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New therapies

A new immunosuppressant: tacrolimus

D Geraint James

Summary
Tacrolimus is the new name for the Japanese immunosuppressant drug FK506. It blocks interleukin 2 transcription thereby inhibiting the CD4 Th-1 lymphocyte response to foreign antigens. It also selectively inhibits cytokine secretion of IL3, IL4 and interferon-gamma. It is metabolised by the cytochrome P-450 enzyme system. The results of two trials indicate that it is similar to cyclosporin in efficacy and toxicity.

Keywords: tacrolimus, immunosuppressant

Tacrolimus is the new name for the Japanese drug FK506, which is competing vigorously with cyclosporin in the expanding world of immunosuppression. Its name suggests its background, constitution and value. The opening letter T stands for Tsukuba, Japan. It is a macrolide, hence the letters ACROL, and the letters IMUS represent its powers of immunosuppression. This macrolide immunosuppressant was isolated in 1984 from *Streptomyces tsukubaensis* by Fujisawa scientists as white crystals or a crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform. It blocks interleukin 2 transcription, thereby inhibiting the CD4T helper lymphocyte response to foreign antigens. It also selectively inhibits cytokine secretion of IL3, IL4 and interferon-gamma. Following absorption from the gastrointestinal tract, tacrolimus has a peak concentration in blood and plasma of 1.5–3.5 hours and a half-life of about five hours. It is metabolised by the cytochrome P-450 enzyme system.

Its safety and value have been assessed following liver transplantation in two multicentre trials, one in the US and the other in Europe. The results were equivalent to cyclosporin-based immunosuppressive regimens. Patient and graft survival were similar for both treatments and also similar, at about 80%, in both US and European trials. It is important to be aware of drugs which may affect tacrolimus blood levels (box 1). As with cyclosporin, there are numerous adverse effects when given by mouth and intravenously (box 2). These are due to overdosage and may respond to a reduction of the dose.

Treatment is initiated within six hours after transplantation by intravenous infusion of 0.05–0.10 mg/kg/day and then converted to oral therapy of 0.15–0.30 mg/kg/day in two divided doses every 12 hours.

At the present time the main indication for tacrolimus is the prevention of rejection after liver transplantation. As with cyclosporin, the list of indications will inevitably broaden. Reports are already appearing of its efficacy in uveitis unresponsive to cyclosporin and for pyoderma gangrenosum.

Drugs which may effect tacrolimus blood levels

Increase
- calcium channel blockers
- antifungal agents
- erythromycin
- clarithromycin
- cyclosporin
- cimetidine
- danazol
- methylprednisolone
- metoclopramide

Decrease
- phenobarbitone
- phenytoin
- carbamazepine
- rifampicin
- rifabutin

Box 1

Adverse effects of tacrolimus

CNS
- headache
- tremor
- insomnia
- paraesthesia

Gastro-intestinal
- nausea
- diarrhoea
- constipation
- anorexia
- vomiting
- abnormal liver function

Cardiovascular
- hypertension

Urogenital
- oliguria
- urinary infection
- kidney damage

Metabolic
- hyperkalaemia
- hypokalaemia
- hyperglycaemia
- hypomagnesia

Haematological
- anaemia
- leucocytosis
- thrombocytopenia

Respiratory
- pleural effusion
- atelactasis
- dyspnoea

Miscellaneous
- rash
- pruritus
- fever
- ascites
- peripheral oedema

Box 2

Royal Free Hospital School of Medicine, University of London, Rowland Hill Street, London NW3 2PF, UK
DG James

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