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Posaconazole and its pharmacologic and clinical uses: an antifungal drugs

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Abstract

Posaconazole (PCZ) is a new broad-spectrum azole antifungal drug, is accepted for the prevention of persistent aspergillosis and candidiasis in addition to the cure of oropharyngeal candidiasis. There is proof of efficacy in the treatment and prevention of rarer, difficult to treat fungal diseases. PCZ oral suspension has revealed limitations with fasting state absorption, raised gastrointestinal pH and high motility. Oral use of PCZ in divided doses increases the bioavailability. The recently approved sustained-release oral tablet and interavenous solutions provide a smart treatment option. PCZ has fungicidal activities against *Aspergillus fumigatus*, *Blastomyces dermatitidis*, *Crytopcoccus neoformans*, some *Candida* species,and *Trichosporon* andfungistaticactivities against *Candida*, *Coccidioides*, some *Fusarium* species, *Scedosporium*, *Histoplasma*, and *Zygomycetes.* PCZ has synergistic effects with caspofungin or amphotericin B against *A. fumigatus*, *C. glabrata* and *C. neoformans*. The absorption of PCZ is enhanced when given with food, nutritional supplements, and carbonated beverages. PCZ is highly protein bound (>95%) and main elimination route is fecal. PCZ is an inhibitor of the CYP3A4 enzyme. Common adverse effects are headache, fatigue, nausea, vomiting and elevated hepatic enzymes. Oral suspension is suggested in immuno compromised patients with functional gastro intestinal tract who not responds to conventional antifungal therapies. Interavenous injection is also available for individuals who are unable to take oral drugs. On the basis of clinical studies, PCZ is a valuable drug for the treatment of life-threatening fungal infections. This review will examine the progress history of PCZ and emphasize the most recent progresses.

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1 Introduction

Progress in chemotherapy and immunotherapy has an incredible impact on continued existence considerably declining disease-associated morbidity. Though, such therapies have raised the figure of patients with a compromised immune system thus predisposing to opportunistic fungal diseases. In spite of presently offered antifungal drugs, mortality rates stay elevated. Drug approvals for HIV, cancer, and transplantation keep on and have considerably outpaced antifungal drug therapy improvement (Richard, 2018). Invasive fungal infections (IFIs) are difficult for seriously ill patients, with augmented threats of morbidity and death. Prophylactic cure is regularly beneficial due to late antifungal treatment has been shown to high death rates (Garey et al., 2006; Morrell et al., 2005). IFIs caused by opportunistic organisms like Candida and Aspergillus species are of considerable concern of immune compromised patients (Baddley, 2011; Bassetti et al., 2018; Muskett et al., 2011). The use of antimicrobial drugs in neutropenic patients with cancer proposed that antifungal drug prophylaxis be used in high-risk patients, together with those undergoing hematopoietic stem-cell transplantation (HSCT) or severe chemotherapy for leukemia (Freifeld et al., 2011). Unfortunately, safety and acceptability concern regularly decrease the use of antifungals. The presently accessible systemic triazole drugs are divided into two groups: the first generation are fluconazole (FCZ) and Itraconazole (ICZ) and the second generation drugs are voriconazole (VCZ), Posaconazole (PCZ) and isavuconazonium (IVZ) (Figure 1). Even though these drugs possess the same mechanism of action, each has differing antifungal action, efficiency, pharmacokinetics and safety reports, leading to exceptional therapeutic positions (Pappas et al., 2009; Walsh et al., 2008).

The treatment of continual fungal infections attempt to target metabolic aspects distinct to the pathogen. In addition, raises in the Mucor-related infections is alike or more relating to as competent treatments are to some levelare alike or more related to as competent treatments are limited (Ibrahim and Kontoyiannis, 2013; Spellberg, 2017). Currently, two main classes of antifungal drugs are usually used to fight constant fungal infections by azole antifungal drugs and echinocandin drugs. The polyene antifungal amphotericin-B (AMB) persists in examining the use of drugin examining drug for fungal infections. The AMB is filled with undesirable effects and bearing the renal toxicity (Laborin and Vargas, 2009). The progress of lipid-based AMB has effort to avoid toxicity and side effects together with infusion-related reactions (Dix and Andriole, 2000). Though, the cost of these doses form is noteworthy. Today's increasing immune compromised people and the necessity for cost-effective, curative antifungal drugs remain at the front of drug expansion. To fight resistance and enlarge spectrum of activity, improvement has been made in the design and progress of newer drugs with improved activity and decreased in cost. Here, this is a brief review of current antifungal therapy as well as new antifungal drugs with novel molecular targets.

1. 1. Azole antifungals

The ideal azole antifungal drug, ketoconazole, was marketed to the USA market in 1981. This imidazole ring containing drug, and all succeeding azole antifungal drugs, targets the fungal CYP-51 enzyme system (also known as 14α-demethylase) (Degreef et al., 1981; Graybill et al., 1980). The CYP-51 catalyzes the removal of a methyl group from lanosterol and symbolized a key enzyme in the synthetic way primary to the formation of the fungal sterol ergosterol. Reserve of CYP-51 causes fungal membrane disruptions primary to a fungicidal action. Ketoconazole was removed from therapeutic use for systemic fungal infections due to the hepatic injury, drug-drug interactions, and decreased human steroid synthesis risks. Fluconazole (FCZ), voriconazole (VCZ), PCZ, and isavuconazole represent the current armory of azole antifungal drugs. The triazole moiety for CYP-51 binding, molecular flexibility in a different aspect of these drugs permits for different affinity for CYP-51 in varying fungal strains (Richardson et al., 1990). For example, FCZ have activity against various Candida species such as *C. albicans*. Though, resistance exists or is an issue when using FCZ to treat C. tropicalis, C. glabrata, and C. krusei (Berkow and Lockhart, 2017). The voriconazole is possessing action against numerous FCZ-resistant Candida strains. Moreover, FCZ lacks action against Aspergillus while VCZ retains use in this infection. Isavuconazole, the prodrug isavuconazonium (IVZ) sulfate, corresponds to a key advance in azole antifungal therapy. This drug approved in the USA in 2015, tolerates the necessary triazole ring along with a distinctive side-chain that affords affinity for both Aspergillus CYP-51 and the CYP-51 enzyme responsible for causing persistent mucormycosis (Mucor, Rhizopus, Cunninghamella) (Denis et al., 2018; Ledoux et al., 2018). PCZhas been used in the treatment of mucormycosis but such use is at present off-label.

