Successful use of posaconazole to treat invasive cutaneous fungal infection in a liver transplant patient on sirolimus

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Fungi are an important and common cause of cutaneous infections affecting solid organ transplant recipients. These infections can represent a primary site of infection with the potential for dissemination, or a manifestation of metastatic infection. The high morbidity and mortality associated with these infections necessitates urgent therapy with antifungal drugs; however, the interaction between these drugs and immunosuppressive therapies can be a major limitation because of drug toxicity. A case of soft tissue infection of the toe caused by *Fusarium chlamydosporum* and *Candida guilliermondii* in a liver transplant patient on sirolimus, who was successfully treated with the new antifungal agent posaconazole, is described. The pharmacokinetic interactions of sirolimus and the new triazoles, and their impact on treatment choices are briefly discussed.

Key Words: Cutaneous fungal infections; Liver transplantation; Posaconazole; Sirolimus

Immunocompromised patients are at increased risk of infections from an environmental source. Fungi are increasingly recognized as major pathogens in transplant patients, with reported incidence rates of between 5% and 40% (1,2). The risk of developing fungal infections in these patients is determined by the interaction between the epidemiological exposure and the degree of immunosuppression. Fungal infections in transplant recipients are generally classified into either primary infection, with high risk for dissemination; reactivation infection, with one of the geographically restricted systemic mycoses; or opportunistic infection by fungal species that rarely cause infection in immunocompetent hosts (2). Treating these infections can be a challenge because of the difficulties encountered with the use of certain antifungal drugs and their toxicity or interaction with immunosuppressive drugs. To our knowledge, the present report is the first published case describing the use of posaconazole to treat cutaneous fungal infection in a liver transplant recipient while continuing sirolimus therapy.

CASE PRESENTATION

A 57-year-old Canadian man was referred to the infectious disease clinic in August 2007, because of painful discolouration of his right fifth toe and the lateral aspect of his left heel. These symptoms started two-and-a-half weeks before presentation and did not improve after two courses of antibiotics. He recollected walking barefoot in the soil at his cottage but did not recall any specific trauma to either foot. There were no complaints of fever, chills or night sweats. He underwent a liver transplantation in 2005 for hepatic failure secondary to Budd-Chiari syndrome, as well as polycythemia rubra vera and hypertension.

L'utilisation fructueuse du posaconazole pour traiter une infection fongique invasive de la peau chez un greffé du foie prenant du sirolimus

Les champignons sont une cause importante et courante d'infections cutanées chez les greffés d'un organe plein. Ces infections peuvent constituer un foyer primaire d'infection ayant le potentiel de se disséminer ou une manifestation d'infection métastatique. Le fort taux de morbidité et de mortalité associé à ces infections exige un traitement urgent aux antifongiques, mais l'interaction entre ces médicaments et les immunosuppresseurs peut constituer une importante limite en raison de la toxicité des médicaments. Est décrit le cas d'un greffé du foie atteint d'une infection des tissus mous de l'orteil causée par un *Fusarium chlamydosporum* et un *Candida guilliermondii* qui prenait du sirolimus et qui a subi un traitement fructueux au posaconazole, un nouvel antifongique. Les auteurs abordent brièvement les interactions pharmacocinétiques du sirolimus et des nouveaux triazoles, ainsi que leurs répercussions sur les choix thérapeutiques.

Post-transplant, he developed chronic kidney failure secondary to calcinuric inhibitors. His medications included sirolimus (2 mg daily), mycophenolate mofetil (750 mg twice daily), trimethoprim-sulfamethoxazole (800 mg/160 mg every other day), hydrochlorothiazide (25 mg daily) and warfarin (9 mg daily). He had no known drug allergies and his family and social history were unremarkable.

On examination, he appeared systemically well, was afebrile and had a heart rate of 78 beats/min, a respiratory rate of 18 breaths/min and an oxygen saturation of 98% on room air. His right fifth toe was purple, mottled and ulcerated with involvement of the nail plate (Figure 1). There was no discharge, but the toe was exquisitely tender to palpation. Mild bilateral ankle edema was present.

