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Posaconazole liquid suspension in solid organ transplant recipients previously treated with voriconazole

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Abstract

Background—Posaconazole (PCZ) has become an attractive alternative to voriconazole (VCZ) in transplant recipients with suspected or proven invasive filamentous fungal infections, given fewer drug interactions. Here, we describe our experience with PCZ after VCZ in solid organ transplant (SOT) recipients.

Methods—VCZ was replaced by PCZ liquid solution in 19 SOT recipients (15 lung, 2 kidney, 1 liver, and 1 heart/lung) with invasive pulmonary aspergillosis (12/19; 63.2%), possible invasive pulmonary fungal infection (2/19; 10.5%), prophylaxis (2/19; 10.5%), or pulmonary scedosporiosis, mucormycosis, and mixed fungal species (1 each). Rationales for switch were suspected adverse reactions to VCZ (17/19; 89.4 %) and desire to broaden spectrum of coverage to include agents of mucormycosis (3/19; 15.8 %).

Results—PCZ was well tolerated in all patients. In those patients with baseline liver enzyme abnormalities, a median change occurred in concentrations of alanine transaminase (–20 IU/L), aspartate aminotransferase (–17.5 IU/L), and alkaline phosphatase (–61.5 IU/L). Clinical success (resolution, stabilization, or prevention of infection) was achieved in 16/19 (84%) people.

Conclusion—PCZ appears to have a reasonable safety and tolerability profile and may be an effective alternative in SOT patients who require an agent with anti-mold activity, but are unable to tolerate VCZ.

Keywords

posaconazole; fungal infection prevention; solid organ transplant; voriconazole

Invasive filamentous fungal infections (IFFI) are a major problem in solid organ transplant (SOT) recipients. Initial treatment is frequently with voriconazole (VCZ), but this agent is associated with multiple potential side effects including hepatic, neurologic, and cutaneous toxicities. In addition, IFFI may prove refractory to VCZ therapy. Posaconazole (PCZ) may be an option for some patients who require an alternative agent because they are either

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unable to tolerate VCZ or whose infection proves refractory to that drug. The drug is comparatively attractive, having a less complicated cytochrome P450 metabolism profile and, potentially, less hepatotoxicity. Data on use of PCZ for such patients, including SOT recipients, are accumulating (1–6). However, published information regarding PCZ use in SOT recipients who were previously treated with VCZ is sparse. Herein, we describe our center's experience with administering PCZ oral suspension after VCZ intolerance or suspected failure.

Methods

The Johns Hopkins Medicine Institutional Review Board (NA_00075845) approved the study. This was a single-center, retrospective study of adult (> 18 years) SOT patients treated with PCZ liquid suspension after having received at least 1 week of VCZ. Subjects were identified using the pharmacy billing detail feature of our hospital's electronic casemix information management system (JHM DataMart). This retrospective study describes 1) the rationale for PCZ vs. VCZ use, 2) antifungal-related adverse drug reactions, and 3) response to therapy. Clinical success was defined as resolution of infection in people receiving PCZ as treatment for an active infection, and 6 months fungal-free survival in those receiving PCZ for prevention of an infection. Alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) levels were compared at the beginning of PCZ treatment and after 2 weeks (when available). Hepatotoxicity was evaluated using Common Terminology Criteria or Adverse Events (CTCAE Version 4.0; National Cancer Institute). Invasive fungal infections (IFI) were defined as proven, probable, and possible according to EORTC/MSG criteria (7).

The following data were collected: basic demographic information, type of transplant, underlying condition and co-morbidities, significant medical history, positive fungal stains and cultures, galactomannan levels, radiographic findings indicative of fungal infections, dates of PCZ and VCZ administration, indication for antifungals, rationale for drug switch, adverse events related to VCZ and PCZ and response to therapy outcomes.

Results

Patient population

During 2006–2012, 23 SOT recipients were identified as having been switched to PCZ liquid suspension after being treated with VCZ. Four of those received < 72 h of PCZ and were excluded from further analysis. All but 1 of the patients was treated with 800 mg of PCZ/day in 2–4 divided doses, and the other patient received 1200 mg/day. The median age was 51 years, and 74% were men. The most common underlying condition was lung transplantation (15/19; 78.9%) followed by kidney (2/19; 10.5%), and liver and heart/lung (1/19; 5.3% each). Immunosuppressive regimens included a calcineurin inhibitor (CNI) (tacrolimus or cyclosporine), and corticosteroids in 18/19 (95%) patients, and mycophenolate or azathioprine in 12/19 (63%) patients. One patient was treated with sirolimus alone. In all patients, the indication for antifungal therapy was to treat pulmonary infection. Twelve patients were treated for invasive pulmonary aspergillosis, 2 for possible IFFI, 2 for prophylaxis following discovery of respiratory tract fungal colonization, and 1

each for scedosporiosis, mucormycosis, and a mixed filamentous fungal infection. Details of the demographics and clinical characteristics of the patients in this study are shown Table 1.