1. 2. New antifungal agents

Both azole antifungals and echinocandins have appreciably contributed to the cure of persistent fungal infections. Though, fungi will develop and resistance is predictable. The continuing expansion of agents which avoid resistance will be serious as we encounter extremely drug-resistant fungal strains like *Candida auris* (Vallabhaneni et al., 2017; Walia et al., 2017). Developing new dosing schemes through improved kinetic and dynamic factors can also positively impact antifungal treatment. All existing echinocandins are used interavenously (i.v) on a daily basis. A novel drug, CD-101 (rezafungin), is in clinical trials and is a once-weekly echinocandin (James et al., 2017). Rezafungin has a like spectrum of activity as other echinocandins have a half-life of up to 130 hours after a single 400 mg dose. Such a dosing may accelerate patient discharge thereby declining healthcare expenditures. SCY-078 is an oral triterpene inhibitor of β(1-3)-glucan synthase and is now in phase 3 development (Lepak et al., 2015). It is also being examined for the emergent treatment of *Candida auris* infections (Larkin et al., 2017). The SCY-078 is the first β(1-3)-glucan synthase inhibitor being developed in both i.v and oral doses forms. The molecular target may overlap with echinocandins and cross-resistance is not predictable. The T-2307 is an arylamidine for the treatment of echinocandin-resistant candida infections. It is structurally similar to the antifungal and antiprotozoal drug pentamidine and possess activity against various fungal pathogens like echinocandin-resistant and azole-resistant Candida spp, *Cryptococcus neoformans* and *Aspergillus fumigatus* (Shibata et

al., 2012; Wiederhold et al., 2016).

1. 3. Posaconazole

Posaconazole (PCZ) is a triazole antifungal have extended-spectrum of activity for prophylaxis and treatment of IFIs. PCZ has showed efficacy as an antifungal prophylactic in HSCT recipients with graft versus host disease (GVHD) and in neutropenic patients with hematologic malignancy. In addition, PCZ has effective salvage treatment alternative for patients who are non approachable to regular antifungal therapies (Kim and Williams, 2014), Overall, PCZ covers a wide collection of IFIs, like aspergillosis, cryptococcosis, fusariosis, candidiasis, mycetoma mucormycosis, chromoblastomycosis, and coccidioidomycosis (Li et al., 2010). Compared with the older azoles [fluconazole (FCZ), Itraconazole (ICZ) and voriconazole (VCZ)], PCZ has a more encouraging safety outline (Chau et al., 2014). Additionally, PCZ's activity expands outside that of other azoles, like VCZ, for example, that does not cover mucormycosis (Marty et al., 2004; Rogers, 2008). PCZ oral suspension (Noxafil) is a U.S. Food and Drug Administration (FDA) approved drug for prophylaxis against persistent aspergillosis and candidiasis in immuno-compromised patients (FDA, 2015; Product monograph–Noxafil, 2014; Schering Corp, 2014). The PCZ is a broad spectrum antifungal drug due to its unique activity against various fungi, majority of yeasts, filamentous fungi and azole resistant *Candida* species (Keating, 2005). The patterns of *Candida* infections have shifted from the common FCZ sensitive *C. albicans* to other FCZ dose-dependent sensitive and FCZ resistant *Candida* species (Pfaller et al., 2002). But not limited to, *C. glabata*, *C. parapsilosis* and *C. tropicalis*. The emergence of breakthroughfungal infections (*fusarium*, *scedosporium* and *zygomycosis*) has occurred secondary to the use of potent immunosuppressive agents and a lack of antifungal effect against these pathogens from current antifungal drugs (Pfaller et al., 2004). Therefore, novel antifungal drugs are needed because of their extended spectrum against a broader range of pathogenic microbes; PCZ is capable of treating fungal infections. This review is provided updated information on PCZ.

1. 4. Pharmacology of posaconazole

Posaconazole (PCZ) and other azoles block ergosterol preparation by 14α-demethylase (CYP51) inhibition. Ergosterol depletion stops fungal cell wall formation and causes the assembled of methylated sterol precursors causing to cell death (Torres et al., 2005). The PCZ suffers irrelevant oxidative Phase I metabolism (<2%); its metabolism is eases instead through a Phase II metabolism via uridine disphosphate-glucuronosyltransferase enzyme pathway. No related active metabolites have been recognized for PCZ (Kim et al., 2003). PCZ is a substrate and an inhibitor of the p-glycoprotein efflux transporter (Nagappan and Deresinski, 2007). The US FDA lists PCZ as a Class II compound, representing that it is well absorbed but dissolves slowly (Gubbins et al., 2006). The noticeable volume of distribution of PCZ from 5-25 l/kg, representative wide distribution and tissue infiltration (Li et al., 2010). PCZ is highly protein bound (>98%), mainly to albumin in a concentration-dependent manners. PCZ is mainly excreted in the feces (77% of the radio labeled dose), maily excreted as parent drug (66% of the radio labeled dose) in healthy persons (Krieter et al., 2004). About 14 % of the radiolabeled dose is excreted in urine, maily in the form of glucuronide conjugates. The mean half-life ($t_{1/2}$) of PCZ

