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Rapamycin-based rescue therapy after chronic rejection in a pediatric liver transplant patient

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Dear Editors:

Liver transplantation is a therapeutic procedure accepted by the scientific community for the treatment of a range of end-stage liver diseases in all age groups. However, acute and chronic graft rejections remain major problems, which lead to re-transplantation in a large number of cases [1]. Much has been published on the management of chronic failure of the transplanted liver, and, thanks to the new immunosuppressive drugs now available, there are many therapeutic approaches [2, 3].

Rapamycin, a macrocyclic lactone produced by *Streptomyces hygroscopicus*, resembles tacrolimus structurally and binds the same immunophilin FK506 12-kDa binding protein (FKBP-12) [4], with potent immunosuppressive properties. Its mechanism of action lies in blocking the signal pathway between the IL-2 receptor and nucleus, thereby suppressing cellular proliferation of T lymphocytes and B lymphocytes without affecting the calcineurin pathway [5]. The use of this new immunosuppressive agent has been reported in several articles on adult liver, kidney, or pancreas transplantation [6, 7, 8, 9, 10, 11]; however, only two reports have been published on children with liver and kidney transplants [12, 13]. The case of a pediatric patient saved from chronic graft rejection by rapamycin-based therapy is described herein.

The patient was a 12-year-old girl with a history of extrahepatic biliary atresia and Kasai porto-enterostomy before the age of 45 days. At 4 years of age she underwent orthotopic liver transplantation and suffered an episode of acute graft rejection 15 days after transplantation, which was managed with steroid pulses, and, because of steroid resistance, OKT 3 after 13 days, with good response. She was discharged and receiving immunosuppression therapy consisting of tacrolimus (FK506) and steroids, which were slowly tapered. She remained complication-free during 7 years of therapy with FK506 and with good blood trough concentrations until the age of 11 years, at which time she developed tonsillitis and cervical lymph node enlargement; malignancy was ruled out by biopsy. One month later, jaundice was observed. Laboratory values were: total bilirubin 40 mg/dl, direct bilirubin 29 mg/dl, AST 819 U/l, ALT 756 U/l, GGT 662 U/l, urea 36 mg/dl, and creatinine 0.3 mg/dl. Prothrombin time was always above 70%. Viral serology tests and CMV antigenemia were all negative. Anti-nuclear antibodies, anti-mitochondrial antibodies, liver-kidney microsomal antibodies, smooth muscle antibodies, peri-nuclear anti-neutrophil cytoplasmic antibodies,

antibodies to sialoglycoprotein receptor, and antibodies to liver cytosol type 1, were all negative.

Abdominal ultrasound showed normal liver parenchyma and normal flow of the porta and hepatic artery. No abdominal masses were observed. Liver biopsy showed liver parenchyma with mild chronic inflammatory component and ductopenia of greater than 50%. The histopathological diagnosis was chronic ductopenic rejection, which was treated with steroid pulses, FK506, and mycophenolate mofetil for 37 days, but with no clinical or laboratory improvement. The patient was, therefore, placed on the waiting list for re-transplantation. Upon parental consent, we decided on the compassionate use of rapamycin at 1 mg/day, which was increased to 1.5 mg/day, with blood levels between 4 and 6 ng/ml (because of simultaneous treatment with FK506 and mycophenolate mofetil), achieving an immediate decrease in altered liver-function values. The girl was discharged 2 months after admission, receiving FK506 at 0.1 mg/kg per day (levels 8–10 ng/ml) and rapamycin at 0.03 mg/kg per day (levels 4–6 ng/ml), with total bilirubin 10 mg/dl, direct bilirubin 6.6 mg/dl, AST 102 U/l, ALT 70 U/l, GGT 412 U/l, urea 33 mg/dl, and creatinine 0.28 mg/dl.

Five days after being discharged, she was re-admitted because of acute kidney failure with preserved diuresis, urea 158 mg/dl, and creatinine 2.5 mg/dl, in the context of the documented chronic liver graft rejection. Blood levels of rapamycin and FK506 were 3.9 ng/ml and 7.5 ng/ml, respectively. It was decided to stop these immunosuppressive agents, since no other possible cause was apparent and no data were available on their association with acute renal failure, and to continue with steroids and mycophenolate mofetil.

