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CASE REPORT

Altered metabolism of tacrolimus in hepatic veno-occlusive disease

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Summary

Tacrolimus is widely used for the prophylaxis and treatment of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (HSCT) and graft rejection in solid organ transplantation. The metabolism of tacrolimus has been reported to be impaired in association with liver dysfunction, mostly as documented in liver transplant recipients. Hepatic veno-occlusive disease (VOD) is one of the serious complications after allogeneic HSCT. It is characterized by jaundice, fluid retention, and painful hepatomegaly, caused by endothelial cell injury resulting from the toxicity of the conditioning regimen. The impaired metabolism of tacrolimus in hepatic VOD has not previously been reported in the literature. Here, we report the notable alteration in the metabolism of tacrolimus in two patients with hepatic VOD, in whom the half-lives of tacrolimus were markedly prolonged (288 and 146 h).

Introduction

Tacrolimus, a potent macrolide immunosuppressive agent, has been frequently used for the prophylaxis of graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). Tacrolimus undergoes an extensive metabolism in the liver, which is mainly mediated by cytochrome P450 (CYP) 3A4 isoenzymes [1]. Therefore, liver dysfunction has been associated with a prolonged half-life and reduced clearance of tacrolimus [2–5]. Veno-occlusive disease (VOD) of the liver is one of the serious early complications after HSCT; it is characterized by a syndrome of jaundice, fluid retention, and painful hepatomegaly. Pathologic changes of hepatic VOD are centered in zone 3 of the liver acinus, and hepatic venular occlusion caused by primary injury to sinusoidal endothelial cells is the main pathogeneic change. In addition, subsequent extensive hepatocyte damage due to reduced hepatic venous outflow is also seen in moderate-to-severe hepatic VOD [6]. We here report two cases of hepatic VOD, in which impaired metabolism of tacrolimus resulted in a markedly prolonged half-life of tacrolimus.

Case report

A 59-year-old female (*Patient 1*) with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) and a 60-year-old male (*Patient 2*) with myelodysplastic syndrome (refractory anemia with excess of blasts) underwent cord blood transplantation from a human leukocyte antigen (HLA) serologically mismatched unrelated donor. The conditioning regimen used for *Patient 1* consisted of total body irradiation (TBI; 1200 cGy), cytarabine (1 g/m^2 every 12 h for 2 days), and cyclophosphamide (60 mg/kg × 2), and the regimen used for *Patient 2* consisted of TBI (400 cGy), fludarabine (125 mg/m^2), and oral busulfan (8 mg/kg). All the laboratory liver function tests were within the normal range in both patients before transplantation. Tacrolimus and short-term methotrexate were used as a prophylaxis against GVHD. Tacrolimus was administered by continuous infusion at an initial

dose of 0.03 mg/kg, and the dose was adjusted to maintain steady-state whole blood levels as measured by automated microparticle enzyme immunoassay (MEIA) between 10 and 20 ng/ml. *Patient 1* achieved hematopoietic engraftment on day 23. Her serum bilirubin level started rising on day 33 (maximum serum bilirubin level 57.1 mg/dl) together with painful hepatomegaly, fluid retention, and progressive thrombocytopenia, and the diagnosis of hepatic VOD was made. Although i.v. administration of tacrolimus was discontinued on day 35, the blood level of tacrolimus remained above 10 ng/ml for 15 days and was detectable for 30 days. The half-life of tacrolimus calculated by a standard technique was 288 h. The patient was treated with recombinant tissue plasminogen activator and hemodialysis for hepatorenal syndrome, which finally improved her hepatic and renal function. *Patient 2* achieved hematopoietic engraftment on day 21. His serum bilirubin level started rising on day 27 (maximum serum bilirubin level 9.0 mg/dl) together with painful hepatomegaly and progressive thrombocytopenia, and the diagnosis of hepatic VOD was made. Although i.v. administration of tacrolimus was discontinued on day 31, the blood level of tacrolimus remained above 10 ng/ml for 6 days and was detectable for 16 days. The half-life of tacrolimus was calculated and found to be 146 h. The patient was managed with a restricted water intake regimen and diuretics to control his body weight, which resulted in the resolution of signs associated with hepatic VOD.

Discussion

Liver dysfunction is one of the most important factors affecting the pharmacokinetics of tacrolimus, as tacrolimus is primarily metabolized in the liver [1]. The possible mechanisms by which liver dysfunction impairs tacrolimus metabolism include a reduction in absolute hepatocyte mass, reduced CYP 450 enzymatic concentration or activity, decreased sinusoidal perfusion, impaired intrahepatic diffusion and mixing, and cholestasis [7,8]. Most previous reports have described the association of impaired tacrolimus metabolism with liver dysfunction in recipients of liver transplantation [2–5]. To the best of our knowledge, alteration of the pharmacokinetics of tacrolimus in patients with hepatic VOD has not been previously reported in the literature. Hepatic VOD is not only involved with impaired sinusoidal perfusion, but also with other multiple factors due to subsequent extensive hepatocyte damage. We found that metabolism of tacrolimus is more severely affected in patients with hepatic VOD than in patients with hepatic dysfunction due to other etiologies. Indeed, the present two patients with hepatic VOD showed notably long half-lives of tacrolimus, 288 and 146 h, when compared with those in healthy individuals (32.0–34.2 h) and HCT recipients (18.2 h) [1,9,10, and an internal report of Astellas Pharma, Inc., Tokyo, Japan]. Furthermore, while liver transplant recipients generally showed a tacrolimus half-life ranging from 11.7 to 12.1 h, patients with impaired graft function showed longer tacrolimus half-lives (40.1–61.5 h) [2–5]. The severity of liver damage may explain the difference of tacrolimus half-life between patients with hepatic VOD and liver transplant recipients with impaired graft function. Another possible explanation is that hepatic VOD could more critically alter the metabolism of tacrolimus than the liver dysfunction due to other etiologies, as hepatic VOD mainly affects area three of the liver acinus, which contains the greatest concentration of CYP.

Ascites, one of the clinical characteristics of hepatic VOD, might play some role in the impaired pharmacokinetics of tacrolimus because of the distribution of tacrolimus into ascitic fluid. However, probably because most of the tacrolimus in the plasma is protein-bound, only a small amount of tacrolimus could accumulate in the ascitic fluid [11]. Because of severe thrombocytopenia and/or the treatment with recombinant tissue plasminogen activator, the concentration of tacrolimus in the ascitic fluid was not examined in our patients. However, in *Patient 1,* who had massive ascites, the concentration of tacrolimus decreased promptly after the treatment improved the clinical signs of hepatic VOD, even though she still had a large volume of ascitic fluid. This strongly suggests that ascites has little effect on the pharmacokinetics of tacrolimus.

We conclude that the pharmacokinetics of tacrolimus is markedly impaired in patients developing hepatic VOD when compared with those with hepatic dysfunction due to other etiologies. Transplant physicians should be fully aware of this phenomenon and should discontinue or reduce the dosage of tacrolimus in patients who develop hepatic VOD as soon as possible.

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