Antifungal therapy

The formulation of the drugs remained consistent throughout the study period for PCZ (oral suspension) and for both routes of administration of VCZ (intravenous and oral). The main reasons for switching to PCZ were suspected adverse reactions to VCZ (17/19; 89.4 %) and desire to broaden spectrum of coverage to include agents of mucormycosis (3/19; 15.8 %). Suspected VCZ toxicities leading to initiation of PCZ were hepatic (9/17; 53%), neuropsychiatric (5/17; 29%), visual (2/17; 12 %), cutaneous (2/17; 12 %), and gastrointestinal (1/17; 6%).

Outcomes and treatment course

Overall, clinical success defined by resolution and stabilization of IFFI was achieved in 15/17 (88%) patients where PCZ was used for treatment, and in 1 of 2 (50%) patients where it was used for prevention. Infection resolved in 10/12 patients with invasive pulmonary aspergillosis and was stabilized in another. Infection resolved in 4/5 patients with proven, probable, or possible other IFI. In the 2 patients in whom PCZ was used for prophylaxis, 1 had breakthrough fungal infection. Neuropsychiatric, cutaneous, visual, and gastrointestinal abnormalities improved and/or resolved in all patients. Liver toxicity grades improved or remained stable in all but 1 patient, who had elevation of ALP from 95 to 125 IU/mL. In those patients with VCZ- associated hepatic injury, the change in liver enzymes during the first 2 weeks after change to PCZ were ALT (–20 IU/mL (range –7 to –86), AST (–17.5 IU/L; range +3 to –27), and ALP (– 61.5 IU/L; range +30 to –656).

Discussion

In this study we report our experience with SOT patients whose antifungal regimen for treatment or prevention of pulmonary IFI was switched from VCZ to PCZ liquid suspension. The most common reason for change to PCZ was development of adverse reactions attributed to VCZ. Less commonly, the switch was driven by a desire for an oral antifungal agent with activity in mucormycosis. Treatment with PCZ was generally well tolerated and was associated with resolution, stabilization, or prevention of infection in 16 of the 19 (84%) patients.

The role of PCZ as treatment for IFFIs has yet to be well defined. At this time, it is approved in the United States for prophylaxis of IFI and for treatment of oropharyngeal candidiasis. However, published guidelines recommend it as possible salvage therapy for a variety of IFI (8–11). The drug is active against multiple important filamentous fungi including *Aspergillus* species, *Scedosporium apiospermum*, and Zygomycetes, and has been used as therapy for invasive aspergillosis and mucormycosis (2, 12–16). In a *post hoc* analysis of a large, open-label, multicenter study of PCZ as salvage therapy in patients with IFI, Alexander et al. (3) described the outcomes of 23 SOT recipients. None of those patients received VCZ as prior antifungal therapy. Complete or partial response rate in that study was 13/23 (57%). Heinz et al. (4) reported on their experience with PCZ after previous

antifungal therapy with VCZ for invasive aspergillosis in a population of patients with hematologic or oncologic malignancy or receipt of hematopoietic stem cell transplantation. The overall response rate in that study was 72.2%, with 15/36 patients showing complete response (41.7%) and 11 patients with partial response (30.6%).

A common rationale for stopping VCZ in our study was development of a neuropsychiatric event and/or elevation of liver function tests while the patient was on VCZ. Both side effects are well-known complications of VCZ (17, 18). Sensory abnormalities may present as enhanced visual perceptions, blurred vision, color vision changes, photophobia, or visual and auditory hallucinations (18, 19). The side effects may be transient and, in the case of most visual symptoms, resolve despite continuation of VCZ. It is frequently unclear whether these adverse patient experiences are related to VCZ, the patients' other medical conditions and therapies, or both. When hallucinations or progressive elevation in liver function tests are present, a reduction in VCZ dosage or its discontinuation altogether may be required. PCZ is not typically associated with neuropsychiatric side effects, but may cause hepatic injury. In our study, transition to PCZ was uniformly associated with resolution of visual symptoms and either resolution or improvement in mental status abnormalities. Moreover, transition to PCZ resulted in resolution or stabilization of liver function study abnormalities in nearly all patients. These findings are in line with previous observations regarding tolerability of PCZ as salvage treatment (3, 4).

Both VCZ and PCZ affect the metabolism of multiple drugs, and can elevate serum levels of CNIs and sirolimus. For this reason, dose adjustment and close monitoring of CNI and sirolimus levels are imperative when starting or stopping either of these antifungal agents. Because of the potential for subtle differences in the impact of VCZ and PCZ upon metabolism of CNI and mammalian target of rapamycin (mTOR) inhibitors, careful monitoring of the levels of those immunosuppressant drugs is needed, and doses may need to be adjusted during transitions between antifungal agents. All patients in this study received tacrolimus, cyclosporine, or sirolimus, and therapeutic drug monitoring was used to assist in dosing of those agents.