25-35 h. PCZ has shown in vitro activity against various fungal pathogens, like Aspergillus spp., Candida spp., Coccidioides immitis and Fonsecaea pedrosoi. Some Fusarium, Rhizopus and Mucor species are susceptible to PCZ. Clinical *A. fumigatus* isolates have been reveal resistance to PCZ, exclusively those that harbor CYP51 mutations (Mavridou et al., 2010). There is no recognized pharmacokinetic strategy with respect to plasma PCZ for get through IFIs (Dolton et al., 2012). A PCZ concentration target greater than 0.50 mg/l is suggested for prophylactic therapy; with others suggesting a focus target greater than 0.70 mg/l. Cardiothoracic transplant patients having PCZ levels constantly exceeding 0.50 mg/l had clinically useful results (Shields et al., 2011). The values above 0.70 mg/l do not give any extra decrease in the clinical failure rate, as established in two randomized, active-controlled clinical studies using PCZ oral suspension (Jang et al., 2010).

1. 5. Chemical development

Posaconazole (PCZ) is chemically as 4-[4-[4-[4-[[(3R,5R)-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one. Its molecular formula is C37H42F2N8O4 and molecular weight is 700.8. It is formed exclusively as the (R, R, S, S) enantiomer with four chiral centers via a three-step synthesis pursued by a micronization step to improve the rate of dissolution. PCZ is highly lipophilic with triazole structurally similar to Itraconazole (ICZ) (Courtney, et al., 2004). The PCZ is consists of a triazole and difluoro phenyl rings with regular orientations feature of other azoles. PCZ is structurally analogous with ICZ. The tetrahydrofuran oxygen of PCZ overlaps the hydroxyl oxygen part of fluconazole (FCZ). Alterations, including fluorine (F) in place of chlorine (Cl) and a furan ring in place of the dioxolane ring, with an extensive range of antifungal activity (Li et al., 2010). The long side chain of PCZ grows inside the space formed by the different structural areas of lanosterol 14α-demethylase, a cytochrome P450 (CYP450) enzyme, which contains helix A′, a β turn connecting strands β4-1 and β4-2, an FG loop, helix B′ and β-strands, β1-4 (Xiao et al., 2004).

1. 6. Mechanism of action

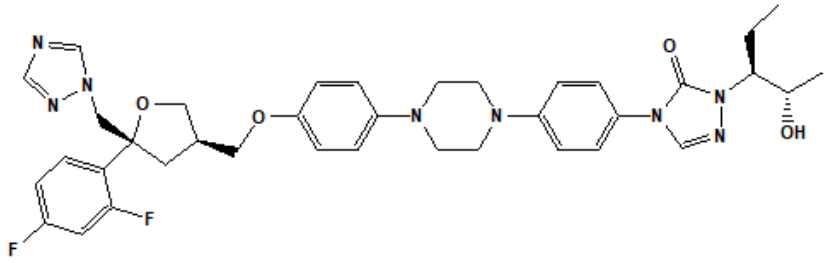
Posaconazole (PCZ) act by inhibiting fungal ergosterol biosynthesis. PCZ binds to heme cofactor situated on the target site of lanosterol 14α-demethylase, which is a CYP450 dependent enzyme (Xiao et al., 2004; Ghannoum and Rice, 1999), it is the product of CYP51A gene expression (ERG11). The fungal cell membrane integrity is maintained by ergosterol. PCZ prevents demethylation of ergosterol at C-14 and/or C-4 positions. The modified structure of ergosterol interferes with plasma membrane function, resulting in fungal cell death.

Various *in vitro* studies have confirmed the antifungal mechanism of PCZ with liquid chromatography (Heimark et al., 2002; Munayyer et al., 2004). *In vitro* PCZ reduces the development of ergosterol in *C. albicans* by inhibiting the enzyme lanosterol 14α-demethylase (Heimark et al., 2002). The depletion of ergosterol in both azole susceptible and resistant *C. albicans* incubated with PCZ [MICs ≤ 0.5 μg/mL] (Munayyer, et al., 2004). Dose dependent inhibition of ergosterol and ergosterol-like compounds (ergosta-5, 8, 22-trien-3-ol) was also examined in most *C. glabrata* strains and strain C110 respectively, when exposed to PCZ (MICs ≤4 μg/mL). Exposure of *Aspergillus fumigatus* and *A. flavus* to PCZ (MICs ≤ 0.06 μg/mL)

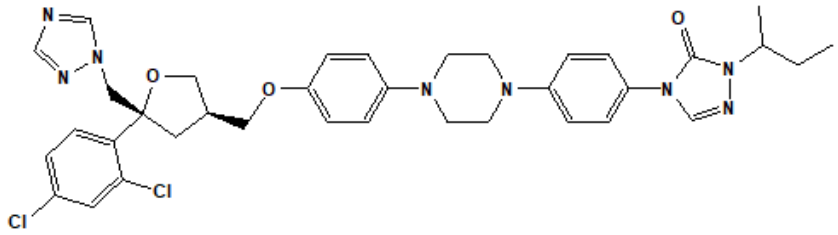
inhibited ergosterol synthesis.

1. 7. Spectrum of activity

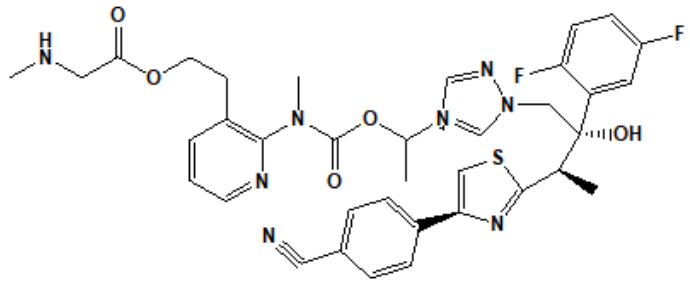
Posaconazole (PCZ) has wide spectrum of antifungal activity, as illustrated in Table 1. It has fungicidal activity *in vitro* and *in vivo*, against *Aspergillus* (*fumigatus*,*flavus*, and *terreus*), *Cryptococcus neoformans*, *Trichosporon*, *Blastomyces dermatitidis* and specific *Candida* spp. *(C. parapsilosis*, *C. krusei*, *C. lusitaniae* and *C. inconspicua*) (Sabatelli et al., 2006). PCZ also has fungistatic effects against other *Candida* spp., *Coccidiodes*, *Scedosporium*, *Zygomycetes* and specific *Fusarium* strains (*F. monilforme* and *F. oxysporum*) (Espinel-Ingroff, 1998). However, unlike antibacterials, activities ofantifungal agents do not relate with clinical outcomes.



