3. Lemos PA, *et al.* Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2003; **41:** 2093–9.
4. Holmes DR, *et al.* Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004; **109:** 634–40.
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6. Cheng-Lai A, Frishman WH. Sirolimus-eluting coronary stents: novel devices for the management of coronary artery disease. *Am J Ther* 2004; **11:** 218–28.
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8. Kastrati A, *et al.* Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356:** 1030–9.
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11. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; **91:** 1176–80.
12. Stettler C, *et al.* Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007; **370:** 937–48.
13. Galløe AM, *et al.* SORT OUT II Investigators. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA* 2008; **299:** 409–16.
14. Stone GW, *et al.* Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356:** 998–1008.
15. Mauri L, *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; **356:** 1020–9.
16. Beohar N, *et al.* Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; **297:** 1992–2000.
17. Win HK, *et al.* Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; **297:** 2001–9.
18. Hausleiter J, *et al.* Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation* 2004; **110:** 790–5.
19. Waksman R, *et al.* Oral rapamycin to inhibit restenosis after stenting of de novo coronary lesions: the Oral Rapamune to Inhibit Restenosis (ORBIT) study. *J Am Coll Cardiol* 2004; **44:** 1386–92.
20. Rodriguez AE, *et al.* ORAR II Investigators. Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the Prospective, Randomized Oral Rapamycin in Argentina (ORAR II) Study. *J Am Coll Cardiol* 2006; **47:** 1522–9.
21. Rodriguez AE, *et al.* Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial). *Heart* 2005; **91:** 1433–7.

Uveitis. Sirolimus has been reported to be effective in the treatment of patients with refractory uveitis.[1]

1. Shanmuganathan VA, *et al.* The efficacy of sirolimus in the treatment of patients with refractory uveitis. *Br J Ophthalmol* 2005; **89:** 666–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Rapamune; ***Austral.:*** Rapamune; ***Austria:*** Rapamune; ***Belg.:*** Rapamune; ***Braz.:*** Rapamune; ***Canad.:*** Rapamune; ***Chile:*** Rapamune; ***Cz.:*** Rapamune; ***Denm.:*** Rapamune; ***Fin.:*** Rapamune; ***Fr.:*** Rapamune; ***Ger.:*** Rapamune; ***Gr.:*** Rapamune; ***Hong Kong:*** Rapamune; ***Hung.:*** Rapamune; ***India:*** Rapamune; ***Irl.:*** Rapamune; ***Israel:*** Rapamune; ***Ital.:*** Rapamune; ***Malaysia:*** Rapamune; ***Mex.:*** Rapamune; ***Neth.:*** Rapamune; ***Norw.:*** Rapamune; ***NZ:*** Rapamune; ***Philipp.:*** Rapamune; ***Pol.:*** Rapamune; ***Port.:*** Rapamune; ***S.Afr.:*** Rapamune; ***Singapore:*** Rapamune; ***Spain:*** Rapamune; ***Swed.:*** Rapamune; ***Switz.:*** Rapamune; ***Thai.:*** Rapamune; ***Turk.:*** Rapamune; ***UK:*** Rapamune; ***USA:*** Rapamune; ***Venez.:*** Rapamune.

Tacrolimus *(BAN, USAN, rINN)*

FK-506; FR-900506; Tacrolimús; Tacrolimusum; Takrolimus; Takrolimuusi; Tsukubaenolide. (−)-(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-8-Allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-{(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl}-14,16,-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone monohydrate.

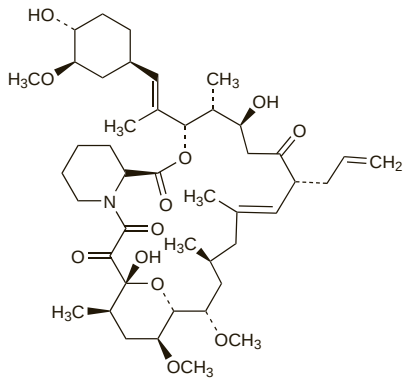
Такролимус

$C_{44}H_{69}NO_{12},H_2O$ = 822.0.

CAS — 104987-11-3 (anhydrous tacrolimus); 109581-93-3 (tacrolimus monohydrate).

ATC — D11AX14; L04AD02.

ATC Vet — QD11AX14; QL04AD02.



Adverse Effects, Treatment, and Precautions

The most common adverse effects after **systemic** use of tacrolimus include tremor, headache, paraesthesias, nausea and diarrhoea, hypertension, insomnia, and impaired renal function. Disturbances of serum electrolytes, notably hyperkalaemia, and hyperglycaemic conditions, including diabetes mellitus, occur frequently. Hyperlipidaemia, hypercholesterolaemia, and hypertriglyceridaemia are common. Anaemia, leucopenia, and thrombocytopenia also occur commonly. Other common adverse effects include mood changes, anxiety, confusion, dizziness, tinnitus, visual disturbances, peripheral neuropathies, and convulsions; constipation, dyspepsia, gastrointestinal perforation and ulceration, and gastrointestinal haemorrhage; dyspnoea, parenchymal lung disorders, pleural effusions, pharyngitis, cough, nasal congestion and inflammation; alopecia, acne, skin rashes, and pruritus; and arthralgia, muscle cramps, asthenia, febrile disorders, oedema, and liver dysfunction. Tachycardia is common; ventricular arrhythmias, cardiac arrest, heart failure, palpitations, and ECG changes are less frequent. Cardiomyopathies, including ventricular hypertrophy have also been reported; most cases have been reversible, and occurring primarily in children with tacrolimus blood concentrations much higher than the recommended maximum levels. Coagulation disorders, neutropenia, and pancytopenia have occurred, as have asthma, acute respiratory distress syndrome, hypoproteinaemia, deep limb venous thrombosis, paralytic ileus, acute and chronic pancreatitis, and haemolytic uraemic syndrome. Coma, CNS haemorrhage, encephalopathy, amnesia, and speech and language abnormalities have also been reported. There are rare reports of thrombotic thrombocytopenic purpura, hypoprothrombinaemia, and hirsutism. Toxic epidermal necrolysis, Stevens Johnson syndrome, hepatic artery thrombosis, and veno-occlusive liver disease have occurred rarely.

Tacrolimus injection is formulated with polyoxyl castor oil: anaphylactoid reactions have occurred, and appropriate means for their management should be available in patients given the injection. Use of tacrolimus should be avoided in patients hypersensitive to macrolides.

Dosage reduction may be necessary in patients with hepatic impairment. Care is also required in patients with pre-existing renal impairment, and dosage reduction may prove advisable in such patients. Monitoring of blood concentrations of tacrolimus is recommended in all patients, especially during episodes of diarrhoea as concentrations may be significantly affected. Renal and hepatic function, blood pressure, serum glucose electrolytes, haematological and cardiac function, as well as neurological and visual status, coagulation values, and plasma protein should be monitored regularly. As with other immunosuppressants, patients receiving tacrolimus are at increased risk of infection and malignancy. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason. Tacrolimus may affect visual or neurological function, and patients so affected should not drive or operate dangerous machinery.

Topical tacrolimus has been associated with local irritation and skin disorders including an increased incidence of herpes simplex and zoster infections; headache and 'flu-like' symptoms have also been reported. Facial flushing and skin irritation has been reported after consumption of alcohol. Exposure of the skin to sunlight should be minimised and the use of artificial sources of ultraviolet light avoided. Carcinogenicity studies in *animals* have reported an increase in the incidence of lymphoma and skin cancers associated with topical tacrolimus and rare cases of skin malignancy and lymphoma have been reported in patients (see also below).

Skin infections should be treated before starting therapy with topical tacrolimus. It should not be used in immunocompromised patients or those with conditions that might increase systemic absorption of tacrolimus. It must also not be applied to pre-malignant or malignant skin conditions; some malignant skin conditions may mimic eczema.

Breast feeding. Tacrolimus is distributed into breast milk. Tacrolimus concentrations were measured in milk from a liver transplant recipient on a dose of 100 micrograms/kg daily. The authors estimated that the infant would ingest only 0.06% (0.06 micrograms/kg daily) of the mother's weight-adjusted dose. No adverse effects were noted in the infant at 2.5 months of age.[1]

Licensed product information recommends that women should avoid breast feeding while taking tacrolimus.

1. French AE, *et al.* Milk transfer and neonatal safety of tacrolimus. *Ann Pharmacother* 2003; **37:** 815–18.

Carcinogenicity. The systemic use of tacrolimus increases the risk of malignancy.

Carcinogenicity studies in *animals* have also reported an increase in the incidence of malignancies associated with the topical calcineurin inhibitors, tacrolimus and pimecrolimus. As of December 2004 the FDA had received reports of 19 cases of lymphoma or cutaneous tumours associated with topical tacrolimus, of which 4 cases were a recurrence or aggravation of a pre-existing malignancy, and 3 other cases were confounded by other possible risk factors. At this same date, the FDA had also received reports of 10 cases of malignancy in patients treated with topical pimecrolimus, including 6 cutaneous tumours. Although the potential for systemic immunosuppression from topical use was unknown and the role of the drug in these cases was uncertain, the FDA recommended that topical calcineurin inhibitors should only be used as a second-line drug for short-term and intermittent treatment of eczema, and that they should not be used in immunocompromised patients or in children younger than 2 years of age.[1,2] Similar warnings have been issued in the European Union.[3] However, there has been some debate about the risk of malignancy associated with the topical use of these drugs, and a number of groups[4-6] have examined the evidence used by the FDA. They found that after topical application in humans the serum concentrations of these drugs were usually low or undetectable, that there was no evidence of systemic immunosuppression as measured by response to childhood immunisation and delayed hypersensitivity, no evidence of an increase in malignancy in clinical studies or compared with the general population, and that none of the reported lymphoma cases resembled the usual presentation and histology seen with systemic immunosuppression-associated lymphoma. They concluded that based on available data the risk of cancer from topical calcineurin inhibitors was theoretical and unknown. A review[7] of skin cancer risk found that there was no conclusive evidence from *rodent* studies to suggest that topical calcineurin inhibitors were associated with an increase in skin cancers, or a potentiation of UV-associated immunosuppression and carcinogenicity. There was also no evidence of an increased risk of skin cancer in human studies. In general, there seems to be agreement that long-term data are still needed to determine the carcinogenic risk, if there is any, from topical tacrolimus and pimecrolimus. Until long-term safety data are available some[8] consider that it would be prudent if topical calcineurin inhibitors were:

- not used in children under 2 years of age
- not used continuously for more than 6 weeks, with an application-free period of up to 2 weeks
- avoided in immunocompromised patients
- avoided in patients with neoplasia
- avoided in those with skin disorders liable to lead to increased systemic absorption

Patients should also be encouraged to use a broad-spectrum sunscreen daily on all sunlight-exposed skin.

