Hepatic veno-occlusive disease resulting in tacrolimus toxicity after allogeneic hematopoietic stem cell transplantation

Seung-Hwan Shin, Seung-Ah Yahng, Jae-Ho Yoon, Sung-Eun Lee, Byung-Sik Cho, Yoo-Jin Kim
Catholic Blood and Marrow Transplantation Center, College of Medicine, The Catholic University of Korea, Seoul, Korea

Abstract
Tacrolimus is a widely used immunosuppressive agent for the prophylaxis of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation (HSCT). Since tacrolimus is primarily metabolized by the liver, hepatic dysfunction may affect its metabolism. Hepatic veno-occlusive disease (VOD) is an early complication of HSCT that results in hepatic dysfunction, suggesting that VOD may affect tacrolimus metabolism. We report a case of hepatic VOD accompanied by a sustained high blood trough level of tacrolimus despite its discontinuation. The findings of this case suggest that the elimination of tacrolimus can be markedly delayed in patients with hepatic VOD, and that the clinician should carefully modulate the drug dosage for these patients.

Key Words Tacrolimus, Veno-occlusive disease, Hematopoietic stem cell transplantation

INTRODUCTION
Tacrolimus is a potent macrolide lactone immunosuppressive agent used in the prophylaxis of graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplantation (HSCT), the prevention or treatment of graft rejection in solid organ transplantations, and the treatment of various autoimmune diseases [1-3]. Tacrolimus is primarily metabolized in the liver; consequently, hepatic dysfunction may affect its metabolism [2]. Hepatic veno-occlusive disease (VOD) is an early complication of HSCT that manifests as hepatomegaly, right upper quadrant pain, jaundice, and ascites, and is characterized by the obstruction of hepatic venous outflow due to the occlusion of the terminal hepatic venules and hepatic sinusoids. In turn, reduced hepatic venous outflow leads to hepatocyte injury and death [4]. There has been only one report regarding prolonged half-life and delayed clearance of tacrolimus due to hepatic dysfunction in VOD [5]. We report a case of hepatic VOD accompanied by a sustained high blood trough level of tacrolimus despite its discontinuation.

CASE REPORT
A 40-year-old man with myelodysplastic syndrome (refractory anemia with excess blasts-2) underwent HSCT from a familial haploidentical donor. The conditioning began with 400 cGy total body irradiation (day –9 to –8), 30 mg/m² fludarabine (day –7 to –3), 3.2 mg/kg intravenous busulfan (day –6 to –5), and 1.25 mg/kg rabbit anti-thymocyte globulin (day –4 to –1). The results of all the baseline liver function tests and Doppler ultrasonography examination were within normal ranges before HSCT. Continuous infusion of low-dose heparin accompanied by administration of ursodeoxycholic acid was conducted for the prophylaxis of VOD. GVHD prophylaxis consisted of tacrolimus and 5 mg/m² methotrexate (day 1, 3, 6, and 11). Tacrolimus was administered by continuous intravenous infusion at an initial dose of 0.03 mg/kg, and the dose was adjusted to maintain a constant blood trough level between 10–20 ng/mL. Neutrophil and platelet engraftment occurred on days 11 and 13, respectively. Intravenous tacrolimus was converted to oral form with a 4-fold increase, and the dose...
was adjusted to maintain a blood trough level between 5–10 ng/mL. The patient was discharged without any early complications. On day 41, the patient visited the emergency room complaining of right upper quadrant pain along with abdominal distension, progressive thrombocytopenia, and weight gain. The patient’s serum bilirubin level began to rise on day 45 (1.55 mg/dL), and his body weight increased consistently. The blood trough level of tacrolimus was 19.2 mg/dL, and the patient complained of depressed mood and suicidal thoughts. We began to taper tacrolimus rapidly, and the drug was substituted with steroids. Examination with Doppler ultrasonography on day 46 showed a flow reversal in the portal vein, presence of ascites, and thickening of the gallbladder wall. These findings led to a diagnosis of hepatic VOD. Patient management included water restriction and diuretics to control body weight in addition to tacrolimus tapering; however, the maximum serum bilirubin level reached 2.32 mg/dL on day 49 (Fig. 1). The low albumin level (3.0 mg/dL) and prolonged prothrombin time (53% of normal) were indicative of concomitant hepatic dysfunction. On day 52, the patient experienced complications associated with acute pancreatitis. Serum amylase and lipase levels were 584.0 mg/dL and 561.3 mg/dL, respectively. Despite rapid tapering and, ultimately, complete discontinuation of tacrolimus due to its sustained high level, the trough level of tacrolimus remained above 9 ng/mL for 7 days. The calculated half-life of tacrolimus was 96 hours. The symptoms and signs associated with hepatic VOD and psychological manifestations gradually disappeared following day 53. The clinical manifestations of acute pancreatitis, serum amylase, and lipase levels also slowly improved after day 62. Doppler ultrasonography examination on day 69 showed regression of hepatic VOD, following which the trough blood level of tacrolimus dropped and eventually became undetectable by day 69.

**DISCUSSION**

Tacrolimus is an effective immunosuppressive agent widely used in the prophylaxis of GVHD in allogeneic HSCT settings. However, tacrolimus requires careful dose adjustment in accordance with therapeutic drug monitoring due to its narrow therapeutic window. Because tacrolimus is primarily metabolized by the cytochrome P450 (CYP) 3A subfamily (mainly, CYP 3A4 and CYP 3A5) in liver microsomes, hepatic dysfunction may impair tacrolimus metabolism [2]. It has been shown that the half-life of tacrolimus is prolonged and its clearance is reduced in patients with hepatic dysfunction [6, 7]. The characteristic pathological findings of VOD are sinusoidal endothelial cell injury in zone 3 of the liver acini, progressive venular occlusion, and occlusion of terminal hepatic venules. These processes ultimately produce widespread zonal liver disruption and centrilobular hemorrhagic necrosis, resulting in extensive hepatocyte damage [8]. Impaired sinusoidal perfusion and hepatocyte damage may affect tacrolimus elimination due to a reduction in absolute hepatocyte mass, reduced CYP 450 enzymatic concentration or activity, and decreased sinusoidal perfusion [9].

Recently, there was a report on a notable alteration of the tacrolimus metabolism in 2 patients with hepatic VOD, in whom the half-lives of tacrolimus were markedly prolonged (288 and 146 hours) [5], when compared with the half-lives reported among HSCT recipients (18.2 hours), liver transplant recipients (12.1 hours), and patients with hepatic dysfunction (38.5 hours) [6, 10, 11]. The tacrolimus half-life recorded in these patients was likely longer than that in our patient because the hepatic VOD in these patients was more severe and persistent. The severely prolonged half-life in patients with hepatic VOD, compared with hepatic dysfunction from other causes, may be explained by the fact that hepatic VOD mainly affects zone 3 of the liver acini, which has the greatest concentration of CYP [5]. Our case was further complicated by psychological manifestations and acute pancreatitis [12, 13].

In conclusion, we describe a case of hepatic VOD accompanied by delayed elimination of tacrolimus despite its immediate discontinuation. This case suggests that tacrolimus-induced complications should be taken into consideration in patients with hepatic VOD because the half-life of tacrolimus can be markedly prolonged by the disease.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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