BRIEF REPORT

Concurrent Administration of Sirolimus and Voriconazole: A Pilot Study Assessing Safety and Approaches to Appropriate Management

Dorothy Surowiec, Pharm.D., Daryl D. DePestel, Pharm.D., and Peggy L. Carver, Pharm.D., FCCP

Study Objectives. To assess the use and safety of concurrent administration of voriconazole and sirolimus—which is contraindicated—and to determine approaches for appropriately managing patients who receive both drugs.

Design. Retrospective medical record review.

Setting. University-affiliated medical center.

Patients. Thirty-one cases in 23 inpatients who received at least one dose of voriconazole and sirolimus concomitantly within a 24-hour period.

Measurements and Main Results. Data on sirolimus and voriconazole indications, doses, routes, frequencies, and administration times; number of days of coadministration; and sirolimus dosage adjustments were collected. In addition, data on laboratory values, adverse events, sirolimus concentrations, and concomitant drugs, including cytochrome P450 (CYP) 3A isoenzyme and P-glycoprotein inhibitors and inducers, were collected for 7 days before, during, and for 14 days after coadministration. No cases of elevated sirolimus concentrations (> 20 mg/ml) occurred in patients stabilized with voriconazole before starting low-dose sirolimus 0.5–1 mg/day, or in those stabilized with sirolimus 0.5–2 mg/day who had baseline sirolimus concentrations of 12 ng/ml or lower and whose sirolimus dose was decreased by 50% before the addition of voriconazole. In contrast, elevated sirolimus concentrations were experienced in patients receiving sirolimus doses of 4 mg/day or higher who had sirolimus concentrations of 12 ng/ml or higher and whose sirolimus dose was not decreased before addition of voriconazole. In a patient who received sirolimus with itraconazole, a strong CYP3A isoenzyme inhibitor, one case of only a minimal increase in the sirolimus concentration occurred after the addition of voriconazole.

Conclusions. Sirolimus and voriconazole can be safely coadministered as long as consideration is given to which agent the patient receives first, the sirolimus dosage, sirolimus concentrations, and concurrent disease states and CYP3A isoenzyme inhibitors. Sirolimus concentrations should be closely and routinely monitored before, during, and after coadministration of voriconazole and other CYP3A isoenzyme inhibitors. Based on the results of this pilot study, a protocol on the management of this drug combination will be implemented and prospectively evaluated for efficacy and safety.

Key Words: voriconazole, sirolimus, transplantation, aspergillosis, drug interaction.

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The incidence of invasive fungal infections has increased dramatically in the United States: among infectious diseases–related deaths, those due to invasive fungal infections increased from the tenth most common in 1980 to the seventh most common in 1997.[1] In particular, patients who have undergone solid organ or hematopoietic stem cell transplantation are susceptible to invasive fungal infections because of multiple risk factors, some of which include treatment with immunosuppressive and/or broad-spectrum antimicrobial agents, graft-versus-host disease (GVHD), neutropenia, or the presence of central venous catheters.[2, 3]

Invasive fungal infections in transplant recipients are frequently caused by *Aspergillus* species. Voriconazole, a second-generation triazole antifungal, is often used for prophylaxis or treatment of these infections in transplant recipients as it provides coverage for *Candida* and *Aspergillus* species.[2, 4] Voriconazole was shown to be efficacious in noncomparative studies as primary or salvage therapy for invasive fungal infections.[5–7] Furthermore, it has emerged as the therapy of choice for these infections caused by *Aspergillus* species, as it demonstrated higher response rates and improved survival compared with amphotericin B in the treatment of invasive aspergillosis.[8]

Voriconazole inhibits cytochrome P450 (CYP)–dependent 14α-lanosterol demethylase, the CYP enzyme responsible for the synthesis of cell membrane ergosterol in fungi. It is both a substrate and an inhibitor of human hepatic CYP2C19, CYP2C9, and CYP3A isoenzymes, increasing the potential for drug interactions with other agents that are substrates of these enzymes, including sirolimus, an antirejection agent used in transplant recipients.[9, 10] Voriconazole drug interactions are dose dependent and are often difficult to predict and manage, in part due to its unpredictable, nonlinear pharmacokinetics and the variability in its concentrations due to genetic polymorphisms of CYP2C19.[10]

From the Department of Pharmacy Services, University of Michigan Health System, and the Department of Clinical Sciences, University of Michigan College of Pharmacy, Ann Arbor, Michigan (all authors).

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Address reprint requests to Peggy L. Carver, Pharm.D., FCCP, University of Michigan College of Pharmacy, 428 Church Street, Ann Arbor, MI 48109-1065; e-mail: peg@umich.edu.

Sirolimus is an immunosuppressive agent that prevents T-lymphocyte activation and proliferation and antibody production. Unlike tacrolimus and cyclosporine, it does not inhibit calcineurin activity but works by inhibiting the activation of the mammalian target of rapamycin. It is indicated for the prophylaxis of organ rejection in patients receiving kidney transplants; however, it has also been used for the prevention or treatment of rejection in other solid organ transplant recipients and GVHD in hematopoietic stem cell transplant recipients.[11–15]

Concomitant use of voriconazole with sirolimus is contraindicated by the manufacturer[9] because voriconazole inhibits CYP3A isoenzymes, the enzymes responsible for metabolizing sirolimus, resulting in greater susceptibility to dose-related adverse effects of sirolimus, including renal dysfunction, leukopenia, thrombocytopenia, and anemia.[11] Repeated doses of oral voriconazole 400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days administered to 15 healthy young men increased the mean maximum plasma concentration and area under the plasma concentration–time curve of a single, oral 2-mg dose of sirolimus by 7- and 11-fold, respectively.[9]