1. FDA. Alert for healthcare professionals: tacrolimus (marketed as Protopic) 03/05. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/ProtopicHCP.pdf (accessed 18/03/08)
2. FDA. Alert for healthcare professionals: pimecrolimus (marketed as Elidel) 03/05. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/ElidelHCP.pdf (accessed 18/03/08)
3. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): reports of malignancies. *Current Problems* 2006; **31:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Fonacier L, *et al.* Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2005; **115:** 1249–53.
5. Bieber T, *et al.* Consensus statement on the safety profile of topical calcineurin inhibitors. *Dermatology* 2005; **211:** 77–8.
6. Berger TG, *et al.* The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol* 2006; **54:** 818–23.
7. Ring J, *et al.* Review of the potential photo-cocarcinogenicity of topical calcineurin inhibitors: position statement of the European Dermatology Forum. *J Eur Acad Dermatol Venereol* 2005; **19:** 663–71.
8. Ring J, *et al.* The US FDA 'black box' warning for topical calcineurin inhibitors: an ongoing controversy. *Drug Safety* 2008; **31:** 185–98.

Effects on the blood. Severe anaemia due to selective depression of erythropoiesis in a patient given tacrolimus resolved when tacrolimus was replaced with ciclosporin.[1] More generalised bone marrow suppression,[2] post-transplant thrombotic microangiopathy,[3] and red cell aplasia[4] have also been reported. Hypoplasia occurring in a liver transplant recipient,[5] was characterised by a slow but complete recovery after substituting tacrolimus with ciclosporin.

1. Winkler M, *et al.* Anaemia associated with FK 506 immunosuppression. *Lancet* 1993; **341:** 1035–6.
2. de-la-Serna-Higuera C, *et al.* Tacrolimus-induced bone marrow suppression. *Lancet* 1997; **350:** 714–15.
3. Trimarchi HM, *et al.* FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation* 1999; **67:** 539–44.
4. Misra S, *et al.* Red cell aplasia in children on tacrolimus after liver transplantation. *Transplantation* 1998; **65:** 575–7.
5. Nosari A, *et al.* Bone marrow hypoplasia complicating tacrolimus (FK506) therapy. *Int J Hematol* 2004; **79:** 130–2.

Effects on carbohydrate metabolism. The development of diabetes mellitus after solid organ transplantation is common,[1,2] which may be attributed to the diabetogenic effects of immunosuppressive drugs. Incidence has appeared to be increased in both adult[3] and paediatric[4] renal transplant recipients given tacrolimus. However, a retrospective review[2] found no significant difference in incidence between patients receiving tacrolimus or ciclosporin but found instead a correlation between the absence of an antiproliferative agent and the development of diabetes. A retrospective study of liver transplant recipients found that, although those given tacrolimus had a greater incidence of diabetes mellitus, hepatitis C infection was the only factor predictive of its development.[1] In contrast, a meta-analysis[5] found the incidence of new-onset diabetes mellitus (NODM) to be significantly higher among patients receiving tacrolimus compared with those receiving ciclosporin after solid organ transplantation. An observational study[6] confirmed this finding, and found it to be unrelated to corticosteroid dosage, although relatively high doses of corticosteroids were used across the study. A retrospective study[7] found tacrolimus to be significantly more diabetogenic than ciclosporin, even when corticosteroid dosing was lower with tacrolimus. An analysis of data for 8839 patients[8] found the risk of NODM to be greatest with high tacrolimus doses, but the increased risk versus ciclosporin was sustained even with lower tacrolimus doses. Higher corticosteroid doses potentiated the diabetogenic effect of tacrolimus, but even the lowest dosage group for tacrolimus and corticosteroids had higher rates of NODM than all ciclosporin groups; there was no association between corticosteroid dose and NODM for any dosage of ciclosporin. In a small, retrospective study,[9] conversion from tacrolimus to ciclosporin resulted in marked improvement of glucose metabolism, and even reversal of diabetes mellitus in a significant proportion of patients.

1. AlDosary AA, *et al.* Post-liver transplantation diabetes mellitus: an association with hepatitis C. *Liver Transpl* 2002; **8:** 356–61.
2. First MR, *et al.* Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. *Transplantation* 2002; **73:** 379–86.
3. Pirsch JD, *et al.* A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation* 1997; **63:** 977–83.
4. Al-Uzri A, *et al.* Posttransplant diabetes mellitus in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation* 2001; **72:** 1020–4.
5. Heisel O, *et al.* New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004; **4:** 583–95.
6. Kamar N, *et al.* Diapason Study Group. Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007; **22:** 1986–93.
7. Hoitsma AJ, Hilbrands LB. Relative risk of new-onset diabetes during the first year after renal transplantation in patients receiving tacrolimus or cyclosporine immunosuppression. *Clin Transplant* 2006; **20:** 659–64.
8. Burroughs TE, *et al.* Influence of early posttransplantation prednisone and calcineurin inhibitor dosages on the incidence of new-onset diabetes. *Clin J Am Soc Nephrol* 2007; **2:** 517–23.
9. Bouchta NB, *et al.* Conversion from tacrolimus to cyclosporin is associated with a significant improvement of glucose metabolism in patients with new-onset diabetes mellitus after renal transplantation. *Transplant Proc* 2005; **37:** 1857–60.

Effects on the cardiovascular system. Hypertrophic cardiomyopathy, and in some cases heart failure, has been described in paediatric patients receiving tacrolimus after organ grafting (small bowel or liver).[1] Symptoms largely resolved on stopping or reducing dosage. A similar case had been found *post mortem* in an adult,[2] and the UK CSM[3] was aware of 29 reported cases worldwide as of July 1995. Echocardiographic monitoring of patients receiving tacrolimus has been recommended, with dose reduction or withdrawal in those who developed hypertrophic changes.[3] However, echocardiographic abnormalities may be quite common after orthotopic liver transplantation in adults, with no obvious relationship to the use of tacrolimus,[4] and a retrospective analysis concluded that tacrolimus is not a risk factor for hypertrophic cardiomyopathy in adult transplant recipients.[5]

Severe hypertension was documented in 5 out of 10 paediatric patients who received intravenous tacrolimus after renal transplant surgery. All patients responded to intravenous labetalol. By contrast none of 11 children who received ciclosporin at the same institution developed hypertension.[6] However, a review[7] concluded that tacrolimus causes less hypertension than ciclosporin, resulting in a better cardiovascular risk profile in renal transplant recipients, and possibly ultimately prolonging graft survival.

1. Atkison P, *et al.* Hypertrophic cardiomyopathy associated with tacrolimus in paediatric transplant patients. *Lancet* 1995; **345:** 894–6.
2. Natazuka T, *et al.* Immunosuppressive drugs and hypertrophic cardiomyopathy. *Lancet* 1995; **345:** 1644.
3. Committee on Safety of Medicines/Medicines Control Agency. Tacrolimus (Prograf) and hypertrophic cardiomyopathy in transplant patients. *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Dollinger MM, *et al.* Tacrolimus and cardiotoxicity in adult liver transplant recipients. *Lancet* 1995; **346:** 507.
5. Coley KC, *et al.* Lack of tacrolimus-induced cardiomyopathy. *Ann Pharmacother* 2001; **35:** 985–9.
6. Booth CJ, *et al.* Intravenous tacrolimus may induce severe hypertension in renal transplant recipients. *Arch Dis Child* 1999; **80** (suppl 1): A27.
7. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; **72** (suppl): S9–12.

Effects on the kidneys. A comparison in patients who had undergone liver transplantation suggested that nephrotoxicity was more of a problem in those receiving tacrolimus than in those given a ciclosporin-based regimen.[1] In particular intravenous tacrolimus during the first week after transplantation was associated with acute renal failure in 4 of 20 patients. Furthermore, on follow-up for 1 year, GFR was somewhat lower in the tacrolimus-treated group. A small study compared GFR and effective renal plasma flow (ERPF), at various stages after transplantation, in renal and liver transplant recipients given tacrolimus.[2] In renal transplant patients, the GFR, although lower than normal, was increased after transplant, and remained stable over 3 months. ERPF, however, was significantly lower at 3 months. In liver transplant recipients, despite being lower than normal, GFR and ERPF were unchanged at 1 year post-transplant.

1. Porayko MK, *et al.* Nephrotoxic effects of primary immunosuppression with FK-506 and cyclosporine regimens after liver transplantation. *Mayo Clin Proc* 1994; **69:** 105–11.
2. Agarwala S, *et al.* Evaluation of renal function in transplant patients on tacrolimus therapy. *J Clin Pharmacol* 2002; **42:** 798–805.

Effects on the nervous system. Although many of the symptoms of neurotoxicity induced by tacrolimus are similar to those of ciclosporin (p.1824), some symptoms such as headaches, tremor, and sleep disturbances, appear to be more prevalent with tacrolimus, and the incidence of tacrolimus-induced neurotoxicity appears to be higher in liver transplant recipients.[1]

Severe peripheral neuropathy together with signs of cerebral dysfunction has been reported in 2 patients receiving tacrolimus.[2] Among other central effects, tacrolimus has also been associated with speech disorders, including severe dysarthria and mutism in 1 patient;[3] some degree of speech dysfunction, in the form of an apparent Norwegian accent, appeared to be permanent in this case.