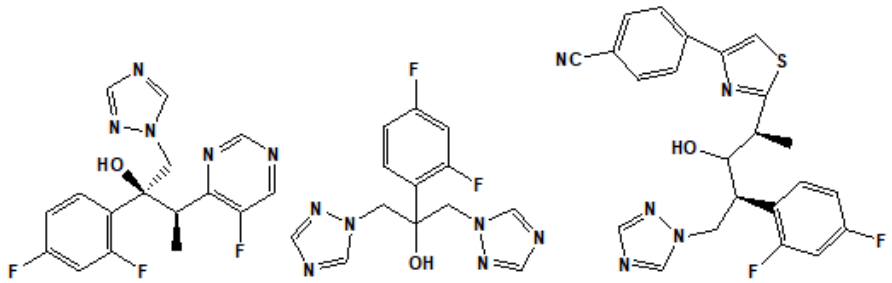
Posaconazole (PCZ)



Itraconazole (ICZ)



Isovuconazonium (IVZ)



Voriconazole (VCZ) **Fluconazole(FCZ)** **Ravuconazole (RCZ)**

Figure 1. Structures of selected triazole antifungal agents.

1. 8. Pharmacodynamics

The *in vitro* activity of PCZ was compared with amphotericin B (AMB), FCZ and ICZ against isolates of *C. neoformans*. Yeasts were inhibit and killed at lower concentrations of PCZ (MICs=0.063–0.25μg/mL) than AMB (MICs=0.25–1 μg/mL). Inhibition at concentrations at least ten fold lower than FCZ (MICs=0.5–16μg/mL) but not for ICZ (MICs =0.008–0.031 μg/mL). The three isolates, clinical strains of *C. neoformans* (T-1, DUMC 133.95, and 89–610), growth was inhibited at high MIC of FCZ (8–16μg/mL) in contrast to low MIC of PCZ (0.125–0.25μg/mL). The *in vivo* activities of PCZ when compared to FCZ were similar in reducing yeast counts in thecerebrospinal fluid in a rabbit model (Perfect et al., 1996). The PCZ compared to AMB, was effectual in prolong survival of mice with *C. neoformans* infection. The PCZ was better to AMB at dropping fungal load in the mice brains infected by two isolates *of Cryptococcal* (Barchiesi et al., 2001). *In vitro* report of voriconazole (VCZ), FCZ and PCZ against *Candida* and *C. neoformans* isolates found that both VCZ and PCZ had maximum activity against *C. albicans*, *C. krusei, C. parapsilosis*, and C. *lusitaniae*, *C. dubliniensis*, *C. tropicalis*, and *C. kefyr* (Pfaller et al., 2004). Furthermore, 97%–98% of *Candida* spp. were vulnerable at MICs ≤ 1 μg/mL. Both PCZ and VCZ were less effective against *C. glabrata* (80% vulnerable at MICs ≤ 1 μg/mL) and PCZ was less effective against *C. pelliculosa* (44% vulnerable at MICs ≤ 1 μg/mL). The FCZ was maximum effective (≥95% vulnerable at MICs ≤ 8 μg/mL) against *C. pelliculosa* (100% vulnerable), *C. albicans* (99% vulnerable), *C. lusitaniae* (98%), *C. tropicalis* (98%), *C. parapsilosis* (95%), and least effective against *C. glabrata* (57%) and *C. krusei* (1%). Both VCZ and PCZ were extremely effetive against *C. neoformans* (98%–100% susceptible at MICs≤ 1μg/mL) when contrast to FCZ (98% of *C. neoformans* vulnerable at MICs ≤ 8 μg/mL). The action of PCZ, ICZ and FCZ against 3312 clinical isolates of *Candida* and 373 isolates of *C. neoformans*, PCZ was exhibited more effective (97% of the *Candida* spp.and 100% of *C. neoformans* were inhibited at MIC ≤ 1 μg/mL) than both triazole antifungal drugs. The *C. neoformans* isolates were inhibited at 78% by FCZ (MICs ≤ 8 μg/mL) contrast to 96% by PCZ and 68% by ICZ (MICs ≤ 0.25 μg/mL). In addition, *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. tropicalis*, *C. lusitaniae*, *C. dubliniensis*, *C. famata* and *C. guilliermondii* were found to be the mostvulnerable to PCZ (99–100% of isolates vulnerable at MICs ≤ 1 μg/mL) whereas *C. glabrata* was least vulnerable (80% vulnerable at MIC ≤ 1 μg/mL) (Pfaller et al., 2001). *In vitro* activities of FCZ, PCZ, ICZ, AMB and 5-fluorocytosine against clinical isolates of *Candida*, all strains were vulnerable to PCZ (MIC range ≤ 0.007–0.125 mg/L) and AMB (MIC ≤0.03–0.5 mg/L) contrast to 97% and 95% of the isolates vulnerable to ICZ (≤0.007–1 mg/L) and FCZ (MIC ≤ 0.125–32 mg/L), respectively (Barchiesi et al., 2003).

