Unique pharmacokinetics for oral tacrolimus administration following allogeneic hematopoietic stem cell transplantation for AML with Shwachman–Diamond syndrome

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Case Report

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Abstract

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive multisystem disease characterized by exocrine pancreatic insufficiency, impaired hematopoiesis, and a predisposition to leukemia [1]. We previously reported successful haploidentical hematopoietic stem cell transplantation (haplo-HSCT) in adult patients with acute myeloid leukemia (AML) and SDS [2]. Herein, we describe the unique pharmacokinetics of orally administered tacrolimus in one such patient.

Full Text

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive multisystem disease characterized by exocrine pancreatic insufficiency, impaired hematopoiesis, and a predisposition to leukemia [1]. We previously reported successful haploidentical hematopoietic stem cell transplantation (haplo-HSCT) in adult patients with acute myeloid leukemia (AML) and SDS [2]. Herein, we describe the unique pharmacokinetics of orally administered tacrolimus in one such patient.

Alloperipheral blood stem cell transplantation was performed from an HLA-haploidentical father to a 21-year-old man with AML caused by SDS. Pancreatic function tests revealed exocrine deficiency. Treatment consisted of intravenous fludarabine (30 mg/m²/d for two days) and busulfan (3.2 mg/kg/d for two days), followed by 4 Gy total body irradiation. Acute graft-versus-host disease (aGvHD) prophylaxis comprised cyclophosphamide, tacrolimus, and mycophenolate mofetil (MMF). Cyclophosphamide (40 mg/kg/d) was administered on post-transplantation days 3 and 4 [3]. Stem cell engraftment was achieved 14 days after transplantation. On day 27, tacrolimus was switched from continuous intravenous infusion to once-daily oral administration (2 mg/d), which is double the recommended infusion dose. Prior to changing the administration route, the whole-blood concentration of tacrolimus was at acceptable therapeutic levels (10.3 ng/ml). Three days after switching to oral administration (post-transplantation day 30), the blood traffic level of tacrolimus was 3.0 ng/ml. On days 32 and 37, the oral dose of tacrolimus was increased to 4 and 6 mg/d, respectively, but the traffic levels remained extremely low at 2.7 and 2.6 ng/ml, respectively. Other drugs were continued without changing the dose or route of administration. No intestinal aGvHD was observed. For pharmacokinetic analysis of oral tacrolimus, blood samples were collected at 0, 1, 2, 3, 5, 10, and 24 h after oral tacrolimus (6 mg) administration on post-transplantation day 40 (Fig. 1). On day 41, the administration route of tacrolimus was switched back to continuous intravenous infusion (1 mg/d), and the blood concentration increased to 9.9 ng/ml. However, the patient developed aGvHD grade 2 (skin stage 3) 45 days after transplantation.

The area under the concentration-time curve (AUC) 0–24 h on day 40 was 149.9 ng h/ml, approximately half the therapeutic AUC0–24 of tacrolimus. The traffic and peak concentrations were extremely low. The bioavailability of oral tacrolimus, calculated as $F = \frac{\text{AUCpo} \times \text{DOSEiv}}{\text{AUCiv} \times \text{DOSEpo}}$, was 10%. Taken together, these data suggested that oral tacrolimus was malabsorbed by the epithelial cells of the patient.
Tacrolimus is absorbed by epithelial cells in the small intestine. Recently, it was reported that glycoprotein 2 (GP2) from pancreatic acinar cells, the functional unit of the exocrine pancreas, plays an important role in anti-inflammation and defense against adhesive and invasive bacteria in intestinal epithelial cells. Studies in GP2-deficient mice have reported severe colitis [4]. GP2 deficiency caused by exocrine pancreatic insufficiency in SDS may cause endothelial damage to the intestine, resulting in malabsorption of oral tacrolimus. Malabsorption may also be caused by polymorphisms in MDR1, which is expressed in epithelial cells and drug transporters [5]. Because SDS is an autosomal recessive multisystem disease, some patients may harbor \( MDR1 \) mutations.

There have been no reports of oral tacrolimus malabsorption in patients with SDS after allogeneic HSCT; however, there are only a few reports on patients with SDS who underwent allogeneic HSCT. In young adults aged 18–40 years, 4% of patients with MDS harbor compound heterozygous mutations in the SDS-associated SBDS gene with concurrent TP53 mutations and poor prognosis; therefore, genetically defined SDS may be underdiagnosed [6]. Many patients with AML or MDS who also have SDS require allogeneic HSCT. Further studies on the pharmacokinetics of oral tacrolimus in patients with SDS after allogeneic HSCT are required to improve patient outcomes.

**Declarations**

**Author contribution**

Y.I: conceptualization and writing of the original manuscript. YU, SK, MK, FS supervising. All authors approved the final version.

**Conflict of interest:**

The authors report no conflict of interest.

**Ethical statement**

This study was conducted according to the Declaration of Helsinki.

**Statements of approval**

The protocol was approved by the institutional review board of St. Marianna University School of Medicine, and the patient gave written informed consent before any study-related procedures were done.

**Consent to participate**

A written informed consent to publish was obtained from father of the patient.

**References**


Figures
Figure 1

Oral tacrolimus concentration curve 40 d after transplantation. AUC0–24 was 149.9 ng h/ml.