Tacrolimus
A Review of its Pharmacology, and Therapeutic Potential in Hepatic and Renal Transplantation

David H. Peters, Andrew Fitton, Greg L. Plosker and Diana Faulds
Adis International Limited, Auckland, New Zealand

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Tacrolimus (FK 506) is a macrolide immunosuppressant which possesses similar but more potent immunosuppressant properties compared with cyclosporin, inhibiting cell-mediated and humoral immune responses. Like cyclosporin, tacrolimus demonstrates considerable interindividual variation in its pharmacokinetic profile. This has caused difficulty in defining the optimum dosage regimen and has highlighted the usefulness of therapeutic drug monitoring. Most clinical studies with tacrolimus have neither been published in their entirety nor subjected to extensive peer review; there is also a paucity of published randomised investigations of tacrolimus versus cyclosporin, particularly in renal transplantation. Despite these drawbacks, tacrolimus has shown notable efficacy as a rescue or primary immunosuppressant therapy when combined with corticosteroids in adult and paediatric recipients following liver or kidney transplantation. Indeed, graft salvage rates in patients experiencing rejection or drug-related toxicity were ≥50%, although data in renal transplantation are limited. Compared with cyclosporin as a primary immunosuppressant, tacrolimus showed comparable or greater patient/graft survival rates in liver allograft recipients (where cost savings associated with reduced hospitalisation costs were evident in one study), and comparable patient/graft survival in patients following kidney transplantation. Worthy of note was the efficacy of tacrolimus as a primary immunosuppressant in patients who received en bloc kidney allografts. The incidence of rejection was largely reduced following rescue therapy with tacrolimus and was generally lower (notably for refractory rejection) than that observed for cyclosporin, at least in liver allograft recipients. This was reflected in less need for adjunct immunotherapy including antilymphocyte preparations for the treatment of rejection episodes. The potential for reduction or withdrawal of corticosteroid therapy with tacrolimus appears to be a distinct advantage compared with cyclosporin, and this may be enhanced by the reduced incidence of infectious complications and of hypertension and hypercholesterolaemia reported by some investigators. In other respects, however, the tolerability profile of tacrolimus appears to be broadly similar to that of cyclosporin.

Against this background, preliminary data indicate that tacrolimus provides a valuable therapeutic alternative to retransplantation in patients experiencing liver or kidney graft rejection or drug-related toxicity. Pending confirmation of initial randomised studies and preliminary results from large randomised investigations, tacrolimus may well be considered as an alternative primary immunosuppressant to cyclosporin in hepatic (particularly) and renal transplantation. Furthermore, the steroid-sparing effects of tacrolimus, although of benefit to all patient groups, may prove to be of particular worth in children and in en bloc kidney recipients. In these patients tacrolimus may well emerge as the drug of choice.

Clearly, further experience in the clinical setting will help clarify the role of tacrolimus in transplantation surgery. Nevertheless, this new immunosuppressant has already demonstrated its usefulness as an addition to the limited immunotherapeutic options available to date.

Pharmacodynamic Properties

The macrolide immunosuppressant, tacrolimus, displays similar, but more potent, immunosuppressive properties to cyclosporin, inhibiting cell-mediated and humoral immune responses. Through its interaction with a specific cytoplasmic immunophilin, tacrolimus inhibits calcium-dependent signal transduction pathways in T cells, thereby preventing transcription of a discrete