- ***Cryptococcus neoformans***

An *in vitro* study, the effects of the interaction of PCZ and flucytosine (FC) against *C. neoformans*. Synergy and additive were observed in 33% and 67% of isolates, respectively. Even when synergy was not reached, the mean MICs of both drugs reduced considerably when they were given in combination (MIC for FC reduced from 1.26–0.39 μg/mL and MIC for PCZ reduced from 0.13–0.02μg/mL). The beneficial interaction was also displayed by a reduction in the numbers of colony forming units (CFU) of *C. neoformans* isolates. Combined therapy of PCZ and FC at sub inhibitory concentrations, eight times lower than the respective MICs,

considerably reduced the counts below those observed with each drug alone. The *in vivo* effect of this combination therapy was not considerably more effectual than every drug alone in terms of continued existence (Barchiesi et al., 2001). The tissue burden study showed that combination therapy reduced the counts considerably below that with each drug used alone. This study only utilized on *C. neoformans* one clinical isolate. Because of the genetic deviations that present among these isolates, further examination of combination therapy using multiple strains is required. Other study observed the *in vitro* interaction of AMB with triazoles against *C.neoformans.* Synergy was observed in 33% of the isolates for PCZ-AMB combined treatment, compared to 7%for ICZ-AMB and FCZ-AMB combinations. Additivism was noted in 53%, 67%, and 73% of the isolates for FCZ-AMB, PCZ-AMB, and ICZ-AMB interactions. Indifference was observed in 20%, 14%, and 26% of the isolates for PCZ-AMB, ICZ-AMB and FCZ-AMB combinations. The *in vivo* interaction of FCZ-AMB combination and compared it to FCZ and AMB therapy alone. The combination therapy was more effective than FCZ therapy and similarly or more efficacious than AMB therapy alone. The *C. neoformans* grown in a medium containing FCZ, with successive contact to AMB, lead to raise in AMB resistance and a positive interaction take placed (Barchiesi et al., 2000).

- ***Candida glabrata***

Terbinafine (TBF) mixed with four triazoles (FCZ, ICZ, VCZ and PCZ) were tested *in vitro* against weakly vulnerable *C. glabrata* strains to azoles. Synergy was found in 17%of the TBF-FCZ mixed therapy, 21% of the TBF-ICZ mixed therapy, 33% of the TBF-VCZ mixed therapy, and 12% of the TBF-PCZ mixed therapy. Combinations where synergy was not found exhibited a reduced in the MIC of one or both drugs when given in mixture (Barchiesi et al., 2000). Other study tested the *in vitro* interaction of PCZ with caspofungin against *C. glabrata* and synergy was observed in 18% of all the isolates together with 4% of the isolates resistant to FCZ (Oliveira et al., 2005). No antagonism was seen between these antigungal drugs. *Candida* resistance has found with the older azoles (FCZ and ICZ) and is currently being reported with caspofungin. PCZ and caspofungin may have a role in declined *Candida* infections and for FCZ-resistant isolates with hig PCZ MICs. Studies are necessary to investigatethe *in vivo* profit of the combination therapy.

- ***Aspergillus* and *Candida* spp.**

The activity of PCZ was tested against *Aspergillus* and *Candida* strains. Overall, PCZ (MICs ≤0.002-0.5 μg/mL) was more active than ICZ (MICs ranged from ≤0.008-1 μg/mL) against some strains of *Aspergillus*. PCZ was also more active (MICs of PCZ ranged from≤ 0.004-16 μg/mL) than FCZ (MICs ranged from ≤0.062 to >64 μg/mL) against 275 strains of *Candida* and nine strains of *C. neoformans* (Cacciapuoti et al., 2000). Compared the *in vitro* effects of PCZ, Ravuconazole (RCZ) and VCZ to ICZ and AMB against 239 isolates of *Aspergillus* and other filamentous fungi, PCZ was most active, inhibiting 94% of isolates at MIC ≤1 μg/mL, followed by VCZ (91%), AMB (89%), RCZ (88%) and ICZ (70%) (Pfaller et al., 2002). The geometric mean MICs of PCZ against *Aspergillus fumigatus* (0.17) and *non-A. fumigatus* (0.16) were considerably lower than AMB, ICZ and VCZ. AMB-resistant *Aspergillus* strains were susceptible to PCZ. ICZ- and VCZ-resistant strains showed low level (2 to 3 time raise in MIC) cross-resistance to PCZ.

Time-kill studies against *Aspergillus* confirmed that the fungicidal action of PCZ is dose and time dependent. The PCZ is more active than ICZ and VCZ (Manavathu et al., 2000).

- ***Blastomyces dermatitidis***

The activity of PCZ was tested against *Blastomyces dermatitidis*. The PCZ was more effective when compared to AMB, ICZ and FCZ [MIC90 of 0.06 μg/mL and least fungicidal concentration (MFC90) of 4μg/mL]. The effect of PCZ treatment was proved in a murine model with pulmonary blastomycosis. Continued existence in mice was prolonged at all PCZ doses (25, 5, or 1 mg/kg) and sterilization of lungs was attained with AMB (1 mg/kg) and PCZ (25 mg/kg/day dosing regimen) but not with ICZ (150 mg/kg/day) and FCZ. The efficacy of PCZ was further at low doses (1 mg/kg/day) where it was revealed to be more active than ICZ (150 mg/kg/day) in prolong survival of mice infected with *B. dermatitidis* (Sugar and Liu, 1996). Further studies with human subjects are needed to explore the roles of PCZ in the treatment of *Cryptococcus*, *Aspergillus*, *Candida* and *Blastomyces* infections.

- ***Aspergillus fumigates***

A study of tested drug combinations of caspofungin with triazoles against *A. fumigatus*. Synergy was tested *in vitro* with PCZ (FICI=0.32) and ICZ (FICI= 0.49). In compared, when caspofungin was combined with RCZ (FICI=0.61) and VCZ (FICI=1.61) there was no interaction (Manavathu et al., 2000). Animal studies are needed to examine the combination of caspofungin with PCZ or ICZ.

