporin oral solution (*Sandimmun*) in an oral gel base was found to be stable[2] for at least 31 days in aluminium-lined ointment tubes stored at 2° to 37°.

1. McLeod HL, *et al.* Stability of cyclosporin in dextrose 5%, NaCl 0.9%, dextrose/amino acid solution, and lipid emulsion. *Ann Pharmacother* 1992; **26:** 172–5.
2. Ghnassia LT, *et al.* Stability of cyclosporine in an extemporaneously compounded paste. *Am J Health-Syst Pharm* 1995; **52:** 2204–7.

Adverse Effects and Treatment

Nephrotoxicity, manifesting as raised serum creatinine and urea, is the major adverse effect of ciclosporin. It is related to drug-plasma concentrations and is usually reversible on reduction of the dose. In renal graft recipients episodes of nephrotoxicity may be difficult to distinguish from graft rejection. Interstitial fibrosis may develop during long-term therapy.

Other frequent adverse effects include hypertension, gastrointestinal disturbances, fatigue, hepatotoxicity, hypertrichosis, gum hyperplasia, tremor, headaches, hyperlipidaemias, hyperkalaemia, hypomagnesaemia, hyperuricaemia, paraesthesia, and muscle cramps and myalgia. Less commonly, anaemia, thrombocytopenia, rashes, weight increase, oedema, pancreatitis, myopathy, neuropathy, and hyperglycaemia have been reported. Glomerular capillary thrombosis has occurred, and may progress to graft failure. Encephalopathy, manifest as convulsions, confusion, visual disturbances including blindness, movement disorders, or psychiatric disturbances, has been reported. Optic disc oedema, including papilloedema with possible visual impairment secondary to benign intracranial hypertension, has occurred rarely.

Anaphylactoid reactions have occurred after intravenous use; it has been suggested that these represent a reaction to the polyoxyl castor oil vehicle of the intravenous preparation.

There is an increased incidence of certain malignancies and a predisposition to infection in patients receiving ciclosporin therapy.

Alopecia. Although ciclosporin is more often associated with reports of hypertrichosis, there have been cases of alopecia areata developing in patients given ciclosporin,[1] sometimes with complete hair loss (alopecia universalis).[2,3]

1. Davies MG, Bowers PW. Alopecia areata arising in patients receiving cyclosporin immunosuppression. *Br J Dermatol* 1995; **132:** 835–6.
2. Monti M, *et al.* Alopecia universalis in liver transplant patients treated with cyclosporin. *Br J Dermatol* 1995; **133:** 663–4.
3. Parodi A, *et al.* Alopecia universalis and cyclosporin A. *Br J Dermatol* 1996; **135:** 657.

Carcinogenicity. The use of ciclosporin in **organ transplant** recipients is associated with an increased incidence of malignancy, notably lymphoma,[1] and also skin cancer and Kaposi's sarcoma. The manufacturers have stated that of an estimated 5550 transplant patients who had been treated with ciclosporin by February 1984, lymphoproliferative disorders had been reported in 40; this represented an overall incidence of 0.7%, varying from 0.2 to 8% in different series.[2] In 1991, a report of 12 cases of lymphoproliferative disorders among 132 paediatric liver graft recipients estimated the incidence at about 2.8% per year for the first 6 years after transplantation, giving a cumulative risk of nearly 20% after 7 years.[3] There is evidence that the incidence of malignancy is related to dose,[2,4] and is greater when ciclosporin is used with other potent immunosuppressants.[2] In addition, the incidence of malignancy varies geographically, possibly reflecting environmental triggers and genetic susceptibility.[5]

It has been suggested that these lymphomas represent proliferation of B-cells under the influence of Epstein-Barr virus, a process normally prevented by the T-cells which are specifically inhibited by ciclosporin.[3] The resultant, usually polyclonal, lymphoproliferative tumours appear to regress on prompt excision of the affected tissue and reduction or withdrawal of the immunosuppressant regimen, in most cases without graft loss.[6] However, the need for vigilance and rapid response to these conditions has been stressed, since the responsive polyclonal disorder may evolve into a monoclonal, frankly malignant form; where the presentation is indistinguishable from a classic non-Hodgkins lymphoma the prognosis is much less good.[3] Interestingly, use of lower dose ciclosporin regimens appears to maintain normal elimination of Epstein-Barr virus-infected B-cells by specific T-cells,[7] and may lead to a reduced incidence of malignancy compared with earlier results.[4,7]

The risk of skin cancers in ciclosporin recipients is further increased by the exposure to sunlight.[8] Prophylactic retinoid therapy may prevent skin cancer in patients with renal transplants.[9]

There is no clear evidence that ciclosporin is associated with an increased incidence of malignancy compared with other immunosuppressants, although in one study dysplastic skin lesions were found in 14 of 64 transplant patients receiving ciclosporin compared with 3 of 33 previous similar patients who had received azathioprine.[10] However, such comparisons are difficult, not least because many transplant patients tend to have received multiple immunosuppressant agents. The safety of ciclosporin in **dermatology** patients has been reviewed.[11] Despite reports of lymphomas and other malignancies in dermatology patients treated with ciclosporin, a 5-year cohort study showed no increased risk of lymphoma or internal malignancies. While there was an increased risk of non-melanoma skin cancers, especially squamous cell carcinoma, many patients had been previously exposed to PUVA, methotrexate, or other immunosuppressants. Adjusting for these variables, more than 2 years of cumulative treatment with ciclosporin was estimated to increase the risk of non-melanoma skin cancer by a factor of 3.3 when compared with less than 2 years of cumulative treatment.

1. Penn I. Cancers following cyclosporine therapy. *Transplantation* 1987; **43:** 32–5.
2. Beveridge T, *et al.* Lymphomas and lymphoproliferative lesions developing under cyclosporin therapy. *Lancet* 1984; **i:** 788.
3. Malatack JJ, *et al.* Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: a growing concern. *J Pediatr* 1991; **118:** 667–75.

4. Dantal J, *et al.* Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; **351:** 623–8.
5. Newstead CG. Assessment of risk of cancer after renal transplantation. *Lancet* 1998; **351:** 610–11.
6. Starzl TE, *et al.* Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984; **i:** 583–7.
7. Crawford DH, Edwards JMB. Immunity to Epstein-Barr virus in cyclosporin A-treated renal allograft recipients. *Lancet* 1982; **i:** 1469–70.
8. Stockfleth E, *et al.* Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. *Recent Results Cancer Res* 2002; **160:** 251–8.
9. Bavinck JN, *et al.* Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995; **13:** 1933–8.
10. Shuttleworth D, *et al.* Epidermal dysplasia and cyclosporine therapy in renal transplant patients: a comparison with azathioprine. *Br J Dermatol* 1989; **120:** 551–4.
11. Behnam SM, *et al.* Review of cyclosporine immunosuppressive safety data in dermatology patients after two decades of use. *J Drugs Dermatol* 2005; **4:** 189–94.

Dysmorphic changes. There was pronounced coarsening of facial features in 11 children who were treated with prednisone and ciclosporin for renal transplantation and followed up for more than 6 months.[1] The changes resembled those seen with phenytoin therapy. In a 13-year-old patient given ciclosporin as part of an immunosuppressive regimen after lung transplantation, facial dysmorphism, which developed along with follicular disturbances, later improved upon conversion to tacrolimus.[2] Similarly, lip hypertrophy associated with ciclosporin use in 2 paediatric patients resolved after therapy was changed to tacrolimus.[3] A 58-year-old renal transplant recipient on long-term ciclosporin therapy developed progressive facial changes, including swelling and distortion of the nose (rhinophyma);[4] surgery or physical ablation of excess tissue may provide cosmetic improvement.

1. Reznik VM, *et al.* Changes in facial appearance during cyclosporin treatment. *Lancet* 1987; **i:** 1405–7.
2. Chastain MA, Millikan LE. Pilomatrix dysplasia in an immunosuppressed patient. *J Am Acad Dermatol* 2000; **43:** 118–22.
3. Cansick JC, Hulton S-A. Lip hypertrophy secondary to cyclosporin treatment. *Pediatr Nephrol* 2003; **18:** 710–11.
4. Brown S, *et al.* [Minerva picture]. *BMJ* 2005; **330:** 1218.

Effects on the blood. Erythraemia[1,2] and thrombocytosis[3] have both been reported with ciclosporin treatment, both of which may contribute to **thromboembolic complications.** One retrospective study reported 17 thromboembolic events (pulmonary embolism, renal-vein or deep-vein thrombosis, or haemorrhoidal thrombosis) in 13 of 90 renal allograft recipients treated with ciclosporin and corticosteroids, compared with only 1 episode of superficial thrombophlebitis in 90 similar patients treated with an azathioprine-based regimen.[4] However, other authors dispute that the incidence of thromboembolic events is any greater after ciclosporin than azathioprine,[5-7] and one group found the reverse.[8]

Other effects that have been associated with ciclosporin therapy include cases of the haemolytic-uraemic syndrome,[9] and thrombocytopenia,[10] or leucopenia.[11] Post-transplant thrombotic microangiopathy has also been reported.[12,13] This syndrome can include haemolytic anaemia and thrombocytopenia, and must be distinguished from rejection in renal transplant recipients. In those patients with a history of thrombotic microangiopathy, the risk of recurrence is high, irrespective of ciclosporin treatment.

1. Tatman AJ, *et al.* Erythraemia in renal transplant recipients treated with cyclosporin. *Lancet* 1988; **i:** 1279.
2. Innes A, *et al.* Cyclosporin and erythraemia. *Lancet* 1988; **ii:** 285.
3. Itami N, *et al.* Thrombocytosis after cyclosporin therapy in child with nephrotic syndrome. *Lancet* 1988; **ii:** 1018.
4. Vanrenterghem Y, *et al.* Thromboembolic complications and haemostatic changes in cyclosporin-treated cadaveric kidney allograft recipients. *Lancet* 1985; **i:** 999–1002.
5. Bergentz S-E, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 101–2.
6. Zazgornik J, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 102.
7. Choudhury N, *et al.* Thromboembolic complications in cyclosporin-treated kidney allograft recipients. *Lancet* 1985; **ii:** 606.
8. Allen RD, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 1004.
9. Bonser RS, *et al.* Cyclosporin-induced haemolytic uraemic syndrome in liver allograft recipient. *Lancet* 1984; **ii:** 1337.
10. Dejong DJ, Sayler DJ. Possible cyclosporine-associated thrombocytopenia. *DICP Ann Pharmacother* 1990; **24:** 1007.
11. Michel F, *et al.* Bone marrow toxicity of cyclosporin in a kidney transplant patient. *Lancet* 1986; **ii:** 394.
12. Pisoni R, *et al.* Drug-induced thrombotic microangiopathy: incidence, prevention and management. *Drug Safety* 2001; **24:** 491–501.
13. Bren A, *et al.* Follow-up of kidney graft recipients with cyclosporine-associated hemolytic-uremic syndrome and thrombotic microangiopathy. *Transplant Proc* 2005; **37:** 1889–91.

Effects on the cardiovascular system. The principal cardiovascular adverse effect of ciclosporin is **hypertension.** This may be severe,[1] appears to be dose-related,[1,2] and is particularly common in recipients of cardiac or heart-lung grafts.[3,4] There may be an association with low serum-magnesium concentrations.[5] Mechanisms that may contribute to ciclosporin-induced hypertension include impaired sodium excretion,[6] enhanced sympathetic nervous activity,[3,7] effects on renal prostaglandin metabolism,[2] and direct damage to endothelial cells[8] with release of the potent vasoconstrictor endothelin,[9] all of which may be due to calcineurin inhibition.[10] Thus hypertension may occur independently of nephrotoxicity,[2,7] and may be difficult to treat with conventional antihypertensive regimens.[6] Calcium-channel blockers are the preferred class of antihypertensives for hypertension that develops after transplantation.[1,11] It is important to choose one that does not interact with ciclosporin (see Cardiovascular Drugs under Interactions, below).[1] Beta blockers may also be used. Diuretics are usually avoided.[11] For mention of the ability of calcium-channel blockers to ameliorate the nephrotoxic effects of ciclosporin, see Transplantation, under Diltiazem, p.1267, Nifedipine, p.1356, and Verapamil, p.1424 Occasionally, hypertension may be irreversible.[2,12]

Raynaud's syndrome has been reported with ciclosporin.[13] Conversely, use of ciclosporin has also reportedly caused erythromelalgia, with painful inflammatory vasodilatation of the extremities.[14] For a discussion of possible thromboembolic complications, see Effects on the Blood, above.

1. Textor SC, *et al.* Cyclosporine-induced hypertension after transplantation. *Mayo Clin Proc* 1994; **69:** 1182–93.
2. Porter GA, *et al.* Cyclosporine-associated hypertension. *Arch Intern Med* 1990; **150:** 280–3.
3. Scherrer U, *et al.* Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990; **323:** 693–9.
4. Weidle PJ, Vlasses PH. Systemic hypertension associated with cyclosporine: a review. *Drug Intell Clin Pharm* 1988; **22:** 443–51.
5. June CH, *et al.* Correlation of hypomagnesemia with the onset of cyclosporine-associated hypertension in marrow transplant patients. *Transplantation* 1986; **41:** 47–51.
6. Weinman EJ. Cyclosporine-associated hypertension. *Am J Med* 1989; **86:** 256–7.
7. Mark AL. Cyclosporine, sympathetic activity, and hypertension. *N Engl J Med* 1990; **323:** 748–50.
8. Zaal MJW, *et al.* Is cyclosporin toxic to endothelial cells? *Lancet* 1988; **ii:** 956–7.
9. Deray G, *et al.* Increased endothelin level after cyclosporine therapy. *Ann Intern Med* 1991; **114:** 809.
10. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; **72:** S9–12.
11. Taler SJ, *et al.* Cyclosporin-induced hypertension: incidence, pathogenesis and management. *Drug Safety* 1999; **20:** 437–49.
12. Sennesael JJ, *et al.* Hypertension and cyclosporine. *Ann Intern Med* 1986; **104:** 729.
13. Deray G, *et al.* Cyclosporin and Raynaud phenomenon. *Lancet* 1986; **ii:** 1092–3.
14. Thami GP, Bhalla M. Erythromelalgia induced by possible calcium channel blockade by ciclosporin. *BMJ* 2003; **326:** 910.

Effects on the gastrointestinal tract. There have been reports[1,2] of severe non-specific colitis associated with both elevated[1] and therapeutic[2] blood or serum concentrations of ciclosporin.

1. Innes A, *et al.* Cyclosporin toxicity and colitis. *Lancet* 1988; **ii:** 957. Correction. *ibid.*; 1094.
2. Bowen JRC, Sahi S. Cyclosporin induced colitis. *BMJ* 1993; **307:** 484.

Effects on glucose tolerance. Ciclosporin, particularly in high doses, may be associated with reduced insulin production,[1] impaired glucose tolerance,[2] and occasional overt diabetes mellitus,[3,4] although ciclosporin has also been tried, with some apparent benefit, in the treatment of recent-onset diabetes mellitus (for mention of the use of immunosuppressants in diabetes mellitus, see p.431). The incidence of fasting hyperglycaemia has been estimated at about 8% in ciclosporin-treated renal transplant recipients, compared with about 5% in those given an azathioprine-based regimen.[4]

1. Scott JP, Higenbottam TW. Adverse reactions and interactions of cyclosporin. *Med Toxicol* 1983; **3:** 107–27.
2. Gunnarsson R, *et al.* Deterioration in glucose metabolism in pancreatic transplant recipients given cyclosporin. *Lancet* 1983; **ii:** 571–2.
3. Bending JJ, *et al.* Diabetogenic effect of cyclosporin. *BMJ* 1987; **294:** 401–2.
4. Yagisawa T, *et al.* Deterioration in glucose metabolism in cyclosporine-treated kidney transplant recipients and rats. *Transplant Proc* 1986; **18:** 1548–51.

Effects on the kidneys. Ciclosporin nephrotoxicity comprises 2 distinct forms of renal injury.[1,2]

Acute nephrotoxicity is dose-related, and reversible.[1-4] It occurs shortly after starting ciclosporin and often presents as an asymptomatic increase in serum creatinine, which improves quickly on dosage adjustment or drug withdrawal.[2,5] It may be difficult to distinguish ciclosporin nephrotoxicity from acute graft rejection after kidney transplantation.[5] Extremely high intravenous doses of ciclosporin (21 mg/kg per 24 hours for 60 hours) have been associated with fatal acute tubular necrosis;[6] in another patient given an overdose of 30 mg/kg per 24 hours, the error was detected after 18 hours, and the necrosis deemed to be partially reversible.[7]

Acute ciclosporin nephrotoxicity appears to be related to a renal imbalance of vasoconstrictor and vasodilator mediators, leading to intense vasoconstriction within the kidney.[1,2] Stimulation of the renin-angiotensin system,[5] free radical damage,[1,2] and activation of the sympathetic nervous system[1,5] have been suggested to play a role; numerous vasoactive mediators, including prostaglandins, thromboxanes, nitric oxide, and endothelin-1, may be implicated.[2,3] However, studies with therapies affecting vasoactive factors have produced equivocal results.[1-3]

Chronic nephrotoxicity is related to long-term exposure to ciclosporin.[2] It may be difficult to distinguish between chronic ciclosporin nephrotoxicity and chronic allograft rejection or nephropathy.[4,5] There is a decline in glomerular filtration rate, which may be irreversible or only partially reversible in transplant patients;[3] Some cardiac transplant patients given higher doses than those used in renal transplantation have developed end-stage renal failure.[3] One study[8] in paediatric heart transplant patients found that the decline in renal function correlated with early exposure to ciclosporin. However, in non-transplant patients, renal function impairment has been reported to be reversible after stopping ciclosporin.[3,9] Long-term follow-up has not shown progressive loss of renal function in these patients.[3] Chronic nephrotoxicity is also associated with typical irreversible histological changes, such as interstitial fibrosis.[1-3] which may occur as a result of ischaemic damage secondary to the prolonged alterations in intrarenal haemodynamics.[3] The mechanism is not completely understood, and chronic nephrotoxicity can occur independently of acute renal dysfunction, dosage, or ciclosporin blood concentrations.[4]

Drugs tried to *ameliorate* the nephrotoxic effects of ciclosporin in patients who have undergone transplantation include calcium-channel blockers (see Transplantation, under Diltiazem, p.1267, Nifedipine, p.1356, and Verapamil, p.1424), clonidine, codergocrine,[10-12] omega-3 triglycerides,[13] misoprostol and other prostaglandin analogues,[14,15] and cilastatin.[16] Although benefits have been reported with some of these, hydration, careful monitoring of ciclosporin concentrations, and the use where possible of low-dose or intermittent regimens of ciclosporin appear to remain the major means of minimising nephrotoxicity. Calcium-channel blockers are used if hypertension occurs (see Effects on the Cardiovascular System, above).

1. Burdmann EA, *et al.* Cyclosporine nephrotoxicity. *Semin Nephrol* 2003; **23:** 465–76.
2. Cattaneo D, *et al.* Nephrotoxic aspects of cyclosporine. *Transplant Proc* 2004; **36** (suppl): 234S–239S.
3. Leaker B, Cairns HS. Clinical aspects of cyclosporin nephrotoxicity. *Br J Hosp Med* 1994; **52:** 529–34.
4. Vítko Š, Viklický O. Cyclosporine renal dysfunction. *Transplant Proc* 2004; **36** (suppl): 243S–247S.
5. Busauschina A, *et al.* Cyclosporine nephrotoxicity. *Transplant Proc* 2004; **36** (suppl): 229S–233S.
6. Shechter P. Acute tubular necrosis following high-dose cyclosporine A therapy. *Eur J Clin Pharmacol* 1996; **49:** 521–3.
7. Dussol B, *et al.* Acute tubular necrosis induced by high level of cyclosporine A in a lung transplant. *Transplantation* 2000; **70:** 1234–6.
8. Hornung TS, *et al.* Renal function after pediatric cardiac transplantation: the effect of early cyclosporin dosage. *Pediatrics* 2001; **107:** 1346–50.
9. Powles AV, *et al.* Renal function after 10 years' treatment with cyclosporin for psoriasis. *Br J Dermatol* 1998; **138:** 443–9.
10. Heinrichs DA, *et al.* The effects of co-dergocrine on cyclosporin A pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1987; **24:** 117–18.
11. Nussenblatt RB, *et al.* Hydergine and cyclosporin nephrotoxicity. *Lancet* 1986; **i:** 1220–1.
12. Kho TL, *et al.* Hydergine and reversibility of cyclosporin nephrotoxicity. *Lancet* 1986; **ii:** 394–5.
13. Stoof TJ, *et al.* Does fish oil protect renal function in cyclosporin-treated psoriasis patients? *Br J Dermatol* 1990; **123:** 535.
14. Moran M, *et al.* Prevention of acute graft rejection by the prostaglandin E analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; **322:** 1183–8.
15. Di Palo FQ, *et al.* Role of a prostaglandin E analogue in the prevention of acute graft rejection by cyclosporine. *N Engl J Med* 1990; **323:** 832.
16. Tejedor A, *et al.* Cilastatin protection against cyclosporin A-induced nephrotoxicity: clinical evidence. *Curr Med Res Opin* 2007; **23:** 505–13.

Effects on lipids. Marked hyperlipidaemia has been associated with ciclosporin therapy, with notable increases reported in low-density lipoprotein cholesterol,[1,2] and triglycerides. An increase in lipoprotein(a) has been reported,[3] but this was disputed.[4-6] Ciclosporin has been reported to have greater effects on lipids than azathioprine[7] or tacrolimus[8] post-transplantation. The use of corticosteroids with ciclosporin appears to have an additive adverse effect on lipids.[9] Lipid regulating drugs are used to decrease hypercholesterolaemia in transplant patients.

