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# Sirolimus-tacrolimus combination immunosuppression.

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### **Sirolimus-tacrolimus combination immunosuppression.**

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#### **Abstract**

A series of 32 recipients of liver, kidney, or pancreas transplants who were treated with sirolimus and low-dose tacrolimus experienced a low rate of rejection and excellent graft function without drug-related toxic effects.

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A series of 32 recipients of liver, kidney, or pancreas transplants who were treated with sirolimus and low-dose tacrolimus experienced a low rate of rejection and excellent graft function without drug-related toxic effects.

Sirolimus is as effective as cyclosporin in preventing renal graft loss due to rejection while maintaining superior graft function.[1] Various studies have shown the safety and efficacy of the combination of sirolimus and cyclosporin, and the potential for cyclosporin dose reduction.[2] Sirolimus is effective when used alone or with cyclosporin after liver transplantation.[3] Sirolimus and tacrolimus have similar structures and compete for the same intracellular binding protein (FKBP12).[4] However, the sirolimus-FKBP12 complex does not inhibit calcineurin and T-cell activation as the tacrolimus-FKBP12 complex does, but it exerts its immunosuppressive effect by inhibiting mTOR, a protein essential for cytokine-driven T-cell proliferation. Experimental transplantation studies suggest synergism between sirolimus and tacrolimus.[5] We investigated whether sirolimus can be given safely to tacrolimus-treated transplant recipients and whether its addition allows the dose of tacrolimus to be decreased.

Between April, 1998, and May, 1999, we recruited 32 transplant recipients (16 female, 16 male) aged 16-69 years (mean 50). (Full details of the patients are available from the investigators.) Tacrolimus and sirolimus treatment was started on the day of transplantation via nasogastric tube at daily doses of 0.03 mg/kg (33% of the recommended dose) and 5 mg, respectively. Doses were subsequently adjusted to maintain trough concentrations of 3-7 [ $\mu$ g/L and 6-12 [ $\mu$ g/L, respectively. Prednisone was given as a 500 mg intravenous bolus during transplantation and subsequently at 25 mg/day tapering to 5-10 mg/day at 1 month. Steroids are being withdrawn from all patients beyond 3 months. Antithymocyte globulin was given to recipients of pancreas grafts for 3-7 days (mean 4.5). All patients received prophylaxis with trimethoprim and sulphamethoxazole against *Pneumocystis carinii*, and those at high risk of cytomegalovirus transmission received ganciclovir. Graft biopsies were done if there was biochemical or clinical evidence of graft dysfunction.

Indications for liver transplantation were cryptogenic cirrhosis (six), primary biliary cirrhosis (six), fulminant liver failure (four), hepatitis C (three), autoimmune hepatitis (two), [ $\alpha$ 1]-antitrypsin deficiency (one), and primary sclerosing cholangitis (one). Two patients received liver and kidney grafts for polycystic disease and for alcoholic cirrhosis with IgA nephropathy. Seven patients received pancreas transplants for diabetic nephropathy, two of whom had previously undergone kidney transplantation; the other five received kidney grafts simultaneously. One patient received an ABO-incompatible liver and another received a cross-match-positive kidney-liver combination.

30 (94%) of the 32 recipients are alive and well with normal function in all grafts 43-450 days (mean 230) after transplantation. 23 (92%) of the liver recipients are alive; five (20%) of these were comatose and on mechanical ventilation at the time of transplantation. A 57-year-old man with alcohol-associated autoimmune hepatitis who remained dependent on mechanical ventilation after liver transplantation died of a subarachnoid haemorrhage 66 days after transplantation. He did not have thrombocytopenia or hypertension. Necropsy showed cytomegalovirus infection of the lung and a normal liver. A 54-year-old woman with primary sclerosing cholangitis who was on treatment for intrahepatic abscesses at the time of transplantation died from hepatic-artery haemorrhage at home 28 days later. An abscess adjacent to the artery was found; the liver was normal.

Only one episode of rejection has occurred. A 52-year-old recipient, of her own volition, stopped all medications, including tacrolimus and sirolimus, for 1 week, because of transient malaise, 233 days after transplantation. She developed grade 1 rejection that was reversed by a 3-day course of prednisolone (500 mg/day) and the resumption of sirolimus and tacrolimus. At the time of rejection, sirolimus and tacrolimus concentrations in her blood were undetectable.

Only one other patient had cytomegalovirus, which was diagnosed by liver biopsy taken because of a symptomless rise in aminotransferases 92 days after transplantation. This 55-year-old cytomegalovirus-negative man had received a cytomegalovirus-positive liver and kidney graft for alcoholic cirrhosis and IgA nephropathy. He was initially thought to have rejection and was treated with bolus steroids before successful treatment with ganciclovir. He remained symptom-free throughout, and the kidney was not affected. The two recipients of pancreas after kidney grafts had culture-negative intra-abdominal abscesses due to peripancreatic fat necrosis 3 weeks and 8 weeks after transplantation; these resolved with operative drainage. Pancreas biopsy samples were both normal. Sirolimus or tacrolimus was transiently withheld in three patients because of infection. The rate and severity of bacterial and viral infection appeared lower than those previously seen in similar patients.

A 31-year-old morbidly obese (body-mass index 51 kg/m<sup>2</sup>) female liver recipient is receiving insulin and treatment for hypertension. No other cases of new-onset diabetes or hypertension have been seen. Only one patient is being treated for hyperlipidaemia. Mean cholesterol and triglyceride concentrations are 5.8 mmol/L (SD 2.2) and 4.5 mmol/L (3.1). Kidney function is near normal in all patients, with current serum creatinine of 92.8 [ $\mu$ ]mol/L (32.2) in liver recipients and 112 [ $\mu$ ]mol/L (25.4) in kidney recipients. These findings compare favourably with previous experience of full-dose tacrolimus or cyclosporin; the mean serum creatinine concentrations 1 year after transplantation were 120 [ $\mu$ ]mol/L and 138 [ $\mu$ ]mol/L respectively.

All patients are taking sirolimus and tacrolimus at doses of 4.2 mg/day (1.7) and 4.6 mg/day (2.5) achieving serum concentrations of 8.0 [ $\mu$ ]g/L (3.5) and 5.7 [ $\mu$ ]g/L (3.2) (IMX, Abbott Diagnostics, Mississauga, Ontario, Canada). There was wide variation between patients in absorption of tacrolimus and sirolimus but trough concentrations of both drugs correlated closely with total drug exposure.

The very low rates of renal dysfunction, hypertension, and diabetes in these patients are explained by the low blood concentrations of tacrolimus. Nevertheless, rejection occurred only in a patient who stopped treatment. The low rate of opportunistic infection suggests that the patients were not excessively immunosuppressed. The combination of sirolimus with low-dose tacrolimus should be investigated further in multicentre controlled trials.

## References

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