- ***Trichosporon* spp.**

The activities of AMB, PCZ, FCZ, VCZ, ICZ, and RCZ were tested against *Trichosporon* spp. *in vitro*. The fungicidal effects against *Trichosporon* with PCZ, VCZ and RCZ were more effective than AMB and FCZ, but like to ICZ (Paphitou et al., 2002). Further *in vivo* studies to determine the role of PCZ in the treatment of *Trichosporon* are needed.

- ***Scedosporium* spp.**

Compared the *in vitro* activities of the azoles [miconazole (MCZ), ICZ, VCZ and PCZ] to the polyenes (AMB and nystatin) and terbinafine against clinical isolates of *S.apiospermum* and clinical isolates of *S. apiospermum, S. prolificans* isolates weremost vulnerable to VCZ (MIC90 of 0.5 μ/mL) followed by MCZ (MIC90 of 1 μg/mL), PCZ (MIC90 of 2 μg/mL) and ICZ (MIC90 of 4 μg/mL). The MIC90 values of AMB (16 μg/mL), nystatin (32 μg/mL) and terbinafine (>32 μ/mL) were high. *S. prolificans* isolates were less vulnerable (MIC90 for all drugs were high (>16) except VCZ, which had a value of 4 μg/mL). Cross-resistance was found among all azoles except PCZ (Meletiadis et al., 2002). *In vitro* activities of triazoles (MCZ, VCZ, RCZ, PCZ and UR-9825) to antifungals (AMB, ketoconazole, ICZ and nystatin) against *S. apiospermum* and *S. prolificans* clinical isolates. The latter group was ineffective against both spp. (MIC90 >16 μg/mL), whereas the triazoles showed activity against *S. apiospermum*. RCZ was more effective (MIC90=0.125 μg/mL) than PCZ or VCZ (MIC 90 0.25 μg/mL). The *S. prolificans* isolates were less vulnerable (MIC90 16 for PCZ and RCZ and 4 μg/mL for VCZ) (Carrillo and Guarro, 2001).

- ***Coccidioides immitis***

ThePCZ exhibited similar *in vitro* activity to ICZ (MIC for PCZ was 0.25 -1 μg/mL, and for ICZ was 0.125-0.5 μg/mL); it was more active against *Coccidioides immitis in vivo*. Cultures of spleens and livers from mice treated with PCZ (10 mg/kg/day) showed ≥70% sterilization, whereas no sterilization was seen with ICZ, even at the higher dose of 30 mg/kg three times daily (Gonzalez et al., 2002).

- ***Mucor* spp.**

The *in vivo* actions of PCZ (5, 15, and 30 mg/kg 2 time/day dose), ICZ (30 mg/kg 3 time/day dose), and AMB (1 mg/kg once daily dose) against *Mucor* spp. were compared in immuno-compromised mice. PCZ at doses of 15 and 30 mg/kg 2 time/day prolonged continued existence and reduced fungal tissue load, while ICZ did not. PCZ given at 30 mg/kg 2 time/day dose (total daily dose 60 mg/kg/day) was as potent as AMB (Sun et al., 2002). The activity of PCZ is efficient in immune-compromised mice; further studies are needed to decided its role in the cure of human coccidioidomycosis and *zygomycosis*.

- ***Pseudallescheria boydil***

An *in vitro* study confirmed that PCZ (MIC90=1μg/mL) was more active against *Pseudallescheria boydil* than ICZ (MIC90=4μg/mL) and FCZ (MIC90 =>64μg/mL). Moreover, there were no statistically important differences on survival between treatment with PCZ (0.5, 1, 5 and 10 mg/kg/day) and ICZ (30 mg/kg 3 time/day). However, PCZ was more efficient in avoiding death (70%–75% endurance) at the higher doses (30 or 50 mg/kg/day and 25 mg/kg 2 time/day), than FCZ (50% survival at a dose of 20 mg/kg 2 time/day). This confirms the relative resistance of PCZ to *Pseudallescheria boydil* (Gonzalez et al., 2003).

1. 9. Dermatophytes

PCZ was considered equally efficacious in vitro against dermatophytes compared to ICZ (MIC90=0.5 and 1 μg/mL, respectively). Though, PCZ (MFC90 of 1 μg/mL) showed a higher fungicidal effect than ICZ (MFC90 2 μg/mL) against isolates of the *Microsporum* genus. *In vivo* studies are needed to examine the potential use of PCZ in the treatment of dermatophytes (Barchiesi et al., 2001).

1. 10. Synergy

The interaction of PCZ with other antifungal regimens against *C. neoformans*, *C. glabrata*, and *A. fumigatus* (Manavathu et al., 2003), synergy is defined as fractional inhibitoryconcentration index (FICI) of ≤0.5, additivism as FICI > 0.5-1.0, indifference as FICI > 1.0 -≤2.0, and antagonism as FICI > 2.0. PCZ has been shown to have synergistic and additivistic activities with other antifungals. These combinations may help evade the emergence of drug resistance, decrease drug related toxicities with the use of lower doses, expand the spectrum of activity and shorten duration of treatment.