Five days later, renal function became normal, urea was 38 mg/dl, and creatinine 0.41 mg/dl, although

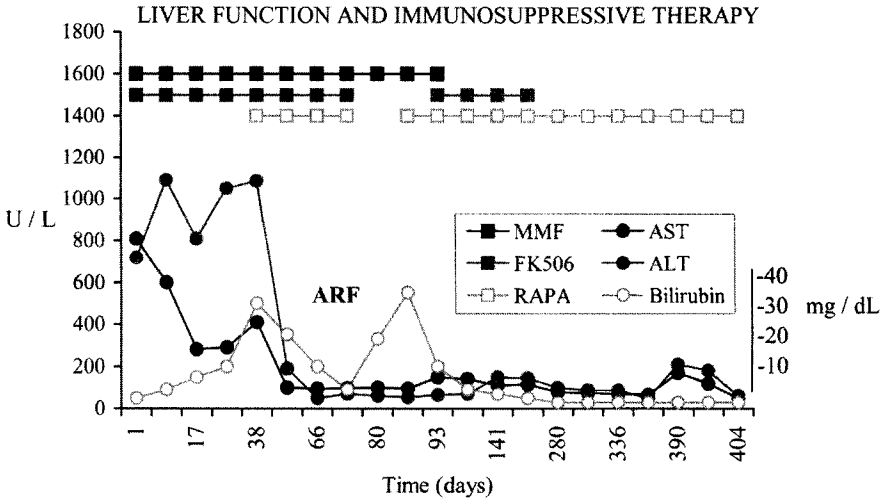

Fig. 1 Course of chronic rejection and treatment with immunosuppressors. Day 1 denotes the day on which clinical diagnosis of rejection was made (*ARF* acute renal failure, *MMF* mycophenolate mofetil, *FK506* tacrolimus, *RAPA* rapamycin)

transaminases and bilirubin were increased: AST 159 U/l, ALT 97 U/l, GGT 662 U/l, total bilirubin 44 mg/dl, and direct bilirubin 26 mg/dl. Again, she was given rapamycin starting at 1 mg/day (levels 2–4 ng/ml) and progressing to 2 mg/day (levels 4–6 ng/ml) (Fig. 1). Since the start of rapamycin management, cholesterol level and leukocyte and platelet counts had been normal. Prior to the introduction of rapamycin, triglyceride levels were between 420 and 640 mg/dl; within the following 3 months, triglyceride levels were between 295 and 810 mg/dl, and normal thereafter. As the clinical course was favorable, with a slow improvement in liver function, she was discharged 1.5 months after admission.

Clinical evolution was good, with normalization of liver function 9 months after the episode of chronic rejection (Fig. 1). At that time a second control biopsy was performed, due to clinical and functional improvement; however, morphological appearance of chronic rejection persisted, but with new cholangiocellular proliferation of the peripheral portal space.

One year after the rejection episode, controls have been periodic and continuous; the patient takes rapamycin at 2.2 mg/day (0.04 mg/kg per day, levels between 4 and 6 ng/ml) and mycophenolate mofetil at 250 mg/day (5.3 mg/kg per day, levels under 1 ng/ml). Liver-function tests now show total bilirubin 1 mg/dl, direct bilirubin 0.4 mg/dl, AST 25 U/l, ALT 58 U/l, GGT 42 U/l, prothrombin time 90%, triglycerides 79 mg/dl, cholesterol 135 mg/dl, leukocytes 7,800, platelet count 392,000, urea 27 mg/dl, and creatinine 0.19 mg/dl. To date, her clinical and general condition have been good, and she is completely involved in daily and school life in accordance with her age.

Experimental transplantation studies suggest a synergy between rapamycin and tacrolimus [10]. The use of rapamycin has been reported in several articles, mainly on adult transplant recipients. The possible indications for use include acute rejection, chronic rejection, hypertrophic cardiomyopathy, nephrotoxicity, treatment-resistant hemolytic anemia, seizures, pancreatitis, and resolving post-transplant lymphoproliferative disease (PTLD) [12, 13].

Notably, no nephrotoxicity, neurotoxicity, or diabetogenesis have

been reported with rapamycin management; however, leukopenia, thrombocytopenia, hypertriglyceridemia, hypercholesterolemia, raised hepatic aminotransferase enzyme levels [3, 4, 5], interstitial pneumonitis, bronchiolitis obliterans and organizing pneumonia, and pulmonary alveolar proteinosis [14] have been described in some patients. Recent data raise concern over an association between rapamycin and hepatic artery thrombosis. Furthermore, rapamycin may increase infection rates in liver transplant recipients in a dose-related fashion; low doses (2–4 mg) may reduce toxicity while warding off infection [15].

However, hypertriglyceridemia was the only problem related to rapamycin use in our patient for the first 3 months; thereafter, triglyceride levels remained normal. We consider that, in this particular case, recovery from chronic rejection was achieved with rapamycin, and, although the histopathology did not vary significantly, her biological and functional status have been very satisfactory, with the avoidance of re-transplantation, which would otherwise have been imminent.

Clinical improvement was the result of a better immunosuppressive management of the patient. Conversion to rapamycin treatment was safely achieved in our pediatric liver transplant recipient. Rapamycin appears to be effective in children who develop chronic rejection while on tacrolimus-based and mycophenolate mofetil-based immunosuppression. The long-term effect of rapamycin will be investigated further with a longer follow-up.

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