Drug interactions between azole antifungals, such as voriconazole, itraconazole, ketoconazole, or fluconazole, and immunosuppressive agents, including sirolimus, have been extensively reported in the literature.[10, 16–19] Although the onset and duration of voriconazole-mediated inhibition of CYP3A isoenzymes is unknown, in studies evaluating other CYP inhibitors, inhibition occurred immediately after administration of the first dose of the CYP inhibitor.[20] The duration of CYP3A isoenzyme inhibition after voriconazole administration is believed to be affected by its half-life, which is variable and dose dependent, and by protein binding.[9, 20]

At our institution, we noted that increasing numbers of patients were receiving the combination of voriconazole and sirolimus. As only very limited data were available regarding the concurrent use of these two agents, and we found no data regarding the management of patients receiving voriconazole before the start of sirolimus, we evaluated all patients treated at our institution in whom both drugs were coadministered. The objective of this retrospective study was to assess the use of concurrent administration of voriconazole and sirolimus, and to determine approaches for appropriately managing patients who receive both drugs. In addition, the safety of concurrent administration of voriconazole and sirolimus was

Table 1. Definitions of Adverse Effects Relative to Baseline Laboratory Values

	Definition	
Adverse Effect	If Baseline Value Normal	If Baseline Value Abnormal
Renal dysfunction	Serum creatinine concentration > 1.5 mg/dl	50% ↑ from baseline
Leukopenia	White blood cell count < 4.0 x 10^3/mm^3	50% ↓ from baseline
Thrombocytopenia	Platelet count < 150 x 10^3/mm^3	25% ↓ from baseline
Anemia	Hemoglobin concentration < 12 g/dl (females) or < 14 g/dl (males) Hematocrit < 35% (females) or < 49% (males)	25% ↓ from baseline
Dyslipidemia	Total cholesterol concentration > 200 mg/dl or triglyceride concentration > 150 mg/dl	Not applicable
Hepatic dysfunction	AST or ALT > 3 x upper limit of normal[a]	50% ↑ from baseline

AST = aspartate aminotransferase; ALT = alanine aminotransferase.
[a]Upper limit of normal for AST is 30 U/L and for ALT is 35 U/L.

assessed by determining whether clinicians prospectively or concurrently adjusted sirolimus doses, and by evaluating whether patients experienced increased adverse events due to elevated sirolimus concentrations after coadministration with voriconazole.

Methods

In this retrospective study, we reviewed the medical records of inpatients who were on a medical service at the University of Michigan Hospital who received coadministration of sirolimus and voriconazole between July 1, 2002, and November 1, 2006. Institutional review board approval was obtained, and informed consent was waived as the study did not involve any direct patient interventions. Patients were included if they were inpatients at the University of Michigan Hospital and had received at least one dose of voriconazole and sirolimus concurrently within a 24-hour period. Patients were excluded if their medical records were unavailable for review or were incomplete. Each patient was assigned a case number, and if the patient was admitted more than one time and received coadministration of the two drugs, the original case number followed by a decimal was used to indicate subsequent admissions (e.g., case 2.2 refers to the second admission for the patient assigned case number 2).

Computerized pharmacy and medical databases were used to identify inpatients at the hospital who had drug orders for voriconazole and sirolimus on the same days. Medical records and medication administration records were then reviewed to confirm the specific doses and administration times of all drugs.

Demographic data were collected, including patients' age, sex, race-ethnicity, type of transplantation, and other comorbidities. The following information was collected 7 days before, during, and 14 days after coadminis-tration of sirolimus and voriconazole: indication for sirolimus and voriconazole based on physician progress notes; dose, route, frequency, and administration times for sirolimus and voriconazole; sirolimus concentrations and time of sample collection; dose, route, frequency, and administration times for other concomitant drugs that had potential to affect the drug interaction; laboratory values; and adverse effects. Data on 30-day mortality after the last day of combination therapy as an inpatient were also collected. The definitions of adverse effects relative to baseline laboratory values are listed in Table 1. Data on rash, neurotoxicity, and death were also assessed.

Sirolimus concentrations were measured by the liquid chromatography with mass spectrometry (LCMS) method; a trough concentration of 5–20 ng/ml was considered therapeutic.[21–23] In this study, concentrations greater than 20 ng/ml were considered elevated based on current clinical practice in our institution and literature citing target trough ranges of 12–20 ng/ml (using the LCMS methodology) after cyclosporine withdrawal in renal transplant recipients.[22–23] At our institution, sirolimus concentrations are generally obtained with the morning laboratory testing in order to minimize collection of blood samples and to provide a consistent sampling time (dosing times are also standardized). In this study, most (92 [79.3%] of 116 concentrations) of the patients had random concentrations obtained. Troughs were defined as plasma concentrations obtained within 3 hours before the next scheduled dose or within 1 hour after the next scheduled dose if the scheduled dose was not administered at the correct time. The