Encephalopathy, sometimes occurring within the reversible posterior leukoencephalopathy syndrome (RPLS), has been reported with use of tacrolimus.[4-8] Presenting symptoms included acute severe headache, seizures, cortical blindness, disorientation, and hypertension.

Miller Fisher syndrome, a variant of Guillain-Barré syndrome, has been attributed to tacrolimus use in a liver transplant recipient.[9] Clinical manifestations included ataxia, ophthalmoplegia, and areflexia.

1. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; **13:** 313–26.
2. Ayres RCS, *et al.* Peripheral neurotoxicity with tacrolimus. *Lancet* 1994; **343:** 862–3.
3. Boeve BF, *et al.* Dysarthria and apraxia of speech associated with FK-506 (tacrolimus). *Mayo Clin Proc* 1996; **71:** 969–72.
4. Kiemeneij IM, *et al.* Acute headache as a presenting symptom of tacrolimus encephalopathy. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1126–7.
5. Nakazato T, *et al.* Reversible posterior leukoencephalopathy syndrome associated with tacrolimus therapy. *Intern Med* 2003; **42:** 624–5.
6. Frühauf NR, *et al.* Late onset of tacrolimus-related posterior leukoencephalopathy after living donor liver transplantation. *Liver Transpl* 2003; **9:** 983–5.
7. Schuuring J, *et al.* Severe tacrolimus leukoencephalopathy after liver transplantation. *Am J Neuroradiol* 2003; **24:** 2085–8.
8. Lavigne CM, *et al.* Tacrolimus leukoencephalopathy: a neuropathologic confirmation. *Neurology* 2004; **63:** 1132–3.
9. Kaushik P, *et al.* Miller Fisher variant of Guillain-Barré syndrome requiring a cardiac pacemaker in a patient on tacrolimus after liver transplantation. *Ann Pharmacother* 2005; **39:** 1124–7.

Effects on skeletal muscle. Severe acute rhabdomyolysis, leading to fatal acute renal failure, developed in an 18-month-old child given tacrolimus after bone marrow transplantation.[1] Seizures, severe rhabdomyolysis, and acute renal failure were reported in a renal transplant patient taking tacrolimus and a monoclonal antibody.[2]

1. Hibi S, *et al.* Severe rhabdomyolysis associated with tacrolimus. *Lancet* 1995; **346:** 702.
2. Fontana I, *et al.* Severe rhabdomyolysis and acute renal failure in a kidney transplant patient treated with tacrolimus and chimaeric CD25 monoclonal antibody. *Transplant Proc* 2004; **36:** 711–2.

Effects on the skin. Three children developed lentigines (small pigmented macules) while receiving long-term (9 months to 4 years) treatment with topical tacrolimus 0.1% for eczema. The lesions developed primarily in the areas where tacrolimus had been applied. Despite withdrawal of tacrolimus, the lentigines still persisted at review 6 to 18 months later. The authors noted that use of tacrolimus was outside the product's licensed indications, and that the clinical implications of their findings remained uncertain.[1]

1. Hickey JR, *et al.* Does topical tacrolimus induce lentigines in children with atopic dermatitis? A report of three cases. *Br J Dermatol* 2005; **152:** 152–4.

Hepatitis. For the suggestion that dosage requirements of tacrolimus may be reduced in children with hepatitis C see Administration, below.

Infection. For a report of an increased incidence of CMV disease in renal transplant recipients given a regimen combining tacrolimus and mycophenolate mofetil see under Interactions, p.1837.

Overdosage. A report[1] of 12 cases of acute overdose with tacrolimus described overdoses of up to 30 times the prescribed dose. Three patients were asymptomatic, while 7 showed mild transient renal and hepatic impairment, nausea, and mild hand tremors. One patient suffered renal failure, histoplasmosis, and sepsis 48 hours after admission for the overdose. The outcome was unknown in one patient. All 8 symptomatic patients recovered when tacrolimus concentrations returned to normal. No specific treatment regimen has been recommended, but patients have been treated with gastric lavage, oral activated charcoal, and phenytoin. The latter is used both to prevent seizures and to enhance tacrolimus metabolism by stimulation of cytochrome P450. Patients should be closely monitored for known signs and symptoms of tacrolimus toxicity. In a further series of 5 cases,[2] acute ingestion of tacrolimus was reported to be well tolerated, and adequately managed with conservative treatment.

1. Curran CF, *et al.* Acute overdoses of tacrolimus. *Transplantation* 1996; **62:** 1376.
2. Mrvos R, *et al.* Tacrolimus (FK 506) overdose: a report of five cases. *J Toxicol Clin Toxicol* 1997; **35:** 395–9.

Porphyria. Data are limited on the use of tacrolimus in patients with porphyria. There has been a report of a patient with acute intermittent porphyria given tacrolimus for 5 days before renal transplantation, and maintenance tacrolimus post-transplantation, without exacerbation of symptoms.[1]

1. Barone GW, *et al.* The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; **41:** 113–5.

Pregnancy. Tacrolimus crosses the placenta. Licensed product information states that, although *systemic* tacrolimus has shown abortifacient and teratogenic properties in *animal* studies, limited data in humans show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy compared with other immunosuppressants. However, use of tacrolimus has been associated with neonatal hyperkalaemia, which appears to normalise spontaneously, and neonatal renal dysfunction; the neonate should be monitored for potential adverse effects.

There are no adequate data from the use of *topical* tacrolimus in pregnancy.

Further references.

1. Kainz A, *et al.* Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000; **70:** 1718–21.
2. Jain AB, *et al.* Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. *Transplantation* 2003; **76:** 827–32.
3. Baumgart DC, *et al.* Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis. *Gut* 2005; **54:** 1822–3.

Interactions

Increased nephrotoxicity may result if tacrolimus is given with other potentially nephrotoxic drugs: use with ciclosporin should be avoided for this reason. Similarly, concurrent use with neurotoxic drugs should be avoided. High potassium intake or potassium-sparing diuretics should also be avoided in patients receiving tacrolimus.

Tacrolimus is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme system, such as azole antifungals, bromocriptine, calcium-channel blockers, cimetidine, some corticosteroids, ciclosporin, danazol, HIV-protease inhibitors, the NNRTI delavirdine, macrolide antibacterials, and metoclopramide, may produce increased blood concentrations of tacrolimus. The metabolism of tacrolimus may also be inhibited by grapefruit juice and they should not be taken together. Equally, inducers of this enzyme system (such as carbamazepine, nevirapine, phenobarbital, phenytoin, rifampicin, and St John's wort) may reduce blood concentrations of tacrolimus. Sirolimus can also decrease blood concentrations of tacrolimus. For a warning concerning the use of live vaccines in patients receiving immunosuppressants see Adverse Effects and Precautions, above.

Facial flushing or skin irritation may occur if alcohol is consumed by patients using topical tacrolimus.

◊ The cytochrome P450 isoenzyme subfamily CYP3A, and P-glycoprotein, are involved in the pharmacokinetic pathways of tacrolimus.[1] Drugs known to interact with these systems will probably affect tacrolimus concentrations, primarily by influencing oral bioavailability rather than clearance.[2] A study[3] *in vitro* found that metabolism of tacrolimus by CYP3A in human liver microsomes was inhibited by bromocriptine, corticosterone, dexamethasone, ergotamine, erythromycin, ethinylestradiol, josamycin, ketoconazole, miconazole, midazolam, nifedipine, omeprazole, tamoxifen, troleandomycin, and verapamil. No effect on tacrolimus metabolism was seen with aspirin, amphotericin B, captopril, cefotaxime, ciprofloxacin, diclofenac, diltiazem, doxycycline, furosemide, glibenclamide, imipramine, lidocaine, paracetamol, prednisolone, progesterone, ranitidine, sulfamethoxazole, trimethoprim, or vancomycin.

1. van Gelder T. Drug interactions with tacrolimus. *Drug Safety* 2002; **25:** 707–12.
2. Christians U, *et al.* Mechanisms of clinically relevant drug interactions associated with tacrolimus. *Clin Pharmacokinet* 2002; **41:** 813–51.
3. Christians U, *et al.* Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; **41:** 187–90.

Antibacterials. Increased concentrations of tacrolimus in plasma have been reported with *erythromycin*;[1] the interaction was accompanied by some evidence of nephrotoxicity. A similar interaction has been reported between tacrolimus and *clarithromycin*.[2,3] For reference to the effects of macrolides on tacrolimus metabolism *in vitro* see above.

Treatment with *rifampicin* has been found to substantially decrease tacrolimus concentrations.[4,5] A pharmacokinetic study found that rifampicin induces metabolism of tacrolimus in both the liver and intestine, probably by induction of the cytochrome P450 isoenzyme subfamily CYP3A and P-glycoprotein.[6] Both *metronidazole*[7,8] and *chloramphenicol*[9,10] increased the blood concentrations of tacrolimus. This is probably due to inhibition of metabolism, and dosage reduction of the immunosuppressant may be necessary when either drug is given with tacrolimus. A pharmacokinetic study[11] found that *levofloxacin* partially inhibited the metabolism of tacrolimus, and recommended that drug concentrations be monitored when these 2 drugs are used together.

Plasma concentrations of tacrolimus are also increased by *quinupristin/dalfopristin*.

