BRIEF ARTICLE

Safety of Posaconazole and Sirolimus Coadministration in Allogeneic Hematopoietic Stem Cell Transplants

David W. Kubiak,[1,4] Sophia Koo,[1,2,3] Sarah P. Hammond,[1,2,3] Philippe Armand,[2,3,5] Lindsey R. Baden,[1,2,3] Joseph H. Antin,[2,3,5] Francisco M. Marty[1,2,3]

Sirolimus is used in allogeneic hematopoietic stem cell transplants (HSCTs) for prevention and treatment of graft-versus-host disease (GVHD). Posaconazole is used in this population for invasive fungal disease (IFD) prophylaxis and treatment. As posaconazole strongly inhibits CYP3A4, concurrent administration of sirolimus, a CYP3A4 substrate, and posaconazole has been reported to increase sirolimus drug exposure substantially. Coadministration of posaconazole and sirolimus is contraindicated by the manufacturer of posaconazole. We identified 15 patients who underwent HSCTs at our institution receiving a steady-state dose of sirolimus who subsequently started posaconazole therapy from January 2006 to March 2009. We recorded baseline characteristics, drug administration details, and potential adverse effects related to either drug. All patients underwent HSCTs for treatment of hematologic malignancy. All patients were initially prescribed sirolimus for GVHD prophylaxis and continued therapy after developing GVHD. Twelve patients (80%) received posaconazole for IFD prophylaxis in the setting of GVHD and 3 (20%) for IFD treatment. Patients received sirolimus and posaconazole concurrently for a median of 78 days (interquartile range [IQR] 25-177; range, 6-503). The median daily dose of sirolimus (2 mg/day) before initiation of posaconazole was reduced 50% to a median daily dose of 1 mg/day at steady state. Six patients experienced sirolimus trough levels greater than 12 ng/mL during coadministration, but only 1 patient experienced an adverse event potentially associated with sirolimus exposure during the first month of coadministration. This patient's sirolimus dose was empirically reduced by only 30% on posaconazole initiation. Concurrent sirolimus and posaconazole use seems to be well tolerated with a 33% to 50% empiric sirolimus dose reduction and close monitoring of serum sirolimus trough levels at the time of posaconazole initiation.

Biol Blood Marrow Transplant 18: 1462-1465 (2012)

KEY WORDS: Posaconazole, Sirolimus, Tacrolimus, Drug interactions, Coadministration

INTRODUCTION

Sirolimus is a macrocyclic lactone immunosuppressive agent increasingly used for prophylaxis and treatment of graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplants (HSCTs) [1,2]. Sirolimus binds uniquely to FK binding protein 12, resulting in the formation of an immunosuppressive complex that inhibits the mammalian target of rapamycin, with down-regulation of T cell proliferation and activation. Sirolimus has synergistic immunosuppressive effects when combined with tacrolimus, without overlapping toxicities or drug interactions [3,4]. Several studies have observed reduced transplantation-associated morbidity and mortality with sirolimus-containing GVHD prophylaxis regimens, with lower rates of grade II to IV GVHD and superior rates of neutrophil and platelet engraftment, compared to methotrexate-containing regimens [5-8].

Sirolimus is extensively metabolized by hepatic and intestinal cytochrome P450-3A4 (CYP3A4) enzymes and is a substrate and inhibitor of P-glycoprotein, and plasma concentrations are known to increase substantially with posaconazole, which strongly inhibits CYP3A4 [9,10]. Posaconazole has demonstrated efficacy in preventing invasive fungal

From the [1]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts; [2]Dana-Farber Cancer Institute, Boston, Massachusetts; [3]Harvard Medical School, Boston, Massachusetts; [4]Department of Pharmacy, Brigham and Women's Hospital, Boston, Massachusetts; and [5]Division of Medical Oncology, Brigham and Women's Hospital, Boston, Massachusetts.

Presented in abstract form at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, 2009: Abstract A1-592.

Financial disclosure: See Acknowledgment on page 1465.

Correspondence and reprint requests: David W. Kubiak, PharmD, BCPS, Division of Infectious Diseases, Brigham and Women's Hospital, 75 Francis Street, PBB-A4, Boston, MA 02115 (e-mail: dwkubiak@partners.org).