Table 2. Demographic Data of the 23 Patients

Characteristic	Value
Age at first admission (yrs), mean ± SD	42.7 ± 16.2
	No. (%) of Patients
Male	15 (65)
Race-ethnicity	
Caucasian	17 (74)
African-American	3 (13)
Asian	1 (4)
Hispanic	1 (4)
Unknown	1 (4)
Dialysis at baseline	0 (0)
Liver disease	7 (30)
Diabetes mellitus	4 (17)
Autoimmune disease	3 (13)
Solid organ cancer	3 (13)
Solid organ transplant	7 (30)
Lung	5 (22)
Kidney	1 (4)
Liver	1 (4)
Hematologic malignancy	16 (70)
Lymphoma	5 (22)
Leukemia	8 (35)
Other	3 (13)
Hematopoietic stem cell transplant	16 (70)

Table 3. Summary of Voriconazole and Sirolimus Therapy in the 31 Cases

Variable	Value
	No. (%) of Cases
Voriconazole indication	
Treatment of a proven or probable invasive fungal infection	10 (32)
Empiric treatment of an invasive fungal infection	11 (35)
Primary prophylaxis	5 (16)
Secondary prophylaxis	5 (16)
Sirolimus indication	
Treatment of GVHD or rejection	26 (84)
Prophylaxis for GVHD or rejection	5 (16)
	Mean ± SD
No. of days of coadministration (range)	4.6 ± 4.2 (1–20)
Weight (kg)	67.1 ± 21.8
	Range
Voriconazole dosing	
mg/kg/dose[a]	2.2–6.3
mg/dose	150–600
Sirolimus dosing	
mg/kg/dose[a]	0.007–0.179
mg/dose	0.5–12

GVHD = graft-versus-host disease.
[a]Based on mean weight of 67.1 kg.

clinical pharmacists on each service interpret the concentrations based on the timing and estimate trough concentrations accordingly.

Table 4. Summary of Coadministration Scenarios and Sirolimus Concentrations in the 31 Cases

Variable	Value
	No. (%) of Cases
Scenario	
Voriconazole administration before addition of sirolimus	9 (29)
Sirolimus administration before addition of voriconazole	13 (42)
Already receiving voriconazole and sirolimus concurrently on admission[a]	9 (29)
Time of sample collection for sirolimus concentrations	
During the admission	30 (97)
Before coadministration	11 (35)
During coadministration	21 (68)
After coadministration	12 (39)
	Mean ± SD
Sirolimus concentration from all collections obtained before, during, and after coadministration (ng/ml)	12.7 ± 12.0
	Range
Sirolimus concentration (ng/ml)	
During the admission	2.3–60.0
Before coadministration	2.6–56.0
During coadministration	2.4–40.1
After coadministration	2.3–60.0

[a]Includes 5 cases from patient 5, 2 cases from patient 9, and 1 case each from patients 7 and 14.

Results

Of 31 patients who had orders for voriconazole and sirolimus on the same day, there were 43 separate cases. After reviewing the medication administration records, 12 cases (in 8 patients) were excluded because the patients had not actually received the agents concomitantly within a 24-hour period. This left 31 cases (in 23 patients) of coadministration of voriconazole and sirolimus for inclusion in the study. In 13 (46.4%) of 28 cases, the patients were discharged from the hospital with the combination of sirolimus and voriconazole. The remaining 3 cases were in patients who died while in the hospital.

Of the 23 patients, seven had undergone solid organ transplantation and 16 had received a hematopoietic stem cell transplant (Table 2). Coadministration of voriconazole and sirolimus occurred for a mean of 4.6 ± 4.2 days and ranged from 1–20 days (Table 3). Three types of case scenarios were identified: in 9 cases (9 patients), voriconazole was administered before the addition of sirolimus; in 13 cases (13 patients), sirolimus was administered before the addition of voriconazole; and in 9 cases (4 patients), patients

were receiving the two agents concurrently on admission to the hospital. Overall, sirolimus concentrations were obtained during the admission in 30 (97%) of the 31 cases (Table 4).

Voriconazole Administration Before the Addition of Sirolimus

In this scenario, sirolimus concentrations were obtained during the period of sirolimus coadministration with voriconazole in 7 (78%) of the 9 cases (Table 5); however, in 2 patients (cases 11 and 23), no sirolimus concentrations were obtained during coadministration. In these 7 cases, the first sirolimus concentration obtained during coadministration was a mean ± SD of 14.8 ± 11.8 ng/ml (range 3.4–36.0 ng/ml) and was obtained 35.1 ± 24.6 hours (range 6–71 hrs) after the start of coadministration. In the 4 cases (1, 3, 7, and 14) in which the initial sirolimus dose was low (0.5–1 mg/day) and in case 20 in which a 6-mg loading dose was given, subsequent sirolimus concentrations were less than 20 ng/ml. In contrast, in 2 cases (2 and 8) in which 12- and 4-mg, respectively, loading doses were given, the patients experienced elevated (> 20 ng/ml) sirolimus concentrations of 24.9 and 36.0 ng/ml, respectively (Table 5). Figure 1 depicts the concentrations of sirolimus in case 8: this patient was receiving voriconazole before administration of a 4-mg loading dose of sirolimus; subsequent sirolimus concentrations were greater than 20 ng/ml.

Sirolimus Administration Before the Addition of Voriconazole

Sirolimus concentrations were obtained both before and during coadministration with voriconazole in 10 of the 13 cases in this scenario (Table 6); however, in 3 patients (cases 13, 16, and 19) no sirolimus concentrations were obtained after the addition of voriconazole. In these 10 cases, the mean ± SD baseline sirolimus concentration was 11.4 ± 8.2 ng/ml (range 3.4–30.8 ng/ml), which was obtained 99.7 ± 114.1 hours (range 2–384 hrs) before the addition of voriconazole. The first sirolimus concentration and its time obtained after addition of voriconazole were 15.7 ± 12.9 ng/ml (range 2.8–39.6 ng/ml) and 37.7 ± 40.3 hours (range 0.5–141 hrs), respectively. In 7 cases in which the patients received sirolimus doses of 0.5–2 mg/day and whose sirolimus concentrations before adding voriconazole ranged from 3.4–13.2 ng/ml, sirolimus concentrations were less than 20 ng/ml after adding voriconazole (Table 6).