1. Luke DR, *et al.* Longitudinal study of cyclosporine and lipids in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1990; **30:** 163–9.
2. Ballantyne CM, *et al.* Effects of cyclosporine therapy on plasma lipoprotein levels. *JAMA* 1989; **262:** 53–6.
3. Webb AT, *et al.* Does cyclosporin increase lipoprotein(a) concentrations in renal transplant recipients? *Lancet* 1993; **341:** 268–70.
4. Kronenberg F, *et al.* Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; **341:** 765.
5. Segarra A, *et al.* Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; **341:** 766.
6. Hunt BJ, *et al.* Does cyclosporin affect lipoprotein(a) concentrations? *Lancet* 1994; **343:** 119–20.
7. Van den Dorpel MA, *et al.* Conversion from cyclosporine A to azathioprine treatment improves LDL oxidation in kidney transplant recipients. *Kidney Int* 1997; **51:** 1608–12.
8. Taylor DO, *et al.* A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. *J Heart Lung Transplant* 1999; **18:** 336–45.
9. Moore R, *et al.* Calcineurin inhibitors and post-transplant hyperlipidaemias. *Drug Safety* 2001; **24:** 755–66.

Effects on the nervous system. Adverse effects of ciclosporin on the CNS include tremor,[1-4] ataxia,[1-3] confusion[1,2,5] or agitation,[2] mental depression,[3] headache,[2,5] sleep disturbances,[2] lethargy,[1,2,6,7] or coma[2,5-7] (in one case coma persisted for 44 days),[8] convulsions,[2,3,5,9-13] leukoencephalopathy,[2,8,9,13] cortical blindness,[2,9] diplopia,[14] and spasticity or paralysis of the limbs.[1,2] Opsoclonus (an involuntary eye movement disorder) has also been reported.[13] In one reported case of posterior leukoencephalopathy, the patient developed irreversible abulia (impairment of ability to perform voluntary actions or make decisions; reduction in speech, movement, thought, and emotional reaction);[15] the patient initially presented with subtle symptoms of decreased appetite and reduced activity. Convulsions have sometimes been associated with hypertension and fluid retention,[11] but this is by no means always the case.[9,10]

Although neurotoxicity usually manifests within a month of beginning treatment, it may be delayed, and in one case occurred only after 3 years of ciclosporin therapy.[16] Severe CNS toxicity has been stated to vary in incidence from 0.1% in renal transplant patients to about 1.6% in bone marrow transplant recipients.[12] There is some evidence for an association of serious neurological effects with low total serum-cholesterol concentrations,[2] and the use of the intravenous formulation.[2] Neurotoxicity may also be associated with the use of lipid solutions.[17] An association with hypomagnesaemia has also been proposed[3] but may just represent concomitant nephrotoxicity.[18] Convulsions may be more likely or more severe in patients with a familial history of epilepsy,[19] subclinical aluminium overload,[20] or in those also given high-dose corticosteroids.[5,21,22]

The mechanism of toxicity is unknown but may be associated with disturbance of the blood-brain barrier;[10,12,23] it has been suggested that the metabolite M-17, or possibly other metabolites, are responsible for neurotoxicity.[6] Ciclosporin may be selectively toxic for glial cells, and alteration of sympathetic outflow by calcineurin inhibition may also mediate neurotoxicity.[24]

1. Atkinson K, *et al.* Cyclosporine-associated central-nervous-system toxicity after allogeneic bone-marrow transplantation. *N Engl J Med* 1984; **310:** 527.
2. de Groen PC, *et al.* Central nervous system toxicity after liver transplantation: the role of cyclosporine and cholesterol. *N Engl J Med* 1987; **317:** 861–6.
3. Thompson CB, *et al.* Association between cyclosporin neurotoxicity and hypomagnesaemia. *Lancet* 1984; **ii:** 1116–20.
4. Munhoz RP, *et al.* Movement disorders secondary to long-term treatment with cyclosporine A. *Arq Neuropsiquiatr* 2005; **63:** 592–6.
5. Taque S, *et al.* Central neurotoxicity of cyclosporine in two children with nephrotic syndrome. *Pediatr Nephrol* 2004; **19:** 276–80.
6. Kunzendorf U, *et al.* Cyclosporin metabolites and central-nervous-system toxicity. *Lancet* 1988; **i:** 1223.
7. Lischke R, *et al.* Cyclosporine-related neurotoxicity in a patient after bilateral lung transplantation for cystic fibrosis. *Transplant Proc* 2004; **36:** 2837–9.
8. Berden JHM, *et al.* Severe central-nervous-system toxicity associated with cyclosporin. *Lancet* 1985; **i:** 219–20.
9. Hughes RL. Cyclosporine-related central nervous system toxicity in cardiac transplantation. *N Engl J Med* 1990; **323:** 420–1.
10. Gottrand F, *et al.* Cyclosporine neurotoxicity. *N Engl J Med* 1991; **324:** 1744–5.
11. Joss DV, *et al.* Hypertension and convulsions in children receiving cyclosporin A. *Lancet* 1982; **i:** 906.
12. Krupp P, *et al.* Encephalopathy associated with fat embolism induced by solvent for cyclosporin. *Lancet* 1989; **i:** 168–9.
13. Marchiori PE, *et al.* Cyclosporine A-induced ocular opsoclonus and reversible leukoencephalopathy after orthotopic liver transplantation: brief report. *Clin Neuropharmacol* 2004; **27:** 195–7.
14. Openshaw H. Eye movement abnormality associated with cyclosporin. *J Neurol Neurosurg Psychiatry* 2001; **70:** 809.
15. Nishie M, *et al.* Posterior encephalopathy subsequent to cyclosporin A presenting as irreversible abulia. *Intern Med* 2003; **42:** 750–5.
16. Welge-Lüssen UC, Gerhartz HH. Late onset of neurotoxicity with cyclosporin. *Lancet* 1994; **343:** 293.
17. De Klippel N. Cyclosporin leukoencephalopathy induced by intravenous lipid solution. *Lancet* 1992; **339:** 1114.
18. Allen RD, *et al.* Cyclosporin and magnesium. *Lancet* 1985; **i:** 1283–4.
19. Velu T, *et al.* Cyclosporin-associated fatal convulsions. *Lancet* 1985; **i:** 219.
20. Nordal KP, *et al.* Aluminium overload, a predisposing condition for epileptic seizures in renal-transplant patients treated with cyclosporin. *Lancet* 1985; **ii:** 153–4.
21. Durrant S, *et al.* Cyclosporin A, methylprednisolone, and convulsions. *Lancet* 1982; **ii:** 829–30.
22. Boogaerts MA, *et al.* Cyclosporin, methylprednisolone, and convulsions. *Lancet* 1982; **ii:** 1216–17.
23. Sloane JP, *et al.* Disturbance of blood-brain barrier after bone-marrow transplantation. *Lancet* 1985; **ii:** 280–1.
24. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; **13:** 313–26.

Effects on skeletal muscle. Ciclosporin has occasionally been associated with myopathy.[1-6] The manufacturer noted that 29 cases had been reported by December 1990, which appeared to be divided into cases of toxic or non-specific myopathy or mild sensory motor neuropathy, which were generally dose-related; and rhabdomyolysis, often, but not always, when used with lovastatin or colchicine.[7] Rhabdomyolysis has also been reported when other statins were used with ciclosporin, see Lipid Regulating Drugs, under Interactions, below.

1. Noppen M, *et al.* Cyclosporine and myopathy. *Ann Intern Med* 1987; **107:** 945–6.
2. Goy J-J. Myopathy as possible side-effect of cyclosporin. *Lancet* 1989; **i:** 1446–7.
3. Grezard O, *et al.* Cyclosporin-induced muscular toxicity. *Lancet* 1990; **335:** 177.
4. Fernandez-Sola J, *et al.* Reversible cyclosporin myopathy. *Lancet* 1990; **335:** 362–3.
5. Wahie S, Meggitt SJ. Myotoxicity occurring with ciclosporin in a patient with atopic dermatitis. *Br J Dermatol* 2005; **153:** 1238.
6. Khan S, *et al.* Musculoskeletal and myotoxic side-effects in a patient treated for psoriasis. *Br J Dermatol* 2006; **155:** 481.
7. Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; **337:** 915.

Hyperplasia. Ciclosporin is well known to be associated with the development of gingival hyperplasia or gingival overgrowth: one review[1] has estimated the incidence at about 30% in transplant patients, while noting that reported values in the literature range from about 7 to 70%. A large study[2] found dosage and serum concentration of ciclosporin to be the most significant risk factors in the development of gingival hyperplasia. The presence of dental plaque may exacerbate the response, and good oral hygiene is important in preventing or minimising of gingival overgrowth.[1] Use with nifedipine (which can itself produce hyperplasia) may exacerbate overgrowth;[3] a cohort study[4] of renal transplant recipients found that amlodipine was associated with a greater prevalence of overgrowth than nifedipine. Overgrowth is generally reversible after dosage reduction or withdrawal of ciclosporin; where this is not feasible, surgical excision is recommended.[1] However, improvement or resolution of the overgrowth may also be produced by a course of azithromycin.[5-7] Similar benefit has been reported for metronidazole in some[8,9] but not all patients.[10] There are reports[11,12] of marked improvement in hyperplasia after changing treatment from ciclosporin to tacrolimus, including a case apparently resistant to azithromycin.[13]

Enlargement of the papillae of the tongue[14] and sebaceous gland hyperplasia[15] have also occurred in association with ciclosporin.

1. Brunet L, *et al.* Gingival enlargement induced by drugs. *Drug Safety* 1996; **15:** 219–31.
2. Thomas DW, *et al.* Risk factors in the development of cyclosporine-induced gingival overgrowth. *Transplantation* 2000; **69:** 522–6.
3. Slavin J, Taylor J. Cyclosporin, nifedipine, and gingival hyperplasia. *Lancet* 1987; **ii:** 739.
4. James JA, *et al.* The calcium channel blocker used with cyclosporin has an effect on gingival overgrowth. *J Clin Periodontol* 2000; **27:** 109–15.
5. Jucglà A, *et al.* The use of azithromycin for cyclosporin-induced gingival overgrowth. *Br J Dermatol* 1998; **138:** 198–9.
6. Nash MM, Zaltzman JS. Efficacy of azithromycin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant recipients. *Transplantation* 1998; **65:** 1611–15.
7. Citterio F, *et al.* Azithromycin treatment of gingival hyperplasia in kidney transplant recipients is effective and safe. *Transplant Proc* 2001; **33:** 2134–5.
8. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; **343:** 986.
9. Cecchin E, *et al.* Treatment of cyclosporine-induced gingival hypertrophy. *Ann Intern Med* 1997; **126:** 409–10.
10. Aufricht C, *et al.* Oral metronidazole does not improve cyclosporine A-induced gingival hyperplasia. *Pediatr Nephrol* 1997; **11:** 552–5.
11. Thorp M, *et al.* The effect of conversion from cyclosporine to tacrolimus on gingival hyperplasia, hirsutism and cholesterol. *Transplantation* 2000; **69:** 1218–20.
12. James JA, *et al.* Reduction in gingival overgrowth associated with conversion from cyclosporin A to tacrolimus. *J Clin Periodontol* 2000; **27:** 144–8.
13. Vallejo C, *et al.* Resolution of cyclosporine-induced gingival hyperplasia resistant to azithromycin by switching to tacrolimus. *Haematologica* 2001; **86:** 110.
14. Silverberg NB, *et al.* Lingual fungiform papillae hypertrophy with cyclosporin A. *Lancet* 1996; **348:** 967.
15. Boschnakow A, *et al.* Ciclosporin A-induced sebaceous gland hyperplasia. *Br J Dermatol* 2003; **149:** 198–200.

Hypersensitivity. Anaphylactoid reactions in 5 of 21 patients given intravenous ciclosporin infusions were found to be associated with improper mixing of the ciclosporin concentrate, which had a polyoxyl castor oil vehicle, with the infusion solution.[1] It was concluded that this had led to an initial bolus of polyoxyl castor oil that had triggered the anaphylactic reactions. Subsequent study indicated that peak concentrations of up to 9 times the intended concentration of ciclosporin and polyoxyl castor oil were present in the first 10 minutes of a poorly mixed infusion.[2] Anaphylactic shock after ingestion of ciclosporin capsules has been reported. The microemulsifying base containing corn oil and polyoxyl 40 hydrogenated castor oil, which is related to the polyoxyl castor oil vehicle used in the intravenous formulation, was considered to be the likely cause.[3]

1. Liau M, *et al.* High incidence of anaphylactoid reactions to iv cyclosporin A caused by improper dissolution of Cremophor EL. *Clin Pharmacol Ther* 1995; **57:** 209.
2. Liau-Chu M, *et al.* Mechanism of anaphylactoid reactions: improper preparation of high-dose intravenous cyclosporine leads to bolus infusion of Cremophor EL and cyclosporine. *Ann Pharmacother* 1997; **31:** 1287–91.
3. Kuiper RAJ, *et al.* Cyclosporine-induced anaphylaxis. *Ann Pharmacother* 2000; **34:** 858–61.

Hyperuricaemia. Ciclosporin therapy may be associated with marked hyperuricaemia,[1-3] which may lead (mainly in male patients[1]) to episodes of severe gouty arthritis.[1-3] It has been suggested that ciclosporin specifically reduces urate clearance by the kidney independently of its effects on glomerular filtration,[4,5] but this has been disputed.[6] Treatment of ciclosporin-induced gout can be difficult since interactions with NSAIDs may lead to enhanced renal toxicity[5] and patients who are also receiving azathioprine may experience increased bone-marrow toxicity if given allopurinol.[7] Benzbromarone appears to be an alternative[8] for treating hyperuricaemia in renal transplant recipients with a creatinine clearance greater than 25 mL/minute.

1. Lin H-Y, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1989; **321:** 287–92.
2. Kahl LE, *et al.* Gout in the heart transplant recipient: physiologic puzzle and therapeutic challenge. *Am J Med* 1989; **87:** 289–94.
3. Burack DA, *et al.* Hyperuricemia and gout among heart transplant recipients receiving cyclosporine. *Am J Med* 1992; **92:** 141–6.
4. Noordzij TC, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; **322:** 335.
5. Farge D, *et al.* Hyperuricemia and gouty arthritis in heart transplant recipients. *Am J Med* 1990; **88:** 553.
6. Zürcher RM, *et al.* Hyperuricaemia in cyclosporin-treated patients: a GFR-related effect. *Nephrol Dial Transplant* 1996; **11:** 153–8.
7. Figg WD. Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; **332:** 334–5.
8. Zürcher RM, *et al.* Excellent uricosuric efficacy of benzbromarone in cyclosporin-A-treated renal transplant patients: a prospective study. *Nephrol Dial Transplant* 1994; **9:** 548–51.

Overdosage. Anxiety, diarrhoea, vomiting, and perspiration, with weak and irregular pulse, occurred in a patient accidentally injected with 250 mg (estimated 6.25 mg/kg) of ciclosporin.[1] The patient subsequently developed atrial fibrillation, which was treated with digoxin, and in the next 36 hours showed signs of slight renal insufficiency. Two days later no adverse effects were apparent. Atrial fibrillation also developed in another patient accidentally given 1 g of microemulsifying oral ciclosporin.[2] No adverse renal, hepatic, or neurological effects were seen in a third patient[3] who took 25 g of ciclosporin over 8 days. There was a mild increase in blood pressure and other symptoms included burning sensations in the mouth and the extremities, dysgeusia, facial flushing, and gastrointestinal disturbances. Symptoms resolved within 2 weeks of stopping ciclosporin.

A patient accidentally given intravenous ciclosporin at 30 mg/hour for 13 hours, developed massive intracerebral oedema and brainstem compression and died despite stopping the infusion.[4]

Although ciclosporin is only minimally dialysable, whole blood exchange (therapeutic erythrocytapheresis followed by plasma exchange) has been used in the management of a patient inadvertently given 3.5 g of ciclosporin orally; the overdose was discovered too late for the use of activated charcoal or gastric lavage, and plasma exchange alone was considered unsuitable because of the partitioning of ciclosporin between plasma and erythrocytes. The patient, who had signs of nephrotoxicity and hepatotoxicity, recovered without long-term sequelae.[5]

For reference to tubular necrosis after extremely high intravenous doses of ciclosporin, see under Effects on the Kidneys, above.

1. Wallemacq PE, Lesne ML. Accidental massive IV administration of cyclosporine in man. *Drug Intell Clin Pharm* 1985; **19:** 29–30.
2. LoVecchio FA, Goltz HR. Atrial fibrillation following acute overdose with oral cyclosporine. *Ann Pharmacother* 2000; **34:** 405.
3. Baumhefner RW, *et al.* Huge cyclosporin overdose with favourable outcome. *Lancet* 1987; **ii:** 332.
4. de Perrot M, *et al.* Massive cerebral edema after i.v. cyclosporin overdose. *Transplantation* 2000; **70:** 1259–60.
5. Kwon SU, *et al.* Successful whole blood exchange by apheresis in a patient with acute cyclosporine intoxication without long-term sequelae. *J Heart Lung Transplant* 2006; **25:** 483–5.

Precautions

Regular monitoring of renal and hepatic function, blood pressure, and serum electrolytes (chiefly potassium and magnesium) is required in patients receiving ciclosporin. Serum lipids should also be monitored. Monitoring of plasma ciclosporin concentrations is mandatory in transplant patients. Dosage adjustment is often necessary in patients with renal impairment or other factors affecting plasma ciclosporin concentrations. Care is required in patients with hyperuricaemia, and intravenous formulations should be given cautiously to those who have previously received parenteral drugs formulated in polyoxyl castor oil, or to those with a history of allergic reactions.

Ciclosporin should not be used to treat atopic dermatitis, psoriasis, or rheumatoid arthritis in patients with persistently raised creatinine, uncontrolled hypertension, uncontrolled infections, or malignancy. An exception is patients with treated malignant or pre-malignant lesions of the skin who may receive ciclosporin as a last resort for psoriasis. Psoriatic patients should not be given concomitant ultraviolet irradiation and should avoid excessive sun exposure. Ciclosporin may increase the risk of benign intracranial hypertension.

The commercially available oral formulations of ciclosporin differ in their bioavailability, and patients should not be transferred from one to another without

appropriate monitoring. Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Immunosuppressants may reduce the response to vaccines and use with live vaccines should generally be avoided as there is a possibility of generalised infection, see below.

Oral formulation. After development of the oral microemulsifying formulation of ciclosporin patients were switched from the old formulation on a 1:1 basis by weight initially, with monitoring of resultant ciclosporin concentrations and subsequent dosage adjustment. Results were generally good, despite some reports of nephrotoxicity or rejection in previously stable grafts,[1-4] and a meta-analysis[5] concluded that of *de novo* transplant recipients, those receiving the microemulsifying formulation had significantly fewer instances of rejection, and, in liver transplant recipients, significantly fewer adverse events.

1. Bennett WM, *et al.* Which cyclosporin formulation? *Lancet* 1996; **348:** 205.
2. Olyaei AJ, *et al.* Switching between cyclosporin formulations: what are the risks? *Drug Safety* 1997; **16:** 366–73.
3. Filler G, Ehrich J. Which cyclosporin formulation? *Lancet* 1996; **348:** 1176–7.
4. Gennery A, *et al.* Which cyclosporin formulation? *Lancet* 1996; **348:** 1177.
5. Shah MB, *et al.* A meta-analysis to assess the safety and tolerability of two formulations of cyclosporine: Sandimmune and Neoral. *Transplant Proc* 1998; **30:** 4048–53.

Breast feeding. The American Academy of Pediatrics considers that ciclosporin may possibly suppress the immune system in a nursing infant.[1] However, a study[2] in the breast-fed infants of 7 women given ciclosporin found that the amounts ingested by the infant produced undetectable blood concentrations. In another case it was estimated that a breast-fed infant received less than 100 micrograms/kg of ciclosporin daily.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/01/08)
2. Nyberg G, *et al.* Breast feeding during treatment with cyclosporine. *Transplantation* 1998; **65:** 253–5.
3. Thiru Y, *et al.* Successful breast feeding while mother was taking cyclosporin. *BMJ* 1997; **315:** 463.

Porphyria. Ciclosporin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*. However, there are reports of patients with acute intermittent porphyria given ciclosporin pre- and post-transplant with no exacerbation of symptoms.[1,2]

1. Barone GW, *et al.* The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; **41:** 113–15.
2. Warholm C, Wilczek H. Renal transplantation in a case of acute intermittent porphyria. *J Clin Pharmacol* 2003; **43:** 1158–60.

Pregnancy. Ciclosporin has been used successfully in pregnant women. However, in common with other immunosuppressants, fetal growth retardation may be a significant problem.[1-4] Patients with hypertension or graft dysfunction are more likely to have adverse outcomes, so patients should have stable graft function and be on maintenance therapy before considering pregnancy.[1,2] Serum ciclosporin concentrations may fall during pregnancy,[2,3,5] but although frequent monitoring is necessary, the altered immune state of pregnancy may protect against rejection episodes.[5] Ciclosporin should be used at the lowest possible dose to maintain efficacy, and one review[3] has recommended that the daily dose should be kept below 5 mg/kg.

One case of osseous malformation, resulting in hypoplasia of the right leg has been reported in an infant born to a ciclosporin-treated mother.[6]

1. Armenti VT, *et al.* Variables affecting birthweight and graft survival in 197 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation* 1995; **59:** 476–9.
2. Armenti VT, *et al.* National Transplantation Pregnancy Registry (NTPR): cyclosporine dosing and pregnancy outcome in female renal transplant recipients. *Transplant Proc* 1996; **28:** 2111–12.
3. Huynh LA, Min DI. Outcomes of pregnancy and the management of immunosuppressive agents to minimize fetal risks in organ transplant patients. *Ann Pharmacother* 1994; **28:** 1355–6.
4. Lamarque V, *et al.* Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. *Transplant Proc* 1997; **29:** 2480.
5. Thomas AG, *et al.* The effect of pregnancy on cyclosporine levels in renal allograft patients. *Obstet Gynecol* 1997; **90:** 916–19.
6. Pujals JM, *et al.* Osseous malformation in baby born to woman on cyclosporin. *Lancet* 1989; **i:** 667.

