LETTER TO THE EDITOR

Tacrolimus–azithromycin interaction in a recipient of allogeneic bone marrow transplantation

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Tacrolimus is a potent macrolide immunosuppressive agent, which is used for the prophylaxis and treatment of organ rejection and graft-versus-host disease (GVHD) after allogeneic organ or stem cell transplantation. Tacrolimus undergoes extensive metabolism in the liver, which is mediated by cytochrome P450 (CYP) 3A4 isoenzymes [1]. Therefore, the metabolism of tacrolimus is affected by the drug interaction with several drugs metabolized by CYP 3A4. There is nearly a complete overlap between its drug interactions and those of cyclosporine A, another calcineurin inhibitor. However, fewer drug interaction studies for tacrolimus have been carried out. Macrolide antibiotics including erythromycin and clarithromycin have been known as the inhibitors of CYP, and their concomitant use with tacrolimus has been reported to increase the whole blood tacrolimus concentration [2–5]. Azithromycin, possessing a unique azalide structure, shows a pharamacokinetics and metabolism different from other macrolides. Indeed, unlike erythromycin and clarithromycin, azithromycin does not affect CYP [6,7]. Thus, its drug interaction with tacrolimus has not been reported, although the interaction between azithromycin and CSA has been described in a renal transplant recipient [8].

A 27-year-old woman with acute myelogenous leukemia underwent allogeneic bone marrow transplantation (BMT) from an human leukocyte antigen matched unrelated donor after the conditioning with total body irradiation and high-dose cytarabine. For the prophylaxis of GVHD, she received continuous intravenous tacrolimus at the initial dose of 0.03 mg/kg starting 1 day before BMT, and short-term methotrexate. The concentration of tacrolimus in the whole blood was measured by an automated microparticle enzyme immunoassay at least two or three times a week during the first 2 months after BMT. Engraftment was achieved on day 17. On day 37, she developed folliculitis on her face and head, and azithromycin (500 mg/day) was given orally on days 38–40. During the 1 week before initiating azithromycin, the dose of intravenous tacrolimus was not changed (0.02 mg/kg/day), and the concentration of tacrolimus had ranged between 15.8 and 17.5 ng/ml. On day 40, 3 days after starting azithromycin, the concentration of tacrolimus exceeded the measurable level without dilution (>30.0 ng/ml), although the dose of tacrolimus was not changed. Intravenous tacrolimus was discontinued for 24 h, and the blood level of tacrolimus decreased to 16.0 ng/ml. Tacrolimus was then restarted at a reduced dose (0.016 mg/kg). On day 44, the dose was increased to 0.02 mg/kg, which kept the blood level between 16.0 and 19.2 ng/ml. During this period, any additional drugs known to affect CYP isoenzyme activity were not given.

Although azithromycin has been reported to have minimal effects on CYP, the marked increase in the tacrolimus blood level after only two doses of azithromycin in this case strongly suggested the possibility of its interaction with tacrolimus. Thus, transplant physicians should be aware of this drug interaction, because the chance of receiving both drugs is not infrequent among organ or stem cell transplant recipients. Further cases should be accumulated in order to evaluate and confirm this drug interaction.

Takehiko Mori, Yoshinobu Aisa, Tomonori Nakazato, Rie Yamazaki, Yauso Ikeda and Shinichiro Okamoto
Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

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