

Sirolimus Conversion in Liver Transplant Recipients With Calcineurin Inhibitor-Induced Complications: Efficacy and Safety

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Abstract

Objectives: To evaluate the efficacy and safety of conversion from calcineurin inhibitors to sirolimus among liver transplant recipients with calcineurin inhibitor-induced complications.

Materials and Methods: After receiving liver transplants, 25 patients with calcineurin inhibitor-induced complications (22 renal dysfunction and 3 new-onset diabetes mellitus) were converted from sirolimus to tacrolimus. The serum creatinine, sirolimus trough level, liver function, acute rejection episodes, and drug-related adverse effects were monitored.

Results: The patients were followed for 12 to 50 months (median, 25 months). The renal function of the 22 patients with renal dysfunction improved after sirolimus conversion. The serum creatinine levels were significantly lower at 3 months after conversion versus before conversion ($113.2 \pm 21.8 \mu\text{mol/L}$ vs $163.2 \pm 45.3 \mu\text{mol/L}$; $P < .05$). At the end of the follow-up, the average serum creatinine level was $101.9 \pm 23.4 \mu\text{mol/L}$ among the 20 living recipients. Diabetes also was under control in 3 diabetic recipients after the conversion. Four patients experienced episodes of acute rejection,

and intravenous steroid bolus therapy was administered in 2 of them. No graft was lost because of acute rejection. The adverse effects of sirolimus included hyperlipidemia (7/25), anemia (8/25), and mouth ulcers (9/25). All these adverse effects were relieved after a short-term symptomatic therapy, and no patient was withdrawn from the conversion trial.

Conclusions: Sirolimus monotherapy is effective and safe in liver transplant recipients. Conversion to sirolimus was associated with a sustained improvement in renal function and diabetes mellitus without an increased incidence of acute rejection episodes.

Key words: Liver transplant, Sirolimus, Calcineurin inhibitors, Complications, Conversion

Introduction

Introduction of calcineurin inhibitors has significantly improved the effectiveness of liver transplants and long-term patient survival. On the other hand, calcineurin inhibitors, themselves, would impair the maximal benefit of liver transplant by inducing various complications including renal function impairment, neurotoxicity, de novo diabetes mellitus, and hypertension. Sirolimus is a novel immunosuppressant without nephrotoxic, neurotoxic and diabetogenic properties, providing an alternate option for immunosuppression regimens. We retrospectively reviewed the clinical course of 25 patients who underwent sirolimus conversion from tacrolimus because of the presence of calcineurin inhibitor-induced complications after liver transplant to evaluate the effectiveness and

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safety of sirolimus monotherapy in liver transplant recipients.

Materials and Methods

Between October 2005 and December 2008, five hundred twenty-six liver transplants were performed in our center. Inclusion criteria in this retrospective study were (1) having undergone a de novo liver transplant, (2) having compatible donor-recipient ABO blood type, (3) having calcineurin inhibitor-induced complications, and (4) receiving sirolimus conversion. Twenty-five recipients were enrolled in this study. We analyzed the medical records of all 25 patients (all male; mean age, 53.1 ± 6.3 y). The study protocol was in accord with the ethical guidelines of the 1975 Helsinki Declaration, and was approved by our local institutional ethics committee. Written, informed consent was obtained from all subjects. The indications for transplant were cirrhosis secondary to hepatitis B virus infection (14/25), severe hepatitis (5/25), primary hepatic carcinoma with cirrhosis (4/25), and alcoholic cirrhosis (2/25). Twenty-two patients developed renal dysfunction, defined as *basal creatinine values* $\geq 132.6 \mu\text{mol/L}$ (1.5 mg/dL) in 3 consecutive tests with the exclusion of other possible causes. The other 3 patients had new-onset diabetes mellitus after the liver transplant, who received high-dose insulin therapy (80 to 130 U/d), but blood glucose levels remained unstable.

Immunosuppressive conversion protocol

A triple immunosuppression regimen consisting of an IL-2 receptor antibody (basiliximab), tacrolimus, and steroids was used in all 25 patients. Two doses of basiliximab (20 mg) were administered intraoperatively on the fourth day after the transplant. A dose of 500 mg methylprednisolone was given intraoperatively and on day 1 after liver transplant, then 240 mg on day 2, and tapered 10 mg every day. At the end of the intravenous steroid reduction, intravenous steroids were converted to methylprednisolone tablets with an initial dosage of 48 mg on day 9 postoperatively, which was reduced by 8 mg every 3 days and maintained at 4 mg/d thereafter, until they were completely stopped 3 months after the liver transplant. Tacrolimus was added on day 4 at an initial dosage of 0.04 mg/kg/d , and the dosage was adjusted to maintain a trough level of 6 to 12 ng/mL. Eleven patients took

mycophenolate mofetil (MMF) (750 mg twice daily), which was withdrawn within 3 to 6 months after liver transplant.