Dramatically elevated sirolimus concentrations (> 20 ng/ml) occurred in 3 cases in this scenario. In case 6, the patient received sirolimus 6 mg/day as an outpatient and had a sirolimus concentration of 12.5 ng/ml 68 hours before the addition of voriconazole. The subsequent sirolimus concentration at hour 102.5 (26 hrs after coadministration) was 32.7 ng/ml (Figure 2). In case 12, the patient received sirolimus 2 mg/day on admission, but the dose was increased to 4 mg/day on

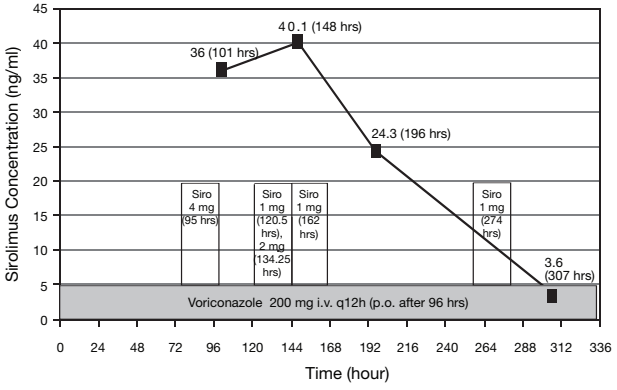

Figure 1. Case 8 is an example of dramatically elevated sirolimus (Siro) concentrations resulting from administration of a loading dose of sirolimus 4 mg in a patient receiving voriconazole. Time 0 is the start of admission.

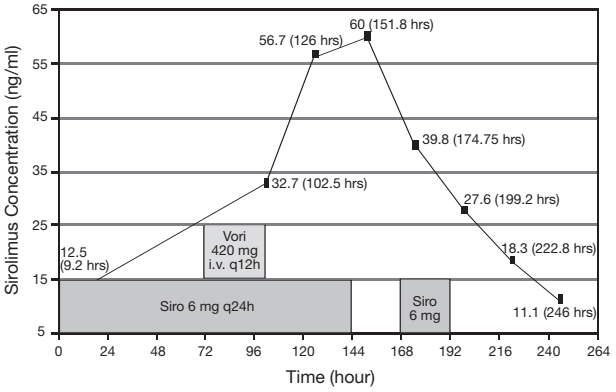

Figure 2. Case 6 is an example of dramatically elevated sirolimus (Siro) concentrations resulting from voriconazole (Vori) administration in a patient previously stabilized with high daily doses of sirolimus (time 0 is 72 hrs before admission). Voriconazole was started at a dose of 420 mg intravenously at hour 76.5 (with time 0 being the time of admission), with a second 420-mg intravenous dose given at hour 91.3. Sirolimus was continued at a dosage of 6 mg/day.

Table 5. Voriconazole Administration Before Addition of Sirolimus

Case No.	Voriconazole Dosage	No. of Days Before Coadministration	Sirolimus Oral Dosage	Concurrent Drugs[b]	No. of Days of Coadministration
1	200 mg i.v. q12h	≥ 7[a]	1 mg/day	None	1
2	200 mg p.o. q12h	≥ 1[a]	12 mg x 1 day, then 2 mg/day	None	7
3	300 mg p.o. q12h	≥ 1[a]	1 mg/day x 2 days, then 0.5 mg/day x 2 days	None	4
7	200 mg p.o. q12h	≥ 4[a]	1 mg/day x 4 days, then 1 mg 3 times/wk x 7 days	None	11
8	200 mg i.v. q12h, then changed to p.o. on day 2 of coadministration	≥ 3[a]	4 mg x 1 day, then skipped 1 day, then 3 mg x 1 day, then 1 mg x 1 day	(A) Rifampin, phenytoin, omeprazole	9
14	150 mg i.v. q12h x 3 doses, then 200 mg i.v. q12h	7	0.5 mg/day	(B, D) Phenytoin	9
20	200 mg p.o. q12h	≥ 7[a]	6 mg x 1 day, then 2 mg/day x 4 days, 4 mg x 1 day, then 3 mg/day x 2 days	None	8

R = random; T = trough; A = after coadministration; B = before coadministration; D = during coadministration.
[a]Number of days the patient received voriconazole as documented on the medication administration record as an inpatient before sirolimus was started; however, the patient may have been taking voriconazole as an outpatient before admission.
[b]Cytochrome P450 3A isoenzyme or P-glycoprotein inducer or inhibitor.
[c]Sirolimus trough concentrations were defined as plasma concentrations obtained within 3 hrs before the next scheduled dose or within 1 hr after the next scheduled dose if the scheduled dose was not administered at the correct time (e.g., if nursing staff waited until the trough was obtained before administration of the next sirolimus dose).
[d]Number of hours after start of coadministration that sirolimus concentration was obtained.
[e]Dose decreased to 0.5 mg/day 24 hrs before sirolimus concentration was obtained.
[f]Dose decreased to 1 mg 3 times/wk 48 hrs after sirolimus concentration was obtained.

the second day of admission; 24 hours after the dose increase the sirolimus concentration was 17.6 ng/ml. Despite a 50% decrease in the sirolimus dose after voriconazole was added, a sirolimus concentration of 27.6 ng/ml was observed 56 hours after the start of coadministration. In case 21, the patient received sirolimus 1 mg every 12 hours in combination with oral itraconazole 200 mg/day (a strong CYP3A isoenzyme inhibitor), thus the patient experienced elevated sirolimus concentrations (30.8–56.0 ng/ml) before coadministration of sirolimus and voriconazole. The total daily dose of sirolimus was reduced by 50% and the sirolimus concentration decreased to 30.8 ng/ml before coadministration of voriconazole and sirolimus. Only a minimal increase in sirolimus concentrations to 39.6 ng/ml was observed with addition of voriconazole (Figure 3).

