—Case Reports—

Hepatotoxicity Caused by Both Tacrolimus and Cyclosporine after Living Donor Liver Transplantation

Nobuhiko Taniai, Koho Akimaru, Yosinori Ishikawa,
Tomohiro Kanada, Daisuke Kakinuma, Yoshiaki Mizuguchi,
Yasuhiro Mamada, Hiroshi Yoshida and Takashi Tajiri

Surgery for Organ Function and Biological Regulation, Graduate School of Medicine, Nippon Medical School

Abstract

We present a case report of a posttransplant patient who had hepatotoxicity due to both tacrolimus and cyclosporine and cholestatic jaundice due to tacrolimus. The patient did not show sustained improvement in enzyme and bilirubin abnormalities after an initial change from tacrolimus to cyclosporine or with a change back to tacrolimus, but he ultimately showed improvement when the blood concentration of tacrolimus was lowered. A 56-year-old man with subacute fulminant hepatitis induced by acarbose was admitted to our hospital for living donor liver transplantation. The liver graft consisted of the left lobe from his ABO-identical son. The early posttransplant course was uneventful. The serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin improved initially, but the ALT and AST levels later increased. A liver biopsy suggested a presumptive diagnosis of drug reaction. All drugs were discontinued, the immunosuppressive agent was changed from tacrolimus to cyclosporine. After initial improvement, the ALT and AST levels increased again. Assuming a reaction to cyclosporine, we decreased the concentration of cyclosporine in the blood. The enzyme levels improved temporarily but again began to rise. We changed the immunosuppressive agent to tacrolimus, which resulted in improvements in the ALT and AST levels; however, the total bilirubin level increased. We interpreted this increase as tacrolimus-induced cholestasis; in response, we decreased the blood concentration of tacrolimus to between 3 and 5 ng/dL and added 1,000 mg of mycophenolate mofetil to the drug regimen. The patient recovered without further complications. Repeated liver biopsies throughout the hospital course suggested that the mild mononuclear cell infiltration observed in a few triads had not been caused by acute rejection but had possibly been drug-induced. (J Nippon Med Sch 2008; 75: 187–191)

Key words: living donor liver transplantation, hepatotoxicity, calcineurin inhibitors

Introduction
cyclosporine are widely used as immunosuppressive agents after liver transplantation. Although its clinical application is limited owing to adverse effects, such as neurotoxicity, nephrotoxicity, and

Correspondence to Nobuhiko Taniai, MD, Department of Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyou-ku, Tokyo 113-8603, Japan
E-mail: Taniai@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

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new-onset diabetes mellitus, tacrolimus is currently prescribed to nearly 90% of liver transplant recipients. Cyclosporine rescue therapy is invaluable in cases of unacceptable side effects, and hepatotoxicity sometimes makes it necessary to switch between these two drugs.

We present a case in which hepatotoxicity was induced by both tacrolimus and cyclosporine, and cholestatic jaundice was induced by tacrolimus. The patient’s hepatic complications did not resolve completely after the immunosuppressive agent was changed from tacrolimus to cyclosporine or vice versa but did ultimately resolve when the dose of tacrolimus was lowered.

**Case Report**

A 56-year-old Japanese man with subacute fulminant hepatitis induced by acarbose was admitted to our hospital for living donor liver transplantation. Before the transplantation, he was negative for autoimmune antibodies and had no evidence of active infection with hepatitis A, B, or C virus; cytomegalovirus; or Epstein-Barr virus. The liver graft consisted of the left lobe and middle hepatic vein from his ABO-identical son, who was negative for hepatitis B core antibodies preoperatively. The donor’s left lobe weighed 639 g, which was equivalent to 56.2% of the recipient’s standard liver volume. The operation took 18 hours and 15 minutes, with a cold ischemic time of 50 minutes and warm ischemic time of 125 minutes. Total blood loss was 9,500 mL, and the patient received transfusions of 2,800 mL of concentrated red blood cells, 4,480 mL of fresh-frozen plasma, and 800 mL of platelet concentrate.

Tacrolimus and methylprednisolone were administered for immunosuppression. The immediate posttransplant course was uneventful. The serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyltransferase (γ-GTP), and total bilirubin improved to 49 U/L, 171 U/L, 141 IU/L, 47 IU/L, and 1.7 mg/dL, respectively, by postoperative day (POD) 6. On POD 8, the total bilirubin level remained at 1 to 2 mg/dL, and the ALP and γ-GTP levels were within normal limits; however, the ALT and AST levels had increased to 170 U/L and 307 U/L, respectively, and a liver biopsy was performed. Histopathological examination of the biopsy specimen revealed swollen hepatic cells and polymuclear cells with scattered areas of necrosis. There was no histological evidence of cholestasis. Drug-induced cytotoxicity was strongly suspected, and the administration of all drugs, including heparin and methylprednisolone, was discontinued.