1. Jensen C, *et al.* Interaction between tacrolimus and erythromycin. *Lancet* 1994; **344:** 825.
2. Wolter K, *et al.* Interaction between FK 506 and clarithromycin in a renal transplant patient. *Eur J Clin Pharmacol* 1994; **47:** 207–8.
3. Ibrahim RB, *et al.* Tacrolimus-clarithromycin interaction in a patient receiving bone marrow transplantation. *Ann Pharmacother* 2002; **36:** 1971–2.
4. Furlan V, *et al.* Interactions between FK506 and rifampicin or erythromycin in pediatric liver recipients. *Transplantation* 1995; **59:** 1217–18.
5. Chenhsu R-Y, *et al.* Renal allograft dysfunction associated with rifampin-tacrolimus interaction. *Ann Pharmacother* 2000; **34:** 27–31.
6. Hebert MF, *et al.* Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 1999; **39:** 91–6.
7. Herzig K, Johnson DW. Marked elevation of blood cyclosporin and tacrolimus levels due to concurrent metronidazole therapy. *Nephrol Dial Transplant* 1999; **14:** 521–3.
8. Page RL, *et al.* Potential elevation of tacrolimus trough concentrations with concomitant metronidazole therapy. *Ann Pharmacother* 2005; **39:** 1109–13.
9. Schulman SL, *et al.* Interaction between tacrolimus and chloramphenicol in a renal transplant recipient. *Transplantation* 1998; **65:** 1397–8.
10. Mathis AS, *et al.* Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; **4:** 169–74.
11. 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.

Antidepressants. Tacrolimus trough concentrations reduced sharply in a patient who took *St John's wort*, and returned to previous levels on stopping the St John's wort.[1] St John's wort induces cytochrome P450 isoenzyme CYP3A4, enhancing the metabolism of tacrolimus. A pharmacokinetic study[2] confirmed this, finding an increase in tacrolimus clearance; the authors concluded that potential consequences of this interaction in transplant recipients are rejection and graft loss.

1. Bolley R, *et al.* Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. *Transplantation* 2002; **73:** 1009.
2. Hebert MF, *et al.* Effects of St. John's wort (Hypericum perforatum) on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 89–94.

Antiepileptics. For the effect of tacrolimus on *phenytoin*, see Immunosuppressants in Phenytoin, p.500.

Antifungals. Elevated plasma-tacrolimus concentrations have been reported in patients given *clotrimazole*,[1] *fluconazole*,[2] or *voriconazole*[3]; a reduction in the dose of tacrolimus was likely to be necessary if it were given with an azole antifungal. A study involving tacrolimus and *ketoconazole* suggested that an increase in the oral bioavailability of tacrolimus from a mean of 14 to 30% when given with the azole was probably due to decreased cytochrome P450 isoenzyme CYP3A4 metabolism in the gut wall, or improved absorption due to inhibition of P-glycoprotein mediated efflux, rather than an effect on hepatic metabolism.[4] Similarly, a 50% reduction in tacrolimus dosage was found to be necessary when the drug was given with *itraconazole*.[5] It has been suggested that the interaction could be exploited to reduce the cost of immunosuppressant regimens.[6] In another study of itraconazole with tacrolimus,[7] 1 patient required a 20% increase in the dose of tacrolimus, 3 patients required no dose adjustment, and 5 patients required tacrolimus dose reductions, ranging from 20 to 76.5%. The authors concluded that the magnitude of the dose reduction is dependent on the initial tacrolimus serum concentration and the final target concentration.

1. Mieles L, *et al.* Interaction between FK506 and clotrimazole in a liver transplant recipient. *Transplantation* 1991; **52:** 1086–7.
2. Mañez R, *et al.* Fluconazole therapy in transplant recipients receiving FK506. *Transplantation* 1994; **57:** 1521–3.
3. Venkataramanan R, *et al.* Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. *Antimicrob Agents Chemother* 2002; **46:** 3091–3.
4. Floren LC, *et al.* Tacrolimus oral bioavailability doubles with coadministration of ketoconazole. *Clin Pharmacol Ther* 1997; **62:** 41–9.
5. Capone D, *et al.* Effects of itraconazole on tacrolimus blood concentrations in a renal transplant recipient. *Ann Pharmacother* 1999; **33:** 1124–5.
6. Kramer MR, *et al.* Dose adjustment and cost of itraconazole prophylaxis in lung transplant recipients receiving cyclosporine and tacrolimus (FK506). *Transplant Proc* 1997; **29:** 2657–9.
7. 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.

Antivirals. Ten- to fiftyfold reductions in tacrolimus dosage were necessary to maintain therapeutic tacrolimus trough concentrations, in 6 HIV-positive liver transplant recipients receiving tacrolimus-based immunosuppressive therapy, when antiretroviral therapy including an HIV-protease inhibitor was started postoperatively.[1] This effect was more pronounced with *nelfinavir* than *indinavir*. In contrast, 4 HIV-positive kidney transplant recipients received antiretroviral therapy without protease inhibitors, and required only conventional doses of tacrolimus. The authors caution that some protease inhibitors can act as both inducers and inhibitors of the cytochrome P450 isoenzyme CYP3A4. While the inhibitory effect appears to predominate when given with tacrolimus, if the protease inhibitor is withdrawn suddenly the CYP3A4 system may remain induced, and a sudden decrease in tacrolimus concentration may occur; this had occurred in one case. For this reason, they concluded that great caution and frequent tacrolimus monitoring are necessary when protease inhibitors are introduced or withdrawn in transplant recipients receiving tacrolimus.

Dramatic increases in tacrolimus blood concentrations have been reported after addition of *lopinavir/ritonavir* in HIV-positive liver transplant recipients.[2-4] Some patients did not need further tacrolimus for up to 3 weeks, even with normal hepatic function; with hepatic dysfunction, 1 mg of tacrolimus provided a therapeutic concentration for up to 5 weeks, and in one patient the tacrolimus concentration increased for the next few days with the introduction of lopinavir/ritonavir without any additional dose of tacrolimus. The authors recommended a pre-emptive decrease in tacrolimus dose by at least 50% one day before starting therapy with lopinavir/ritonavir, and withholding tacrolimus for the next few days; therapy should then be guided by therapeutic drug monitoring of tacrolimus blood concentrations.[3] The usual dose of tacrolimus while a patient is on lopinavir/ritonavir is expected to be about 0.5 to 1 mg weekly.[2,3] In contrast, *efavirenz* did not appreciably affect tacrolimus pharmacokinetics.[4]

1. Jain AKB, *et al.* The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transpl* 2002; **8:** 841–5.
2. Schonder KS, *et al.* Tacrolimus and lopinavir/ritonavir interaction in liver transplantation. *Ann Pharmacother* 2003; **37:** 1793–6.
3. Jain AB, *et al.* Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl* 2003; **9:** 954–60.
4. Teicher E, *et al.* Effect of highly active antiretroviral therapy on tacrolimus pharmacokinetics in hepatitis C virus and HIV coinfected liver transplant recipients in the ANRS HC-08 study. *Clin Pharmacokinet* 2007; **46:** 941–52.

Calcium-channel blockers. Dosage requirements for tacrolimus were substantially reduced in 22 liver graft recipients who also received *nifedipine*, compared with 28 patients given tacrolimus alone, in a 1-year retrospective study.[1]

Tacrolimus toxicity has been reported in a liver transplant patient shortly after starting *diltiazem*.[2]

1. Seifeldin RA, *et al.* Nifedipine interaction with tacrolimus in liver transplant recipients. *Ann Pharmacother* 1997; **31:** 571–5.
2. Hebert MF, Lam AY. Diltiazem increases tacrolimus concentrations. *Ann Pharmacother* 1999; **33:** 680–2.

Danazol. Nephrotoxicity and tremors associated with elevated concentrations of tacrolimus developed in a patient given danazol with the immunosuppressant.[1] The effect might have been due to inhibition of the metabolism of tacrolimus.

1. Shapiro R, *et al.* FK 506 interaction with danazol. *Lancet* 1993; **341:** 1344–5.

Deoxyschizandrin. Mean blood concentrations of tacrolimus in 12 healthy subjects rose from 22.2 to 66.4 nanograms/mL after they had received 13 days of treatment with SchE (*Hezheng Pharmaceutical Company, China*), an extract of *Schisandra sphenanthera* containing amongst other ingredients deoxyschizandrin.[1] During the study the area under the concentration-time curve (AUC) of tacrolimus also rose by 164.2% while oral clearance fell by 49%. It was suggested that constituents of *Schisandra sphenanthera* may act as inhibitors of the cytochrome P450 isoenzyme CYP3A4 and/or P-glycoprotein.

1. Xin H-W, *et al.* Effects of *Schisandra sphenanthera* extract on the pharmacokinetics of tacrolimus in healthy volunteers. *Br J Clin Pharmacol* 2007; **64:** 469–75.

Gastrointestinal drugs. In 2 renal transplant recipients, tacrolimus trough concentrations increased markedly after introduction of *lansoprazole* and returned to normal after it was stopped.[1,2] One of the patients was later given *rabeprazole* with no effect on tacrolimus concentration.[2] The same effects were apparent in a study of healthy subjects,[3] with lansoprazole increasing the concentration and decreasing the clearance of tacrolimus, but the degree of interaction was found to depend, at least partly, upon the genetic status of the patients. The authors supposed that certain ethnic groups might be at higher risk for this interaction. In contrast, rabeprazole appears less affected by genotypic status, and had minimal effect on tacrolimus pharmacokinetics; the authors considered it a safer proton pump inhibitor than lansoprazole for those with cytochrome P450 isoenzyme CYP2C19 gene mutation who were receiving tacrolimus. An *in-vitro* study suggested that omeprazole inhibited the metabolism of tacrolimus.[4] Despite a study reporting no clinically relevant interaction between omeprazole and tacrolimus in renal transplant recipients,[5] increased tacrolimus concentrations were reported when a paediatric liver transplant patient was started on omeprazole.[6]

1. Takahashi K, *et al.* Lansoprazole-tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. *Ann Pharmacother* 2004; **38:** 791–4.
2. Homma M, *et al.* Effects of lansoprazole and rabeprazole on tacrolimus blood concentration: case of a renal transplant recipient with CYP2C19 gene mutation. *Transplantation* 2002; **73:** 303–4.
3. Itagaki F, *et al.* Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. *J Pharm Pharmacol* 2004; **56:** 1055–9.
4. Christians U, *et al.* Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; **41:** 187–90.
5. Pascual J, *et al.* Interaction between omeprazole and tacrolimus in renal allograft recipients: a clinical-analytical study. *Transplant Proc* 2005; **37:** 3752–3.
6. Moreau C, *et al.* Interaction between tacrolimus and omeprazole in a pediatric liver transplant recipient. *Transplantation* 2006; **81:** 487–8.