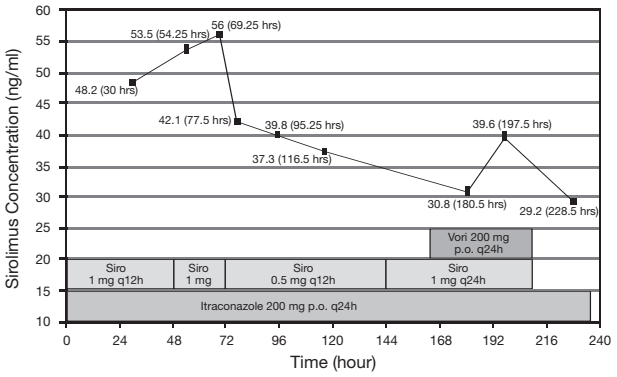

Figure 3. Case 21 is an example of the minimal effect of voriconazole (Vori) administration on plasma sirolimus (Siro) concentrations in a patient already receiving a potent inhibitor of cytochrome P450 3A4 isoenzymes (itraconazole). Time 0 is 168 hours before coadministration of sirolimus and voriconazole.

Voriconazole and Sirolimus Already Being Received Concurrently on Admission

In 9 cases (in 4 patients), patients were already receiving the combination of voriconazole and sirolimus on admission. Combination therapy was also started as inpatients in cases 5, 7, and 14, whereas in case 9 it had been started only as

Table 5. (continued)

Sirolimus Concentration (ng/ml)[c]	Time Sirolimus Concentration Obtained (hrs)[d]	Comments
10.2 (R)	71	Discharged with combination therapy
24.9 (R)	21	Sirolimus doses held and dosed by concentration; voriconazole later discontinued
8.3[e] (T)	63	Discharged with combination therapy
5.4[f] (R)	32	Discharged with combination therapy
36.0 (R)	6	Sirolimus dosed by concentration then discontinued
3.4 (R)	40	Discharged with combination therapy
15.1 (R)	13	Voriconazole changed to micafungin; discharged with sirolimus

an outpatient. In case 5, the patient received the combination for approximately 1 year (the patient was admitted 5 times during a 1-yr period); sirolimus concentrations were successfully maintained at less than 20 ng/ml (mean sirolimus concentration of 7.8 ± 1.8; range 3.6–9.4 ng/ml) throughout this period with a regimen of oral sirolimus 1 mg/day and voriconazole 200 mg every 12 hrs.

Concurrent Use of Cytochrome P450 3A Isoenzyme or P-glycoprotein Inducers or Inhibitors

In 2 cases, the patients were concurrently receiving a CYP3A isoenzyme inducer before and during coadministration of voriconazole and sirolimus (Tables 5 and 6). In no cases did the patients receive a concomitant P-glycoprotein inducer, but in 9 cases the patients received a P-glycoprotein inhibitor (itraconazole, cyclosporine, or omeprazole[10, 24]) during coadministration.

Adverse Effects of Combination Therapy

Adverse effects potentially attributable to elevated sirolimus concentrations (> 20 ng/ml) occurred in 2 (8%) of 25 cases; sirolimus concentrations were not available in 6 cases. In case 2, the patient developed thrombocytopenia with no other identifiable causes. In case 8, the patient developed renal dysfunction requiring hemodialysis and leukopenia, although tacrolimus may have contributed to these toxicities; however, the patient's tacrolimus concentrations were within normal limits (4–6.7 ng/ml).

The 30-day mortality rate after the last day of combination therapy as an inpatient was 30% (7 of 23 patients). Six (86%) of these seven patients were not receiving combination therapy at the time of death. The causes of death were infectious complications in three patients and transplant complications in four patients.

Discussion

Although the voriconazole prescribing information states that its use with sirolimus is contraindicated,[9] clinicians have been faced with the challenge of still needing to use the two agents together. Despite a lack of prospective, randomized, controlled studies evaluating the concurrent use of voriconazole and sirolimus in the transplant population, several published case reports describe the concomitant use of these two agents. In one case report, in which a patient received sirolimus 1 mg/day while receiving voriconazole, the area under the plasma concentration–time curve of sirolimus increased by 4.5-fold during concurrent administration with voriconazole; on discontinuation of voriconazole, the sirolimus dose had to be increased to 3 mg/day to maintain therapeutic sirolimus concentrations.[17] This report also described increased sirolimus concentrations when voriconazole was administered concomitantly in two other transplant recipients. The sirolimus concentration increased by 2.5-fold when a patient, who had been stabilized with sirolimus 4 mg/day, began to receive voriconazole despite a slow taper of the sirolimus dose to 1 mg/day. The other patient had been maintained with sirolimus 1.5 mg/day (concentrations ranged from 17–19 ng/ml before the addition of voriconazole), and the concentration (sirolimus was continued at 1.5 mg/day) increased to 29 ng/ml 2 weeks after the addition of voriconazole.