Sirolimus was initiated at a dosage of 4 mg/d after weeks 4 to 6 after the liver transplant and the dosage was adjusted to achieve a target trough level of 5 to 10 ng/mL. Simultaneously, the dosage of tacrolimus used was halved and withdrawn within 1 to 2 weeks after conversion. At the beginning of sirolimus conversion, all patients were still on methylprednisolone (4 mg once daily). In the 11 patients who took MMF remained on MMF (750 mg twice daily). And at the end of the follow-up, all patients were off steroids and MMF, unless they were being used for treatment of acute rejection.

Follow-up

The serum creatinine (Cr), serum lipids (cholesterol, triglycerides), blood glucose, liver function tests (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]), drug adverse effects, and acute rejection episodes were evaluated before conversion to sirolimus at 1, 3, and 6 months, and at the end of follow-up.

Statistical Analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 13.0, IBM Corporation, Armonk, New York, USA). Continuous variables were tested for normal distribution and expressed as means $\pm$ standard deviation (SD) or median (range) as appropriate. The *t* test was applied to compare differences between the groups. For all analyses, a *P* value $< .05$ was considered statistically significant.

Results

Calcineurin inhibitor-induced complications

Twenty-two patients had renal dysfunction at 7 to 32 months after the transplant. In 15 of the 22 patients, serum creatinine decreased at 1 month after conversion. In the remaining 7 patients, the serum creatinine remained stable at the value before conversion, and no progressive increment was observed. The average serum creatinine began to decrease but without significant difference at this time. At 3 months after conversion, the serum creatinine of all 22 patients decreased significantly before versus after conversion. At 6 months after conversion, a

further decrement was observed. Two patients died of tumor recurrence at 11 and 18 months after conversion, while the other 20 patients had stable and improved renal function at the end of follow-up (Table I).

Table 1. Change of serum creatinine before and after conversion.

Time	Serum Cr ($\mu\text{mol/L}$)	t value	P value
Preconversion	163.2 $\pm$ 45.3		
1 mo after conversion	143.5 $\pm$ 44.1	1.87	> .05
3 mo after conversion	113.2 $\pm$ 21.8	5.37	< .05
6 mo after conversion	99.6 $\pm$ 20.8	6.15	< .05
End of follow-up (12 to 50 mo)	101.9 $\pm$ 23.4	6.23	< .05

Three patients developed de novo diabetes mellitus at 8 to 14 months after the liver transplant and received insulin therapy. The conversion to sirolimus was initiated at 13 to 21 months after the liver transplant when the dosage of insulin had reached 80 to 130 U/d but the blood glucose levels were still out of control. At 1 month after conversion, hyperglycemia improved, and the dosage of insulin used was reduced gradually. Until then, we reported the patients had been followed for 12 to 28 months, the dosage of insulin used was 24 to 32 U/d, and the blood glucose was stable.

Acute rejection episodes

Sirolimus was given to 22 patients at a dosage of 0.5 to 2.5 mg/d, with blood trough levels of 4.5 to 10.6 ng/mL. Four patients (16%), including 3 with liver cirrhosis secondary to hepatitis B virus infection and 1 with severe hepatitis, developed a biopsy-proven acute rejection within 6 months after conversion. Two patients were treated by the readdition of tacrolimus. The other 2 patients were treated with intravenous steroid bolus therapy, and then tapered until complete withdrawal. Sirolimus was not withdrawn in all above 4 cases, and no graft loss happened because of acute rejection.

Toxicity and adverse effects of sirolimus

During follow-up, 7 patients (28.0%) had hypercholesterolemia, and 3 were treated with statins. Eight patients (32.0%) had anemia or thrombocytopenia and were treated with blood transfusion and granulocyte colony-stimulating factor. Nine patients (36.0%) had aphthous ulcers and were cured by a dosage reduction of sirolimus, vitamin C administration, and regional treatment. No patient was withdrawn from the conversion trial.