Received March 18, 2012; accepted April 30, 2012

1083-8791/$36.00
doi:10.1016/j.bbmt.2012.04.015

disease (IFD), especially invasive aspergillosis in patients who undergo HSCT with acute GVHD [11]. The manufacturer of posaconazole currently contraindicates the coadministration of sirolimus with posaconazole (Noxafil; Schering Corporation, Kenilworth, NJ). Voriconazole a triazole antifungal agent and potent CYP3A4, CYP2C9, and CYP2C19 inhibitor, has been used to prevent IFD in patients who undergo HSCT with GVHD [12]. The manufacturer of voriconazole also contraindicates coadministration with sirolimus (Vfend IV; Roerig, New York, NY); however, feasibility of coadministration with sirolimus has been reported. Marty et al. [13] found that with an empiric initial 90% sirolimus dose reduction along with careful systematic monitoring of sirolimus trough levels, coadministration was safe and feasible.

There are no clinical data to guide the appropriate initial empiric dose reduction of sirolimus when coadministration with posaconazole may be clinically indicated. We present a consecutive series of patients at our institution who required concomitant sirolimus and posaconazole administration and report the feasibility and safety of such an approach.

PATIENTS AND METHODS

Patients who received posaconazole oral suspension and sirolimus concurrently were identified by searching medical records of all allogeneic HSCT recipients at our institution from January 2006 to March 2009. Demographics and transplantation details were recorded. Details of sirolimus and posaconazole use were recorded, including indications for use; empiric sirolimus dose adjustments with initiation of posaconazole, posaconazole daily dose, steady-state dose of sirolimus 1 month after the onset of coadministration, sirolimus trough levels, and any concomitant medications that might interact with sirolimus. We also collected data on concomitant tacrolimus use, tacrolimus trough levels, and empiric dose adjustments with initiation of posaconazole. Any potential adverse effects related to sirolimus, tacrolimus, or posaconazole were recorded. The Partners Healthcare Human Research Committee approved this study.

RESULTS

Fifteen patients were receiving a steady-state dose of sirolimus, and 14 of these patients were also receiving a steady-state dose of tacrolimus when they initiated posaconazole treatment. Demographic data and transplantation details are summarized in Table 1. Median age at time of coadministration was 50 years, most patients were men, the most common malignancy requiring HSCT was acute myelogenous leukemia, and a high proportion were at high risk for GVHD, with unrelated or mismatched donors. Sirolimus, tacrolimus, and posaconazole treatment characteristics are summarized in Table 2. Patients received sirolimus and posaconazole concurrently for a median of 78 days (interquartile range [IQR] 25-177; range, 6-503). All patients were initially prescribed sirolimus for GVHD prophylaxis, and those who developed GVHD continued to receive sirolimus as a part of their GVHD treatment regimen. Most patients (80%) received posaconazole for IFD prophylaxis in the setting of GVHD; the remainder received posaconazole for IFD treatment. Nine patients had gastrointestinal involvement by acute GVHD, but were able to take oral medications. No patients received fluconazole prophylaxis or any other concomitant medications with the potential to induce or inhibit CYP3A4 isozymes or cause a relevant pharmacokinetic (PK) drug interaction with either sirolimus or tacrolimus during the study period.

Table 1. Baseline Demographics and Transplantation Characteristics

Cohort Characteristics	No. of Patients (%)
Cohort (N)	15
Median age, years (range)	50 (23-63)
Male	9 (60)
Primary underlying disease	
AML	5 (33)
Myelodysplastic syndrome	2 (13)
CLL	2 (13)
CML	2 (13)
ALL	2 (13
Aplastic anemia	1 (6)
T cell lymphoblastic lymphoma	1 (6)
HSCT type	
Matched related	2 (13)
Matched unrelated	8 (53)
Mismatched related	1 (6)
Mismatched unrelated	4 (26)

AML indicates acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplant.

The median daily dose of sirolimus before initiation of posaconazole was 2 mg (range, 1-3 mg). At initiation of posaconazole and sirolimus coadministration, the daily sirolimus dose was empirically reduced by a median of 50% (IQR, 0%-50%; range, 0%-90%) in the cohort. After 7 days of coadministration, the median daily sirolimus dose was 33% (IQR, 0%-50%; range, −50% to 83%) less than the baseline sirolimus dose before coadministration. A single patient required a 50% sirolimus dose increase from baseline. There were no differences in the percent reduction in sirolimus dose among the 9 patients with gastrointestinal involvement with GVHD when compared to the rest of the cohort.

At initiation of posaconazole and tacrolimus coadministration, the median daily tacrolimus dose was empirically reduced by 33% (IQR, 0%-50%; range, 0%-67%). The median steady-state dose was 30% (IQR, 0%-50%; range, −100% to 70%) less than the