Immunosuppressants. *Sirolimus* may decrease blood concentrations of tacrolimus; in stable renal transplant recipients given both drugs, mean exposure and trough concentrations of tacrolimus decreased by about 30% relative to tacrolimus alone. Tacrolimus may inhibit *ciclosporin* metabolism *in vitro*, with the possibility of increased nephrotoxicity (see under Ciclosporin, p.1828). Tacrolimus may also increase concentrations of mycophenolic acid, a metabolite of *mycophenolate mofetil* (see under Mycophenolate Mofetil, p.1837), and the risk of infection may be increased if used together.

Pharmacokinetics

Absorption of tacrolimus after oral doses is reported to be erratic. Oral bioavailability varies very widely; the mean value is in the range of 20 to 25%. The rate and extent of absorption of tacrolimus is decreased by the presence of food, with the effect most pronounced after a high-fat meal. There is little or no systemic exposure to tacrolimus after topical use (but see Absorption, below). After intravenous doses it is widely distributed to the tissues; it is extensively bound to erythrocytes in the blood, and variations in red cell binding account for much of the variability in pharmacokinetics. The portion in plasma is about 99% bound to plasma proteins. Tacrolimus is extensively metabolised in the liver, principally by cytochrome P450 isoenzyme CYP3A4, and excreted, primarily in bile, almost entirely as metabolites. Considerable metabolism also occurs in the intestinal wall. Whole-blood elimination half-life has been reported to average 43 hours in healthy subjects, and to range from about 12 to 16 hours in transplant patients.

◊ References.

1. Gruber SA, *et al.* Pharmacokinetics of FK506 after intravenous and oral administration in patients awaiting renal transplantation. *J Clin Pharmacol* 1994; **34:** 859–64.
2. Jusko WJ, *et al.* Pharmacokinetics of tacrolimus in liver transplant patients. *Clin Pharmacol Ther* 1995; **57:** 281–90.
3. Venkataramanan R, *et al.* Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* 1995; **29:** 404–30.
4. Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. *Clin Pharmacokinet* 2001; **40:** 283–95.
5. Bekersky I, *et al.* Comparative tacrolimus pharmacokinetics: normal versus mildly hepatically impaired subjects. *J Clin Pharmacol* 2001; **41:** 628–35.
6. Reding R, *et al.* Efficacy and pharmacokinetics of tacrolimus oral suspension in pediatric liver transplant recipients. *Pediatr Transplant* 2002; **6:** 124–6.
7. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* 2004; **43:** 623–53.
8. Kuypers DRJ, *et al.* Time-related clinical determinants of long-term tacrolimus pharmacokinetics in combination therapy with mycophenolic acid and corticosteroids: a prospective study in one hundred de novo renal transplant recipients. *Clin Pharmacokinet* 2004; **43:** 741–62.
9. Iwasaki K. Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. *Drug Metab Pharmacokinet* 2007; **22:** 328–35.
10. Antignac M, *et al.* Population pharmacokinetics and bioavailability of tacrolimus in kidney transplant patients. *Br J Clin Pharmacol* 2007; **64:** 750–7.

Absorption. A single topical application of a 0.1% tacrolimus ointment to an infant for the treatment of chronic dermatitis, resulted in high serum-tacrolimus concentrations (24 nanograms/mL). Tacrolimus levels decreased over 7 days, after which another smaller, single application of 0.03% tacrolimus ointment again resulted in high serum concentrations. The authors cautioned against its use in young children and diseases with decreased skin barrier function.[1] In another report,[2] elevated blood tacrolimus concentrations were seen after application of 0.1% tacrolimus ointment to a large area of the body of a patient with erythroderma; again, caution in conditions where the skin barrier is disrupted was advised.

1. Kameda G, *et al.* Unexpected high serum levels of tacrolimus after a single topical application in an infant. *J Pediatr* 2003; **143:** 280. Correction. *ibid.*; 462.
2. Teshima D, *et al.* Increased topical tacrolimus absorption in generalized leukemic erythroderma. *Ann Pharmacother* 2003; **37:** 1444–7.

Bioavailability. Bioavailability of tacrolimus appears to be influenced by the type and timing of meals. Food, particularly high-fat meals, significantly reduced bioavailability, compared with the fasting state.[1] Ingestion of tacrolimus up to 1.5 hours after a meal also considerably reduced absorption.[2] UK licensed product information states that tacrolimus should be taken on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. Gastrointestinal metabolism of tacrolimus is thought to be extensive, significantly affecting its bioavailability,[3] and differences in this metabolism may account for apparent differences in availability according to ethnic origin.[4]

1. Bekersky I, *et al.* Effect of low- and high-fat meals on tacrolimus absorption following 5 mg single oral doses to healthy human subjects. *J Clin Pharmacol* 2001; **41:** 176–82.
2. Bekersky I, *et al.* Effect of time of meal consumption on bioavailability of a single oral 5 mg tacrolimus dose. *J Clin Pharmacol* 2001; **41:** 289–97.
3. Tuteja S, *et al.* The effect of gut metabolism on tacrolimus bioavailability in renal transplant recipients. *Transplantation* 2001; **71:** 1301–7.
4. Mancinelli LM, *et al.* The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. *Clin Pharmacol Ther* 2001; **69:** 24–31.

Genetic factors. Renal transplant recipients homozygous for CYP3A5*3 required lower doses to reach target trough concentrations of tacrolimus compared with CYP3A5*1 allele carriers;[1] the latter group can be expected to have a tacrolimus clearance 25 to 45% greater than that of homozygotes.[2] Determination of the cytochrome P450 isoenzyme genotype before transplantation may identify patients at risk for underimmunosuppression or toxicity.

1. 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.
2. Utecht KN, *et al.* Effects of genetic polymorphisms on the pharmacokinetics of calcineurin inhibitors. *Am J Health-Syst Pharm* 2006; **63:** 2340–8.

Therapeutic drug monitoring. There is a good correlation between tacrolimus trough concentrations and systemic exposure, and analysis at other time points is not considered to offer any advantage.[1] However, since tacrolimus 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.[2]

Microparticle enzyme immunoassay (MEIA) and enzyme-linked immunosorbent assay (ELISA) have both been used to measure tacrolimus whole blood concentrations. A study[3] of liver transplant recipients found that increasing trough tacrolimus concentrations, as measured by the ELISA, correlated with decreasing risk of acute rejection, but increasing risk of nephrotoxicity. The authors suggested a trough blood concentration of less than 15 nanograms/mL to minimise nephrotoxicity. While several studies have shown that adverse effects are more closely correlated with tacrolimus concentrations than with dose, the correlation between concentrations and allograft rejection has not been established. There is some suggestion that measuring the unbound concentration of tacrolimus may be a better correlate for rejection than whole blood concentrations.[4]

Licensed product information states that blood trough concentrations of tacrolimus should be monitored during the post-transplantation period; blood should be drawn about 12 hours after dosing, just before the next dose. Samples which are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they may be frozen at –20° for up to 12 months. The frequency of monitoring is based on clinical need; about twice-weekly during the early post-transplant period is recommended, followed by periodic monitoring during maintenance therapy. Trough concentrations should also be monitored after dose adjustment, although it may take several days before changes become apparent. Monitoring is also recommended after changes in the immunosuppressive regimen, or when other drugs are given which may alter tacrolimus blood concentrations. The majority of patients can be successfully managed if blood concentrations are maintained below 20 nanograms/mL. In practice, in the early post-transplant period, whole blood trough concentrations have generally been in the range of 5 to 20 nanograms/mL in liver transplant recipients, and 10 to 20 nanograms/mL in kidney and heart transplant recipients. During maintenance therapy, blood concentrations have generally been between 5 to 15 nanograms/mL in liver, kidney, and heart transplant patients.

Bayesian forecasting has also been used.[5]

UK licensed product information states that the relationship between tacrolimus trough concentrations and systemic exposure is similar for the standard formulation (*Prograf, Astellas*) and the prolonged-release formulation (*Advagraf, Astellas*).

1. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
2. Baraldo M, Furlanut M. Chronopharmacokinetics of ciclosporin and tacrolimus. *Clin Pharmacokinet* 2006; **45:** 775–88.
3. Venkataramanan R, *et al.* Clinical utility of monitoring tacrolimus blood concentrations in liver transplant patients. *J Clin Pharmacol* 2001; **41:** 542–51.
4. Zahir H, *et al.* Factors affecting variability in distribution of tacrolimus in liver transplant recipients. *Br J Clin Pharmacol* 2004; **57:** 298–309.
5. Fukudo M, *et al.* Forecasting of blood tacrolimus concentrations based on the Bayesian method in adult patients receiving living-donor liver transplantation. *Clin Pharmacokinet* 2003; **42:** 1161–78.

Uses and Administration

Tacrolimus is a potent macrolide (macrolactam) immunosuppressant derived from *Streptomyces tsukubaensis*, and has actions similar to those of ciclosporin (see p.1830). Tacrolimus binds to an intracellular protein, FKBP-12, and then forms a complex with calcium, calmodulin, and calcineurin, which inhibits the activity of calcineurin. This interferes with the production of lymphokines such as interleukin-2 and inhibits T-lymphocyte activation, resulting in immunosuppression.

Tacrolimus is used to prevent or manage rejection in patients receiving organ transplants, as indicated by the cross-references given in Organ and Tissue Transplantation, below. Tacrolimus has been tried in a few patients with refractory auto-immune or immune-mediated disorders; in some countries it is licensed for use in myasthenia gravis, in rheumatoid arthritis that is unresponsive to conventional therapy, and in lupus nephritis where corticosteroids are ineffective or contra-indicated. Tacrolimus is also applied topically in the management of moderate to severe atopic eczema. Tacrolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

UK licensed product information recommends that oral tacrolimus should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximum absorption.