Discussion

Introduction of calcineurin inhibitors has significantly improved the effectiveness of liver transplant. However, various adverse effects of calcineurin inhibitors have undesirable effects on the quality of life and long-term survival of liver transplant recipients. The most-frequent adverse effects of calcineurin inhibitors include renal dysfunction, neurotoxicity, new-onset diabetes mellitus, and hypertension. Twenty percent of liver transplant recipients receiving calcineurin inhibitors would develop renal dysfunction at 5 years after the liver transplant.¹ Withdrawal or reduction of calcineurin inhibitors can limit the occurrence of these adverse effects but may yield a higher risk of acute rejection episodes, which may result in graft failure or even death.

Sirolimus is a novel immunosuppressant without nephrotoxic, neurotoxic, and diabetogenic properties.² Sirolimus was introduced to liver transplant to minimize the use of calcineurin inhibitors recently, especially for reducing calcineurin inhibitor-induced renal dysfunction. Sirolimus can limit or even avoid the adverse effects of calcineurin inhibitors and simultaneously guarantee adequate immunosuppression.³⁻⁶

There are 2 regimens for converting to sirolimus from calcineurin inhibitors in liver transplant.⁵ One is partial conversion by combining low-dose sirolimus with reduced calcineurin inhibitors, which was used in most studies of the early trials. The other is complete conversion by cessation of calcineurin inhibitors and addition of sirolimus monotherapy or in combination with steroids and/or MMF. We initiated a research project on partial conversion to sirolimus in liver transplant recipients with calcineurin inhibitor-induced renal dysfunction and satisfactory results were achieved.⁷ This study is to evaluate the effectiveness and safety of converting from calcineurin inhibitors to sirolimus monotherapy among liver transplant recipients with calcineurin inhibitor-induced complications.

This study summarizes use of sirolimus conversion in 25 liver transplant recipients who developed calcineurin inhibitor-related complications. After conversion, renal function was significantly improved. In the following 12 to 50 months, the curative effects were stable and no deterioration of renal function was observed. The

blood glucose levels of 3 patients with calcineurin inhibitor-induced diabetes mellitus were under control after conversion, and the insulin dosage was decreased, and hyperglycemia was well-controlled in the 12- to 28-month follow-up. However, some researchers argue against sirolimus monotherapy because it may increase the risk of acute rejection. A rejection rate of up to 75% after sirolimus monotherapy has been reported.⁸ Therefore, they suggest that sirolimus should be added to, but not completely replace, calcineurin inhibitors to reduce episodes of acute rejection. However, more and more studies proved that sirolimus monotherapy was safe and did not increase the risk of acute rejection.^{5,9} In this study, only 4 in 25 patients (16.0%) developed acute rejection. Among them, 2 patients received re-addition of calcineurin inhibitors, and intravenous steroid bolus therapy was initiated in the other 2 patients. No hormone-resistant refractory rejection occurred.

The adverse effects of sirolimus include liver dysfunction, anemia, leukopenia, thrombocytopenia, hyperlipidemia, aphthous ulcers, and delayed wound healing.¹⁰ Hyperlipidemia is a common adverse effect in long-term use of sirolimus. In the current study, 7 patients developed hyperlipidemia at 6 to 20 months after conversion and were given a low-fat diet and dosage reduction of sirolimus, among which 3 cases still received lipid-lowering drug therapy. Hyperlipidemic patients experienced increased risk of cardiocerebral vascular accidents. Therefore, blood lipid levels should be monitored in patients with long-term use of sirolimus and given lipid-lowering medications when necessary. Eight cases developed anemia or thrombocytopenia and were relieved after blood infusion and medications. Nine patients developed aphthous ulcers and were relieved after reducing sirolimus and use of vitamin C. The US Food and Drug Administration had issued a warning that sirolimus may increase the risk of hepatic artery thrombosis and delay wound healing. But most reports did not show that the application of sirolimus was associated with increased risk of hepatic artery thrombosis.¹¹ In this study, no hepatic artery thrombosis was observed.

In conclusion, in line with most current research, this study supports that sirolimus monotherapy is

effective and safe in liver transplant recipients. For patients with calcineurin inhibitor-induced complications after a liver transplant, sirolimus conversion can provide enough immunosuppression and yield a sustained improvement in renal function and diabetic status without an increased incidence of acute rejection episodes. Nonetheless, for patients receiving long-term therapy with sirolimus, adverse effects should be monitored. Most sirolimus-related adverse effects are mild and can be well controlled by adjusting sirolimus dosage and symptomatic treatment. Further prospective studies should be conducted to confirm the benefit of sirolimus in liver transplant recipients with calcineurin inhibitor-induced complications.

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