1. 11. Postantifungal effect

Postantifungal effect (PAFE) is defined as fungal growth inhibition that persists after contact to an antifungal drug. It reflects the time it takes for an organism to recover from the exposure to the drug and continue normal growth. This effect varies depending on the microbes' interaction and the antifungal drugs. The fungistatic drugs are anticipated to create shorter PAFE compared to fungicidal drugs. This is because fungistatic drugs, unlike the fungicidal drugs, do not cause stable damage to the fungal cell wallbecause fungistatic drugs, unlike the fungicidal drugs, do not cause stable ones damage to the fungal cell wall, which improves as soon as the drug is uninvolved. PCZ formed a short PAFE against *A. fumigatus* (0.75hr) and *C. albicans* (≤0.5 h) compared to the long PAFE of AMB (7.5 hr and 5.3 hr). Though PCZ has fungicidal effect against *Aspergillus*, it has a short PAFE. The fungicidal actiion of triazoles is slow (12–24 h for ≥90% killing of cells) due to the extended time required for the reduction of lanosterol in the fungal cell by inhibition of CYP450 reliant lanosterol 14α-demethylase. The slow fungicidal effect of PCZ elucidated the short PAFE, in distinction to the rapid fungicidal action and the long PAFE of AMB (Manavathu et al., 2004).

1. 12. Use in special populations

Posaconazole (PCZ) kinetics is comparable regardless of gender and is not appreciably affected by ethnicity. PCZ kinetics does not differ considerably with age. PCZ is selected pregnancy category C, such that no adequate clinical studies have examined. PCZ use has led to skeletal malformations in rats at relative conc lower than human therapeutic dosing. PCZ use produced higher rates of bone resorption to occur in rabbits, with higher dosages cause a decrease in body weight gain. PCZ may excrete into breast milk of lactating females. PCZ average conc is consistent in the pediatrics with that of adults. For prophylaxis of candidiasis, PCZ has been indicate in several clinical context in pediatrics (Hope et al., 2012). For allogenic HSCT, PCZ oral suspension (200 mg TID) is suggested for patients greater than grade II GVHD who are at least 13 years of age. PCZ oral suspension (200 mg TID) is suggested for AML and recurrent leukemia patients ages 13 and older after the last dose of therapy until neutrophil recovery. DRO PCZ tablets are now indicated for patients 13 years or older. The use of PCZ i.v injection is not suggested for patients under the age of 18 due to preclinical safety concern (Product monograph–Noxafil, 2014). No PCZ kinetic effects have been seen in patients used 400 mg single-dose PCZoral suspension with mild-to-moderate renal harm; thus, no further dose correction necessities are suggested for patients with mild-to-moderate renal harm. Close monitoring for IFI is suggested for patients with severe renal harm (eGFR: <20 ml/min). Similar studies have not been conducted with DRO PCZ tablets, no dose adjustments are suggested for mild-to-moderate renal harm. PCZi.vinjection should be avoided in patients with moderate or severe renal harm as excess accumulation of the i.v vehicle, sulfobutylether-β-cyclodextrin, may be problematic. The serum creatinine levels of these patients should be closely monitored. No PCZoral suspension dose adjustments are suggested for patients with mild-to-severe hepaticharm. Mean AUC values of a single dose of 400-mg PCZoral suspension range from 21 to 43% higher for patients with hepatic harms. Respective Cmax and $t_{1/2}$ values for hepatic harm patients vary with normal persons. Similar studies have not been performed with the DRO tablets or i.v injection; however, no dose adjustments are suggested for either of these doses

form in patients with mild-to-severe hepatic harm (Product monograph–Noxafil, 2014). Immuno suppressant drugs, specifically cyclosporine and tacrolimus, need to have levels observed when given in combination with PCZ (Sansone-Parsons et al., 2007). Concurrent use of PCZand sirolimus is contraindicated; a study has shown that PCZcan be given in combination with sirolimus in a liver solid organ transplant patient (Dahlan et al., 2012). It is imperative that sirolimus concentration levels are monitored when given in combination with PCZ.

1. 13. Oral suspension formulation

The Posaconazole (PCZ) oral suspension has been evaluated extensively (Lipp, 2010); its use has been covered by the newer doses form. There are various challenges with respect to the PCZ oral suspension. In a clinical study in healthy men, PCZ oral suspension dose form given 400 mg every 12 hr or 200 mg every 6 hr resulted in 98 and 220% raised in bioavailability and compared with 800 mg given in a single dose (Ezzet et al., 2005). It is also important kinetic variability in nutrition as bioavailability improves at a low gastric pH and high-fat foods (Krishna et al., 2009). Acidic carbonated beverages causes increase the bioavailability of PCZ oral suspension (Walravens et al., 2011).

1. 14. Delayed-release oral tablet

The FDA approved a delayed-release oral (DRO) PCZ tablet in November 2013. This DRO tablet was designed to overcome the absorption limitations linked with the oral suspension in the clinic studies. The PCZ DRO tablet is designed to reduce active drug release at low gastric pH, while rising release at the high pH of the intestine with a bioavailability of 54% for the DRO tablet. The DRO tablet be taken with food, even though it is not known if the oral bioavailability of the tablet get better under fed conditions (Product monograph–Noxafil, 2014; Krishna et al., 2012). During the single 100 mg dose study, the DRO tablet form had a higher maximum serum concentration (Cmax) than the oral suspension in the fasted state (0.39 vs 0.08 mg/l). In the fed state, the DRO tablet doses formstill sustain a higher Cmax compared with the oral suspension (0.33 vs 0.24 mg/l). For the multidose subjects were randomized to one of two groups. Group 1 consisted of either placebo or PCZ 200 mg only dose on day 1, a 5-day wash period, and then 200 mg twice on day 6, 200 mg QD on days 7–14 and 200 mg twice on days 15–22. Group 2 taken 400 mg, as opposed to 200 mg, and had the same plan as group 1 until day 14. Median time to maximum conc. (Tmax) was 4 hr for the 200-mg dose and 5 hr for the 400-mg dose, while mean $t_{1/2}$ was similar for both doses (25 and 26 hr for the 200- and 400-mg dose). With the 400-mg dose, the DRO tablet showed linear kinetics and steady-state conc were attained after 7 days. Higher inter subject unpredictability was noted in exposure values for the 400-mg dose compared with the 200-mg dose (54 vs 32%) (Duarte et al., 2014). The two groups were used PCZ tablets, 200 or 300 mg daily. The 300-mg group reached the steady-state conc goal of 0.50 and 2.50 mg/l in 97% of patients, whereas 79% of patients reached the goal in the 200-mg group. A Phase III trial used the 300-mg DRO tablet to further examine the kinetics in myelodysplasia patients along with recent HSCT recipients (Cornely et al., 2013). During the 28-day trial period, the steady-state conc goal, set at 0.50–3.75 mg/l, was attained in 96% of patients, with 81% falling in the between 0.50 and 2.50 mg/l. These conc goals are in line with targeted proposals

for get through IFIs.