Interactions

Ciclosporin is extensively metabolised in the liver and plasma-ciclosporin concentrations may be affected by inducers or competitive inhibitors of hepatic enzymes, particularly cytochrome P450 isoenzyme CYP3A4. For example, use of carbamazepine, nevirapine, phenytoin, phenobarbital, rifampicin, St John's wort, and other inducers of hepatic enzymes may lead to lower plasma concentrations of ciclosporin, and increased plasma concentrations have been reported with some antifungals, macrolide antibacterials, HIV-protease inhibitors, the NNRTI delavirdine, some calcium-channel blockers, sex hormones, corticosteroids and grapefruit juice. In transplant patients frequent measurement of plasma ciclosporin and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of other drugs.

Concurrent use of statins may increase the risk of myopathy and rhabdomyolysis. Potassium-sparing diuretics should be avoided because of the risk of hyperkalaemia, and patients taking ciclosporin should avoid a high dietary intake of potassium. The risk of gingival hyperplasia may be increased by amlodipine or nifedipine.

During treatment with ciclosporin, vaccination may be less effective, and the use of live vaccines should generally be avoided.

Care should be taken when ciclosporin is given with other nephrotoxic drugs.

◊ Reviews of the interactions of ciclosporin.

1. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin. *Clin Pharmacokinet* 1990; **19:** 319–32 and 400–15.
2. Lake KD, Canafax DM. Important interactions of drugs with immunosuppressive agents used in transplant recipients. *J Antimicrob Chemother* 1995; **36** (suppl B): 11–22.
3. Campana C, *et al.* Clinically significant drug interactions with cyclosporin: an update. *Clin Pharmacokinet* 1996; **30:** 141–79.
4. Chan L-N. Drug-nutrient interactions in transplant recipients. *J Parenter Enteral Nutr* 2001; **25:** 132–41.

Antibacterials. ***AMINOGLYCOSIDES.*** Increased nephrotoxicity has been reported after the use of aminoglycosides with ciclosporin.[1,2] However, a retrospective analysis in 21 patients given ciclosporin for allogeneic bone marrow transplant, in whom aminoglycosides were used if fever and neutropenia developed, showed no greater incidence of nephrotoxicity than in 20 autologous bone marrow recipients who did not receive ciclosporin, suggesting that these drugs can be given together provided careful monitoring is maintained.[3]

1. Termeer A, *et al.* Severe nephrotoxicity cause by the combined use of gentamicin and cyclosporine in renal allograft recipients. *Transplantation* 1986; **42:** 220–1.
2. Morales JM, *et al.* Reversible acute renal toxicity by toxic sinergic effect between gentamicin and cyclosporine. *Clin Nephrol* 1988; **29:** 272.
3. Chandrasekar PH, Cronin SM. Nephrotoxicity in bone marrow transplant recipients receiving aminoglycoside plus cyclosporine or aminoglycoside alone. *J Antimicrob Chemother* 1991; **27:** 845–9.

CHLORAMPHENICOL. Marked rises in plasma-ciclosporin concentrations have been reported when chloramphenicol was given.[1-3] Ciclosporin trough concentrations should be monitored if these drugs are used together.[3]

1. Steinfort CL, McConachy KA. Cyclosporin-chloramphenicol drug interaction in a heart-lung transplant recipient. *Med J Aust* 1994; **161:** 455.
2. Bui LL, Huang DD. Possible interaction between cyclosporine and chloramphenicol. *Ann Pharmacother* 1999; **33:** 252–3.
3. Mathis AS, *et al.* Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; **4:** 169–74.

MACROLIDES. Markedly raised blood concentrations of ciclosporin have been reported in patients also given *erythromycin*.[1-4] The mechanism involved appears to be a combination of decreased hepatic metabolism of ciclosporin and increased gastrointestinal absorption.[5] Similar elevations of ciclosporin concentrations have been noted after use with other macrolide antibacterials, including *clarithromycin*,[6-8] *josamycin*,[9,10] *midecamycin*,[11] *midecamycin acetate*,[12] and the structurally-related streptogramins, *pristinamycin*[13] and *quinupristin/dalfopristin*.[14] Small increases in ciclosporin concentrations have been seen with *roxithromycin*.[15] Increases in ciclosporin concentrations were attributed to *azithromycin* in 2 patients,[16,17] but a study in 6 patients found no effect.[18] *Spiramycin* does not appear to affect the pharmacokinetics of ciclosporin.[19,20]

1. Ptachcinski RJ, *et al.* Effect of erythromycin on cyclosporine levels. *N Engl J Med* 1985; **313:** 1416–17.
2. Martell R, *et al.* The effects of erythromycin in patients treated with cyclosporine. *Ann Intern Med* 1986; **104:** 660–1.
3. Wadhwa NK, *et al.* Interaction between erythromycin and cyclosporine in a kidney and pancreas allograft recipient. *Ther Drug Monit* 1987; **9:** 123–5.
4. Gupta SK, *et al.* Cyclosporin-erythromycin interaction in renal transplant patients. *Br J Clin Pharmacol* 1989; **27:** 475–81.
5. Ignoffo RJ, Kim LE. Erythromycin and cyclosporine drug interaction. *DICP Ann Pharmacother* 1991; **25:** 30–1.
6. Ferrari SL, *et al.* The interaction between clarithromycin and cyclosporine in kidney transplant recipients. *Transplantation* 1994; **58:** 725–7.
7. Treille S, *et al.* Kidney graft dysfunction after drug interaction between clarithromycin and cyclosporin. *Nephrol Dial Transplant* 1996; **11:** 1192–3.
8. Sádaba B, *et al.* Concurrent clarithromycin and cyclosporin A treatment. *J Antimicrob Chemother* 1998; **42:** 393–5.
9. Kreft-Jais C, *et al.* Effect of josamycin on plasma cyclosporine levels. *Eur J Clin Pharmacol* 1987; **32:** 327–8.
10. Azanza JR, *et al.* Possible interaction between cyclosporine and josamycin: a description of three cases. *Clin Pharmacol Ther* 1992; **51:** 572–5.
11. Alfonso I, *et al.* Interaction between cyclosporine A and midecamycin. *Eur J Clin Pharmacol* 1997; **52:** 79–80.
12. Couet W, *et al.* Effect of ponsinomycin on cyclosporin pharmacokinetics. *Eur J Clin Pharmacol* 1990; **39:** 165–7.
13. Garraffo R, *et al.* Pristinamycin increases cyclosporin blood levels. *Med Sci Res* 1987; **15:** 461.
14. Stamatakis MK, Richards JG. Interaction between quinupristin/dalfopristin and cyclosporine. *Ann Pharmacother* 1997; **31:** 576–8.
15. Billaud EM, *et al.* Interaction between roxithromycin and cyclosporin in heart transplant patients. *Clin Pharmacokinet* 1990; **19:** 499–502.
16. Ljutic D, Rumboldt Z. Possible interaction between azithromycin and cyclosporin: a case report. *Nephron* 1995; **70:** 130.
17. Page RL, *et al.* Possible interaction between intravenous azithromycin and oral cyclosporine. *Pharmacotherapy* 2001; **21:** 1436–43.
18. Gomez E, *et al.* Interaction between azithromycin and cyclosporin? *Nephron* 1996; **73:** 724.
19. Vernillet L, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1989; **27:** 789–94.
20. Kessler M, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1990; **29:** 370–1.

PENICILLINS. Decreased plasma-ciclosporin concentrations and effect were seen in a patient given *nafcillin*.[1] Conversely, another study reported increased nephrotoxicity from the use of ciclosporin with nafcillin but no apparent increase in ciclosporin concentrations.[2]

1. Veremis SA, *et al.* Subtherapeutic cyclosporine concentrations during nafcillin therapy. *Transplantation* 1987; **43:** 913–15.
2. Jahansouz F, *et al.* Potentiation of cyclosporine nephrotoxicity by nafcillin in lung transplant recipients. *Transplantation* 1993; **55:** 1045–8.

QUINOLONES. A number of reports have indicated that the quinolone *ciprofloxacin* has no effect on the pharmacokinetics of ciclosporin.[1-3] However, there is a report of enhanced nephrotoxicity without a change in ciclosporin concentrations in a patient given ciprofloxacin,[4] and another report showing both enhanced nephrotoxicity and increased ciclosporin concentrations.[5] Furthermore, a small case-control study suggested an increase in transplant rejection with ciprofloxacin.[6] *Norfloxacin* has been reported to decrease clearance and increase blood concentrations of ciclosporin in paediatric patients,[7] probably by inhibition of ciclosporin metabolism. *Levofloxacin* did not alter ciclosporin pharmacokinetics in healthy subjects,[8] but a study in renal transplant patients found that levofloxacin partially inhibited the metabolism of ciclosporin;[9] no adverse effects and no supratherapeutic concentrations of ciclosporin were seen.

1. Hooper TL, *et al.* Ciprofloxacin: a preferred treatment for legionella infections in patients receiving cyclosporin A. *J Antimicrob Chemother* 1988; **22:** 952–3.
2. Tan KKC, *et al.* Co-administration of ciprofloxacin and cyclosporin: lack of evidence for a pharmacokinetic interaction. *Br J Clin Pharmacol* 1989; **28:** 185–7.
3. Krüger HU, *et al.* Investigation of potential interaction of ciprofloxacin with cyclosporine in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1990; **34:** 1048–52.
4. Elston RA, Taylor J. Possible interaction of ciprofloxacin with cyclosporin A. *J Antimicrob Chemother* 1988; **21:** 679–80.
5. Nasir M, *et al.* Interaction between ciclosporin and ciprofloxacin. *Nephron* 1991; **57:** 245–6.
6. Wrishko RE, *et al.* Investigation of a possible interaction between ciprofloxacin and cyclosporine in renal transplant patients. *Transplantation* 1997; **64:** 996–9.
7. McLellan RA, *et al.* Norfloxacin interferes with cyclosporine disposition in pediatric patients undergoing renal transplantation. *Clin Pharmacol Ther* 1995; **58:** 322–7.
8. Doose DR, *et al.* Levofloxacin does not alter cyclosporine disposition. *J Clin Pharmacol* 1998; **38:** 90–93.
9. Federico S, *et al.* Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; **45:** 169–75.

RIFAMYCINS. Use with *rifampicin* has been associated with marked decreases in blood-ciclosporin concentrations,[1-5] and has resulted in graft rejection.[1,3] Although it has been assumed that this effect represents induction of the hepatic metabolism of ciclosporin by rifampicin, there is some suggestion that rifampicin may decrease the absorption of ciclosporin or induce intestinal metabolism, resulting in reduced bioavailability.[6] Topical application of *rifamycin* has also been associated with a decrease in blood-ciclosporin concentrations in another patient;[7] ciclosporin concentrations rose immediately after withdrawal of rifamycin, suggesting that the effect was not due to enzyme induction.

1. Langhoff E, Madsen S. Rapid metabolism of cyclosporin and prednisone in kidney transplant patient receiving tuberculostatic treatment. *Lancet* 1983; **ii:** 1031.
2. Daniels NJ, *et al.* Interaction between cyclosporin and rifampicin. *Lancet* 1984; **ii:** 639.
3. Allen RDM, *et al.* Cyclosporin and rifampicin in renal transplantation. *Lancet* 1985; **i:** 980.
4. Freitag VL, *et al.* Effect of short-term rifampin on stable cyclosporine concentrations. *Ann Pharmacother* 1999; **33:** 871–2.
5. Zelunka EJ. Intravenous cyclosporine-rifampin interaction in a pediatric bone marrow transplant recipient. *Pharmacotherapy* 2002; **22:** 387–90.

6. Hebert MF, *et al.* Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. *Clin Pharmacol Ther* 1992; **52:** 453–7.
7. Renoult E, *et al.* Effect of topical rifamycin SV treatment on cyclosporin A blood levels in a renal transplant recipient. *Eur J Clin Pharmacol* 1991; **40:** 433–4.

STREPTOGRAMINS. Increased plasma concentrations of ciclosporin have occurred after therapy with *pristinamycin* and *quinupristin/dalfopristin* (see Macrolides, above).

SULFONAMIDES. Intravenous, but not oral, therapy with *sulfadimidine* and *trimethoprim* has been associated with falls in ciclosporin concentrations to subtherapeutic values.[1,2] Oral *sulfadiazine* has had a similar effect.[3] Conversely, *trimethoprim* and *co-trimoxazole* can cause rises in serum creatinine, and therefore may contribute to ciclosporin-induced nephrotoxicity.[4,5]

1. Wallwork J, *et al.* Cyclosporin and intravenous sulphadimidine and trimethoprim therapy. *Lancet* 1983; **i:** 366–7.
2. Jones DK, *et al.* Serious interaction between cyclosporin A and sulphadimidine. *BMJ* 1986; **292:** 728–9.
3. Spes CH, *et al.* Sulfadiazine therapy for toxoplasmosis in heart transplant recipients decreases cyclosporine concentration. *Clin Investig* 1992; **70:** 752–4.
4. Thompson JF, *et al.* Nephrotoxicity of trimethoprim and cotrimoxazole in renal allograft recipients treated with cyclosporine. *Transplantation* 1983; **36:** 204–6.
5. Ringden O, *et al.* Nephrotoxicity by co-trimoxazole and cyclosporin in transplanted patients. *Lancet* 1984; **i:** 1016.

Antidepressants. Giving *fluoxetine* to a patient receiving ciclosporin as part of an immunosuppressant regimen after cardiac transplantation was associated with a subsequent marked increase in ciclosporin trough blood concentrations to about twice their original value, necessitating a reduction in ciclosporin dosage.[1] After withdrawal of fluoxetine, ciclosporin concentrations fell, and dosage had to be increased. However, a study in 13 other patients given ciclosporin with fluoxetine failed to find any evidence of altered ciclosporin concentrations.[2] A nearly tenfold increase in ciclosporin concentration was seen in a cardiac transplant patient after use of *nefazodone*,[3] and there are 2 case reports[4] of ciclosporin toxicity due to interactions with nefazodone and *fluvoxamine* in renal transplant recipients. Ciclosporin concentrations decreased in a 10-year-old African American heart transplant recipient 22 days after starting *bupropion*. Despite an increase in ciclosporin dosage, ciclosporin concentrations decreased even further, necessitating another increase in ciclosporin dose, and withdrawal of bupropion.[5]

1. Horton RC, Bonser RS. Interaction between cyclosporin and fluoxetine. *BMJ* 1995; **311:** 422.
2. Strouse TB, *et al.* Fluoxetine and cyclosporine in organ transplantation: failure to detect significant drug interactions or adverse clinical events in depressed organ recipients. *Psychosomatics* 1996; **37:** 23–30.
3. Wright DH, *et al.* Nefazodone and cyclosporine drug-drug interaction. *J Heart Lung Transplant* 1999; **18:** 913–15.
4. Vella JP, Sayegh MH. Interactions between cyclosporine and newer antidepressant medications. *Am J Kidney Dis* 1998; **31:** 320–3.
5. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; **11:** 193–8.

ST JOHN'S WORT. Ciclosporin plasma levels are reduced by St John's wort.[1] This has lead to acute rejection episodes in transplant patients,[2] and the two drugs should not be used together.[3]

1. Bauer S, *et al.* Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br J Clin Pharmacol* 2003; **55:** 203–11.
2. Ernst E. St John's wort supplements endanger the success of organ transplantation. *Arch Surg* 2002; **137:** 316–19.
3. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)

Antiepileptics. Use with the antiepileptics *carbamazepine*,[1-3] *phenobarbital*,[4] and *phenytoin*,[5] which are all inducers of hepatic cytochrome P450, has been associated with a reduction in blood-ciclosporin concentrations. *Oxcarbazepine* also decreased ciclosporin trough concentrations in a kidney transplant recipient with epilepsy; concentrations were corrected by an increase in ciclosporin dose. The dose of oxcarbazepine also had to be reduced due to hyponatraemia, and ciclosporin concentrations remained stable thereafter.[6] *Valproate* has been successfully used in ciclosporin-treated patients without apparent interaction.[1,2]

1. Hillebrand G, *et al.* Valproate for epilepsy in renal transplant recipients receiving cyclosporine. *Transplantation* 1987; **43:** 915–16.
2. Schofield OMV, *et al.* Cyclosporin A in psoriasis: interaction with carbamazepine. *Br J Dermatol* 1990; **122:** 425–6.
3. Cooney GF, *et al.* Effects of carbamazepine on cyclosporine metabolism in pediatric renal transplant recipients. *Pharmacotherapy* 1995; **15:** 353–6.
4. Carstensen H, *et al.* Interaction between cyclosporin A and phenobarbitone. *Br J Clin Pharmacol* 1986; **21:** 550–1.
5. Freeman DJ, *et al.* Evaluation of cyclosporin-phenytoin interaction with observations on cyclosporin metabolites. *Br J Clin Pharmacol* 1984; **18:** 887–93.
6. Rösche J, *et al.* Possible oxcarbazepine interaction with cyclosporine serum levels: a single case study. *Clin Neuropharmacol* 2001; **24:** 113–16.

Antifungals. The imidazole *ketoconazole* is a potent inhibitor of hepatic cytochrome P450 and markedly increased blood-ciclosporin concentrations have resulted when conventional formulations of the latter were given with the antifungal.[1-4] The interaction has been used, similarly to the calcium-channel blockers (see below), to permit therapeutic blood concentrations of ciclosporin to be achieved at lower doses;[5-8] however, this method may result in considerable variations in ciclosporin pharmacokinetics, and has been criticised on several grounds.[9] It was noted[10] that this improved bioavailability of ciclosporin was not seen when the microemulsifying formulation (see Absorption under Pharmacokinetics, below) was given with ketoconazole, suggesting that bioavailability was already maximal. Increased ciclosporin concentrations have also been reported with *itraconazole*,[11,12] and it has also been suggested[13] that use be made of this interaction, similarly to ketoconazole, to allow for decreased ciclosporin doses. *Voriconazole* also increases exposure to ciclosporin, and ciclosporin concentrations should be closely monitored.[14,15] There is a single report of increased ciclosporin plasma concentrations with use of *miconazole*.[16] However, although such an interaction has also been reported with *fluconazole*,[17,18] a small study has failed to note any significant interaction;[19,20] it has been suggested that an interaction may take place only at high doses of fluconazole,[21] or that sex and ethnicity may play a role.[18]

Increased nephrotoxicity may occur if ciclosporin is used with *amphotericin B*,[22,23] while liposomal amphotericin B has been reported possibly to exacerbate ciclosporin neurotoxicity.[24] There is a report of decreased ciclosporin concentrations in a patient after addition of *griseofulvin* to therapy.[25] Modest decreases have also been seen in ciclosporin concentrations when *terbinafine* was given.[26] *Micafungin* modestly inhibits ciclosporin metabolism; however, in a minority of patients it may cause a significant increase in ciclosporin concentrations.[27]

1. Ferguson RM, *et al.* Ketoconazole, cyclosporin metabolism, and renal transplantation. *Lancet* 1982; **ii:** 882–3.
2. Dieperink H, Møller J. Ketoconazole and cyclosporin. *Lancet* 1982; **ii:** 1217.
3. Shepard JH, *et al.* Cyclosporine-ketoconazole: a potentially dangerous drug-drug interaction. *Clin Pharm* 1986; **5:** 468.
4. Gomez DY, *et al.* The effects of ketoconazole on the intestinal metabolism and bioavailability of cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 15–19.
5. First MR, *et al.* Concomitant administration of cyclosporin and ketoconazole in renal transplant recipients. *Lancet* 1989; **ii:** 1198–1201.
6. Keogh A, *et al.* Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. *N Engl J Med* 1995; **333:** 628–33.
7. El-Husseini A, *et al.* Concomitant administration of cyclosporine and ketoconazole in idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2004; **19:** 2266–71.
8. El-Husseini A, *et al.* Co-administration of cyclosporine and ketoconazole in idiopathic childhood nephrosis. *Pediatr Nephrol* 2004; **19:** 976–81.
9. Frey FJ. Concomitant cyclosporin and ketoconazole. *Lancet* 1990; **335:** 109–10.
10. Akhlaghi F, *et al.* Pharmacokinetics of cyclosporine in heart transplant recipients receiving metabolic inhibitors. *J Heart Lung Transplant* 2001; **20:** 431–8.
11. Kramer MR, *et al.* Cyclosporine and itraconazole interaction in heart and lung transplant recipients. *Ann Intern Med* 1990; **113:** 327–9.
12. Leather H, *et al.* Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12:** 325–34.
13. Florea NR, *et al.* Beneficial pharmacokinetic interaction between cyclosporine and itraconazole in renal transplant recipients. *Transplant Proc* 2003; **35:** 2873–7.
14. Romero AJ, *et al.* Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. *Clin Pharmacol Ther* 2002; **71:** 226–34.
15. Groll AH, *et al.* Pharmacokinetic interaction between voriconazole and ciclosporin A following allogeneic bone marrow transplantation. *J Antimicrob Chemother* 2004; **53:** 113–14.
16. Horton CM, *et al.* Cyclosporine interactions with miconazole and other azole-antimycotics: a case report and review of the literature. *J Heart Lung Transplant* 1992; **11:** 1127–32.
17. Collignon P, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; **i:** 1262.
18. Mathis AS, *et al.* Sex and ethnicity may chiefly influence the interaction of fluconazole with calcineurin inhibitors. *Transplantation* 2001; **71:** 1069–75.
19. Krüger HU, *et al.* Absence of significant interaction of fluconazole with cyclosporin. *J Antimicrob Chemother* 1989; **24:** 781–6.
20. Ehninger G, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; **ii:** 104–5.
21. López-Gil JA. Fluconazole-cyclosporine interaction: a dose-dependent effect? *Ann Pharmacother* 1993; **27:** 427–30.
22. Kennedy MS, *et al.* Acute renal toxicity with combined use of amphotericin B and cyclosporine after marrow transplantation. *Transplantation* 1983; **35:** 211–15.
23. Furrer K, *et al.* Nephrotoxicity of cyclosporine A and amphotericin B-deoxycholate as continuous infusion in allogenic stem cell transplantation. *Swiss Med Wkly* 2002; **132:** 316–20.
24. Ellis ME, *et al.* Is cyclosporin neurotoxicity enhanced in the presence of liposomal amphotericin B? *J Infect* 1994; **29:** 106–7.
25. Abu-Romeh SH, *et al.* Ciclosporin A and griseofulvin: another drug interaction. *Nephron* 1991; **58:** 237.
26. Lo ACY, *et al.* The interaction of terbinafine and cyclosporine A in renal transplant patients. *Br J Clin Pharmacol* 1997; **43:** 340–1.
27. Hebert MF, *et al.* Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45:** 954–60.