For **transplantation**, in adult patients in the UK, the initial ***oral*** daily doses, to be given in 2 divided doses, are:

- *liver* transplantation: 100 to 200 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 200 to 300 micrograms/kg, starting within 24 hours of completion of surgery
- *heart* transplantation: 75 micrograms/kg, after antibody induction, and within 5 days of completion of surgery, and when the patient is stable

Alternatively, tacrolimus has been given orally within 12 hours of transplantation, in patients without other organ dysfunction, at an initial oral dose of 2 to 4 mg daily, with mycophenolate mofetil and corticosteroids, or with sirolimus and corticosteroids

If the patient's condition does not permit oral use, therapy may be started ***intravenously***, by continuous 24-hour infusion; suggested initial adult daily doses are:

- *liver* transplantation: 10 to 50 micrograms/kg
- *kidney* transplantation: 50 to 100 micrograms/kg
- *heart* transplantation: 10 to 20 micrograms/kg

For rejection therapy, increased tacrolimus doses, supplemental corticosteroid therapy, and short courses of monoclonal or polyclonal antibodies have been used. For conversion to tacrolimus from another immunosuppressant, in liver and kidney transplant recipients treatment should begin with the initial oral dose recommended for primary immunosuppression. For heart transplant patients converted to tacrolimus, an initial oral dose of 150 micrograms/kg daily, in 2 divided doses, is recommended. UK dose recommendations for rejection therapy in other allografts are based on limited data. The following initial ***oral*** daily doses of tacrolimus have been used:

- *lung* transplantation: 100 to 150 micrograms/kg
- *pancreatic* transplantation: 200 micrograms/kg
- *intestinal* transplantation: 300 micrograms/kg

In the USA, the following initial ***oral*** daily doses, given in 2 divided doses, are recommended for adult patients:

- *liver* transplantation: 100 to 150 micrograms/kg, starting about 6 hours after transplantation
- *kidney* transplantation: 200 micrograms/kg, starting within 24 hours of transplantation, but delayed if necessary until renal function has recovered
- *heart* transplantation: 75 micrograms/kg, starting no sooner than 6 hours after transplantation

For most transplant patients, initial oral therapy is recommended. If ***intravenous*** tacrolimus therapy is need-

ed, the recommended starting daily doses, to be given as a continuous infusion, are:

- *liver* transplantation: 30 to 50 micrograms/kg
- *kidney* transplantation: 30 to 50 micrograms/kg
- *heart* transplantation: 10 micrograms/kg

Tacrolimus doses are usually reduced in the post-transplant period; in some cases other immunosuppressant therapy can be stopped, leading to tacrolimus monotherapy or tacrolimus-based dual therapy. Maintenance dosage should be adjusted according to whole-blood trough concentrations in individual patients: it is suggested that most patients can be satisfactorily maintained at whole-blood concentrations below 20 nanograms/mL. (see Therapeutic Drug Monitoring, above)

Prolonged-release capsules of tacrolimus are also available in some countries for the prevention of rejection in adult liver or kidney transplantation, and the treatment of allograft rejection. Patients maintained on the twice-daily standard formulation are converted to once daily prolonged-release capsules at the same total daily dose; the prolonged-release formulation should be given in the morning, and tacrolimus trough concentrations should be monitored to maintain similar systemic exposure.

For doses used in paediatric transplant recipients, see Administration in Children, below.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, tacrolimus may be applied twice daily as a 0.03 or 0.1% ointment; an attempt should be made to use the lower strength or reduce the frequency of application when possible. Either strength may be used in adults; for treatment in children, see Administration in Children, below. Treatment should be continued only until resolution of signs and symptoms. UK licensed product information recommends that if no signs of improvement are seen after 2 weeks of treatment, further treatment options should be considered; in the USA, if clinical manifestations do not improve within 6 weeks, diagnosis of atopic eczema should be confirmed through re-examination.

◊ Reviews.

1. Winkler M, Christians U. A risk-benefit assessment of tacrolimus in transplantation. *Drug Safety* 1995; **12:** 348–57.
2. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. *Drugs* 2000; **59:** 323–89.
3. Skaehill PA. Tacrolimus in dermatologic disorders. *Ann Pharmacother* 2001; **35:** 582–8.
4. Woo DK, James WD. Topical tacrolimus: a review of its uses in dermatology. *Dermatitis* 2005; **16:** 6–21.
5. Simpson D, Noble S. Tacrolimus ointment: a review of its use in atopic dermatitis and its clinical potential in other inflammatory skin conditions. *Drugs* 2005; **65:** 827–58.
6. First MR, Fitzsimmons WE. Modified release tacrolimus. *Yonsei Med J* 2004; **45:** 1127–31.
7. Wente MN, *et al.* Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; **20** (suppl 17): 80–4.
8. Chisholm MA, Middleton MD. Modified-release tacrolimus. *Ann Pharmacother* 2006; **40:** 270–5.
9. Cross SA, Perry CM. Tacrolimus once-daily formulation: in the prophylaxis of transplant rejection in renal or liver allograft recipients. *Drugs* 2007; **67:** 1931–43.
10. First MR. First clinical experience with the new once-daily formulation of tacrolimus. *Ther Drug Monit* 2008; **30:** 159–66.

Administration. The mean dose of tacrolimus required to produce a standard trough concentration of 10 to 15 nanograms/mL was reported to be 96% higher in 7 black renal graft recipients than in 20 such patients of white or Asian descent.[1] (For mention of the effect of ethnicity on the bioavailability of tacrolimus see under Pharmacokinetics, above.)

Children generally require relatively higher doses than adults to achieve the same blood concentrations (see Administration in Children, below). There is limited evidence that children with hepatitis C required on average one-third of the dose of tacrolimus needed by children without the virus.[2]

1. Andrews PA, *et al.* Racial variation in dosage requirements of tacrolimus. *Lancet* 1996; **348:** 1446.
2. Moreno M, *et al.* Monitoring of tacrolimus as rescue therapy in pediatric liver transplantation. *Ther Drug Monit* 1998; **20:** 376–9.

Administration in children. For **transplantation** in paediatric patients in the UK, tacrolimus is given in the following initial **oral** daily doses, in 2 divided doses:

- *liver* transplantation: 300 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 300 micrograms/kg, starting within 24 hours of completion of surgery; a lower dose of 200 micrograms/kg has been used in adolescents to prevent very high trough concentrations
- *heart* transplantation, *after antibody induction*: 100 to 300 micrograms/kg

If the patient's condition does not allow for oral use, therapy may be started ***intravenously***, by continuous 24-hour infusion; intravenous therapy may be given for up to 7 days, but should be converted to oral therapy as soon as clinically possible. Suggested daily doses are:

- *liver* transplantation: 50 micrograms/kg
- *kidney* transplantation: 75 to 100 micrograms/kg

For *heart* transplantation *without antibody induction*, patients may be started on intravenous doses of 30 to 50 micrograms/kg daily, as a continuous 24-hour infusion. The first oral dose should be started 8 to 12 hours after stopping intravenous infusion, at a dose of 300 micrograms/kg daily, given in 2 divided doses.

For rejection therapy after *liver* and *kidney* transplantation, treatment is as for adults (see Uses and Administration, above). For paediatric *heart* transplant patients converted to tacrolimus, an initial oral dose of 200 to 300 micrograms/kg daily, in 2 divided doses, is recommended.

In the USA, the following ***oral*** daily doses, given in 2 divided doses, are recommended for children:

- *liver* transplantation: 150 to 200 micrograms/kg, starting about 6 hours after transplantation

Intravenous doses are as for adults (see Uses and Administration, above).

Doses are adjusted according to whole-blood trough concentrations (see Therapeutic Drug Monitoring, above); children generally require doses per kg 1⁄ to 2 times higher than adults to achieve the same concentrations.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, the following treatment schedules have been recommended in children:

- 2 to 16 years: apply 0.03% ointment thinly twice daily, for up to 3 weeks, then reduce to once daily until lesion clears. The 0.1% ointment is not licensed for use in children under 16, although it has been used (see Eczema, below).

  For reference to the development of lentigines in children given long-term treatment with the higher strength preparation see Effects on the Skin under Adverse Effects, above
- 16 years and older: as for adults (see Uses and Administration, above)

Treatment duration is as for adults (see Uses and Administration, above).

Eczema. Topical tacrolimus has been found to be safe and effective[1-3] for short-term use in the treatment of moderate to severe atopic eczema (p.1579). In adult patients, the efficacy of 0.1% tacrolimus ointment was similar to that of 0.1% hydrocortisone butyrate ointment in one study[4] and more effective than a combination of 0.1% hydrocortisone butyrate ointment (applied to the trunk and extremities) and 1% hydrocortisone acetate ointment (applied to the head and neck) in another study.[5] In paediatric patients 2 to 15 years of age,[6,7] both 0.03 and 0.1% tacrolimus were significantly more effective than 1% hydrocortisone acetate ointment. In 18 of 19 patients with facial atopic eczema resistant to 0.03% tacrolimus ointment,[8] there was significant improvement upon application of a 0.03% lotion formulation, and 6 patients were positive to a patch test for white petrolatum, an ingredient of the commercial ointment. A meta-analysis concluded that topical tacrolimus 0.1% was as effective as potent topical corticosteroids and more effective than mild topical corticosteroids for the treatment of eczema; however, tacrolimus was significantly more likely to cause skin burning than corticosteroids.[9]

Results from a small, open-label study suggest that long-term intermittent use of tacrolimus ointment may reverse the skin atrophy induced by topical corticosteroids.[10] In another study,[11] adult and paediatric patients (2 to 15 years of age) with atopic eczema were treated continuously or intermittently with tacrolimus 0.1% ointment for up to 4 years; almost 60% of patients were evaluated for at least 2 years and about 38% for at least 3 years. The majority of patients received tacrolimus monotherapy, although some used topical corticosteroids at some point. There was no indication of an increased risk of adverse effects with the long-term use of tacrolimus, nor was there an indication of an increased risk for any cutaneous infection with increased duration of exposure to tacrolimus. In general, however, long-term use of topical tacrolimus should be avoided because of concerns about potential carcinogenicity (see under Adverse Effects, above).

