

Everolimus

A Viewpoint by Udo Vester

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Major problems after solid organ transplantation are chronic graft dysfunction, cardiovascular morbidity and malignancies, all of which are at least partially due to the adverse effects of conventional immunosuppressive therapy.

Everolimus is a novel inhibitor of the p70 S6 kinase which arrests the cell cycle of lymphocytes and vascular smooth muscle cells in the G₁ phase. In pre-clinical and clinical studies everolimus has proven its immunosuppressive activity in solid organ transplantation. A synergistic action is suspected with ciclosporin, mycophenolate mofetil (MMF) and FTY720. Pharmacokinetic data have shown drug exposure with an intra- and interindividual variability of up to 50%. Therefore, therapeutic drug monitoring is advisable. The lower effective pre-dose blood concentration was 3 ng/mL in renal graft recipients.

Everolimus was well tolerated in transplant patients. The rate of viral infection including cytome-

galovirus was reduced in comparison to azathioprine or MMF, but bacterial infections were more frequent. The incidences of thrombocytopenia and leukopenia were modest. No long-term data on malignancies are available so far.

The main adverse effect of concern is hyperlipidaemia, which peaks in the first months of treatment and is responsive to lipid-lowering therapy. Surprisingly, despite this, everolimus ameliorates vascular remodeling in animal models and cardiac transplant recipients compared to other immunosuppressive drugs.

In conclusion, everolimus is an attractive new supplement or alternative to conventional immunosuppressive therapy in solid organ transplant patients. Future studies should explore the potential for synergy with other drugs as part of combination protocols. Data from larger cohorts on long-term effects on cardiovascular risks and chronic graft vasculopathy are awaited. Tolerability and adverse effects should be evaluated further in the early and stable phases after transplantation. Data on everolimus in the treatment of autoimmune diseases are also expected in the future. ▲