Antigout drugs. A patient who had been receiving maintenance doses of ciclosporin for some years, with consistent whole-blood trough concentrations of around 130 nanograms/mL at doses of 175 mg twice daily had a rise in ciclosporin concentrations to 410 nanograms/mL after 2 months of treatment with *allopurinol* 200 mg daily.[1] Ciclosporin concentrations returned to their previous levels over several weeks after stopping allopurinol, and rose again on rechallenge. Dosage of ciclosporin was then reduced. For a report of a low dose of allopurinol being added to a ciclosporin-containing immunosuppressive regimen, see Organ and Tissue Transplantation, p.554.

UK licensed product information states that *colchicine* may increase ciclosporin concentrations.

In a report of 120 heart transplant recipients with hyperuricaemia, *sulfinpyrazone* reduced ciclosporin concentrations, and 2 patients needed treatment for acute rejection.[2]

1. Gorrie M, *et al.* Allopurinol interaction with cyclosporin. *BMJ* 1994; **308:** 113.
2. Caforio ALP, *et al.* Sulfinpyrazone reduces cyclosporine levels: a new drug interaction in heart transplant recipients. *J Heart Lung Transplant* 2000; **19:** 1205–8.

Antimalarials. A large rise in serum-ciclosporin concentration was seen on 2 occasions in a renal graft recipient when *chloroquine* was added to his medication for malaria prophylaxis.[1] *Quinine* has been reported to reduce ciclosporin concentrations.[2]

1. Finielz P, *et al.* Interaction between cyclosporin and chloroquine. *Nephron* 1993; **65:** 333.
2. Tan HW, Ch'ng SL. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. *Singapore Med J* 1991; **32:** 189–90.

Antineoplastics. Elevated plasma-ciclosporin concentrations and an increased incidence of nephrotoxic effects and hypertension have been reported in patients receiving ciclosporin for psoriasis who had been previously,[1] or concurrently,[2] treated with *methotrexate*. Conversely, methotrexate has been used effectively with reduced-dose ciclosporin in graft-versus-host disease.[3] Severe renal failure has been reported when standard oral doses of ciclosporin were given after high-dose intravenous *melphalan* (used as a bone marrow conditioning agent before allogeneic bone marrow transplantation).[4] A retrospective analysis of allogeneic haematopoietic stem cell transplant patients taking ciclosporin found that, in those given a conditioning regimen containing *cyclophosphamide*, mean serum-ciclosporin concentrations were reduced; no effect on the incidence of graft-versus-host disease could be established.[5]

UK licensed product information states that *imatinib* may increase ciclosporin concentrations.

Ciclosporin increases plasma-*doxorubicin* concentrations and toxicity (see p.714), and has been used to increase oral absorption of *paclitaxel* (see p.760). For the effects of ciclosporin on the pharmacokinetics of *teniposide* and *etoposide*, see p.778 and p.719, respectively.

Ciclosporin and its analogues have been given with antineoplastics for their ability to inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, thus resulting in raised intracellular concentrations of the other drug.

1. Powles AV, *et al.* Cyclosporin toxicity. *Lancet* 1990; **i:** 610.
2. Korstanje MJ, *et al.* Cyclosporine and methotrexate: a dangerous combination. *J Am Acad Dermatol* 1990; **23:** 320–1.
3. Stockschlaeder M, *et al.* A pilot study of low-dose cyclosporin for graft-versus-host prophylaxis in marrow transplantation. *Br J Haematol* 1992; **80:** 49–54.
4. Morgenstern GR, *et al.* Cyclosporin interaction with ketoconazole and melphalan. *Lancet* 1982; **ii:** 1342.
5. Nagamura F, *et al.* Effect of cyclophosphamide on serum cyclosporine levels at the conditioning of hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **32:** 1051–8.

Antiobesity drugs. A reduction in ciclosporin concentrations to subtherapeutic levels has been reported[1-3] in transplant recipients given *orlistat*. It was postulated[2] that the interaction was a result of reduced absorption of ciclosporin in the presence of orlistat and that at least 2 hours should elapse between doses of these two drugs. However, despite this dosing interval, there has been a further report[3] of subtherapeutic plasma levels of ciclosporin. The patient had had severe diarrhoea, and the subsequent decreased absorption of fats was thought to have decreased the absorption of ciclosporin.

An increase in ciclosporin trough concentrations occurred when a renal transplant patient was given *sibutramine*;[4] both drugs are metabolised by cytochrome P450 isoenzyme 3A4.

1. Nägele H, *et al.* Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. *Eur J Clin Pharmacol* 1999; **55:** 667–9.
2. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. *N Engl J Med* 2000; **342:** 1141–2.
3. Barbaro D, *et al.* Obesity in transplant patients: case report showing interference of orlistat with absorption of cyclosporine and review of literature. *Endocr Pract* 2002; **8:** 124–6.
4. Clerbaux G, *et al.* Interaction between sibutramine and cyclosporine. *Am J Transplant* 2003; **3:** 906.

Antivirals. For a report of mutual elevations in the area under the plasma concentration-time curves for ciclosporin and the HIV-protease inhibitor *saquinavir*, see Indinavir, p.883.

Bifendate. In 2 patients given maintenance doses of ciclosporin, trough whole-blood concentrations decreased from 97.7 nanograms/mL to 49.0 nanograms/mL and from 127.5 nanograms/mL to 45.0 nanograms/mL respectively when

bifendate was given. Ciclosporin concentrations returned to pre-treatment levels over several weeks once bifendate was stopped.[1]

1. Kim YS, *et al.* The effect of diphenyl-dimethyl-dicarboxylate on cyclosporine-A blood level in kidney transplants with chronic hepatitis. *Korean J Intern Med* 1997; **12:** 67–9.

Cardiovascular drugs. ***ACE INHIBITORS.*** There may be an increased risk of hyperkalaemia when ACE inhibitors are used with ciclosporin. Acute renal failure, associated with use of *enalapril*, has been reported in 2 patients given ciclosporin after renal transplantation.[1] Renal function recovered when the ACE inhibitor was withdrawn.

1. Murray BM, *et al.* Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* 1990; **16:** 66–9.

ANTIARRHYTHMICS. Marked rises in serum-ciclosporin concentrations despite reductions in dose have been noted in recipients of organ transplants after treatment with *amiodarone*.[1-3] A rise in serum ciclosporin has similarly been seen in a patient given both ciclosporin and *propafenone*.[4]

1. Mamprin F, *et al.* Amiodarone-cyclosporine interaction in cardiac transplantation. *Am Heart J* 1992; **123:** 1725–6.
2. Egami J, *et al.* Increase in cyclosporine levels due to amiodarone therapy after heart and heart-lung transplantation. *J Am Coll Cardiol* 1993; **21:** 141A.
3. Chitwood KK, *et al.* Cyclosporine-amiodarone interaction. *Ann Pharmacother* 1993; **27:** 569–71.
4. Spes CH, *et al.* Ciclosporin-propafenone interaction. *Klin Wochenschr* 1990; **68:** 872.

ANTICOAGULANTS. Treatment with *warfarin* for deep-vein thrombosis in a patient maintained on ciclosporin for pure red cell aplasia resulted in a relapse of the latter and a significant fall in ciclosporin blood concentrations.[1] Increase in the ciclosporin dose restored control of the aplasia but resulted in a marked increase in prothrombin activity requiring an increase in warfarin dosage. The results suggest that each drug interferes with the activity of the other. The influence of the patient's other medications (including phenobarbital and folic acid), if any, is unknown, although it has been suggested[2,3] that the phenobarbital had enhanced the metabolism of both drugs. In another report,[2] a patient on long-term warfarin for deep-vein thrombosis was started on ciclosporin for lymphoma relapse, and subsequently required larger doses of warfarin. During use of *acenocoumarol* with ciclosporin, the dose of ciclosporin had to be increased[3] in one patient and both drugs decreased[4] in another. It appears that the interaction between ciclosporin and anticoagulants is unpredictable[3] and dependent on the anticoagulant used.[2]

1. Snyder DS. Interaction between cyclosporine and warfarin. *Ann Intern Med* 1988; **108:** 311.
2. Turri D, *et al.* Oral anticoagulants and cyclosporin A. *Haematologica* 2000; **85:** 893–4.
3. Borrás-Blasco J, *et al.* Interaction between cyclosporine and acenocoumarol in a patient with nephrotic syndrome. *Clin Nephrol* 2001; **55:** 338–40.
4. Campistol JM, *et al.* Interaction between ciclosporin A and Sintrom. *Nephron* 1989; **53:** 291–2.

ANTIPLATELET DRUGS. *Ticlopidine* decreased serum-ciclosporin concentrations in isolated cases,[1-3] but a study in 20 heart transplant patients failed to show any interaction between ciclosporin and low-dose ticlopidine.[4] For reports of rhabdomyolysis occurring in patients stabilised on ciclosporin and a statin when *clopidogrel* was added to their treatment, see p.1250.

1. Birmelé B, *et al.* Interaction of cyclosporin and ticlopidine. *Nephrol Dial Transplant* 1991; **6:** 150–1.
2. Verdejo A, *et al.* Probable interaction between cyclosporin A and low dose ticlopidine. *BMJ* 2000; **320:** 1037.
3. Feriozzi S, *et al.* Treatment with ticlopidine is associated with reduction of cyclosporin A blood levels. *Nephron* 2002; **92:** 249–50.
4. Boissonnat P, *et al.* A drug interaction study between ticlopidine and cyclosporin in heart transplant recipients. *Eur J Clin Pharmacol* 1997; **53:** 39–45.

BETA BLOCKERS. Ciclosporin plasma concentrations increased when *carvedilol* was added to treatment regimens of renal[1] and cardiac[2] transplant patients. Considerable interindividual variation was seen in one study,[1] so it is recommended that ciclosporin concentrations should be monitored carefully if the drugs are used together.

1. Kaijser M, *et al.* Elevation of cyclosporin A blood levels during carvedilol treatment in renal transplant patients. *Clin Transplant* 1997; **11:** 577–81.
2. Bader FM, *et al.* The effect of β-blocker use on cyclosporine level in cardiac transplant recipients. *J Heart Lung Transplant* 2005; **24:** 2144–7.

BOSENTAN. There is a complex interaction between ciclosporin and bosentan. If the drugs are given together reduced ciclosporin concentrations and increased bosentan concentrations may occur; further details are given on p.1235.

CALCIUM-CHANNEL BLOCKERS. The calcium-channel blockers *diltiazem*,[1-3] *lercanidipine*, *nicardipine*,[4,5] and *verapamil*[6,7] have all been associated with increases in ciclosporin blood concentrations. It has been suggested that such an interaction can be used to obtain effective ciclosporin concentrations with lower doses.[8] In addition, there is some evidence of mitigation of ciclosporin-induced nephrotoxicity when calcium-channel blockers are given (see Effects on the Kidneys, above), and they are useful for ciclosporin-induced hypertension (see Effects on the Cardiovascular System, above). However, some caution is required: one report has pointed out that diltiazem does not increase ciclosporin concentrations in all cases,[9] while others have found that use together alters the pattern of ciclosporin metabolites, and that pharmacokinetic changes are greater in female than in male patients.[10] Therefore, some prefer a calcium-channel blocker that does not alter ciclosporin pharmacokinetics for hypertension and renal protection. *Nifedipine* has not been shown to increase blood-ciclosporin concentrations.[6] For a report of increased nifedipine toxicity with ciclosporin see Immunosuppressants, p.1353. Other calcium-channel blockers that do not appear to affect ciclosporin pharmacokinetics include *felodipine*[7,11] and *isradipine*.[7,12] Ciclosporin concentrations have been reported to increase or to remain unchanged with *amlodipine*.[13] Use of amlodipine or nifedipine with ciclosporin may exacerbate the problem of gingival hyperplasia—see Hyperplasia under Adverse Effects, above.

1. Brockmöller J, *et al.* Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; **38:** 237–42.
2. Bourge RC, *et al.* Diltiazem-cyclosporine interaction in cardiac transplant recipients: impact on cyclosporine dose and medication costs. *Am J Med* 1991; **90:** 402–4.
3. Åsberg A, *et al.* Pharmacokinetic interactions between microemulsion formulated cyclosporine A and diltiazem in renal transplant recipients. *Eur J Clin Pharmacol* 1999; **55:** 383–7.
4. Todd P, *et al.* Nicardipine interacts with cyclosporin. *Br J Dermatol* 1989; **121:** 820.
5. Kessler M, *et al.* Influence of nicardipine on renal function and plasma cyclosporin in renal transplant patients. *Eur J Clin Pharmacol* 1989; **36:** 637–8.
6. Tortorice KL, *et al.* The effects of calcium channel blockers on cyclosporine and its metabolites in renal transplant patients. *Ther Drug Monit* 1990; **12:** 321–8.
7. Yildiz A, *et al.* Interaction between cyclosporine A and verapamil, felodipine, and isradipine. *Nephron* 1999; **81:** 117–18.
8. Sketris IS, *et al.* Effect of calcium-channel blockers on cyclosporine clearance and use in renal transplant patients. *Ann Pharmacother* 1994; **28:** 1227–31.
9. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; **42:** 642–4.
10. Bleck JS, *et al.* Diltiazem increases blood concentrations of cyclized cyclosporine metabolites resulting in different cyclosporine metabolite patterns in stable male and female renal allograft recipients. *Br J Clin Pharmacol* 1996; **41:** 551–6.
11. Cohen DJ, *et al.* Influence of oral felodipine on serum cyclosporine concentrations. *Clin Transplant* 1994; **8:** 541–5.
12. Endresen L, *et al.* Lack of effect of the calcium antagonist isradipine on cyclosporine pharmacokinetics in renal transplant patients. *Ther Drug Monit* 1991; **13:** 490–5.
13. Schrama YC, Koomans HA. Interactions of cyclosporin A and amlodipine: blood cyclosporin A levels, hypertension and kidney function. *J Hypertens* 1998; **16** (suppl): S33–S38.

CARDIAC GLYCOSIDES. For reference to the effect of ciclosporin on serum-digoxin concentrations, see under Digoxin, p.1262.

CLONIDINE. Addition of clonidine to the regimen of a 3-year-old child who had developed hypertension after a renal transplant resulted in a marked increase in whole blood ciclosporin concentrations, despite a reduction in ciclosporin dose.[1] Ciclosporin concentrations fell rapidly on withdrawal of clonidine.

1. Gilbert RD, *et al.* Interaction between clonidine and cyclosporine A. *Nephron* 1995; **71:** 105.

DIURETICS. Enhanced nephrotoxicity, without apparent change in ciclosporin blood concentrations, has been seen in individual patients after addition of *metolazone*[1] or *amiloride* with *chlorothiazide*[2] to their regimen. Severe nephrotoxicity, resulting in loss of graft function, has been seen in a renal transplant patient given *mannitol* with ciclosporin;[3] graft function recovered on withdrawal of the diuretic.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; **294:** 578.
2. Deray G, *et al.* Enhancement of cyclosporin nephrotoxicity by diuretic therapy. *Clin Nephrol* 1989; **32:** 47.
3. Brunner FP, *et al.* Mannitol potentiates cyclosporine nephrotoxicity. *Clin Nephrol* 1986; **25** (suppl 1): S130–6.

LIPID REGULATING DRUGS. A study in 10 renal transplant recipients indicated that use of ciclosporin with *probucol* markedly reduced the whole blood and plasma concentrations of the former in 9 of them, compared with use of ciclosporin alone.[1] *Bezafibrate* has been reported to increase blood concentrations of ciclosporin, with resultant nephrotoxicity.[2] However, other studies with bezafibrate have found a small decrease in ciclosporin concentrations,[3] or no effect,[4,5] despite an increase in serum creatinine in each study. Conflicting effects have also been reported with other fibrates: decreased[6] and unchanged[7] ciclosporin concentrations have occurred with *fenofibrate*, and both a decrease[8] and lack of effect[9] have also occurred with *gemfibrozil*.

In 1 study, *simvastatin* increased the unbound fraction of ciclosporin in the blood, resulting in a modest increase in apparent ciclosporin clearance.[10] In renal transplant recipients, *atorvastatin* increased ciclosporin blood concentrations in 4 out of 10 patients in one study[11] but was deemed to have minimal clinical effect in others.[12,13] Ciclosporin concentrations were unaffected by *cerivastatin*,[11,14] *fluvastatin*,[15] *lovastatin*,[16] and *pravastatin*.[16,17] A literature review concluded that the statins do not interact with ciclosporin to a clinically relevant degree. However, given the narrow therapeutic range of ciclosporin, the increase in systemic exposure to statins, and reports of rhabdomyolysis when used together, the authors advise that ciclosporin levels be monitored when starting statin therapy, and that lower doses of statins be used.[18] For the effects of ciclosporin on plasma levels of statins and reports of rhabdomyolysis, see Immunosuppressants, under Interactions of Simvastatin, p.1393.

1. Gallego C, *et al.* Interaction between probucol and cyclosporine in renal transplant patients. *Ann Pharmacother* 1994; **28:** 940–3.
2. Hirai M, *et al.* Elevated blood concentrations of cyclosporine and kidney failure after bezafibrate in renal graft recipient. *Ann Pharmacother* 1996; **30:** 883–4.
3. Barbir M, *et al.* Maxepa versus bezafibrate in hyperlipidemic cardiac transplant recipients. *Am J Cardiol* 1992; **70:** 1596–1601.
4. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; **341:** 371.
5. Jespersen B, Tvedegaard E. Bezafibrate induced reduction of renal function in a renal transplant recipient. *Nephrol Dial Transplant* 1995; **10:** 702–3.
6. Boissonnat P, *et al.* The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. *Transplantation* 1994; **58:** 245–7.
7. de Lorgeril M, *et al.* Pharmacokinetics of cyclosporine in hyperlipidaemic long-term survivors of heart transplantation: lack of interaction with the lipid-lowering agent, fenofibrate. *Eur J Clin Pharmacol* 1992; **43:** 161–5.
8. Fehrman-Ekholm I, *et al.* Decreased cyclosporine levels during gemfibrozil treatment of hyperlipidemia after kidney transplantation. *Nephron* 1996; **72:** 483.
9. Pisanti N, *et al.* Lack of effect of gemfibrozil on cyclosporine blood concentrations in kidney-transplanted patients. *Am J Nephrol* 1998; **18:** 199–203.
10. Akhlaghi F, *et al.* Effect of simvastatin on cyclosporine unbound fraction and apparent blood clearance in heart transplant recipients. *Br J Clin Pharmacol* 1997; **44:** 537–42.
11. Renders L, *et al.* Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. *Nephrol Dial Transplant* 2001; **16:** 141–6.
12. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; **1:** 382–6.
13. Taylor PJ, *et al.* Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. *Ann Pharmacother* 2004; **38:** 205–8.
14. Mück W, *et al.* Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients. *Clin Pharmacol Ther* 1999; **65:** 251–61.
15. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996; **62:** 1559–64.
16. Olbricht C, *et al.* Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997; **62:** 311–21.
17. Regazzi MB, *et al.* Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc* 1993; **25:** 2732–4.
18. Åsberg A. Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients. *Drugs* 2003; **63:** 367–78.

Colchicine. Use of ciclosporin with colchicine may result in myopathy or rhabdomyolysis—see Effects on Skeletal Muscle, under Adverse Effects, above. For reports of adverse effects and increased serum-ciclosporin concentrations when given with colchicine, see also p.556.

Corticosteroids. It has been suggested that use of ciclosporin with corticosteroids increases plasma concentrations of both drugs, but not all studies support this—see Immunosuppressants, p.1495.

Gastrointestinal drugs. Giving *cisapride*[1] or *metoclopramide*[2] to renal transplant recipients receiving ciclosporin has been reported to increase peak ciclosporin concentrations and increase the speed of absorption. *Cimetidine*,[3,4] *ranitidine*,[3] or *famotidine*,[4] do not appear to affect ciclosporin pharmacokinetics. A literature review[5] noted that although there are reports of cimetidine influencing peak concentrations of ciclosporin, there is no support for a pharmacokinetic interaction. A pharmacodynamic interaction between ciclosporin and histamine H_2-receptor antagonists, resulting in a potentiation of nephrotoxicity, is also unlikely.

