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CASE REPORT

Clotrimazole troches induce supratherapeutic blood levels of sirolimus and tacrolimus in an allogeneic hematopoietic cell-transplant recipient resulting in acute kidney injury

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Abstract
Allogeneic hematopoietic cell transplantation is a potential curative treatment option for various malignant and nonmalignant hematologic disorders. Patients undergoing an allogeneic hematopoietic cell transplant are prescribed immune-suppressant therapies to facilitate hematopoietic donor-cell engraftment and prevent graft-versus-host disease. Drug–drug interactions may occur, owing to exposure to complex multidrug regimens with narrow therapeutic windows and high toxicity profiles. Here, we describe a unique case of a 65-year-old man with poor-risk acute myeloid leukemia who underwent a matched-sibling hematopoietic cell allograft. Sirolimus and tacrolimus were used for graft-versus-host disease prophylaxis. He developed oral thrush requiring treatment with clotrimazole troches, which subsequently resulted in serious renal toxicity attributed to supratherapeutic levels of sirolimus and tacrolimus. Patient renal function improved after temporarily holding both immune suppressants, and administering phenytoin to help induce sirolimus and tacrolimus metabolism. This case highlights sudden

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and serious toxicities that resulted from clotrimazole–sirolimus and clotrimazole–tacrolimus drug–drug interactions, even when administered topically.

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potential curative treatment option for various malignant and nonmalignant hematologic disorders [1–5]. Patients undergoing allo-HCT are prescribed immune suppressive therapies to facilitate hematopoietic donor-cell engraftment and prevent graft-versus-host disease (GVHD) [6]. For several years, the combination of a calcineurin inhibitor, namely cyclosporine, with methotrexate was the most commonly used regimen to prevent acute GVHD. Later, data showed a lower incidence of Grades 2–4 acute GVHD when using tacrolimus versus cyclosporine in unrelated donor allografting [7]. Combining tacrolimus with sirolimus has become a popular regimen for GVHD prophylaxis at various transplant programs worldwide, owing to a lower incidence of severe mucositis when compared to methotrexate [8–10].

During allo-HCT, it is imperative to maintain blood levels of immune suppressants within a desirable therapeutic range to ensure engraftment, prevent GVHD, and avoid drug-related toxicity and consequent morbidity [11]. Drug–drug interactions may occur as a result of exposure to medications with narrow therapeutic windows and high toxicity profiles. Understanding the mechanism(s) associated with metabolism of such drugs is important to help avoid unwanted and potentially serious drug–drug interactions [11].

Tacrolimus (FK506), a calcineurin inhibitor, is primarily metabolized by the CYP4503A4 system in the liver and intestinal wall, and is well-known for its inter- and intrapatient pharmacokinetic variability [12]. Sirolimus, an inhibitor of the mammalian target of rapamycin (MTOR) enzyme, exerts its function by reducing DNA transcription and translation, and inducing cell cycle arrest in the G1 phase in activated lymphocytes, among others [11]. Similar to tacrolimus, sirolimus is predominantly metabolized by the hepatic CYP4503A4 [13,14].

Azole antifungal agents are CYP3A4 inhibitors commonly used in the setting of allo-HCT for anti-fungal prophylaxis and treatment of fungal infections [15–20]. Systemic triazoles, such as fluconazole, posaconazole, and voriconazole, are used consistently in allo-HCT patients to inhibit fungal cytochrome P450 14-α-sterol demethylase [21]. Drug–drug interactions with these agents are well documented for CYP3A4 inhibition, requiring dose reductions in other concomitant CYP3A4-substrate medications by 25–90%, depending on which azole antifungal is being prescribed [11]. Inhibition of CYP450 enzymes by azole antifungals primarily occurs through intestinal and hepatic CYP3A4. Conflicting data regarding inhibitory or inducing effects of oral clotrimazole exist between laboratory and human studies [21]. However, oral administration of a CYP3A4 substrate in combination with clotrimazole may result in the inhibition of presystemic (intestinal) versus systemic (hepatic) metabolism by CYP3A4 [21].

Empiric dose-reduction of calcineurin inhibitors and sirolimus is necessary when azole antifungals are prescribed [11]. Vigilant monitoring of immunosuppressant blood levels is imperative to ensure therapeutic benefit and avoid toxicities. Several case reports have described renal toxicity occurring when combining azoles with calcineurin inhibitors or sirolimus [22–25]. The potential adverse drug–drug interaction between oral clotrimazole troches and tacrolimus was anecdotally described in a liver-transplant recipient [26]. Here, we present the first case, to our knowledge, of an allo-HCT recipient who developed acute kidney injury as a result of elevated levels of both sirolimus and tacrolimus following use of clotrimazole troches for treatment of oral thrush.

Case report

A 65-year-old man with poor-risk acute myeloid leukemia with associated complex karyotype underwent an allo-HCT in first complete remission from a human leukocyte antigen-matched-sibling donor (Class I: A–C; Class II: DRB1) using granulocyte-colony stimulating factor-mobilized peripheral blood stem cells. The HCT-comorbidity index of the patient at the time of transplantation was two [27]. The preparative regimen for allo-HCT consisted of 40 mg/m^2 intravenous fludarabine (Day −5, Day −4, Day −3, and Day −2) and 130 mg/m^2 intravenous busulfan aimed at a target area-under-the curve (AUC) dose of 3,500 mmol min/L per dose × four doses (Day −5, Day −4, Day −3, and Day −2). GVHD prophylaxis consisted of tacrolimus started on Day −3 at a dose of 0.01 mg/kg (ideal body weight), given initially as a 24-hour continuous intravenous infusion and later converted to an oral formulation using a 1:4 ratio on Day +12 post-allografting. A 12-mg loading dose of sirolimus was given on Day −1, followed by 4 mg/d beginning on Day 0. The immunosuppressant-goal range for tacrolimus was ~3–7 ng/mL, and ~8–14 ng/mL for sirolimus. Antimicrobial prophylaxis consisted of 800 mg acyclovir orally twice a day, 400 mg ciprofloxacin orally twice a day, and 50 mg micafungin once daily, started on Day 0. The dose of infused CD34 cells was 9.41 × 10^6/kg of recipient body weight. The clinical course of the patient was complicated by diarrhea associated with *Clostridium difficile*, which developed on Day −2 and required 125 mg vancomycin orally four times per day. On Day +9 post-transplantation, the patient developed oral mucositis, which progressed to Grade 3 by Day +12 and required intravenous hydromorphone for pain control. On Day +15, the patient had evidence of oral thrush. At that time, the oral mucositis had improved slightly, and there were no

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