This study had multiple limitations inherent to its non-comparative, single-center, and retrospective design. For example, because of the complexity of the patients' medical conditions, changes in liver function may have been caused by other factors, besides the transition from VCZ to PCZ, which were not detected by our study procedures. In some patients, PCZ was stopped and alternative treatments started without specific evidence for drug toxicity or clinical failure, but rather owing to concerns about potential for side effects and pharmacokinetic considerations. In addition, none of the patients in this study received the delayed release formulation of PCZ, which is increasingly replacing the PCZ solution used in our study. Importantly, the experience reported herein, cannot be extrapolated to patients who had clinical failure while on VCZ and were switched to 'salvage' PCZ.

Despite these limitations, this study provides a "real world" view of PCZ use in SOT patients and provides useful information regarding alternative therapy, particularly in cases of VCZ toxicity.

In conclusion, this study demonstrates that PCZ can serve as a viable alternative for SOT patients who require an agent with anti-mold activity, but are unable to tolerate VCZ.

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References

1. Raad, Graybill JR, Bustamante AB, et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clin Infect Dis*. 2006; 42:1726–1734. [PubMed: 16705579]
2. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis*. 2007; 44:2–12. [PubMed: 17143808]
3. Alexander BD, Perfect JR, Daly JS, et al. Posaconazole as salvage therapy in patients with invasive fungal infections after solid organ transplant. *Transplantation*. 2008; 86:791–796. [PubMed: 18813103]
4. Heinz WJ, Egerer G, Lellek H, Boehme A, Greiner J. Posaconazole after previous antifungal therapy with voriconazole for therapy of invasive aspergillus disease, a retrospective analysis. *Mycoses*. 2013; 56:304–310. [PubMed: 23170837]
5. Segal BH, Barnhart LA, Anderson VL, Walsh TJ, Malech HL, Holland SM. Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis*. 2005; 40:1684–1688. [PubMed: 15889369]
6. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. *Clin Infect Dis*. 2006; 42:e61–e65. [PubMed: 16511748]
7. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008; 46:1813–1821. [PubMed: 18462102]
8. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. *Clin Microbiol Infect*. 2014; 20(Suppl 3):27–46. [PubMed: 24548001]
9. Cornely OA, Arikan-Akdoglu S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect*. 2014; 20(Suppl 3):5–26. [PubMed: 24479848]
10. Chowdhary A, Meis JF, Guarro J, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. *Clin Microbiol Infect*. 2014; 20(Suppl 3):47–75. [PubMed: 24483780]
11. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008; 46:327–360. [PubMed: 18177225]
12. Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. *J Clin Microbiol*. 1998; 36:2950–2956. [PubMed: 9738049]
13. Carrillo AJ, Guarro J. In vitro activities of four novel triazoles against *Scedosporium* spp. *Antimicrob Agents Chemother*. 2001; 45:2151–2153. [PubMed: 11408242]
14. Vehreschild JJ, Birtel A, Vehreschild MJ, et al. Mucormycosis treated with posaconazole: review of 96 case reports. *Crit Rev Microbiol*. 2013; 39:310–324. [PubMed: 22917084]
15. Kim JH, Williams K. Posaconazole salvage treatment for invasive fungal infection. *Mycopathologia*. 2014; 178:259–265. [PubMed: 25103141]

16. Felton TW, Baxter C, Moore CB, Roberts SA, Hope WW, Denning DW. Efficacy and safety of posaconazole for chronic pulmonary aspergillosis. *Clin Infect Dis*. 2010; 51:1383–1391. [PubMed: 21054179]
17. Luong ML, Hosseini-Moghaddam SM, Singer LG, et al. Risk factors for voriconazole hepatotoxicity at 12 weeks in lung transplant recipients. *Am J Transplant*. 2012; 12:1929–1935. [PubMed: 22486950]
18. Zonios D, Yamazaki H, Murayama N, et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. *J Infect Dis*. 2014; 209:1941–1948. [PubMed: 24403552]
19. Zrenner E, Tomaszewski K, Hamlin J, Layton G, Wood N. Effects of multiple doses of voriconazole on the vision of healthy volunteers: a double-blind, placebo-controlled study. *Ophthalmic Res*. 2014; 52:43–52. [PubMed: 24925440]

Table 1

Demographics and patient characteristics

	N (%)
Age, median, years	51
Male gender	14 (74)
Transplant type ¹	
Lung	15 (78.9)
Kidney	2 (10.5)
Liver	1 (5.2)
Heart/lung	1 (5.2)
Indication for antifungal ²	
IPA	12 (63.2)
Other IFFI ³	3(15.8)
Possible IFFI	2 (10.5)
Prophylaxis	2 (10.5)

IPA, invasive pulmonary aspergillosis; IFFI, invasive filamentous fungal infection.

¹ Percentages exceed 100% as one patient had both heart and lung transplantation.

² Unless otherwise specified, all infections were proven or probable invasive fungal infections.

³ *Scedosporium apiospermum*, *Mucor* species, and mixed filamentous fungal infection in 1 patient each.