1. Finet L, *et al.* Effects of cisapride on the intestinal absorption of cyclosporine in renal transplant recipients. *Gastroenterology* 1991; **100:** A209.
2. Wadhwa NK, *et al.* The effect of oral metoclopramide on the absorption of cyclosporine. *Transplant Proc* 1987; **19:** 1730–3.
3. Barri YM, *et al.* Cimetidine or ranitidine in renal transplant patients receiving cyclosporine. *Clin Transplant* 1996; **10:** 34–8.
4. Shaefer MS, *et al.* Evaluation of the pharmacokinetic interaction between cimetidine or famotidine and cyclosporine in healthy men. *Ann Pharmacother* 1995; **29:** 1088–91.
5. Lewis SM, McCloskey WW. Potentiation of nephrotoxicity by H -antagonists in patients receiving cyclosporine. *Ann Pharmacother* 1997; **31:** 363–5.

Grapefruit juice. Grapefruit juice increases the bioavailability of oral ciclosporin,[1-4] including the microemulsion formulation,[5] leading to marked increases in blood-ciclosporin concentrations; intravenous ciclosporin is unaffected. The effect appears to be due to inhibition of cytochrome P450 enzymes in the gut wall by substances present in grapefruit juice,[3] resulting in transiently reduced ciclosporin metabolism. Although it has been suggested that the effect might be used similarly to that of calcium-channel blockers or ketoconazole in reducing the required dose of ciclosporin,[2] others have pointed out that grapefruit juice is not standardised and its effects are variable.[6]

Pomelo juice has also reportedly increased ciclosporin bioavailability; pomelo is a citrus fruit closely related to grapefruit.[7]

1. Proppe DG, *et al.* Influence of chronic ingestion of grapefruit juice on steady-state blood concentrations of cyclosporine A in renal transplant patients with stable graft function. *Br J Clin Pharmacol* 1995; **39:** 337–8.
2. Yee GC, *et al.* Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; **345:** 955–6.
3. Hollander AAMJ, *et al.* The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients. *Clin Pharmacol Ther* 1995; **57:** 318–24.
4. Ducharme MP, *et al.* Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. *Clin Pharmacol Ther* 1995; **57:** 485–91.
5. Ku Y-M, *et al.* Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter? *J Clin Pharmacol* 1998; **38:** 959–65.
6. Johnston A, Holt DW. Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; **346:** 122–3.
7. Grenier J, *et al.* Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans. *Clin Pharmacol Ther* 2006; **79:** 255–62.

Hypoglycaemic drugs. Use of *glibenclamide* with ciclosporin in 6 patients was associated with a mean 57% increase in the steady-state plasma concentration of ciclosporin, suggesting that dosage adjustment may be necessary when both drugs are given.[1]

Troglitazone decreased ciclosporin-blood concentrations by 32%, necessitating an increase in ciclosporin dosage.[2]

For the effect of ciclosporin on *repaglinide*, see under Interactions of Repaglinide, p.458.

1. Islam SI, *et al.* Possible interaction between cyclosporine and glibenclamide in posttransplant diabetic patients. *Ther Drug Monit* 1996; **18:** 624–6.
2. Burgess SJ, *et al.* Effect of troglitazone on cyclosporine whole blood levels. *Transplantation* 1998; **66:** 272–3.

Immunosuppressants. There has been a report of altered ciclosporin requirements in paediatric renal graft patients treated with *basiliximab*,[1] but others have failed to note such an effect,[2] and whether an interaction exists is unclear.

Treatment of acute rejection of kidney grafts in 10 patients using *muromonab-CD3* resulted in increases in mean trough ciclosporin concentrations, despite a reduction in ciclosporin dosage.[3] Once muromonab-CD3 was withdrawn the dosage of ciclosporin had to be increased again to provide adequate concentrations. In a retrospective study[4] of renal transplant recipients given ciclosporin and either muromonab-CD3 or antilymphocyte immunoglobulin, ciclosporin trough concentrations were found to be raised on day 5 postoperatively in the patients receiving muromonab-CD3. Although no differences were found in trough concentrations on days 7 and 10, the doses of ciclosporin had by then been adjusted based on the levels obtained on day 5.

For the effects of ciclosporin on the pharmacokinetics of *everolimus*, *mycophenolate mofetil*, and *sirolimus*, see p.1834, p.1837, and p.1841 respectively.

Tacrolimus inhibits ciclosporin metabolism *in vitro*[5] but did not alter the pharmacokinetics of intravenous ciclosporin in 7 liver transplant patients.[6] However, there is a possibility of increased nephrotoxicity when the drugs are used together, so licensed product information contraindicates such use.

1. Strehlau J, *et al.* Interleukin-2 receptor antibody-induced alterations of ciclosporin dose requirements in paediatric transplant recipients. *Lancet* 2000; **356:** 1327–8.
2. Vester U, *et al.* Basiliximab in paediatric liver-transplant recipients. *Lancet* 2001; **357:** 388–9.
3. Vrahnos D, *et al.* Cyclosporin levels during OKT3 treatment of acute renal allograft rejection. *Pharmacotherapy* 1991; **11:** 278.
4. Vasquez EM, Pollak R. OKT3 therapy increases cyclosporine blood levels. *Clin Transplant* 1997; **11:** 38–41.
5. Venkataramanan R, *et al.* Pharmacokinetics of FK 506 in transplant patients. *Transplant Proc* 1991; **23:** 2736–40.
6. Jain AB, *et al.* Pharmacokinetics of cyclosporine and nephrotoxicity in orthotopic liver transplant patients rescued with FK 506. *Transplant Proc* 1991; **23:** 2777–9.

Methoxsalen. In a pharmacokinetic study, a single oral dose of methoxsalen significantly increased the oral bioavailability of ciclosporin.[1]

1. Rheeders M, *et al.* Drug-drug interaction after single oral doses of the furanocoumarin methoxsalen and cyclosporine. *J Clin Pharmacol* 2006; **46:** 768–75.

Methylphenidate. Methylphenidate led to an increase in ciclosporin concentrations in a 10-year-old African American boy, necessitating reduction of the ciclosporin dose.[1] The patient had previously had to stop bupropion because of decreased ciclosporin concentrations.

1. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; **11:** 193–8.

NSAIDs. Raised serum-ciclosporin trough concentrations, together with small increases in serum creatinine and BUN concentrations, followed the use of *sulindac* in a previously-stabilised renal graft recipient taking an immunosuppressive regimen including ciclosporin.[1] Increased renal impairment was seen when sulindac or *naproxen* were added to ciclosporin therapy in patients with rheumatoid arthritis.[2] Nephrotoxicity, in the absence of significantly raised blood-ciclosporin concentrations, has been reported in other patients given *diclofenac* with ciclosporin.[3] Ciclosporin may also increase plasma-diclofenac concentrations, see p.45. In general, because of the known potential of NSAIDs to adversely affect renal function, careful monitoring of renal function is advised if these drugs are added to ciclosporin therapy or their dosages altered.

1. Sesin GP, *et al.* Sulindac-induced elevation of serum cyclosporine concentration. *Clin Pharm* 1989; **8:** 445–6.
2. Altman RD, *et al.* Interaction of cyclosporine A and nonsteroidal anti-inflammatory drugs on renal function in patients with rheumatoid arthritis. *Am J Med* 1992; **93:** 396–402.
3. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; **337:** 252.

Octreotide. A marked reduction in ciclosporin serum concentrations was seen in 10 diabetic patients with pancreatic transplants when octreotide was also given;[1] it was suggested that if these 2 drugs are used together the oral dosage of ciclosporin needs to be increased on average by 50%.

1. Landgraf R, *et al.* Effect of somatostatin analogue (SMS 201-995) on cyclosporine levels. *Transplantation* 1987; **44:** 724–5.

Quercetin. In a small study in healthy males, pre-treatment with the flavonoid quercetin significantly increased the peak concentration and bioavailability of ciclosporin.[1]

1. Choi JS, *et al.* Effect of quercetin on the pharmacokinetics of oral cyclosporine. *Am J Health-Syst Pharm* 2004; **61:** 2406–9.

Retinoids. After a report of increased whole-blood ciclosporin concentrations and nephrotoxicity in a patient given *etretinate* with ciclosporin, *in-vitro* results indicated that etretinate inhibited hepatic microsomal metabolism of ciclosporin, as did *acitretin* and *isotretinoin*.[1] However, a study failed to find evidence of such an interaction *in vitro*.[2]

1. Shah IA, *et al.* The effects of retinoids and terbinafine on the human hepatic microsomal metabolism of cyclosporin. *Br J Dermatol* 1993; **129:** 395–8.
2. Webber IR, Back DJ. Effect of etretinate on cyclosporin metabolism in vitro. *Br J Dermatol* 1993; **128:** 42–4.

Sex hormones. Raised ciclosporin concentrations in blood have been seen when therapy with *danazol*,[1] *methyltestosterone*,[2] or *norethisterone*[1] was given with ciclosporin, and clinical evidence of both nephrotoxicity[1,2] and hepatotoxicity[2] has been seen. Severe hepatotoxicity and raised plasma-ciclosporin trough values also resulted when an oral contraceptive containing *levonorgestrel* and *ethinylestradiol* was taken by a woman receiving ciclosporin;[3] she had taken the same contraceptive before beginning ciclosporin without ill-effects.

1. Ross WB, *et al.* Cyclosporin interaction with danazol and norethisterone. *Lancet* 1986; **i:** 330.
2. Møller BB, Ekelund B. Toxicity of cyclosporine during treatment with androgens. *N Engl J Med* 1985; **313:** 1416.
3. Deray G, *et al.* Oral contraceptive interaction with cyclosporin. *Lancet* 1987; **i:** 158.

Ursodeoxycholic acid. In a heart transplant patient with short bowel syndrome, ursodeoxycholic acid increased the trough concentrations of ciclosporin by enhancing its absorption.[1] In an attempt to determine whether this interaction would aid the attainment of therapeutic ciclosporin concentrations after heart transplantation, a patient with a jejunoileal bypass was given ciclosporin both with and without ursodeoxycholic acid; no difference was noted in the bioavailability of ciclosporin.[2] Small studies in liver transplant recipients found no alteration in ciclosporin pharmacokinetics when given single doses of ursodeoxycholic acid,[3] nor any difference in ciclosporin requirements between patients given ursodeoxycholic acid and those given placebo.[4] Another study in 12 liver transplant patients, 6 of whom had cholestatic liver dysfunction, found that ursodeoxycholic acid increased the rate of absorption of ciclosporin, but that peak concentrations and bioavailability did not change significantly.[5] In a study using microemulsifying ciclosporin in liver transplant recipients, ursodeoxycholic acid reduced the absorption rate and bioavailability of ciclosporin in 9 patients without cholestasis, but increased absorption rate and bioavailability in 3 cholestatic patients.[6] UK licensed product information for the microemulsifying formulation states that ursodeoxycholic acid increases ciclosporin concentrations.

1. Gutzler F, *et al.* Ursodeoxycholic acid enhances the absorption of cyclosporine in a heart transplant patient with short bowel syndrome. *Transplant Proc* 1992; **24:** 2620–1.
2. Kino KJ, Wittkowsky AK. Influence of bile acid replacement on cyclosporine absorption in a patient with jejunoileal bypass. *Pharmacotherapy* 1995; **15:** 350–2.
3. Maboundou CW, *et al.* A single dose of ursodiol does not affect cyclosporine absorption in liver transplant patients. *Eur J Clin Pharmacol* 1996; **50:** 335–7.
4. Söderdahl G, *et al.* Ursodeoxycholic acid increased bile flow and affects bile composition in the early postoperative phase following liver transplantation. *Transpl Int* 1998; **11** (suppl): S231–S238.
5. Al-Quaiz MN, *et al.* Variable effect of ursodeoxycholic acid on cyclosporin absorption after orthotopic liver transplantation. *Transpl Int* 1994; **7:** 190–4.
6. Caroli-Bosc F-X, *et al.* Ursodeoxycholic acid modulates cyclosporin A oral absorption in liver transplant recipients. *Fundam Clin Pharmacol* 2000; **14:** 601–9.

Vaccines. Efficacy of immunoprophylaxis may be expected to be reduced during ciclosporin therapy, and use of live virus vaccines, in particular, is contra-indicated in immunocompromised patients;[1] there has also been concern that vaccine antigens given during ciclosporin therapy might induce tolerance and result in increased rather than decreased susceptibility to diseases.

1. Grabenstein JD, Baker JR. Comment: cyclosporine and vaccination. *Drug Intell Clin Pharm* 1985; **19:** 679–80.

Vitamins. For reference to increased absorption of ciclosporin when given with a water-soluble macrogol derivative of *vitamin E*, see Absorption, under Pharmacokinetics, below.

Pharmacokinetics

The pharmacokinetics of ciclosporin are variable and difficult to determine. Results vary depending on the assay used, and values obtained by different methods are not strictly comparable.

Absorption of conventional formulations of ciclosporin from the gastrointestinal tract is variable and incomplete. An oral microemulsifying formulation with improved absorption characteristics is available and is more rapidly and completely absorbed, with peak concentrations achieved about 1.5 to 2 hours after a dose.

Ciclosporin is widely distributed throughout the body. Distribution in the blood is concentration-dependent, with between 41 and 58% in erythrocytes and 10 to 20% in leucocytes; the remainder is found in plasma, about 90% protein-bound, mostly to lipoprotein. Because of distribution into blood cells whole blood concentrations are higher than, and not comparable with, plasma concentrations; where peak plasma concentrations are reported to be about 1 nanogram/mL (by specific HPLC assay) for each mg of oral ciclosporin, whole blood concentrations for each mg range from about 1.4 to 2.7 nanograms/mL. Ciclosporin is reported to cross the placenta, and to be distributed into breast milk.

Clearance from the blood is biphasic. The terminal elimination half-life of an oral dose is reported to range from about 5 to 20 hours; clearance in children is more rapid.

Ciclosporin is extensively metabolised in the liver and primarily excreted in faeces via the bile. About 6% of a dose is reported to be excreted in urine, less than 0.1% unchanged.

Absorption. Ingestion of conventional *oral* formulations of ciclosporin with food may increase its bioavailability, although the effect only appears to be significant when the meal is high in fat;[1] ingestion with food and added bile acids may also increase absorption moderately.[2] A micelle-forming macrogol derivative of vitamin E (tocofersolan) has also been reported to markedly increase ciclosporin absorption.[3,4]

Because of the problems of variable oral absorption, an oral microemulsifying formulation has been developed that offers greatly improved and more predictable bioavailability,[5-8] particularly in liver transplant patients with impaired bile flow.[5] It should be noted that the formulation of this product in fact includes a vitamin E compound.

However, a study[9] has suggested that contrary to previous assumptions, conventional formulations of ciclosporin are quite well absorbed, and that the low bioavailability is due to extensive cytochrome-mediated metabolism in the gut wall (see also Metabolism, below). If this were the case, the improved bioavailability seen with the microemulsifying formulation is presumably less to do with improved absorption than with protection from such metabolism.

Very little drug is absorbed after application to the *eye*; ciclosporin accumulates on the ocular surface and cornea, achieving concentrations considered suitable for local immunomodulation. Corneal concentrations are affected by the choice of vehicle, but intra-ocular penetration is low. Little or no ocular metabolism is considered to occur in humans.[10]

1. Gupta SK, *et al.* Effect of food on the pharmacokinetics of cyclosporine in healthy subjects following oral and intravenous administration. *J Clin Pharmacol* 1990; **30:** 643–53.
2. Lindholm A, *et al.* The effect of food and bile acid administration on the relative bioavailability of cyclosporin. *Br J Clin Pharmacol* 1990; **29:** 541–8.
3. Sokol RJ, *et al.* Improvement of cyclosporin absorption in children after liver transplantation by means of water-soluble vitamin E. *Lancet* 1991; **338:** 212–15.
4. Chang T, *et al.* The effect of water-soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 1996; **59:** 297–303.
5. Trull AK, *et al.* Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion. *Br J Clin Pharmacol* 1995; **39:** 627–31.
6. van den Borne BEEM, *et al.* Relative bioavailability of a new oral form of cyclosporin A in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1995; **39:** 172–5.
7. Friman S, Bäckman L. A new microemulsion formulation of cyclosporin: pharmacokinetic and clinical features. *Clin Pharmacokinet* 1996; **30:** 181–93.

8. Schädeli F, *et al.* Population pharmacokinetic model to predict steady-state exposure to once-daily cyclosporin microemulsion in renal transplant recipients. *Clin Pharmacokinet* 2002; **41:** 59–69.
9. Wu C-Y, *et al.* Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 492–7.
10. Tang-Liu DD-S, Acheampong A. Ocular pharmacokinetics and safety of ciclosporin, a novel topical treatment for dry eye. *Clin Pharmacokinet* 2005; **44:** 247–61.

Distribution. The distribution characteristics of ciclosporin are clinically important; binding in blood and plasma is of importance in determining immunosuppressive activity after organ transplantation.[1] The unbound concentration of ciclosporin may have a closer association with both renal and cardiac allograft rejection than the total (bound plus unbound) concentration.

1. Akhlaghi F, Trull AK. Distribution of cyclosporin in organ transplant recipients. *Clin Pharmacokinet* 2002; **41:** 615–37.

Ethnicity and sex. Gender-dependent racial differences in the pharmacokinetics of ciclosporin have been suggested.[1] African American women showed larger clearances of intravenous and oral ciclosporin (microemulsifying formulation) than African American men, and white women. There were no significant differences in clearance between men of different ethnic origin, or between white men and women. Overall bioavailability was also lower in African Americans compared with white subjects. However, other studies[2,3] found no differences in relative bioavailability between races.

Differences in hepatic cytochrome P450 isoenzyme CYP3A and intestinal P-glycoprotein activity may account for interindividual variability in ciclosporin disposition, and it has been speculated that polymorphic CYP3A5 expression might contribute to interracial differences.[4] However, most studies[5,6] have found little or no association between CYP3A4 or CYP3A5 genotype and ciclosporin pharmacokinetics, although one study found that patients with a CYP3A4 variant allele had a small but significantly higher oral clearance of ciclosporin.[7] However, black and Asian transplant recipients were found to have a reduced oral clearance in this study, independent of their CYP3A genotype, and in apparent contradiction to the literature. The authors commented that most of the studies had been conducted with the older oil-based products, and use of the microemulsifying formulation had not been associated with significant differences in ciclosporin pharmacokinetics between ethnic groups.[7] Genotyping of transplant recipients was considered unlikely to be of use in optimising ciclosporin dosage in clinical practice.[6,7]

1. Min DI, *et al.* Gender-dependent racial difference in disposition of cyclosporine among healthy African American and white volunteers. *Clin Pharmacol Ther* 2000; **68:** 478–86.
2. Stein CM, *et al.* Cyclosporine pharmacokinetics and pharmacodynamics in African American and white subjects. *Clin Pharmacol Ther* 2001; **69:** 317–23.
3. Pollak R, *et al.* Cyclosporine bioavailability of Neoral and Sandimmune in white and black de novo renal transplant recipients. *Ther Drug Monit* 1999; **21:** 661–3.
4. Yates CR, *et al.* The effect of CYP3A5 and MDR1 polymorphic expression on cyclosporine oral disposition in renal transplant patients. *J Clin Pharmacol* 2003; **43:** 555–64.
5. Hesselink DA, *et al.* Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; **74:** 245–54.
6. Anglicheau D, *et al.* CYP3A5 and MDR1 genetic polymorphisms and cyclosporine pharmacokinetics after renal transplantation. *Clin Pharmacol Ther* 2004; **75:** 422–33.
7. Hesselink DA, *et al.* Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. *Clin Pharmacol Ther* 2004; **76:** 545–56.

Metabolism. *In vitro*[1] and *in vivo*[2-4] evidence indicates that the low oral bioavailability of ciclosporin is due to first-pass metabolism in the gastrointestinal tract rather than the liver.

1. Tjia JF, *et al.* Cyclosporin metabolism by the gastrointestinal mucosa. *Br J Clin Pharmacol* 1991; **31:** 344–6.
2. Kolars JC, *et al.* First-pass metabolism of cyclosporin by the gut. *Lancet* 1991; **338:** 1488–90.
3. Hoppu K, *et al.* Evidence for pre-hepatic metabolism of oral cyclosporine in children. *Br J Clin Pharmacol* 1991; **32:** 477–81.
4. Wu C-Y, *et al.* Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 492–7.

Therapeutic drug monitoring. Considerable debate has attended the necessity for therapeutic monitoring of ciclosporin concentrations and also on the questions of which assay methods to use and whether to measure drug concentrations in whole blood or plasma.

Before the introduction of specific monoclonal radio-immunoassay the high performance liquid chromatography (HPLC) assay for ciclosporin had the advantage of being specific for the parent compound, and some suggested it to be the method of choice.[1,2] However, it is a more complex procedure, is not universally available, and is slower to perform than radio-immunoassay.[1,3-5] Specific monoclonal radio-immunoassays are now widely available; a comparative study of specific and non-specific radio-immunoassays, HPLC, and polyclonal fluorescence polarisation immunoassay (FPIA) found that the specific assays, used on whole blood samples, gave the best correlation with clinical events.[6]

Because the distribution of ciclosporin between blood cells and plasma is temperature-dependent,[7] plasma concentrations may be twice as high at 37° as at 21°. The temperature at which samples are stored and processed may therefore considerably influence results. In consequence, measurement of drug concentrations in whole blood is to be preferred.[1,3,4,8] However, many, particularly early, clinical studies have given plasma or serum concentrations, which makes comparison of literature data difficult. This problem is compounded by a considerable degree of variation between laboratories,[9,10] even when the same technique is used,[10] and by circadian variations in ciclosporin metabolism which mean that samples should be taken at the same time of day.[11] Since ciclosporin concentrations appear to be generally higher in the morning than the evening, some have suggested that the morning might be the best time for therapeutic drug monitoring.[12]

Because of the variability in results caused by difficulties in monitoring it has proved difficult to determine precisely the ciclosporin concentrations associated with therapeutic benefit and toxicity,[1,3-5] and it has been suggested that measurement of the therapeutic concentrations is unnecessary (provided the patient's clinical condition and renal function are monitored) when low-dose ciclosporin is being given (for example, in psoriasis).[13] However, others consider that it is always critical that ciclosporin blood trough concentrations are regularly measured,[14] in addition to other monitoring. A study in paediatric haematopoietic stem cell transplant recipients found a significant relationship between ciclosporin blood trough concentrations and the severity of acute graft-versus-host disease (GVHD); with lower trough concentrations, GVHD was more severe during the early post-transplantation period.[15] It has been suggested[16] that trough ciclosporin concentrations (C_0), measured by a specific method in whole blood, should not be less than 150 nanograms/mL during the first month after renal transplantation, although lower concentrations are subsequently acceptable; trough concentrations of 250 to 300 nanograms/mL are recommended in the 3 months after liver transplantation.