A second case report noted that in two patients treated with voriconazole and sirolimus concurrently, the sirolimus dose had to be decreased by 75–87.5% in order to maintain therapeutic trough concentrations of sirolimus.[18] A case series reviewed 11 patients who received the two agents together for a median of 33 days (range 3–100 days).[16] In the 8 patients whose sirolimus dose was decreased by 90% after the addition of

Table 6. Sirolimus Administration Before Addition of Voriconazole

Case No.	Oral Sirolimus Dosage	No. of Days Before Coadministration	Sirolimus Concentration Before Coadministration (ng/ml)	Time Sirolimus Concentration Obtained Before Coadministration (hrs)	Voriconazole Dosage	Sirolimus Dosage Adjustment During Coadministration
4	1 mg q.d.	≥ 1[a]	4.0[e]	384	300 mg p.o. x 1, then 200 mg p.o. q12h x 2 doses, then 400 mg i.v. q12h	↓ to 0.5 mg q.d.
5	1 mg q.d.[f]	≥ 2[a]	11.0[e]	99	200 mg p.o. q12h	↓ 0.5 mg q.d. 2 days before voriconazole added
6	6 mg q.d.	≥ 1[a]	12.5	68	420 mg i.v. q12h x 2 doses	No
10	1 mg q.d.	≥ 7[a]	3.7	14	200 mg p.o. q12h	↓ to 1 mg q.o.d. x 5 days, then ↑ to 1.5 mg q.d. x 5 days, then ↓ 1 mg q.d. x 4 days, then ↓ to 1 mg q.o.d. x 6 days
12	2 mg x 1 day, then 4 mg q.d. x 5 days	≥ 6[a]	17.6	112[g]	450 mg i.v. x 1 dose	↓ to 2 mg q.d.
15	2 mg x 1 day, then 1 mg q.d. (missed 1 dose)	6	13.2	20	175 mg i.v. q12 h x 2 doses	No
17	1 mg q.d. x 5 days, then 1.5 mg q.d.[j]	≥ 7[a]	3.4[e]	101	200 mg p.o. q12h	↑ to 2 mg q.d. x 3 days, then ↓ to 0.5 mg q.d.
18	2 mg q.d. x 5 days	≥ 7[a]	8.2[k]	176	600 mg i.v. q12h x 3 doses	↓ to 1 mg q.d. x 2 days before voriconazole added
21	1 mg q12h x 2 days, then 0.5 mg q12h x 4 days	≥ 7[a]	30.8	2	200 mg p.o. q.d.	Changed to 1 mg q.d. 1 day before adding voriconazole
22	1 mg q.d.	≥ 1[a]	9.8	21	200 mg p.o. q12h	↑ to 3 mg x 1 dose, then 1 mg q12h

R = random; T = trough; B = before coadministration; D = during coadministration; A = after coadministration.
[a]Number of days the patient received sirolimus as documented on the medication administration record as an inpatient before voriconazole was started; however, the patient may have been taking sirolimus as an outpatient before admission.
[b]Cytochrome P450 3A isoenzyme or P-glycoprotein inducer or inhibitor.
[c]Sirolimus trough concentrations were defined as plasma concentrations obtained within 3 hrs before the next scheduled dose or within 1 hr after the next scheduled dose if the scheduled dose was not administered at the correct time (e.g., if nursing staff waited until the trough was obtained before administration of the next sirolimus dose).
[d]Number of hours after start of coadministration that sirolimus concentration was obtained.
[e]Reflects sirolimus 1-mg/day dosing.
[f]Sirolimus 1 mg/day according to admission note; no doses given for first 2 days of admission, then restarted at 0.5 mg/day.
[g]Sirolimus concentration that was obtained 24 hrs after dose increased from 2 to 4 mg/day.
[h]44 hrs after voriconazole was discontinued.
[i]0.5 hrs after sirolimus was given.
[j]No sirolimus dose given x 1 day before increasing sirolimus dose to 1.5 mg/day.
[k]Reflects sirolimus 2-mg/day dosing.

voriconazole, no toxicity was observed, and sirolimus trough concentrations remained within 3–12 ng/ml, the target trough range in that study. The three patients who did not have their sirolimus doses reduced when voriconazole was added had sirolimus trough concentrations above the upper limit of the target trough range; however, it was not reported whether these patients were also receiving other CYP3A isoenzyme inhibitors during that time.

Table 6. (continued)

Concomitant Drugs[b]	No. of Days of Coadministration	Sirolimus Concentration After Start of Coadministration (ng/ml)[c]	Time Sirolimus Concentration Obtained (hrs)[d]	Comments
None	1	12.4 (R)	8	Sirolimus discontinued
(B, D) Itraconazole	2	7.2 (R)	141	Discharged with combination therapy
None	1	32.7 (R)	26	Voriconazole discontinued
(A) Fluconazole	20	2.8 (R)	33	Sirolimus concentration ranged from 2.8–18 ng/ml during 20 days of coadministration
(B, D) Phenobarbital (B, D, A) Cyclosporine (A) Fluconazole	2	27.6 (R)	56[h]	Sirolimus continued, voriconazole changed to fluconazole, voriconazole changed to fluconazole
(B, D, A) Cyclosporine (B, D) Fluconazole	2	13.2 (R)	0.5[i]	Sirolimus continued, voriconazole changed to caspofungin
None	5	3.8 (R)	44	Sirolimus discontinued, discharged with voriconazole
(A) Omeprazole (1 dose)	2	7.4 (R)	41	Sirolimus and voriconazole discontinued
(B, D, A) Itraconazole (A) Cyclosporine	1	39.6 (R)	15	Patient received itraconazole during entire admission, discharged with voriconazole
(D, A) Cyclosporine	4	10.4 (T)	12.5	Sirolimus discontinued, discharged with voriconazole