Owing to continued increases in the levels of ALT and AST, cyclosporine was started for immunosuppression on POD 10. The ALT, AST, and total bilirubin levels improved to 35 U/L, 56 U/L, and 0.6 mg/dL, respectively, by POD 21. The ALP, γ-GTP, and total bilirubin levels remained within normal limits; however, the ALT and AST levels increased again. Suspecting cyclosporine cytotoxicity, we decreased the cyclosporine blood concentration to 150 ng/dL. The enzyme levels improved, but the improvement was not sustained. The immunosuppressive agent was changed back to tacrolimus on POD 46, and the ALT and AST levels improved; however, the ALP, γ-GTP, and total bilirubin levels increased to 454 U/L, 170 IU/L, and 10 mg/dL, respectively, by POD 60. At that time, abdominal computed tomography and ultrasonography showed no bile duct dilatation, and we diagnosed tacrolimus-induced cholestasis. We reduced the blood concentration of tacrolimus to between 3 and 5 ng/dL and added 1,000 mg mycophenolate mofetil to the drug regimen. The remainder of the patient’s recovery was uncomplicated, and he was discharged on POD 90 (Fig. 1).

During the postoperative course, other possible causes of the abnormal enzyme and bilirubin levels were investigated. Postoperatively, there was no evidence of active infection with hepatitis A, B, or C virus; cytomegalovirus; Epstein-Barr; *Candida*; or *Aspergillus*. Throughout the postoperative period, Doppler ultrasonography showed normal blood flow in the hepatic artery, portal veins, and hepatic veins. Liver biopsies were performed on POD 8, 24, 46, and 52 to investigate possible causes of the elevated
ALT, AST, and total bilirubin levels.

In the biopsy specimen obtained on POD 8, most of the portal triads showed no cellular infiltration; there was no endothelialitis of the portal vein and no bile duct destruction. A few triads showed mononuclear cell infiltration. No hemorrhage or congestion was seen in the lobules. However, in zones 2 and 3, we found focal necrosis consisting of apoptotic hepatocytes and thinner hepatocytes with eosinophilic cytoplasm, which had accumulated mononuclear cells and histiocytes. Occasional hemorrhage and collapse were observed in all zones. No endothelialitis of the hepatic vein was seen (Fig. 2).

The biopsies suggested that the mild mononuclear cell infiltration occurring in a few triads had not been caused by acute rejection but was possibly drug-induced focal necrosis. This possibility is consistent with the clinical course and findings.

Discussion

Although tacrolimus-based immunosuppression is currently accepted as the main therapy in several transplant centers worldwide, major side effects associated with its use are sometimes encountered following solid organ transplantation. In many cases, the side effects can be severe and do not resolve with dosage reduction alone. Conversion to cyclosporine therapy offers an option to patients having adverse effects, which include neurotoxicity, nephrotoxicity, hepatotoxicity, and new-onset diabetes mellitus. In most reports, tacrolimus hepatotoxicity has been characterized by elevated levels of hepatocellular enzymes, either alone or with minimal cholestasis and hyperbilirubinemia. Recently, Ganschow et al. have reported tacrolimus-induced cholestatic syndrome following pediatric liver transplantation.

Cyclosporine hepatotoxicity has also been
reported to cause cholestasis\textsuperscript{11,12}, but reduction of the cyclosporine dosage alone has been sufficient to resolve the presumed hepatotoxicity\textsuperscript{11}. Most cases involving conversion from cyclosporine to tacrolimus are related to graft rejection\textsuperscript{13,14}, but the immunosuppressive activity of cyclosporine is poor compared with that of tacrolimus.

In our case, the liver biopsies did not reveal acute rejection but suggested a chemical disorder. Reducing the cyclosporine dose by 75% did not resolve the presumed cyclosporine-related hepatotoxicity. Therefore, we changed back to tacrolimus, using a lower dosage because the antirejection dosage required on POD 46 was lower than the dosage required during the earlier postoperative period. Although the levels of hepatocellular enzymes gradually decreased, tacrolimus induced severe intrahepatic cholestasis. Only a few studies have reported that tacrolimus causes severe cholestatic complications\textsuperscript{9,10}. Nevertheless, we believed that this side effect was related to tacrolimus because the patient had no signs of rejection, no septic complications, and no vascular or bile duct strictures and had not received other potentially cholestatic agents, such as antibiotics, antifungals, phenytoin, atenolol, and captopril.

Fearing acute graft rejection if tacrolimus were discontinued completely, we decreased the blood concentration of tacrolimus by reducing the dosage by 75%. The total bilirubin level gradually normalized.

**Summary**

Few cases have been reported in which both tacrolimus and cyclosporine caused hepatotoxicity and tacrolimus induced cholestasis. Our patient recovered after we switched from tacrolimus to cyclosporine and back to tacrolimus and changed doses and blood concentrations of each drug in response to clinical, biochemical, and histopathological monitoring. In cases such as this one, the nature and cause of the hepatotoxicity must be accurately determined to maximize the benefits and minimize the morbidity of the immunosuppressant agents tacrolimus and cyclosporine.

**References**


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