Other methods of monitoring ciclosporin therapy include monitoring the area under the concentration-time curve (AUC), limited sampling strategies, and Bayesian forecasting.[14,17-21] However, these methods also have limitations, often requiring several samples at inconvenient times for the patient, and can involve complex calculations.

Maximum calcineurin inhibition occurs in the first 1 to 2 hours after ciclosporin dosing, and it was hypothesised that AUC in the first 4 hours after a dose, or the blood concentration at 2 hours after a dose (C_2) might better predict immunosuppressive efficacy than trough concentrations (C_0) or AUC over 12 hours.[22] A large study[23] in liver transplant recipients found that measuring C_2 was superior to C_0 monitoring, resulting in a reduction of the incidence and severity of rejection. It was pointed out that these results could not necessarily be extrapolated to different transplant groups and that analysis when sampling high ciclosporin concentrations needed to be extremely accurate.[24] Data from lung transplant recipients found measurements of C_0 but not C_2 or C_6 to be associated with the risk of acute lung allograft rejection.[25] However, there was some suggestion that C_2 predicted rejection better than C_0 in renal[26] and heart[27] transplant recipients also. In paediatric renal transplant recipients,[22] C_2 monitoring was found to be a better predictor of ciclosporin exposure during the absorption phase than C_0.

An international consensus group considered C_2 to be the best time-point predictor of exposure to ciclosporin during the first 4 hours postdose.[28] This was based on data from studies in adult renal, liver, heart, and lung transplant recipients, as well as in paediatric renal and liver transplant patients; patients had received microemulsifying ciclosporin. C_2 monitoring was also able to identify high, intermediate, or low absorbers of ciclosporin. Additional monitoring beyond the C_2 time point was considered necessary in low absorbers to identify true low absorbers from slow absorbers. Target C_2 concentrations at various times post-transplantation were recommended for adult renal and liver transplant patients receiving ciclosporin microemulsion.

For adult renal transplant recipients:

- 1 month post-transplant: C_2 1.5 to 2 micrograms/mL (this should be achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 2 months post-transplant: C_2 1.5 micrograms/mL;
- 3 months post-transplant: C_2 1.3 micrograms/mL;
- 4 to 6 months post-transplant: C_2 1.1 micrograms/mL;
- 7 to 12 months post-transplant: C_2 0.9 micrograms/mL;
- 12 months post-transplant or more: C_2 0.8 micrograms/mL

For adult liver transplant recipients:

- 0 to 6 months post-transplant: C_2 1 micrograms/mL (initially achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 6 to 12 months post-transplant: C_2 0.8 micrograms/mL;
- more than 12 months post-transplant: C_2 0.6 micrograms/mL

Data on long-term clinical benefit of monitoring in terms of rejection prophylaxis and overall safety profile were lacking, and target levels were not established for other transplant groups. A 15-minute 'window of opportunity' before and after the 2-hour time point was considered to provide an acceptable (10%) margin of error, during which time the C_2 sample could be taken.[28] Findings from a 3-year prospective study of C_2 monitoring in stable renal transplant recipients suggested that this method offered clinical benefits in terms of control of hypertension and dyslipidaemia, and protection against chronic renal allograft dysfunction.[29] Australasian guidelines[30] stated that definitive target ciclosporin C_2 concentrations in various organ types or times post-transplant remained to be finalised, and that further evidence supporting C_2 monitoring was needed before C_0 monitoring could be definitively replaced. They recommended that samples clearly indicate which sampling time had been used, that concentrations be preferably reported in units of micrograms/litre, and that each report state the assay method used for analysis. Monitoring practices based on one formulation should not be applied to another formulation unless there was clear evidence of bioequivalence in patients. A subsequent study of C_2 monitoring in heart transplant patients[31] found that higher C_2 concentrations were associated with less episodes of acute cellular rejection. However, in renal transplant patients,[32,33] C_2 concentrations did not predict rejection. A multicentred, retrospective French study[34] determined that, in renal transplant patients monitored on C_0, most patients had C_2 concentrations below the target ranges recommended by the international consensus group; the authors suggested that lower C_2 ranges might be targeted in the early- and long-term post-transplantation periods for those given interleukin-2 receptor antibodies, and that optimal therapeutic windows for ciclosporin monitoring based on C_2 needed more definition. A review of limited sampling strategies in liver transplant patients[35] concluded that, while C_2 monitoring might be better than C_0 monitoring to improve acute rejection rate in the early post-transplantation period, the evidence was not strong, and that further well-designed studies were needed. A review of ciclosporin monitoring after allogeneic stem cell transplantation[36] acknowledged that C_2 monitoring might be preferable to trough concentration monitoring in these patients, but also stated that optimal strategies remained to be defined and that randomised studies were needed.

There has been concern that differences in blood ciclosporin results from various assay systems would necessitate assay-specific target ranges for monitoring. Most transplant centres have developed target ciclosporin ranges that reflect the methodology in use. A study[37] of 5 different assay methods, including radio-immunoassay, HPLC, and FPIA, found that when measuring C_0, this would indeed be the case, but that with C_2 monitoring, differences in the results from the various assay methods were not statistically significant, and were unlikely to be of clinical significance. Different proportions of parent ciclosporin and metabolites were thought to be the reason for this disparity at the two time points. The authors considered that a single target therapeutic range could be adopted when monitoring C_2 concentrations, regardless of the assay method used.

1. Ptachcinski RJ, *et al.* Cyclosporine concentration determinations for monitoring and pharmacokinetic studies. *J Clin Pharmacol* 1986; **26:** 358–66.
2. Varghese Z, *et al.* How to measure cyclosporin. *Lancet* 1984; **i:** 1407–8.
3. Faynor SM, *et al.* Therapeutic drug monitoring of cyclosporine. *Mayo Clin Proc* 1984; **59:** 571–2.
4. Burkle WS. Cyclosporine pharmacokinetics and blood level monitoring. *Drug Intell Clin Pharm* 1985; **19:** 101–5.
5. Rodighiero V. Therapeutic drug monitoring of cyclosporin: practical applications and limitations. *Clin Pharmacokinet* 1989; **16:** 27–37.
6. Lindholm A, *et al.* A prospective study of cyclosporine concentration in relation to its therapeutic effect and toxicity after renal transplantation. *Br J Clin Pharmacol* 1990; **30:** 443–52.
7. Dieperink H. Temperature dependency of cyclosporin plasma levels. *Lancet* 1983; **i:** 416.
8. Bandini G, *et al.* Measuring cyclosporin in plasma. *Lancet* 1983; **i:** 762.
9. Moyer TP. Measurement of cyclosporine: a challenge to the professional laboratory organizations. *Ther Drug Monit* 1985; **7:** 123–4.
10. Johnston A, *et al.* The United Kingdom Cyclosporin Quality Assessment Scheme. *Ther Drug Monit* 1986; **8:** 200–204.
11. Venkataramanan R, *et al.* Diurnal variation in cyclosporine kinetics. *Ther Drug Monit* 1986; **8:** 380–1.
12. Baraldo M, Furlanut M. Chronopharmacokinetics of ciclosporin and tacrolimus. *Clin Pharmacokinet* 2006; **45:** 775–88.
13. Heydendael VMR, *et al.* Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; **147:** 122–9.
14. Dumont RJ, Ensom MHH. Methods for clinical monitoring of cyclosporin in transplant patients. *Clin Pharmacokinet* 2000; **38:** 427–47.
15. Martin P, *et al.* Relationship between CsA trough blood concentration and severity of acute graft-versus-host disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. *Bone Marrow Transplant* 2003; **32:** 777–84.
16. Lindholm A. Therapeutic monitoring of cyclosporin—an update. *Eur J Clin Pharmacol* 1991; **41:** 273–83.
17. David O, Johnston A. Limited sampling strategies. *Clin Pharmacokinet* 2000; **39:** 311–13.
18. Leger F, *et al.* Maximum A Posteriori Bayesian estimation of oral cyclosporin pharmacokinetics in patients with stable renal transplants. *Clin Pharmacokinet* 2002; **41:** 71–80.
19. Bourgoin H, *et al.* Bayesian estimation of cyclosporin exposure for routine therapeutic drug monitoring in kidney transplant patients. *Br J Clin Pharmacol* 2005; **59:** 18–27.
20. Tokui K, *et al.* Dose adjustment strategy for oral microemulsion formulation of cyclosporine: population pharmacokinetics-based analysis in kidney transplant patients. *Ther Drug Monit* 2004; **26:** 287–94.

21. Saint-Marcoux F, *et al.* Patient characteristics influencing ciclosporin pharmacokinetics and accurate Bayesian estimation of ciclosporin exposure in heart, lung and kidney transplant patients. *Clin Pharmacokinet* 2006; **45:** 905–22.
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23. Levy G, *et al.* Improved clinical outcomes for liver transplant recipients using cyclosporine monitoring based on 2-hr post-dose levels (C). *Transplantation* 2002; **73:** 953–9.
24. Holt DW. Cyclosporine monitoring based on C sampling. *Transplantation* 2002; **73:** 840–1.
25. Trull A, *et al.* Randomized, trough blood cyclosporine concentration-controlled trial to compare the pharmacodynamics of Sandimmune and Neoral in de novo lung transplant recipients. *Ther Drug Monit* 1999; **21:** 17–26.
26. Pescovitz MD, *et al.* Two-hour post-dose cyclosporine level is a better predictor than trough level of acute rejection of renal allografts. *Clin Transplant* 2002; **16:** 378–82.
27. Solari SG, *et al.* Cyclosporine monitoring with 2-hour postdose levels in heart transplant recipients. *Ther Drug Monit* 2005; **27:** 417–21.
28. Levy G, *et al.* Patient management by Neoral C monitoring: an international consensus statement. *Transplantation* 2002; **73** (suppl): S12–S18.
29. Citterio F, *et al.* Results of a three-year prospective study of C monitoring in long-term renal transplant recipients receiving cyclosporine microemulsion. *Transplantation* 2005; **79:** 802–6.
30. Morris RG, *et al.* Cyclosporin monitoring in Australasia: 2002 update of consensus guidelines. *Ther Drug Monit* 2002; **24:** 677–88.
31. Delgado DH, *et al.* Monitoring of cyclosporine 2-hour post-dose levels in heart transplantation: improvement in clinical outcomes. *J Heart Lung Transplant* 2005; **24:** 1343–6.
32. Gotti E, *et al.* Blood cyclosporine level soon after kidney transplantation is a major determinant of rejection: insights from the Mycophenolate Steroid-Sparing Trial. *Transplant Proc* 2005; **37:** 2037–40.
33. Einecke G, *et al.* Limitations of C monitoring in renal transplant recipients. *Nephrol Dial Transplant* 2005; **20:** 1463–70.
34. Loichot C, *et al.* Cyclosporine monitoring in renal transplant recipients with induction therapy: C levels in patients monitored on C . *Fundam Clin Pharmacol* 2006; **20:** 91–6.
35. Marin JG, *et al.* Is C2 monitoring or another limited sampling strategy superior to C0 monitoring in improving clinical outcomes in adult liver transplant recipients? *Ther Drug Monit* 2006; **28:** 637–42.
36. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; **38:** 169–74.
37. Johnston A, *et al.* Monitoring cyclosporin in blood: between-assay differences at trough and 2 hours post-dose (C2). *Ther Drug Monit* 2003; **25:** 167–73.

Uses and Administration

Ciclosporin is a powerful immunosuppressant that appears to act specifically on lymphocytes, mainly helper T-cells. It forms a complex with the receptor protein cyclophilin; this complex binds to and inhibits the activation of calcineurin, an important step in the production of lymphokines, including interleukin-2, and results in a depression of cell-mediated immune response. Unlike cytotoxic immunosuppressants such as cyclophosphamide it has little effect on bone marrow.

Ciclosporin is used, usually with corticosteroids (and often with other immunosuppressants), in organ and tissue transplantation for the prophylaxis of graft rejection, or in the management of graft rejection in patients previously treated with other immunosuppressants. It is also used in severe forms of atopic dermatitis, psoriasis, or rheumatoid arthritis, usually when conventional therapy is ineffective or inappropriate, and is used in nephrotic syndrome.

Ciclosporin has been tried in other diseases considered to have an auto-immune component, as indicated by the cross-references given below; they include aplastic anaemia, asthma, Behçet's syndrome, chronic active hepatitis, multiple sclerosis, myasthenia gravis, sarcoidosis, scleritis or uveitis, scleroderma, and various skin disorders.

Ciclosporin is given orally as liquid-filled capsules or as an oily solution, which may be diluted with milk or fruit juice (not grapefruit) immediately before use to improve palatability. Microemulsifying formulations with improved bioavailability are available in a number of countries. When changing between preparations, the initial dose of the new formulation should be the same (mg for mg), and should subsequently be adjusted as necessary based on blood-ciclosporin concentrations, serum creatinine, and blood pressure monitoring. The daily dose of ciclosporin is taken in 2 divided doses, although the conventional formulation is sometimes given as a single daily dose.

In **organ transplantation** the usual initial oral dose of ciclosporin is 10 to 15 mg/kg daily, beginning 4 to 12 hours before transplantation, and continued for 1 to 2 weeks; lower initial doses may be given with other immunosuppressants (e.g. with corticosteroids or as part of 'triple' or 'quadruple' therapy). Dosage may subsequently be reduced gradually to a daily maintenance dose of 2 to 6 mg/kg.

Kidney function and blood pressure should be monitored regularly, as well as blood concentrations of ciclosporin (see Therapeutic Drug Monitoring, above), and dosage should be adjusted as necessary. Hepatic function should also be monitored.

Ciclosporin may also be given intravenously, at one-third of the oral dose, in patients in whom oral dosage is not feasible. It is given by slow intravenous infusion over 2 to 6 hours, the 5% concentrate being diluted 1:20 to 1:100 in sodium chloride 0.9% or glucose 5%, to give a 0.05 to 0.25% solution of ciclosporin. Because of the risk of anaphylactoid reactions, which have been attributed to the polyoxyl castor oil vehicle, patients should be transferred to oral therapy as soon as possible.

For the prevention of graft rejection in **bone marrow transplantation**, and prevention and treatment of graft-versus-host disease, an initial dose of 3 to 5 mg/kg daily by the intravenous route is recommended, starting the day before transplantation and continuing for up to 2 weeks until maintenance by mouth, in doses of 12.5 mg/kg daily can be instituted. If oral treatment is used to begin therapy the recommended dose is 12.5 to 15 mg/kg daily followed by 12.5 mg/kg daily for maintenance. The maintenance dose is continued for at least 3 to 6 months, then gradually reduced until ciclosporin is withdrawn altogether; this may take up to a year after transplantation.

Ciclosporin given by inhalation is under investigation for the prevention and treatment of graft rejection after lung transplantation in some countries.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

In the treatment of **psoriasis**, ciclosporin may be given in usual initial oral doses of 2.5 mg/kg daily (a maximum of 5 mg/kg daily is recommended in the UK and 4 mg/kg daily in the USA), in 2 divided doses, reduced once remission is achieved to the lowest effective maintenance dose. Treatment should be stopped if there is insufficient response to the maximum dose within 6 weeks. A similar dosage range may be given for a maximum of 8 weeks in the treatment of severe **atopic dermatitis**.

In **rheumatoid arthritis** oral ciclosporin may be given in initial daily doses of 2.5 mg/kg, divided into two doses, for a period of 6 or 8 weeks. If the clinical effect is insufficient dosage may then be gradually increased to a maximum of 4 mg/kg daily; if there is no response after 3 to 4 months, treatment should be stopped.

For **nephrotic syndrome** secondary to glomerular kidney disease (minimal change nephropathy, focal glomerulosclerosis, or membranous nephropathy) dosage of ciclosporin depends on age and renal function. To induce remission in patients with normal renal function 5 mg/kg daily may be given to adults, in 2 divided doses orally. In patients with renal impairment the initial dose should not exceed 2.5 mg/kg daily. Treatment may be stopped if there is no response after 3 months (or 6 months in patients with membranous nephropathy). In patients who do respond, maintenance doses should be gradually reduced to the minimum effective value.

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

Eye drops containing ciclosporin 0.05% are used in the management of **dry eye** associated with ocular inflammation. A topical emulsion of ciclosporin is under investigation for the treatment of vernal keratoconjunctivitis, a severe form of chronic allergic conjunctivitis.

Ciclosporin can inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, and has been given with antineoplastics to raise their intracellular concentrations. Nonimmunosuppressive ciclosporin analogues such as valspodar (p.2410) are also being investigated for their ability to reverse multidrug resistance.

Administration. It has been suggested that calculating doses in mg/kg may not be the best way to achieve the desired blood concentrations of ciclosporin.[1] (See also Therapeutic Drug Monitoring, above) Retrospective study of 1071 renal transplant recipients indicated that blood ciclosporin concentrations were not significantly correlated with patient weight, the best prediction of trough blood concentration being given by the formula:

$$\text{Blood concentration (nanograms/mL)} = \frac{\text{dose in mg/day}}{} \times (1.34 + 0.00011 \times \text{days after transplant} - 0.0049 \times \text{height in cm})$$

This formula appeared useful in predicting blood concentrations in prospective studies; from the seventh day after transplantation target trough concentrations could be expected to be about 0.3 times the daily ciclosporin dose in mg.

1. Bock HA, *et al.* Weight-independent dosing of cyclosporine—an alternative to the mg/kg doctrine. *Transplantation* 1994; **57:** 1484–9.

INHALATION. Aerosolised ciclosporin given by inhalation has proved effective[1,2] in the management of acute graft rejection in lung transplantation (p.1815). Doses were up to 300 mg daily via a nebuliser, in either propylene glycol or ethanol solvents.[3] Pulmonary delivery of ciclosporin has been reviewed.[3,4] A positive association between deposited aerosolised ciclosporin dose and improvement in lung function was found in 15 subjects treated over 2 years postoperatively.[5] In a case-control study,[6] aerosolised ciclosporin improved survival among lung transplant recipients with bronchiolitis obliterans. In a randomised controlled study, inhaled ciclosporin given prophylactically did not improve the rate of acute rejection, but it did improve chronic rejection-free survival and overall survival.[7]

A dry powder formulation of ciclosporin for inhalation use has been developed in order to overcome problems of local irritation with propylene glycol; feasibility and efficacy studies with this new formulation are needed.[8]

1. Keenan RJ, *et al.* Efficacy of inhaled cyclosporine in lung transplant recipients with refractory rejection: correlation of intragraft cytokine gene expression with pulmonary function and histologic characteristics. *Surgery* 1995; **118:** 385–91.
2. Iacono AT, *et al.* Dose-related reversal of acute lung rejection by aerosolized cyclosporine. *Am J Respir Crit Care Med* 1997; **155:** 1690–8.
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7. Iacono AT, *et al.* A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med* 2006; **354:** 141–50.
8. Zijlstra GS, *et al.* Characterization of a cyclosporine solid dispersion for inhalation. *AAPS J* 2007; **9:** E190–E199.

OCULAR. Topical ciclosporin, in strengths ranging from 0.05 to 2% has been shown to be effective[1,2] in the treatment of various ocular surface disorders, particularly dry eye (see below) and atopic keratoconjunctivitis. It has also been used for corneal ulcers, glaucoma (see below), as adjunctive therapy in corneal allograft rejection, and for the ocular manifestations of graft-versus-host disease.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

1. Tatlipinar S, Akpek EK. Topical ciclosporin in the treatment of ocular surface disorders. *Br J Ophthalmol* 2005; **89:** 1363–7.
2. Foulks GN. Topical cyclosporine for treatment of ocular surface disease. *Int Ophthalmol Clin* 2006; **46:** 105–22.

ORAL. The microemulsifying formulation of ciclosporin has been reviewed.[1,2] For discussion of the potential problems involved in converting from conventional to microemulsion oral formulations see under Precautions, above.

1. Noble S, Markham A. Cyclosporin: a review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral). *Drugs* 1995; **50:** 924–41.
2. Dunn CJ, *et al.* Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral) in organ transplantation. *Drugs* 2001; **61:** 1957–2016.

Administration in children. UK licensed product information states that, while experience with ciclosporin in children is limited, **transplant** patients from 3 months of age have received the drug at the same doses recommended for adults (see Uses and Administration, above). However, at doses above the recommended range, children seem to be more susceptible to fluid

retention, convulsions, and hypertension. These effects respond to dose reduction.

In contrast, US licensed product information states that, while data in children are lacking, transplant recipients as young as 6 months and 1 year have received the standard formulation and microemulsifying formulation, respectively, with no unusual adverse effects, and that children have generally required and tolerated higher doses of the standard formulation than those used in adults.

The *BNFC* advises to consult local treatment protocols for details of use in organ transplantation.

For the treatment of **psoriasis** and **atopic dermatitis** doses recommended by the *BNFC* for children from 1 month of age are the same as for adults (see Uses and Administration, above).

In the treatment of **nephrotic syndrome** UK licensed product information states that children may be given 6 mg/kg daily by mouth, in 2 divided doses, if renal function is normal. The dose should not exceed 2.5 mg/kg daily in patients with impaired renal function. The *BNFC* specifies use from 1 month of age.