1. Gianni LM, Sulli MM. Topical tacrolimus in the treatment of atopic dermatitis. *Ann Pharmacother* 2001; **35:** 943–6.
2. Allen BR. Tacrolimus ointment: its place in the therapy of atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 401–3.
3. Anonymous. Topical tacrolimus—a role in atopic dermatitis? *Drug Ther Bull* 2002; **40:** 73–5.
4. Reitamo S, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 547–55.
5. Reitamo S, *et al.* A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol* 2005; **152:** 1282–9.
6. Reitamo S, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 539–46.
7. Reitamo S, *et al.* 0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomized double-blind controlled trial. *Br J Dermatol* 2004; **150:** 554–62.
8. Sugiura H, *et al.* An open study of a lotion formulation to improve tolerance of tacrolimus in facial atopic dermatitis. *Br J Dermatol* 2001; **145:** 795–8.
9. Ashcroft DM, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; **330:** 516–22.
10. Kyllönen H, *et al.* Effects of 1-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis. *Br J Dermatol* 2004; **150:** 1174–81.
11. Hanifin JM, *et al.* US Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. *J Am Acad Dermatol* 2005; **53** (suppl 2): S186–S194.

Encephalitis. Compared with historical untreated controls, 7 patients with Rasmussen encephalitis (a progressive neurological disorder thought to have an auto-immune origin) had a superior outcome in terms of neurological function and progression rate of cerebral hemiatrophy after treatment with tacrolimus, but no better seizure outcome.[1] The control patients had more severe disease, but since only 1 patient on tacrolimus showed a cognitive decline, and none became eligible for hemispherectomy, the authors concluded prospective studies would be useful.

1. Bien CG, *et al.* An open study of tacrolimus therapy in Rasmussen encephalitis. *Neurology* 2004; **62:** 2106–9.

Glomerular kidney disease. Tacrolimus has been reported[1-5] to be effective in inducing remission in patients with glomerular kidney disease (p.1504); it has been used as monotherapy from first presentation, as well as in patients refractory to standard therapy, and in those with corticosteroid-dependent disease. However, a small, longitudinal study[6] in children with severe corticosteroid-dependent nephrotic syndrome given tacrolimus after inadequate response to ciclosporin, reported no better management of disease with tacrolimus, although it was beneficial for some children.

1. Segarra A, *et al.* Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol Dial Transplant* 2002; **17:** 655–62.
2. Duncan N, *et al.* Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. *Nephrol Dial Transplant* 2004; **19:** 3062–7.
3. Westhoff TH, *et al.* Tacrolimus in steroid-resistant and steroid-dependent nephrotic syndrome. *Clin Nephrol* 2006; **65:** 393–400.
4. Bhimma R, *et al.* Management of steroid-resistant focal segmental glomerulosclerosis in children using tacrolimus. *Am J Nephrol* 2006; **26:** 544–51.
5. Praga M, *et al.* Grupo Español de Estudio de la Nefropatía Membranosa. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. *Kidney Int* 2007; **71:** 924–30.
6. Sinha MD, *et al.* Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. *Nephrol Dial Transplant* 2006; **21:** 1848–54.

Hepatitis. In auto-immune chronic active hepatitis (p.1501), some evidence suggests that tacrolimus may offer an alternative therapy when corticosteroids alone or with azathioprine do not suffice.

Ichthyosis. For mention of the use of tacrolimus in ichthyosis see p.1580.

Inflammatory bowel disease. There are reports of response to tacrolimus in patients with inflammatory bowel disease (IBD; p.1697). Tacrolimus has been given orally,[1-4] intravenously,[1] or topically,[5,6] in the treatment of ulcerative colitis[1,3,4] and Crohn's disease,[1-3,5,6] refractory to standard therapy. A systematic review[7] of 23 reports of tacrolimus use in 286 patients concluded that oral tacrolimus was a reasonable and effective alternative for fistulising Crohn's disease, although the evidence base was poor and comparative studies with infliximab were needed. Tacrolimus was also a possible alternative in IBD cases unresponsive to corticosteroids. Intravenous use was not deemed to confer any advantage over oral dosage; topical tacrolimus might be an option in certain cases.

1. Fellermann K, *et al.* Tacrolimus: a new immunosuppressant for steroid refractory inflammatory bowel disease. *Transplant Proc* 2001; **33:** 2247–8.
2. Ierardi E, *et al.* Oral tacrolimus long-term therapy in patients with Crohn's disease and steroid resistance. *Aliment Pharmacol Ther* 2001; **15:** 371–7.
3. Bousvaros A, *et al.* Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 2000; **137:** 794–9.

4. Ogata H, *et al.* A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55:** 1255–62. Correction. *ibid.*; 1684. [dosage error in abstract]
5. Casson DH, *et al.* Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; **47:** 436–40.
6. Hart AL, *et al.* Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007; **13:** 245–53.
7. Gonzalez-Lama Y, *et al.* The role of tacrolimus in inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2006; **51:** 1833–40.

Myasthenia gravis. Tacrolimus has been reported to be effective in the management of myasthenia gravis (p.629) in patients resistant to conventional therapy, or for whom standard therapy is contra-indicated.[1,2] In an open-label study, 79 patients with myasthenia gravis, who had undergone thymectomy and were on high doses of prednisone and ciclosporin, were switched from ciclosporin to tacrolimus. Initial doses of tacrolimus were 0.1 mg/kg daily, given in 2 divided doses. Dosage was subsequently adjusted to achieve plasma concentrations between 7 and 8 nanograms/mL; tacrolimus doses of 6 to 10 mg daily were needed. After 1 year doses were reduced to achieve concentrations of about 6 nanograms/mL. Doses of prednisone were reduced, and finally withdrawn in all but 2 patients; 73 patients received tacrolimus for more than 3 years. All patients were able to resume normal daily activities.[3] Tacrolimus is licensed for use for myasthenia gravis in some countries, in a usual dose of 3 mg once daily by mouth. Tacrolimus (initial daily dose 3 mg orally) was also reported to reduce corticosteroid dosage in another small study; treatment was continued long-term and efficacy was maintained for up to 3 years.[4] There is some suggestion that tacrolimus may be more effective in thymomatous myasthenia gravis than in non-thymomatous disease.[5]

Tacrolimus has also been used as first-line adjunctive therapy with prednisolone; it was reported to decrease the daily prednisolone dose, and the need for plasmapheresis and high-dose intravenous methylprednisolone.[6]

1. Evoli A, *et al.* Successful treatment of myasthenia gravis with tacrolimus. *Muscle Nerve* 2002; **25:** 111–14.
2. Shimojima Y, *et al.* Tacrolimus in refractory patients with myasthenia gravis: coadministration and tapering of oral prednisolone. *J Clin Neurosci* 2006; **13:** 39–44.
3. Ponseti JM, *et al.* Long-term results of tacrolimus in cyclosporine- and prednisone-dependent myasthenia gravis. *Neurology* 2005; **64:** 1641–3.
4. Tada M, *et al.* Long-term therapeutic efficacy and safety of low-dose tacrolimus (FK506) for myasthenia gravis. *J Neurol Sci* 2006; **247:** 17–20.
5. Mitsui T, *et al.* Beneficial effect of tacrolimus on myasthenia gravis with thymoma. *Neurologist* 2007; **13:** 83–6.
6. Nagane Y, *et al.* Efficacy of low-dose FK506 in the treatment of Myasthenia gravis—a randomized pilot study. *Eur Neurol* 2005; **53:** 146–50.

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

Organ and tissue transplantation. Tacrolimus has been used both for primary immunosuppression and for the control of graft rejection. Much of the initial experience with the drug was for liver grafts, (p.1815), but it is also used in the transplantation of heart (p.1812), kidney (p.1813), lung (p.1815), pancreas (p.1816), and intestines (p.1813). It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811).

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

1. European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994; **344:** 423–8.
2. The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; **331:** 1110–15.
3. Gruessner RW. Tacrolimus in pancreas transplantation: a multicenter analysis. *Clin Transplant* 1997; **11:** 299–312.
4. Gruessner RWG, *et al.* Suggested guidelines for the use of tacrolimus in pancreas/kidney transplantation. *Clin Transplant* 1998; **12:** 260–2.
5. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002; **359:** 741–6.
6. O'Grady JG, *et al.* Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; **360:** 1119–25.
7. Scott LJ, *et al.* Tacrolimus: a further update of its use in the management of organ transplantation. *Drugs* 2003; **63:** 1247–97.
8. Kelly D, *et al.* Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. *Lancet* 2004; **364:** 1054–61.
9. Webster AC, *et al.* Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005; **331:** 810–14.
10. McCormack PL, *et al.* Tacrolimus: in heart transplant recipients. *Drugs* 2006; **66:** 2269–79.
11. Haddad EM, *et al.* Cyclosporin versus tacrolimus for liver transplanted patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/03/08).
12. Wente MN, *et al.* Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; **20** (suppl 17): 80–4.
13. Patel JK, Kobashigawa JA. Tacrolimus in heart transplant recipients: an overview. *BioDrugs* 2007; **21:** 139–43.
14. Joseph A, *et al.* Tacrolimus immunosuppression in high-risk corneal grafts. *Br J Ophthalmol* 2007; **91:** 51–5.