To coadminister these two agents safely, consideration must be given to which agent (sirolimus or voriconazole) the patient is receiving first, the dosage of sirolimus, the sirolimus concentration before the addition of voriconazole if the patient is already receiving sirolimus, and concurrent CYP3A isoenzyme inhibitors or inducers. As illustrated by our cases 2 and 8 and the drug interaction study in healthy subjects reported in the voriconazole package insert,[9] large loading doses of sirolimus are generally not necessary in patients who have been receiving voriconazole before the addition of sirolimus. The CYP3A isoenzyme activity of patients receiving voriconazole will be inhibited already, and thus, they will have lower amounts of active enzyme to metabolize sirolimus. As illustrated in cases 1, 3, 7, and 14, these patients should begin to receive sirolimus at lower doses (0.5–1 mg/day) and sirolimus concentrations should be monitored closely.

In patients receiving sirolimus before the addition of voriconazole, the management strategy should be based on the daily dose of sirolimus, the sirolimus concentration before addition of voriconazole, and whether the patient has been receiving other CYP3A isoenzyme inhibitors. Patients stabilized with low doses of sirolimus (0.5–2 mg/day) and with prevoriconazole sirolimus concentrations of 12 ng/ml or lower may need only a 50% decrease in their sirolimus dose before addition of voriconazole, as demon-

strated by cases 4, 5, 10, and 18. These patients may have lower baseline amounts of CYP3A isoenzymes; thus, the addition of a CYP3A isoenzyme inhibitor may not have as dramatic an effect as that in patients who have higher amounts of CYP3A isoenzymes at baseline.

In contrast, based on previous literature and cases 6 and 12 in our series, patients receiving high sirolimus doses (≥ 4 mg/day) who have prevoriconazole sirolimus concentrations of 12 ng/ml or higher, should undergo a preemptive sirolimus dosage adjustment of approximately 70–90% after addition of voriconazole.[10–12] These patients may have higher amounts of baseline CYP3A isoenzymes (perhaps due to the presence of CYP3A inducers, such as rifampin, phenytoin, or phenobarbital) and thus need higher doses of sirolimus to reach target sirolimus concentrations. Inhibition of CYP3A isoenzymes in these patients may cause a significant decrease in the amount of active CYP3A isoenzymes, inhibiting the metabolism of sirolimus and resulting in significant elevations in sirolimus concentrations.

Patients receiving other CYP3A isoenzyme inhibitors concurrently with sirolimus, as in case 21 who had been receiving itraconazole, may only need minor sirolimus dosage adjustments with the addition of or change to another CYP3A isoenzyme inhibitor. Adding another CYP3A isoenzyme inhibitor or changing to another agent with a similar degree of CYP3A isoenzyme inhibition will likely cause very little change in CYP3A isoenzyme activity because the patient's enzyme activity may be maximally inhibited by the first inhibitor.

It is important for clinicians to remember that the duration of enzyme inhibition produced (and thus the effect on substrate concentrations) may be quite prolonged, in particular if both the substrate and the inhibitor have long half-lives. This can be readily observed in case 6 (Figure 2), where administration of only two doses of voriconazole resulted in prolonged inhibition of sirolimus.

Nevertheless, sirolimus concentrations should be monitored routinely during coadministration with voriconazole and when any other CYP3A isoenzyme inhibitors are added to or deleted from the patient's drug regimen, as not all interactions are predictable. For example, the patient in case 20, who had been receiving voriconazole, did not experience as elevated a sirolimus concentration as expected after administration of a loading dose of sirolimus of 6 mg; the measured concentration was 15.1 ng/ml after coadministration. The patients in cases 17 and 22 had to have their sirolimus doses increased, despite the addition of voriconazole, to maintain therapeutic sirolimus concentrations. These patients may not have been fully absorbing the voriconazole or sirolimus (case 17 had GVHD of the gastrointestinal tract, case 20 had been receiving total parenteral nutrition, and case 22 had cystic fibrosis) or may have had altered voriconazole metabolism (as described below). Case 15 had a sirolimus concentration of 13.2 ng/ml before and after the addition of voriconazole. The postvoriconazole concentration was obtained 0.5 hour after the dose of sirolimus was given; thus, the patient may not have fully absorbed the sirolimus as the time to peak sirolimus absorption is 1–2 hours, and this patient also had GVHD of the gastrointestinal tract.

Plasma voriconazole concentrations are unpredictable due to inconsistent absorption and genetic polymorphisms in CYP2C19, the isoenzyme primarily responsible for voriconazole's metabolism. Variations in plasma voriconazole concentrations may in turn affect its degree of CYP3A isoenzyme inhibition, resulting in inconsistencies in sirolimus concentrations. Furthermore, whether sirolimus, a weak CYP3A isoenzyme inhibitor, affects voriconazole concentrations is not known. Voriconazole concentrations were not monitored in our study patients. However, we recognize that measuring voriconazole concentrations would be helpful in future studies assessing the drug interaction between these two agents.