The investigations included normal electrolytes, and a white blood cell count of $9.8 \times 10^9/L$ with a lymphocyte count of $1.4 \times 10^9/L$. His urea and creatinine levels were 8.0 mmol/L and 139 mmol/L, respectively. He had a normal foot and ankle x-ray, and a magnetic resonance imaging scan of his feet showed no evidence of osteomyelitis. A skin biopsy of the right fifth toe showed parakeratosis, mild acanthotic hyperplasia with reactive atypia, microvascular dilation and mild lymphocytic infiltration of the upper dermis, changes consistent with a dermatitis reaction with no evidence of neoplasm. However, mycology culture and susceptibility testing identified *Candida guilliermondii* and *Fusarium chlamydosporum*, which are recognized pathogens in the context of cutaneous infections with nail involvement in transplant recipients, as seen in our patient, rather than a simple colonizer. The susceptibility results were obtained using the YeastOne (TREK Diagnostic Systems, Inc, USA) method for *C. guilliermondii*, and the

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Figure 1) A and B Right fifth toe at time of presentation with swelling, discolouration and ulceration. C and D Right fifth toe after treatment with complete healing

TABLE 1
Results of the mycology culture and the susceptibility profile from the biopsy of the right fifth toe

<i>Fusarium chlamydosporum</i>		<i>Candida guilliermondii</i>	
Antifungal drug	MIC, mg/L	Antifungal drug	MIC, mg/L
Amphotericin B	0.5	Amphotericin B	0.5
Fluconazole	32.0	Fluconazole	2
Ketoconazole	1.0	5-flucytosine	0.03
Itraconazole	2.0	Itraconazole	0.25
Voriconazole	0.5	Voriconazole	0.12
		Gaspofungin	0.25

MIC Minimum inhibitory concentration

Clinical and Laboratory Standards Institute method for *F. chlamydosporum* (Table 1). Susceptibility to posaconazole was not performed because it was not a routine test at that time.

The lipid formulation of amphotericin B could not be used due to concern of worsening of the patient's chronic renal insufficiency, and voriconazole was relatively contraindicated at that time because the patient was on sirolimus. As an alternative, the new antifungal agent posaconazole (400 mg orally twice daily) was used, and the patient was instructed to take it with meals. The sirolimus dose was reduced to 1 mg daily then to 1 mg every other day, and drug levels were followed closely by the patient's transplant centre to compensate for the cytochrome P450 (CYP) interaction between sirolimus and posaconazole. During the course of therapy, liver function tests remained normal

and the sirolimus levels were stable between 3.6 µg/L and 5.3 µg/L. Posaconazole drug level was not tested. The patient received a six-month course of posaconazole with complete recovery (Figure 1).

DISCUSSION

Fungal infections are occurring with increasing frequency secondary to medical advances in the areas of transplantation, cancer management and autoimmune diseases. Yeasts most frequently isolated in clinical practice are *Candida* species and *Cryptococcus* species (3). *F. chlamydosporum* and *C. guilliermondii* are uncommon pathogens that can present with cutaneous infections with a potential risk for dissemination in immunocompromised hosts. *C. guilliermondii* has been isolated from numerous human cutaneous infections but systemic infections are rare. *Fusarium* species are soil saprophytes that use the skin as a portal of entry causing soft tissue infection including superficial (onychomycosis and keratitis), locally invasive or disseminated infections (4). Inhalation of spores is another major portal of entry, leading to fungal sinusitis and pneumonia. A previous review of 259 patients with fusarial infection showed that 72% of immunocompromised hosts had skin involvement, which was described as papules, nodules with or without necrosis and gangrenous changes, cellulitis, onychomycosis, ulcers, keratotic lesions or subcutaneous abscesses (5). The presentation varies according to the extent of infection (localized versus disseminated) and the presence or absence of a history of skin breakdown. Skin involvement was associated with a higher mortality rate (70%), particularly with patients whose lesions were disseminated (5).