Psoriasis. Tacrolimus has been shown to be effective in the treatment of psoriasis (p.1583) when used orally[1] or topically.[2-4]

1. The European FK 506 Multicentre Psoriasis Study Group. Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996; **132:** 419–23.
2. Remitz A, *et al.* Tacrolimus ointment improves psoriasis in a microplaque assay. *Br J Dermatol* 1999; **141:** 103–7.
3. Clayton TH, *et al.* Topical tacrolimus for facial psoriasis. *Br J Dermatol* 2003; **149:** 419–20.
4. Brune A, *et al.* Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. *Pediatr Dermatol* 2007; **24:** 76–80.

Pyoderma gangrenosum. There are reports of response to tacrolimus, given orally,[1-3] or topically,[4-9] or both,[10,11] in patients with pyoderma gangrenosum (p.1583). A small study[12] found topical tacrolimus 0.3% in carmellose sodium paste to be more effective than clobetasol propionate 0.05% for peristomal pyoderma gangrenosum.

Systemic absorption, resulting in tacrolimus blood concentrations equivalent to oral dosing, has been reported in patients with pyoderma gangrenosum in whom tacrolimus was applied directly onto ulcerated areas;[13,14] therapeutic drug monitoring has been suggested for patients treated with topical tacrolimus over large skin areas or with impaired skin barriers.

1. Abu-Elmagd K, *et al.* Resolution of severe pyoderma gangrenosum in a patient with streaking leukocyte factor disease after treatment with tacrolimus (FK 506). *Ann Intern Med* 1993; **119:** 595–8.
2. D'Incà R, *et al.* Tacrolimus to treat pyoderma gangrenosum resistant to cyclosporine. *Ann Intern Med* 1998; **128:** 783–4.
3. Lyon CC, *et al.* Recalcitrant pyoderma gangrenosum treated with systemic tacrolimus. *Br J Dermatol* 1999; **140:** 562–4.
4. Schuppe H-C, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Lancet* 1998; **351:** 832.
5. Reich K, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Br J Dermatol* 1998; **139:** 755–7.
6. Vidal D, Alomar A. Successful treatment of periostomal pyoderma gangrenosum using topical tacrolimus. *Br J Dermatol* 2004; **150:** 387–8.
7. Lally A, *et al.* Penile pyoderma gangrenosum treated with topical tacrolimus. *Arch Dermatol* 2005; **141:** 1175–6.
8. Chiba T, *et al.* Topical tacrolimus therapy for pyoderma gangrenosum. *J Dermatol* 2005; **32:** 199–203.
9. Kontos AP, *et al.* An open-label study of topical tacrolimus ointment 0.1% under occlusion for the treatment of pyoderma gangrenosum. *Int J Dermatol* 2006; **45:** 1383–5.
10. Jolles S, *et al.* Combination oral and topical tacrolimus in therapy-resistant pyoderma gangrenosum. *Br J Dermatol* 1999; **140:** 564–5.
11. Deckers-Kocken JM, Pasmans SG. Successful tacrolimus (FK506) therapy in a child with pyoderma gangrenosum. *Arch Dis Child* 2005; **90:** 531.
12. Lyon CC, *et al.* Topical tacrolimus in the management of peristomal pyoderma gangrenosum. *J Dermatol Treat* 2001; **12:** 13–17.
13. Ghislain P-D, *et al.* Efficacy and systemic absorption of topical tacrolimus used in pyoderma gangrenosum. *Br J Dermatol* 2004; **150:** 1052–3.
14. Pitarch G, *et al.* Systemic absorption of topical tacrolimus in pyoderma gangrenosum. *Acta Derm Venereol* 2006; **86:** 64–5.

Reperfusion and revascularisation procedures. References to the use of tacrolimus-eluting stents.

1. García-Tejada J, *et al.* Carbo-stent liberador de tacrolimus Janus : resultados inmediatos y seguimiento clínico a medio plazo. *Rev Esp Cardiol* 2007; **60:** 197–200.
2. Han Y-L, *et al.* Midterm outcomes of prospective, randomized, single-center study of the Janus tacrolimus-eluting stent for treatment of native coronary artery lesions. *Chin Med J (Engl)* 2007; **120:** 552–6.

Rheumatoid arthritis. In a small, open-label study[1] of 12 patients with rheumatoid arthritis (p.11) refractory to other disease-modifying antirheumatic drugs including ciclosporin, 7 had significant response to tacrolimus after treatment for 6 months, with 4 of these patients maintaining this response after 2 years of therapy. In a larger controlled study,[2] tacrolimus improved disease activity in patients with rheumatoid arthritis resistant to methotrexate. Similarly, an open-label multicentre study involving 80 patients with active disease inadequately responsive to methotrexate alone, addition of tacrolimus 3 mg daily by mouth to methotrexate therapy produced a clinical improvement in about half. The regimen was considered to be generally well tolerated.[3] Tacrolimus in an oral dose of 3 mg once daily has been licensed for use in refractory rheumatoid arthritis in some countries; elderly patients may be given 1.5 mg once daily.[4,5]

1. Gremillion RB, *et al.* Tacrolimus (FK506) in the treatment of severe, refractory rheumatoid arthritis: initial experience in 12 patients. *J Rheumatol* 1999; **26:** 2332–6.
2. Furst DE, *et al.* Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis Rheum* 2002; **46:** 2020–8.
3. Kremer JM, *et al.* Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate: a six-month, open-label study. *Arthritis Rheum* 2003; **48:** 2763–8.
4. Curran MP, Perry CM. Tacrolimus: in patients with rheumatoid arthritis. *Drugs* 2005; **65:** 993–1001.
5. Kawai S, Yamamoto K. Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. *Rheumatology (Oxford)* 2006; **45:** 441–4.

Scleroderma. There are reports of response to tacrolimus in patients with scleroderma (p.1817).

Skin disorders. Topical tacrolimus has been used to treat various skin disorders. Aside from its licensed use in eczema (above), and use in psoriasis and pyoderma gangrenosum (see above), there are reports of benefit in granuloma annulare,[1,2] lichen sclerosus,[3] lichen striatus,[4] pityriasis alba,[5] pityriasis lichenoides,[6] seborrhoeic dermatitis,[7] as well as the skin manifestations of angiolymphoid hyperplasia,[8] pruritus due to primary biliary cirrhosis,[9] and facial cutaneous lupus erythematosus.[10]

1. Harth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 2004; **150:** 792–4.
2. Jain S, Stephens CJM. Successful treatment of disseminated granuloma annulare with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1042–3.
3. Hengge UR, *et al.* Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. *Br J Dermatol* 2006; **155:** 1021–8.
4. Sorgentini C, *et al.* Lichen striatus in an adult: successful treatment with tacrolimus. *Br J Dermatol* 2004; **150:** 776–7.
5. Rigopoulos D, *et al.* Tacrolimus ointment 0.1% in pityriasis alba: an open-label, randomized, placebo-controlled study. *Br J Dermatol* 2006; **155:** 152–5.
6. Simon D, *et al.* Successful treatment of pityriasis lichenoides with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1033–5.
7. Braza TJ, *et al.* Tacrolimus 0.1% ointment for seborrhoeic dermatitis: an open-label pilot study. *Br J Dermatol* 2003; **148:** 1242–4.
8. Mashiko M, *et al.* A case of angiolymphoid hyperplasia with eosinophilia successfully treated with tacrolimus ointment. *Br J Dermatol* 2006; **154:** 803–4.
9. Aguilar-Bernier M, *et al.* Successful treatment of pruritus with topical tacrolimus in a patient with primary biliary cirrhosis. *Br J Dermatol* 2005; **152:** 808–9.
10. Tzung T-Y, *et al.* Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, double-blind, bilateral comparison study. *Br J Dermatol* 2007; **156:** 191–2.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Prograf; Protopic; Tacraf; Tacro-Tic; Tacroinmun; ***Austral.:*** Prograf; ***Austria:*** Prograf; Protopic; ***Belg.:*** Progaft; Protopic; ***Braz.:*** Prograf; Protopic; ***Canad.:*** Prograf; Protopic; ***Chile:*** Cromidin; Prograf; Protopic; T-Inmun; ***Cz.:*** Advagraf; Prograf; Protopic; Protopy; ***Denm.:*** Prograf; Protopic; ***Fin.:*** Prograf; Protopic; ***Fr.:*** Advagraf; Prograf; Protopic; ***Ger.:*** Prograf; Protopic; ***Gr.:*** Prograf; Protopic; ***Hong Kong:*** Prograf; Protopic; ***Hung.:*** Prograf; Protopic; ***India:*** Mustopic; PanGraf; Tacroz†; ***Indon.:*** Protopic; ***Irl.:*** Prograf; Protopic; ***Israel:*** Prograf; Protopic; ***Ital.:*** Prograf; Protopic; ***Jpn:*** Prograf; Protopic; ***Malaysia:*** Prograf; Protopic; ***Mex.:*** Limustin; Proalid; Prograf; ***Neth.:*** Prograf; Progaft; Protopic; Protopy; ***Norw.:*** Prograf; Protopic; ***NZ:*** Prograf; ***Philipp.:*** Prograf; Protopic; ***Pol.:*** Prograf; Protopic; ***Port.:*** Prograf; Protopic; Protopy; ***Rus.:*** Prograf (Програф); ***S.Afr.:*** Prograf; ***Singapore:*** Prograf; Protopic; ***Spain:*** Prograf; Protopic; ***Swed.:*** Prograf; Protopic; ***Switz.:*** Prograf; Protopic; ***Thai.:*** Prograf; Protopic; ***Turk.:*** Prograf; ***UK:*** Advagraf; Prograf; Protopic; ***USA:*** Prograf; Protopic; ***Venez.:*** Prograf.

Voclosporin *(USAN, rINN)*

ISA-247; ISATX-247; LX-211; R-1524; Voclosporina; Voclosporine; Voclosporinum. Cyclo{L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)nona-6,8-dienoyl]-(2*S*)-2-aminobutanoyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl}.

Вокльоспорин

$C_{63}H_{111}N_{11}O_{12}$ = 1214.6.

CAS — 515814-01-4.