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Everolimus

A Viewpoint by Howard J. Eisen

Cardiology Section, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

Everolimus is a novel oral immunosuppressive agent which inhibits vascular smooth muscle cell proliferation by inhibiting activation of the p70 S6 kinase. It also has immunosuppressive effects via inhibition of interleukin (IL)-2- and IL-15-mediated T- and B-cell proliferation. Everolimus is a 40-*O*-(2-hydroxyethyl) congener of rapamycin, which is administered twice daily.

The cytochrome P450 enzymes 3A4, 3A5 and 2C8 are the major sites of metabolism of everolimus. As ciclosporin is metabolised by the same isoenzyme system, there is the potential for drug interactions with an increase in everolimus exposure. Clearance of everolimus is reduced by the macrolide antibiotics and itraconazole and increased by rifampicin. No effect was seen with calcium channel blockers, quinolones, trimethoprim-sulfamethoxazole or atorvastatin or pravastatin.

Everolimus has shown synergistic effects with ciclosporin in studies of rat orthotopic renal and heterotopic cardiac allografts, with a reduction in the ciclosporin dose needed to prevent rejection. Everolimus in combination with ciclosporin also prevented chronic cardiac and renal allograft rejection in rats with a reduction in intimal thickness. Bronchiolitis obliterans was prevented in porcine bronchial allografts.

In a large randomised, double-blind, multicentre trial in 634 cardiac allograft recipients, two dosages of everolimus (1.5 or 3 mg/day) were more effective than azathioprine in preventing biopsy-proven allograft rejection at grade 3 or above and the composite endpoint of allograft rejection, rejection with haemodynamic compromise, death or loss to follow-up, and graft loss or retransplantation. Both everolimus doses were also more successful in reducing the incidence of cardiac allograft vasculopathy (CAV) and markers of CAV severity determined by intravascular ultrasound.

The composite endpoint of biopsy-proven acute rejection, graft loss, death or loss to follow-up was similar between everolimus and MMF in clinical trials of renal transplant recipients at 1 year but lower for everolimus at 3 years with fewer cytomegalovirus infections.

Major adverse events in the clinical trials included elevated serum creatinine and triglycerides, thrombocytopenia and leukopenia. These were successfully managed in these clinical trials.

In conclusion, everolimus represents a new, well tolerated therapeutic approach for the prevention of acute and chronic rejection in cardiac and renal allograft recipients. ▲