Although ciclosporin is not licensed in the UK for use in **ulcerative colitis**, the *BNFC* recommends the following initial doses in refractory disease in children, which are then adjusted according to ciclosporin blood concentrations and response:

- orally in those aged 2 to 18 years: 2 mg/kg twice daily (maximum 5 mg/kg twice daily)
- by intravenous infusion in those aged 3 to 18 years: 0.5 to 1 mg/kg twice daily

Aplastic anaemia. Ciclosporin, usually combined with antilymphocyte immunoglobulin, is used in patients with aplastic anaemia when bone marrow transplantation is unsuitable (see p.1042).

Asthma. Ciclosporin is being considered as a potential treatment for some cases of refractory asthma (p.1108). A controlled study[1] in patients with chronic severe asthma requiring long-standing oral corticosteroid treatment found that addition of ciclosporin in an initial dose of 5 mg/kg daily to their regimen resulted in significant improvement in lung function and a reduced frequency of disease exacerbation, compared with placebo. The results were interesting because of the improvement in what had been considered 'irreversible' airflow obstruction. A subsequent study[2] from the same centre involving 39 patients with severe corticosteroid-dependent asthma found that low-dose ciclosporin by mouth (an initial dose of 5 mg/kg daily) permitted a reduction in the daily dosage of prednisolone, from a median of 10 to 3.5 mg daily. However, a systematic review[3] considered that, given the adverse effects of ciclosporin, any clinical benefit was debatable.

1. Alexander AG, *et al.* Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. *Lancet* 1992; **339:** 324–8.
2. Lock SH, *et al.* Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. *Am J Respir Crit Care Med* 1996; **153:** 509–14.
3. Evans DJ, *et al.* Cyclosporin as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).

Behçet's syndrome. Ciclosporin has been tried in Behçet's syndrome, see p.1499.

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

Corneal ulcer. Ciclosporin 1% eye drops, with lamellar keratoplasty, proved effective in treating Mooren's ulcer, a possibly auto-immune corneal disease that is difficult to manage and can lead to blindness.[1] Treatment with topical ciclosporin alone may also be useful[2] in patients with sterile corneal ulcers associated with rheumatoid disease.

1. Chen J, *et al.* Mooren's ulcer in China: a study of clinical characteristics and treatment. *Br J Ophthalmol* 2000; **84:** 1244–9.
2. Gottsch JD, Akpek EK. Topical cyclosporin stimulates neovascularization in resolving sterile rheumatoid central corneal ulcers. *Trans Am Ophthalmol Soc* 2000; **98:** 81–90.

Dermatomyositis. Ciclosporin may be of benefit in refractory dermatomyositis, see Polymyositis and Dermatomyositis, below.

Diabetes mellitus. Immunosuppressants have been used in attempts to prolong the so called 'honeymoon period' in recently diagnosed diabetics (p.431). Ciclosporin has apparently produced modest benefits in such a context,[1-3] but its overall value remains to be determined.

1. Bougneres PF, *et al.* Factors associated with early remission of type 1 diabetes in children treated with cyclosporine. *N Engl J Med* 1988; **318:** 663–70.
2. The Canadian-European Randomized Control Trial Group. Cyclosporin-induced remission of IDDM after early intervention: association of 1 yr of cyclosporin treatment with enhanced insulin secretion. *Diabetes* 1988; **37:** 1574–82.
3. Carel JC, *et al.* Cyclosporine delays but does not prevent clinical onset in glucose intolerant pre-type 1 diabetic children. *J Autoimmun* 1996; **9:** 739–45.

Diffuse parenchymal lung disease. There are reports of benefit from the use of ciclosporin in diffuse parenchymal lung disease (p.1502), although data are too limited to support its use.

Dry eye. Topical ciclosporin has been found to be beneficial[1,2] for keratoconjunctivitis sicca (dry eye—see p.2140). Further studies[3,4] found ciclosporin 0.05% and 0.1% to be the most appropriate formulations since no additional benefit was found with higher concentrations[3] and both were significantly better than placebo.[4]

Topical ciclosporin has also been reported to be beneficial for patients with dry eyes secondary to graft-versus-host disease.[5]

1. Laibovitz RA, *et al.* Pilot trial of cyclosporine 1% ophthalmic ointment in the treatment of keratoconjunctivitis sicca. *Cornea* 1993; **12:** 315–23.
2. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. *Ophthalmology* 2007; **114:** 76–9.
3. Stevenson D, *et al.* Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. *Ophthalmology* 2000; **107:** 967–74.
4. Sall K, *et al.* Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology* 2000; **107:** 631–9.
5. Lelli GJ, *et al.* Ophthalmic cyclosporine use in ocular GVHD. *Cornea* 2006; **25:** 635–8.

Eczema. Ciclosporin is effective in atopic eczema (atopic dermatitis),[1-3] where it is used as adjunctive therapy (see p.1579). It is generally reserved for short-term treatment (up to 8 weeks) in patients with severe disease unresponsive to all conventional therapies, although reports have described long-term use in adult patients.[4] It has also been suggested[5] that long-term remission is possible, even in those treated with short courses. Ciclosporin has been used for both short courses[6,7] and continuous therapy in children.[8] A systematic review and meta-analysis[9] that incorporated most of these studies concluded that the mean clinical improvement in disease severity after 6 to 8 weeks of ciclosporin treatment is about 55%; however, the true benefit may be somewhat lower due to publication bias. Higher initial doses of 4 to 5 mg/kg led to a more rapid response, and the mean benefit after 2 weeks at this dose was about 40%. In a small, open, crossover study,[10] the microemulsifying form was considered equivalent or superior in tolerability and efficacy when compared with the conventional formulation. Responses have also been reported in severe eczematisation associated with Darier's disease[11] (p.1578).

1. van Joost T, *et al.* Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. *Br J Dermatol* 1994; **130:** 634–40.
2. Munro CS, *et al.* Maintenance treatment with cyclosporin in atopic eczema. *Br J Dermatol* 1994; **130:** 376–80.
3. Granlund H, *et al.* Cyclosporin in atopic dermatitis: time to relapse and effect of intermittent therapy. *Br J Dermatol* 1995; **132:** 106–12.
4. Berth-Jones J, *et al.* Long-term efficacy and safety of cyclosporin in severe adult atopic dermatitis. *Br J Dermatol* 1997; **136:** 76–81.
5. Granlund H, *et al.* Long-term follow-up of eczema patients treated with cyclosporine. *Acta Derm Venereol (Stockh)* 1998; **78:** 40–3.
6. Zaki I, *et al.* Treatment of severe atopic dermatitis in childhood with cyclosporin. *Br J Dermatol* 1996; **135** (suppl 48): 21–4.
7. Berth-Jones J, *et al.* Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol* 1996; **34:** 1016–21.
8. Harper JI, *et al.* Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; **142:** 52–8.
9. Schmitt J, *et al.* Cyclosporin in the treatment of patients with atopic eczema—a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; **21:** 606–19.
10. Chawla M, *et al.* Comparison of the steady state pharmacokinetics of two formulations of cyclosporin in patients with atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 48): 9–14.
11. Shahidullah H, *et al.* Darier's disease: severe eczematization successfully treated with cyclosporin. *Br J Dermatol* 1994; **131:** 713–16.

Glaucoma. Topical ciclosporin has produced some encouraging results[1] when used as an adjunct to reduce formation of scar tissue and improve outcome of glaucoma filtering surgery. It has been suggested[2] that topical ciclosporin 0.5% may be substituted for topical corticosteroids in the treatment of postkeratoplasty glaucoma.

1. Turaçli E, *et al.* A comparative clinical trial of mitomycin C and cyclosporin A in trabeculectomy. *Eur J Ophthalmol* 1996; **6:** 398–401.
2. Perry HD, *et al.* Topical cyclosporin A in the management of postkeratoplasty glaucoma. *Cornea* 1997; **16:** 284–8.

Glomerular kidney disease. Ciclosporin has been tried in a number of forms of glomerular kidney disease (p.1504) but use has been cautious because of fears about nephrotoxicity. Nonetheless, responses have been seen in patients with corticosteroid-resistant minimal change nephropathy,[1,2] focal glomerulosclerosis,[1-3] and membranous nephropathy.[4-6]

1. Nyrop M, Olgaard K. Cyclosporin A treatment of severe steroid resistant nephrotic syndrome in adults. *J Intern Med* 1990; **227:** 65–8.
2. Niaudet P, *et al.* Steroid-resistant idiopathic nephrotic syndrome and ciclosporin. *Nephron* 1991; **57:** 481.
3. Chishti AS, *et al.* Long-term treatment of focal segmental glomerulosclerosis in children with cyclosporine given as a single daily dose. *Am J Kidney Dis* 2001; **38:** 754–60.
4. Cattran DC, *et al.* A controlled trial of cyclosporine in patients with progressive membranous nephropathy. *Kidney Int* 1995; **47:** 1130–5.
5. Cattran DC, *et al.* Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int* 2001; **59:** 1484–90.
6. Goumenos DS. What have we learned from the use of ciclosporin A in the treatment of nephrotic patients with idiopathic membranous nephropathy? *Expert Opin Pharmacother* 2008; **9:** 1695–1704.

Hepatitis. In chronic active hepatitis (p.1501), some evidence suggests that ciclosporin may offer an alternative therapy in patients with severe auto-immune (non-viral) disease where corticosteroids alone or with azathioprine do not suffice.

Histiocytic syndromes. As mentioned in the discussion on p.650 ciclosporin has been tried in patients with advanced Langerhans-cell histiocytosis.

Inflammatory bowel disease. Ciclosporin has been tried with variable success as a second-line drug in inflammatory bowel disease (p.1697). Intravenous high-dose ciclosporin has shown some efficacy in refractory ulcerative colitis,[1] and a review[2] concluded that intravenous ciclosporin should be offered to selected patients as an alternative to surgery. Treatment should be started at 2 mg/kg daily, as it appears to be as effective as 4 mg/kg daily. A systematic review,[3] which included only 2 studies, concluded that short-term ciclosporin may be used where surgery is the only option, but that this is not based on strong evidence.

Benefit from ciclosporin in Crohn's disease is less clear. A systematic review[4] concluded that low dose (5 mg/kg daily) oral ciclosporin is not effective for induction of remission in Crohn's disease. While some studies suggest that higher oral doses or intravenous ciclosporin might be beneficial, these are not considered to be useful alternatives for long-term management due to the risk of nephrotoxicity and the availability of other proven therapy.

1. Loftus CG, *et al.* Cyclosporin for refractory ulcerative colitis. *Gut* 2003; **52:** 172–3.
2. Pham CQD, *et al.* Cyclosporine for severe ulcerative colitis. *Ann Pharmacother* 2006; **40:** 96–101.
3. Shibolet O, *et al.* Cyclosporine A for induction of remission in severe ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 15/01/08).
4. McDonald JWD, *et al.* Cyclosporine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/01/08).

Leprosy. For mention of the use of ciclosporin in the management of type 1 lepra reactions in patients with leprosy, see p.176.

Lichen planus. Lichen planus is a skin disorder generally controlled with corticosteroids (see p.1580), although ciclosporin has also been used. Ciclosporin has been given successfully in relatively low doses (3 to 5 mg/kg by mouth) to produce remission of severe lichen planus,[1] but such therapy may be associated with the development of hypertension and impairment of renal function. Use of topical ciclosporin for oral lichen planus has been tried, but results have been variable.[2-8] One such study failed to note any benefit long-term from either ciclosporin mouthwash or corticosteroid oral paste.[7]

1. Pigatto PD, *et al.* Cyclosporin A for treatment of severe lichen planus. *Br J Dermatol* 1990; **121:** 121–3.
2. Eisen D, *et al.* Cyclosporin wash for oral lichen planus. *Lancet* 1990; **335:** 535–6.
3. Eisen D, *et al.* Effect of topical cyclosporine rinse on oral lichen planus: a double-blind analysis. *N Engl J Med* 1990; **323:** 290–4.
4. Levell NJ, *et al.* Lack of effect of cyclosporin mouthwash in oral lichen planus. *Lancet* 1991; **337:** 796–7.
5. Ho VC, Conklin RJ. Effect of topical cyclosporine rinse on oral lichen planus. *N Engl J Med* 1991; **325:** 435.
6. Porter SR, *et al.* The efficacy of topical cyclosporin in the management of desquamative gingivitis due to lichen planus. *Br J Dermatol* 1993; **129:** 753–5.
7. Sieg P, *et al.* Topical cyclosporin in oral lichen planus: a controlled, randomized prospective trial. *Br J Dermatol* 1995; **132:** 790–4.
8. Conrotto D, *et al.* Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; **154:** 139–45.

Lupus nephritis. Ciclosporin has been investigated for SLE (p.1513), particularly lupus nephritis. Significant reductions in proteinuria have been reported,[1-6] although controlled studies are needed.

1. Fu LW, *et al.* Clinical efficacy of cyclosporin A Neoral in the treatment of paediatric lupus nephritis with heavy proteinuria. *Br J Rheumatol* 1998; **37:** 217–21.
2. Tam LS, *et al.* Long-term treatment of lupus nephritis with cyclosporin A. *Q J Med* 1998; **91:** 573–80.
3. Hallegua D, *et al.* Cyclosporine for lupus membranous nephritis: experience with ten patients and review of the literature. *Lupus* 2000; **9:** 241–51.
4. Fujinaga S, *et al.* Treatment of steroid-resistant membranous lupus nephritis with plasmapheresis and low-dose cyclosporine. *Pediatr Nephrol* 2007; **22:** 616–17.
5. Rihova Z, *et al.* Treatment of lupus nephritis with cyclosporine—an outcome analysis. *Kidney Blood Press Res* 2007; **30:** 124–8.
6. Ogawa H, *et al.* Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. *Mod Rheumatol* 2007; **17:** 92–7.

Multiple sclerosis. As noted on p.892, immunosuppressants, including ciclosporin, have produced modest benefit in patients with multiple sclerosis. However, it has been concluded that the scanty benefits of therapy are outweighed by the toxicity of the doses required.

Muscular dystrophies. A study in 15 boys with Duchenne muscular dystrophy (p.1507) given ciclosporin 5 mg/kg daily by mouth in divided doses, adjusted according to trough serum concentrations of ciclosporin, found that muscular force generation was improved during treatment, but declined again once treatment ceased.[1] The clinical significance, if any, of this effect remains to be established.

1. Sharma KR, *et al.* Cyclosporine increases muscular force generation in Duchenne muscular dystrophy. *Neurology* 1993; **43:** 527–32.

Myasthenia gravis. Ciclosporin may be of use as an alternative to azathioprine in the management of myasthenia gravis (p.629) for its corticosteroid-sparing effect[1] or when patients are intolerant of or unresponsive to corticosteroids and azathioprine.[2-4] It appears to be of similar efficacy to azathioprine[5] with a more rapid effect but serious adverse effects such as nephrotoxicity may limit its use.

1. Tindall RSA, *et al.* A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Ann N Y Acad Sci* 1993; **681:** 539–51.
2. Bonifati DM, Angelini C. Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. *J Neurol* 1997; **244:** 542–7.
3. Ciafaloni E, *et al.* Retrospective analysis of the use of cyclosporine in myasthenia gravis. *Neurology* 2000; **55:** 448–50.
4. Lavrnic D, *et al.* Cyclosporine in the treatment of myasthenia gravis. *Acta Neurol Scand* 2005; **111:** 247–52.
5. Schalke BCG, *et al.* Ciclosporin A vs azathioprine in the treatment of myasthenia gravis: final results of a randomized, controlled double-blind clinical trial. *Neurology* 1988; **38** (suppl 1): 135.

Organ and tissue transplantation. Ciclosporin has greatly improved the prospects for successful organ and tissue transplantation, and is a mainstay of regimens used to prevent rejection of solid organ grafts as well as being used for the prevention of graft-versus-host disease in bone marrow transplantation. For more detailed discussion of organ and tissue transplantation and the role of ciclosporin, see p.1810. Ciclosporin has also occasionally been used for corneal graft rejection (p.1502) in high-risk patients, where corticosteroids alone are insufficient. An ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation. Inhaled ciclosporin is under investigation in lung transplantation, see p.1815 and under Administration, above.

A few selected references to the use of ciclosporin in transplantation are given below.

1. Frei UA, *et al.* Randomized, double-blind, one-year study of the safety and tolerability of cyclosporine microemulsion compared with conventional cyclosporine in renal transplant patients. *Transplantation* 1998; **65:** 1455–60.
2. Eisen HJ, *et al.* Safety, tolerability, and efficacy of cyclosporine microemulsion in heart transplant recipients: a randomized, multicenter, double-blind comparison with the oil-based formulation of cyclosporine—results at 24 months after transplantation. *Transplantation* 2001; **71:** 70–78.
3. Thervet E, *et al.* Benefit-risk assessment of ciclosporin withdrawal in renal transplant recipients. *Drug Safety* 2004; **27:** 457–76.
4. Hesselink DA, *et al.* The use of cyclosporine in renal transplantation. *Transplant Proc* 2004; **36** (suppl): 99S–106S.
5. Pape L, *et al.* Cyclosporine in pediatric kidney transplantation. *Transplant Proc* 2004; **36** (suppl): 203S–207S.
6. Banner NR, Yacoub MH. Cyclosporine in thoracic organ transplantation. *Transplant Proc* 2004; **36** (suppl): 302S–308S.
7. Patel JK, Kobashigawa JA. Cardiac transplant experience with cyclosporine. *Transplant Proc* 2004; **36** (suppl): 323S–330S.
8. Johnston A, *et al.* Potential clinical implications of substitution of generic cyclosporine formulations for cyclosporine microemulsion (Neoral) in transplant recipients. *Eur J Clin Pharmacol* 2004; **60:** 389–95.
9. Schrem H, *et al.* Update on liver transplantation using cyclosporine. *Transplant Proc* 2004; **36:** 2525–31.
10. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; **38:** 169–74.

Pemphigus. Although pemphigus is usually treated with corticosteroids (see p.1582), ciclosporin has also been tried in a few patients with pemphigus vulgaris, with variable results.[1-3] A small, randomised study[4] found that use of corticosteroids with ciclosporin had no advantage over corticosteroids alone.

1. Luisi AF, Stoukides CA. Cyclosporine for the treatment of pemphigus vulgaris. *Ann Pharmacother* 1994; **28:** 1183–5.
2. Vardy DA, Cohen AD. Cyclosporine therapy should be considered for maintenance of remission in patients with pemphigus. *Arch Dermatol* 2001; **137:** 505.
3. Gooptu C, Staughton RCD. Use of topical cyclosporin in oral pemphigus. *J Am Acad Dermatol* 1998; **38:** 860–1.
4. Ioannides D, *et al.* Ineffectiveness of cyclosporine as an adjuvant to corticosteroids in the treatment of pemphigus. *Arch Dermatol* 2000; **136:** 868–72.

Polymyositis and dermatomyositis. Ciclosporin may be of benefit[1] in refractory polymyositis and dermatomyositis (see p.1510).

1. Qushmaq KA, *et al.* Cyclosporin A in the treatment of refractory adult polymyositis/dermatomyositis: population based experience in 6 patients and literature review. *J Rheumatol* 2000; **27:** 2855–9.

Primary biliary cirrhosis. In primary biliary cirrhosis (p.2408) some benefit has been reported with ciclosporin, but there are problems with toxicity. A systematic review[1] concluded that, despite improvements in pruritus and liver biochemical variables, ciclosporin did not delay the progression of the disease, and that its use outside of clinical studies could not be recommended.

1. Gong Y, *et al.* Cyclosporin A for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 15/01/08).

Psoriasis. Ciclosporin is used to induce remission or prevent relapse in severe refractory psoriasis (p.1583). Response to ciclosporin has been reported for virtually all the clinical manifestations of the disease,[1] including pustular psoriasis of pregnancy.[2-4] Benefit has also been reported in children with severe refractory psoriasis,[1,5] although exposure should be limited in view of the potential for cumulative toxicity.

Doses of 2.5 to 5 mg/kg daily given for up to 12 weeks produced marked improvement in the majority of patients with severe plaque psoriasis.[6] This intermittent therapy allows for a lower cumulative dose of ciclosporin and in turn decreases the risk of nephrotoxicity or hypertension.[7] Recommendations have been made in the UK for the use of ciclosporin in the management of psoriasis;[8] for those with severe stable disease, an initial starting dose of 2.5 mg/kg daily is suggested, with dose increases of 0.5 to 1 mg/kg daily made at intervals of 2 to 4 weeks, according to clinical response, and up to a maximum of 5 mg/kg daily. Treatment is given for about 12 weeks, and use of adjunctive topical therapy is recommended. Ciclosporin should be stopped once remission is achieved, and restarted at the previous effective dose if the patient relapses. In acute flares of the disease, ciclosporin may be started at higher doses (maximum 5 mg/kg daily) and titrated down as symptoms improve. The patient's renal function and blood pressure should be monitored before and during treatment. In a minority of patients requiring long-term continuous therapy, the duration of treatment should be limited to a maximum of 2 years, and an annual assessment of the patient's glomerular filtration rate is recommended. In most studies, maintenance doses were less than 3.5 mg/kg daily.