TABLE 2
Comparative pharmacokinetics of different triazoles and sirolimus

Agent	Dosage form	Metabolism (%)	Bioavailability, %	Cytochrome P4503A4	Elimination (%)
Fluconazole	Intravenous, oral	Hepatic (20)	95	Substrate	Renal (80)
Itraconazole	Intravenous, oral	Hepatic (extensive)	50	Substrate and inhibitor	Hepatic
Posaconazole	Oral	Hepatic (<30)	Variable	Inhibitor	Feces (77)
Voriconazole	Intravenous, oral	Hepatic (98)	98	Substrate and inhibitor	Renal (83)
Sirolimus	Oral	Hepatic (extensive)	15	Substrate	Feces (91)

Early identification of localized skin disease and institution of therapy with debridement, antifungal agents, or both are crucial and can be life-saving. Despite the reported efficacy of liposomal amphotericin B in treating fusarial skin infection in a liver transplant patient (6), it could not be used in our case because of impaired renal function, and the only other option was to use triazole agents. No two triazole agents offer the same pharmacodynamic profile and choosing among different agents can be difficult (7) (Table 2). Newer azole agents (voriconazole and posaconazole) are emerging as first-line therapies for severe fungal infections because of superior pharmacokinetics and pharmacodynamics, improved safety profiles and clinical efficacy in the treatment of systemic and localized mycoses (7-9).

Posaconazole, as with other triazole antifungal agents, works by binding to the heme cofactor located on the active site of the cytochrome CYP-dependent 14- α -demethylase. This enzyme is responsible for the conversion of lanosterol to 14- α -dimethyl lanosterol in the ergosterol biosynthetic pathway. Ergosterol is an essential component of the fungal cell membrane. The net result is disruption of the integrity and function of the fungal cell membrane, as well as inhibition of fungal growth. Posaconazole is available only in oral formulation (trials of intravenous formulations are upcoming), and its absorption is highly enhanced by concurrent food intake. Therefore, it should be administered during or within 20 min following a full meal or an oral liquid nutritional supplement. Posaconazole is primarily eliminated via the fecal route, and approximately 14% of an administered dose undergoes non-CYP hepatic metabolism to inactive metabolites and is excreted in urine (10). Therefore, only minimal amounts are recovered in the urine and dose reductions are not required for patients with chronic kidney disease. Gastrointestinal symptoms, including diarrhea, nausea and abdominal pain are the most common side effects of this drug and occur in approximately 1% to 10% of users (10).

Although posaconazole does not undergo any appreciable phase I biotransformation reactions, it is an inhibitor of CYP3A4 metabolism and is a substrate and inhibitor of P glycoprotein transport (Table 2). Drug-drug interactions similar to those seen with other inhibitors of CYP3A4 can occur (11,12). For example, sirolimus is metabolized by cytochrome CYP3A4 and is a substrate of the P glycoprotein drug efflux pump. Patients on sirolimus may have up to a sevenfold increase in trough level when treated with drugs such as triazoles because of a decrease in the metabolic activity of this enzymatic system (13). Moton et al (14) evaluated the effects of posaconazole on sirolimus pharmacokinetics in 12 healthy subjects and found that coadministration of these two drugs can lead to an increase in sirolimus C_{max} and area under the curve (AUC) by 6.7- and 8.9-fold, respectively. Therefore, it is essential to monitor blood sirolimus concentrations and to adjust the sirolimus doses before and after coadministration of these drugs. A recent in vitro study assessing drug interactions found significant antagonism with the concurrent use of sirolimus and posaconazole (15).

In comparison, voriconazole is both a substrate and an inhibitor of CYP3A4 with a net effect of increasing sirolimus's AUC. This effect is not easily managed by dose adjustment due to its unpredictable nonlinear pharmacokinetics. In addition, voriconazole is also metabolized by other isoenzymes, namely CYP2C19 and CYP2C9. The latter can exhibit some genetic polymorphisms leading to subject-to-subject variability in voriconazole pharmacokinetics. However, the safety

of coadministration of sirolimus and voriconazole has been previously reported with an initial empirical 90% sirolimus dose reduction combined with systematic monitoring of trough levels (16). In addition, a pilot study (17) assessing the concurrent use of sirolimus and voriconazole confirmed the safety of coadministration, provided that the sirolimus drug level is closely monitored.

CONCLUSION

The new triazole antifungal drugs offer an expanded spectrum of activity over other members of its class, and understanding subtle differences among drugs within this class is essential to safely and effectively using these agents. We described a case of invasive cutaneous fungal infection in a liver transplant recipient on sirolimus that was successfully treated with posaconazole.

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