Several limitations must be considered when evaluating this study. As it is a retrospective study based on medical record reviews, we could only report data that had been documented in the patients' medical records, and we did not have access to patients' outpatient medical records. Although we collected data on other CYP3A isoenzymes and P-glycoprotein inhibitors and inducers that the patients received, we were not able to fully characterize the cumulative effects of these inhibitors and inducers on sirolimus concentrations. Target sirolimus concentrations range depending on what type of transplantation the patient receives, the other immunosuppressive agents the patient is receiving concurrently, and how much time has elapsed since the transplantation. The use of other ranges would affect the need for and amount of dosage adjustments. The average turnaround time for sirolimus concentrations at our institution is 1–2 days. Other

hospitals may have to send patient samples to another institution for analysis, resulting in a turnaround time of more than 1 week, hindering therapeutic drug monitoring of sirolimus. Finally, the study was limited in terms of the number of patients receiving voriconazole and sirolimus concurrently. Nevertheless, the number of patients in our study is far greater than has been previously reported in the literature.

Conclusion

We evaluated 31 cases (in 23 patients) of voriconazole and sirolimus coadministration. There were only 2 cases in which adverse effects occurred, possibly attributable to elevated sirolimus concentrations. Based on the results of this study and previous literature, the drug interaction between voriconazole and sirolimus is clinically manageable despite the significant CYP3A isoenzyme drug interaction with the potential for elevated sirolimus concentrations. Based on the results of this pilot study, a protocol on the management of the combination of sirolimus and voriconazole will be implemented and prospectively evaluated for efficacy and safety.

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References

1. **McNeil MM, Nash SL, Hajjeh RA, et al**. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. Clin Infect Dis 2001;33:641–7.
2. **Marik PE**. Fungal infections in solid organ transplantation. Expert Opin Pharmacother 2006;7:297–305.
3. **De La Rosa GR, Champlin RE, Kontoyiannis DP**. Risk factors for the development of invasive fungal infections in allogeneic blood and marrow transplant recipients. Transpl Infect Dis 2002;4:3–9.
4. **Strasfeld L, Weinstock DM**. Antifungal prophylaxis among allogeneic hematopoietic stem cell transplant recipients: current issues and new agents. Expert Rev Anti Infect Ther 2006;4:457–68.
5. **Sambatakou H, Dupont B, Lode H, Denning DW**. Voriconazole treatment for subacute invasive and chronic pulmonary aspergillosis [online exclusive article]. Am J Med 2006;119:527.e17–24. Available from http://dx.doi.org/10.1016/j.amjmed.2005.11.028.
6. **Perfect JR, Marr KA, Walsh TJ, et al**. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003;36:1122–31.
7. **Denning DW, Ribaud P, Milpied N, et al**. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002;34:563–71.
8. **Herbrecht R, Denning DW, Patterson TF, et al**. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408–15.
9. **Pfizer Inc**. Vfend (voriconazole) package insert. New York, NY; 2003.
10. **Saad AH, DePestel DD, Carver PL**. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy 2006;26:1730–44.
11. **Wyeth Pharmaceuticals Inc**. Rapamune (sirolimus) package insert. Philadelphia, PA; 2006.
12. **Perez-Simon JA, Sanchez-Abarca I, Diez-Campelo M, Caballero D, San Miguel J**. Chronic graft-versus-host disease: pathogenesis and clinical management. Drugs 2006;66:1041–57.
13. **Mehrabi A, Fonouni H, Kashfi A, et al**. The role and value of sirolimus administration in kidney and liver transplantation. Clin Transplant 2006;20:30–43.
14. **Lischke R, Simonek J, Matousovic K, et al**. Initial single-center experience with sirolimus after lung transplantation. Transplant Proc 2006;38:3006–11.
15. **Aranda-Dios A, Lage E, Sobrino JM, et al**. Sirolimus experience in heart transplantation. Transplant Proc 2006;38:2547–9.
16. **Marty FM, Lowry CM, Cutler CS, et al**. Voriconazole and sirolimus coadministration after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2006;12:552–9.
17. **Sadaba B, Campanero MA, Quetglas EG, Azanza JR**. Clinical relevance of sirolimus drug interactions in transplant patients. Transplant Proc 2004;36:3226–8.
18. **Mathis AS, Shah NK, Friedman GS**. Combined use of sirolimus and voriconazole in renal transplantation: a report of two cases. Transplant Proc 2004;36:2708–9.
19. **Said A, Garnick JJ, Dieterle N, Peres E, Abidi MH, Ibrahim RB**. Sirolimus-itraconazole interaction in a hematopoietic stem cell transplant recipient. Pharmacotherapy 2006;26:289–95.
20. **Venkatakrishnan K, Von Moltke LL, Greenblatt DJ**. Human drug metabolism and the cytochromes P450: application and relevance of in vitro models. J Clin Pharmacol 2001;41:1149–79.
21. **Annesley TM, Clayton L**. Simple extraction protocol for analysis of immunosuppressant drugs in whole blood. Clin Chem 2004;50:1845–8.
22. **Holt DW, Denny K, Lee TD, Johnston A**. Therapeutic monitoring of sirolimus: its contribution to optimal prescription. Transplant Proc 2003;35:S157–61.
23. **Stenton SB, Partovi N, Ensom MH**. Sirolimus: the evidence for clinical pharmacokinetic monitoring. Clin Pharmacokinet 2005;44:769–86.
24. **Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF**. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol 2001;364:551–7.