Reviews[1,9] have concluded that patients on short-term ciclosporin therapy for psoriasis do not require routine therapeutic drug monitoring (see above). However, some consider that monitoring of trough concentrations is necessary in those treated with greater than 3 mg/kg daily, or in those at risk of renal impairment.[9] Monitoring may also be useful when compliance is questionable, or drug interactions are suspected.[1]

1. Berth-Jones J. The use of ciclosporin in psoriasis. *J Dermatol Treat* 2005; **16:** 258–77.
2. Edmonds EVJ, *et al.* Pustular psoriasis of pregnancy treated with ciclosporin and high-dose prednisolone. *Clin Exp Dermatol* 2005; **30:** 709–10.
3. Kura MM, Surjushe AU. Generalized pustular psoriasis of pregnancy treated with oral cyclosporin. *Indian J Dermatol Venereol Leprol* 2006; **72:** 458–9.
4. Kapoor R, Kapoor JR. Cyclosporine resolves generalized pustular psoriasis of pregnancy. *Arch Dermatol* 2006; **142:** 1373–5.
5. Pereira TM, *et al.* Cyclosporin A treatment in severe childhood psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20:** 651–6.
6. Faerber L, *et al.* Cyclosporine in severe psoriasis: results of a meta-analysis in 579 patients. *Am J Clin Dermatol* 2001; **2:** 41–7.
7. Ho VC. The use of ciclosporin in psoriasis: a clinical review. *Br J Dermatol* 2004; **150** (suppl. 67): 1–10.
8. Griffiths CEM, *et al.* Ciclosporin in psoriasis clinical practice: an international consensus statement. *Br J Dermatol* 2004; **150** (suppl. 67): 11–23.
9. Heydendael VMR, *et al.* Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; **147:** 122–9.

Psoriatic arthritis. One study[1] has shown that low-dose ciclosporin effectively improves joint complaints in psoriatic arthritis (see under Spondyloarthropathies, p.13), and another[2] found ciclosporin to be more effective than sulfasalazine.

1. Mahrle G, *et al.* Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis: a prospective multicentre study. *Br J Dermatol* 1996; **135:** 752–7.
2. Salvarani C, *et al.* A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; **28:** 2274–82.

Pyoderma gangrenosum. There have been reports[1-5] of responses to ciclosporin in patients with pyoderma gangrenosum (p.1583).

1. Sassolas B, *et al.* Pyoderma gangrenosum with pathergic phenomenon in pregnancy. *Br J Dermatol* 2000; **142:** 827–8.
2. Vena GA, Cassano N. Can we still suggest the topical cyclosporin treatment in cutaneous disorders? *J Eur Acad Dermatol Venereol* 2001; **15:** 18–19.
3. Schöfer H, Baur S. Successful treatment of postoperative pyoderma gangrenosum with cyclosporin. *J Eur Acad Dermatol Venereol* 2002; **16:** 148–51.
4. Patrone P, *et al.* Pyoderma gangrenosum of the scalp treated with cyclosporine A. *Int J Dermatol* 2002; **41:** 916–18.
5. Park H-J, *et al.* Recalcitrant oral pyoderma gangrenosum in a child responsive to cyclosporine. *J Dermatol* 2003; **30:** 612–16.

Rheumatoid arthritis. Various disease-modifying antirheumatic drugs (DMARDs) are used in rheumatoid arthritis (p.11) in an attempt to modify the disease process. Ciclosporin has produced responses in active disease,[1-4] and there is some evidence that it can slow radiological progression of disease[4] as well as providing symptomatic relief; a systematic review[5] has concluded it has an important clinical benefit in the short-term (up to one year) treatment of progressive disease. There has been some concern about associated nephrotoxicity,[1] but the use of low-dose regimens may help to minimise this.

Ciclosporin has also been combined with other DMARDs. Use with methotrexate has reportedly produced responses in patients unresponsive to methotrexate alone,[6] but some investigators found that a combination of methotrexate, ciclosporin and intra-articular corticosteroids was no more effective than standard DMARD therapy.[7] Others consider that ciclosporin monotherapy is of limited benefit, but that combination therapy with methotrexate is one of the best options to control aggressive disease.[8]

International consensus recommendations for the use of ciclosporin in rheumatoid arthritis[9] suggest that it may be considered in patients who are candidates for DMARDs and who do not have risk factors such as malignancy, uncontrolled hypertension, renal dysfunction, cytopenias, or marked disorder of liver function. They recommend a starting dose of between 2.5 and 3 mg/kg daily, increased if necessary after 4 to 8 weeks, in increments of 0.5 or 1 mg/kg at 1 to 2 month intervals, up to a maximum of 5 mg/kg daily, particular care being taken at doses over 4 mg/kg daily. Once the patient's disease has been stable for at least 3 months the daily dose should be decreased monthly or bimonthly in decrements of 0.5 mg/kg to the lowest effective dose. If it is only partially effective after 3 months at the maximum tolerable dose another medication should be considered instead or in addition; if there is no response to the maximum tolerable dose after 3 months, ciclosporin should be stopped. Patients should be carefully monitored before and during therapy.

Ciclosporin has been shown to have a corticosteroid-sparing effect and control the fever of juvenile idiopathic arthritis.[10] In patients with refractory juvenile idiopathic arthritis, adding ciclosporin to methotrexate therapy has been reported to elicit significant clinical improvement.[11]

1. Yocum DE, *et al.* Cyclosporin A in severe, treatment-refractory rheumatoid arthritis: a randomized study. *Ann Intern Med* 1988; **109:** 863–9.
2. Tugwell P, *et al.* Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. *Lancet* 1990; **335:** 1051–5.
3. Landewé RBM, *et al.* A randomized, double-blind, 24-week controlled study of low-dose cyclosporine versus chloroquine for early rheumatoid arthritis. *Arthritis Rheum* 1994; **37:** 637–43.
4. Førre Ø, *et al.* Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine: results of a 48-week multicenter study comparing low-dose cyclosporine with placebo. *Arthritis Rheum* 1994; **37:** 1506–12.
5. Wells G, *et al.* Cyclosporine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 15/01/08).
6. Tugwell P, *et al.* Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; **333:** 137–41.
7. Proudman SM, *et al.* Treatment of poor-prognosis early rheumatoid arthritis. *Arthritis Rheum* 2000; **43:** 1809–19.
8. Gremese E, Ferraccioli GF. Benefit/risk of cyclosporine in rheumatoid arthritis. *Clin Exp Rheumatol* 2004; **22** (suppl 35): S101–S107.
9. Panayi GS, Tugwell P. The use of cyclosporin A microemulsion in rheumatoid arthritis: conclusions of an international review. *Br J Rheumatol* 1997; **36:** 808–11.
10. Gerloni V, *et al.* Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis: results of a 10-year prospective study. *Rheumatology (Oxford)* 2001; **40:** 907–13.
11. Ravelli A, *et al.* Combination therapy with methotrexate and cyclosporine A in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002; **20:** 569–72.

Sarcoidosis. Corticosteroids are the usual therapy for symptomatic sarcoidosis (p.1512), and other agents are very much second-line; ciclosporin is one of a number of immunosuppressants that have been tried with variable results.

Scleritis. Ciclosporin is used alone or with corticosteroids in the treatment of scleritis (see p.1512).

Scleroderma. There are a few reports of responses to ciclosporin in patients with scleroderma (p.1817).

Toxic epidermal necrolysis. Ciclosporin, given either enterally[1] or intravenously,[2] has been reported to be of benefit in toxic epidermal necrolysis.

1. Arévalo JM, *et al.* Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000; **48:** 473–8.
2. Hashim N, *et al.* Early cyclosporine treatment of incipient toxic epidermal necrolysis induced by concomitant use of lamotrigine and sodium valproate. *Acta Derm Venereol* 2004; **84:** 90–1.

Uveitis. Ciclosporin is used in uveitis, see p.1515.

Vasculitic syndromes. For the use of ciclosporin in Takayasu's arteritis and Wegener's granulomatosis, see p.1514 and p.1515, respectively.

Preparations

USP 31: Cyclosporine Capsules; Cyclosporine Injection; Cyclosporine Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Cermox; Gengraf†; Restasis; Sandimmun; ***Austral.:*** Cicloral; Cysporin; Neoral; Sandimmun; ***Austria:*** Cicloralhexal; Neoimmun; Sandimmun; ***Belg.:*** Neoral-Sandimmun; Sandimmun; ***Braz.:*** Gengraf; Restasis; Sandimmun; Sigmasporin; Zinograf†; ***Canad.:*** Neoral; Sandimmune; ***Chile:*** Gengraf; Modusik-A; Restasis; Sandimmun; ***Cz.:*** Consupren†; Equoral; Sandimmun; Sigmasporon; ***Denm.:*** Sandimmun; ***Fin.:*** Sandimmun; ***Fr.:*** Ne-

oral; Sandimmun; ***Ger.:*** Ciclorat; Immunosporin; Sandimmun; ***Gr.:*** Restasis; Sandimmun; ***Hong Kong:*** Gengraf; Sandimmun; ***Hung.:*** Sandimmun; ***India:*** Imusporin; Panimun Bioral; Sandimmun; ***Indon.:*** Sandimmun; ***Irl.:*** Neoral; Sandimmun; ***Israel:*** Deximune; Sandimmun; Sangcya; ***Ital.:*** Sandimmun; ***Jpn:*** Papilock; ***Malaysia:*** Gengraf; Sandimmun; ***Mex.:*** Immulem; Modusik-A; Restasis; Sandimmun; Supremunn; ***Neth.:*** Neoral; Sandimmune; ***Norw.:*** Sandimmun; ***NZ:*** Gengraf; Neoral; Sandimmun; ***Philipp.:*** Restasis; Sandimmun; ***Pol.:*** Equoral; Sandimmun; ***Port.:*** Ciclostar; Sandimmun; ***Rus.:*** Consupren (Консупрен); Sandimmun (Сандиммун); ***S.Afr.:*** Ciclohexal; Sandimmun; ***Singapore:*** Gengraf; ***Spain:*** Sandimmun; ***Swed.:*** Sandimmun; ***Switz.:*** Ciclosol; Sandimmun; ***Thai.:*** Consupren; Equoral; Gengraf; Restasis; Sanda; Sandimmun; ***Turk.:*** Gengraf; Sandimmun; ***UAE:*** Sigmasporin; ***UK:*** Neoral; Sandimmun; ***USA:*** Gengraf; Neoral; Restasis; Sandimmune; ***Venez.:*** Imusporin; Restasis; Sandimmun.

Daclizumab *(BAN, USAN, rINN)*

Dacliximab; Daclizumabum; Daklitsumabi; Daklizumab; Humanised Anti-Tac Antibody; Ro-24-7375. Immunoglobulin G 1, (human-mouse monoclonal 1H4 γ-chain, anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer.

Даклизумаб

CAS — 152923-56-3.

ATC — L04AC01.

ATC Vet — QL04AC01.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with daclizumab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, hypotension, hypoxia, tachycardia, cardiac arrest, wheezing, dyspnoea, bronchospasm, pulmonary oedema, peripheral oedema, laryngeal oedema, and respiratory failure. Injection site reactions have also been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Therapy should be permanently stopped if a severe reaction occurs.

Effects on mortality. Increased mortality was reported in cardiac transplant recipients given an immunosuppressive regimen of daclizumab with ciclosporin, mycophenolate mofetil, and corticosteroids. Some deaths were associated with severe infection and use with antilymphocyte immunoglobulins.[1,2]

1. Roche, USA. 2003 safety alert: Zenapax (daclizumab). Available at: http://www.fda.gov/medwatch/SAFETY/2003/zenapax.htm (accessed 15/01/08)
2. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.

Pharmacokinetics

The recommended regimen of daclizumab (see below) should result in serum concentrations sufficient to saturate interleukin-2 receptors for about 90 days post-transplantation in adult patients, and 120 days in paediatric patients. The terminal elimination half-life of daclizumab has ranged from 11 to 38 days.

Uses and Administration

Daclizumab is a humanised monoclonal murine antibody that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen, Tac subunit) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection after kidney transplantation as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. It is given in a dose of 1 mg/kg intravenously over 15 minutes within 24 hours before surgery and repeated at intervals of 2 weeks for a total of 5 doses. The required dose is diluted in 50 mL of sodium chloride 0.9%, and may be infused either centrally or peripherally. Daclizumab is also under investigation for its immunosuppressant properties in other forms of transplantation (see below) and in various diseases with an auto-immune component.

Administration in children. The dose for daclizumab in children aged 1 year and over is the same as in adults (see Uses and Administration, above).

Multiple sclerosis. Daclizumab has been tried[1-4] in patients with relapsing-remitting or secondary progressive multiple sclerosis; benefit has been reported.

1. Bielekova B, *et al.* Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon β. *Proc Natl Acad Sci U S A* 2004; **101:** 8705–8.
2. Rose JW, *et al.* Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neurol* 2004; **56:** 864–7.
3. Rose JW, *et al.* Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. *Neurology* 2007; **69:** 785–9.
4. Martin R. Humanized anti-CD25 antibody treatment with daclizumab in multiple sclerosis. *Neurodegener Dis* 2008; **5:** 23–6.

Ocular disorders. There have been reports of benefit with daclizumab in ocular inflammatory disorders[1] including scleritis, ocular cicatricial pemphigoid, and uveitis, all of which had been resistant to conventional therapy.

1. Papaliodis GN, *et al.* Treatment of ocular inflammatory disorders with daclizumab. *Ophthalmology* 2003; **110:** 786–9.

Organ and tissue transplantation. Daclizumab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p.1813);[1-4] it is usually given as part of an immunosuppressive regimen that includes a calcineurin inhibitor and corticosteroids.

There are reports of successful corticosteroid withdrawal and corticosteroid-free regimens using daclizumab.[5] An attempt at using daclizumab to avoid use of ciclosporin after renal transplantation was unsuccessful, with a high rate of overall acute rejection in the daclizumab group.[6]

Daclizumab has also been investigated for the prevention of acute rejection after heart,[7] liver,[8,9] and lung[10] transplantation (see p.1812) but increased mortality has followed its use in patients receiving heart grafts[11] (see also under Adverse Effects and Precautions, above).

Daclizumab has also been tried in the management of acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p.1811). While some consider it a viable alternative for corticosteroid-refractory acute GVHD,[12] others found that when daclizumab was used with corticosteroids to treat acute GVHD, this combination had a significantly deleterious effect on patient survival.[13]

Controlled studies that directly compare 2 doses of daclizumab with the standard 5-dose regimen in kidney transplantation are lacking; despite this, many centres use a 2-dose regimen.[14] In a small, retrospective analysis[15] of simultaneous kidney-pancreas transplant recipients (p.1816), patients receiving 1 to 3 doses of daclizumab in addition to triple therapy had a significantly higher incidence of rejection than those receiving 4 to 5 doses. There was no difference in patient or graft survival. A larger multicentre study[16,17] found that simultaneous kidney-pancreas recipients given daclizumab 2 mg/kg every 14 days for 2 doses had a similar incidence of rejection to those given the standard 5-dose regimen; mean time to onset of rejection was delayed in the 2-dose regimen but there was no beneficial effect of daclizumab on graft survival at 3 years. A small comparative study[18] in heart transplant recipients found 2 doses of daclizumab to be at least as effective as the 5-dose regimen; no significant differences were observed for mortality. A novel 3-dose regimen has been investigated in liver transplantation.[19]

1. Vincenti F, *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. *N Engl J Med* 1998; **338:** 161–5.
2. Nashan B, *et al.* Reduction of acute renal allograft rejection by daclizumab. *Transplantation* 1999; **67:** 110–15.
3. Bumgardner GL, *et al.* Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001; **72:** 839–45.
4. Ciancio G, *et al.* Daclizumab induction, tacrolimus, mycophenolate mofetil and steroids as an immunosuppression regimen for primary kidney transplant recipients. *Transplantation* 2002; **73:** 1100–6.
5. ter Meulen CG, *et al.* Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor α therapy: a prospective, randomized, multicenter study. *Am J Transplant* 2004; **4:** 803–10.
6. Åsberg A, *et al.* Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. *Transplantation* 2006; **82:** 62–8.
7. Beniaminovitz A, *et al.* Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med* 2000; **342:** 613–19.
8. Niemeyer G, *et al.* Long-term safety, tolerability and efficacy of daclizumab (Zenapax) in a two-dose regimen in liver transplant recipients. *Am J Transplant* 2002; **2:** 454–60.
9. Figueras J, *et al.* Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts. *Transpl Int* 2006; **19:** 641–8.
10. Garrity ER, *et al.* Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. *Transplantation* 2001; **71:** 773–7.
11. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.
12. Bordigoni P, *et al.* Daclizumab, an efficient treatment for steroid-refractory acute graft-versus-host disease. *Br J Haematol* 2006; **135:** 382–5.
13. Lee SJ, *et al.* Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood* 2004; **104:** 1559–64.
14. van Gelder T, *et al.* Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? *Drugs* 2004; **64:** 1737–41.
15. Bruce DS, *et al.* Multicenter survey of daclizumab induction in simultaneous kidney-pancreas transplant recipients. *Transplantation* 2001; **72:** 1637–43.
16. Stratta RJ, *et al.* One-year outcomes in simultaneous kidney-pancreas transplant recipients receiving an alternative dosing regimen of daclizumab. *Transplant Proc* 2004; **36:** 1080–1.
17. Stratta RJ, *et al.* A prospective, randomized, multicenter study evaluating the safety and efficacy of two dosing regimens of daclizumab compared to no antibody induction in simultaneous kidney-pancreas transplantation: results at 3 years. *Transplant Proc* 2005; **37:** 3531–4.
18. Ortiz V, *et al.* Induction therapy with daclizumab in heart transplantation—how many doses? *Transplant Proc* 2006; **38:** 2541–3.
19. Washburn WK, *et al.* A novel three-dose regimen of daclizumab in liver transplant recipients with hepatitis C: a pharmacokinetic and pharmacodynamic study. *Liver Transpl* 2006; **12:** 585–91.

Skin disorders. There are reports of successful treatment with daclizumab in psoriasis (p.1583),[1,2] pemphigus vulgaris,[3] bullous pemphigoid[4] (see Pemphigus and Pemphigoid, p.1582), and epidermolysis bullosa acquisita[5] (p.1579). Cutaneous manifestations of adult T-cell leukaemia/lymphoma have also been reported to respond to daclizumab.[6]

1. Wohlrab J, *et al.* Treatment of recalcitrant psoriasis with daclizumab. *Br J Dermatol* 2001; **144:** 209–10.
2. Dichmann S, *et al.* Humanized monoclonal anti-CD25 antibody as a novel therapeutic option in HIV-associated psoriatic erythroderma. *J Am Acad Dermatol* 2002; **47:** 635–6.
3. Renkl A, *et al.* A novel therapeutic option in pemphigus vulgaris: humanized monoclonal anti-CD25 antibody. *Br J Dermatol* 2004; **150:** 1220–2.
4. Mockenhaupt M, *et al.* Daclizumab: a novel therapeutic option in severe bullous pemphigoid. *Acta Derm Venereol* 2005; **85:** 65–6.
5. Egan CA, *et al.* Treatment of epidermolysis bullosa acquisita with the humanised anti-Tac mAb daclizumab. *Clin Immunol* 2001; **101:** 146–51.
6. Osborne GEN, *et al.* Novel treatment of Sézary-like syndrome due to adult T-cell leukaemia/lymphoma with daclizumab (humanized anti-interleukin-2 receptor α antibody). *Br J Dermatol* 2006; **155:** 617–20.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zenapax; ***Austral.:*** Zenapax; ***Austria:*** Zenapax; ***Belg.:*** Zenapax†; ***Braz.:*** Zenapax; ***Canad.:*** Zenapax; ***Chile:*** Zenapax; ***Cz.:*** Zenapax; ***Denm.:*** Zenapax; ***Fin.:*** Zenapax; ***Fr.:*** Zenapax; ***Ger.:*** Zenapax; ***Gr.:*** Zenapax; ***Hong Kong:*** Zenapax; ***Hung.:*** Zenapax; ***Irl.:*** Zenapax; ***Israel:*** Zenapax; ***Ital.:*** Zenapax; ***Mex.:*** Zenapax; ***Neth.:*** Zenapax; ***NZ:*** Zenapax; ***Philipp.:*** Zenapax; ***Pol.:*** Zenapax; ***Port.:*** Zenapax; ***S.Afr.:*** Zenapax; ***Singapore:*** Zenapax†; ***Spain:*** Zenapax; ***Swed.:*** Zenapax; ***Switz.:*** Zenapax; ***Thai.:*** Zenapax; ***Turk.:*** Zenapax; ***UK:*** Zenapax; ***USA:*** Zenapax; ***Venez.:*** Zenapax.

Everolimus *(USAN, rINN)*

Évérolimus; Everolimús; Everolimusum; NVP-RAD-001; RAD-001; SDZ-RAD; SDZ-RAD-666. (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,-17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,-26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone.

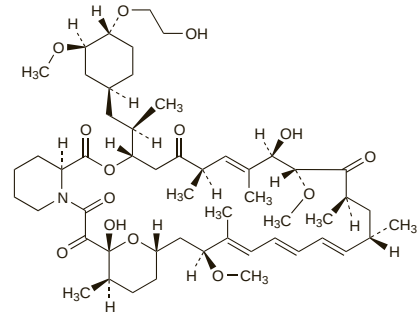
Эверолимус

$C_{53}H_{83}NO_{14}$ = 958.2.

CAS — 159351-69-6.

ATC — L04AA18.

ATC Vet — QL04AA18.



Adverse Effects

Leucopenia, thrombocytopenia, and anaemia occur commonly with everolimus. Haemolysis has been reported rarely. Other common adverse effects include hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypertension, lymphocele, venous thromboembolism, and gastrointestinal upsets. Pneumonia, pneumonitis, hepatitis, jaundice, renal tubular necrosis, and pyelonephritis may occur. Acne and oedema occur frequently; rashes and myalgia occur rarely.

Effects on the lungs. Pulmonary toxicity is a well-known adverse effect in patients given sirolimus (p.1841) and similar toxicity has occurred[1] in patients given everolimus.

1. Expósito V, *et al.* Everolimus-related pulmonary toxicity in heart transplant recipients. *J Heart Lung Transplant* 2008; **27:** 797–800.

Interactions

Everolimus is metabolised in the liver and to some extent in the gastrointestinal wall; plasma concentrations may be affected by