1. 15. Interavenous formulation

An interavenous (i.v) Posaconazole (PCZ) doses form developed as an aqueous solution having the solubilizer sulfobutyl ether beta-cyclodextrin has been approved in the USA (Maertens et al., 2014). Initially, a single-center, two-part rising single- and multiple-dose study in healthy humans was executed to test the kinetics and safety of i.v PCZ (Kersemaekers et al., 2015). First part of the study, six groups covered a single-dose PCZdose 50 to 300 mg by 30 min by peripheral infusion. PCZ i.v dose showed a greater-than-dose-proportional raise in exposure, whereby Cmax values were from 0.31 to 2.84 mg/l for the 50- and 300-mg single-dose use. To increase the kinetic and safety profile of i.v PCZ, a two-part study was performed, one part is as Phase Ib and the other as Phase III to bridge the PCZ i.v solution to the approved PCZ suspension (Maertens et al., 2014). The main purpose of the Phase Ib trial was to recognize the PCZ dose that would attain an exposure goal of 0.50–2.50 mg/l. A single-dose and two multiple-dose groups were recognized for the study, with the multiple dose groups used to test the 200 or 300 mg once daily after a twice-daily loading dose on the first day. Steady-state exposure goals were 94 and 95% for the 200- and 300-mg dosing groups. Mean conc average was 1.19 and 1.43 mg/l for the 200- and 300-mg dosing groups on day 14. PCZ i.v dose showed a similar safety profile to the oral suspension. A 300-mg QD dose was suggested for the Phase III study. The kinetics and safety of the PCZ i.v doses form have also been tested (NDA 205-596-FDA, 2014). Patients with AML, myelodysplastic syndrome or HSCT were tested the PCZ i.v doses form (Cornely et al., 2013). PCZ was i.v used 300 mg twice daily on day 1 and 300 mg once daily for 4–13 days afterward. Then, they were switched to PCZ oral suspension 600 or 800 mg in divided doses for up to 23 days for treatment period of 28 days. The i.v doses form in higher trough conc of PCZ than either of the dosages of oral suspension. The PCZ solution can be dosed at a level to reach suitable exposure for the treatment or prophylaxis of fungal infections.

1. 16. Safety and tolerability

Posaconazole (PCZ) has a good safety and tolerability profile (Chandrasekar, 2009; Jacinto and Chandrasekar, 2013). The tolerability of oral suspension PCZ in doses up to 400 mg twice daily in a Phase I study (Courtney et al., 2003). Adverse effects were mild, like fatigue and dry mouth. PCZ was also particularly well tolerated, the main side effects were gastrointestinal (GIT) distress (nausea, vomiting and diarrhea), neutropenia and high liver enzymes (Skiest et al., 2007; Ullmann et al., 2007). Patients may suffer from mucositis, diarrhea, or early on post-transplant period in hematopoietic stem cell transplant therapy had reduced PCZ levels when using the oral suspension (Dolton et al., 2012). Overall, PCZ has safety profile compared with other approved systemic triazole antifungal drugs (Chau et al., 2014). The i.v PCZ had few additional adverse effects other than infusion site reactions. Infusion site reactions, thrombophlebitis, were clinically satisfactory at 30 min compared with 90 min for single-dose peripheral use (Kersemaekers et al., 2015). Though, a reduced in infusion time from 90 to 30 min did not decrease infusion site reactions for multiple-dose use. The infusion be performed by central line when multiple-dose PCZ use is essential. Healthy volunteers and patients receiving PCZ oral suspension indicated low potential to prolong the corrected QT (QTc) interval, among

other side effects (Moton et al., 2009). The minimal safety concerns regarding high hepatic function tests and QTc prolongation for the PCZ DRO tablets (Duarte et al., 2014). The DRO tablet high hepatic enzyme levels in addition to prolonging the QTc interval (Pettit et al., 2014).

1. 17. Drug interactions

The other triazole antifungal drus have various drug–drug interactions (DDIs) because they inhibit the p-glycoprotein transporter in addition to CYP P450 enzymes, thus resulting in high conc of other drugs (Neofytos et al., 2010). However, Posaconazole (PCZ) and fluconazole (FCZ) are less potent inhibitors than voriconazole (VCZ) and Itraconazole (ICZ). PCZ inhibits CYP3A4 and p-glycoprotein, whereas other triazole druss may also affect CYP2C9 and CYP2C19 (Lipp, 2010). This has vital implications for therapy selection. Immunosuppressive drugs, cyclosporine and tacrolimus, are commonly used; as they are CYP 3A4 substrates, PCZ will likely increase their plasma conc, potentially resulting in toxicity. The coadministration of PCZwith several CYP3A4 substrates is contraindicated, including substrates known to prolong the QTc interval (terfenadine, cisapride), in addition to HMG-CoA reductase inhibitors (statins) and ergot alkaloids (Product monograph–Noxafil, 2014). Reduced PCZoral suspension exposure is noted with the simultaneous use of metoclopramide, phenytoin or rifampin, and the H_2 antihistamine ranitidine (Dolton et al., 2012). Because the PCZoral suspension is more readily absorbed at a lower pH, proton pump inhibitors (PPIs) and cimetidine have shown to reduce the area under the curve (AUC) of PCZ (Cojutti et al., 2013). Other histamine H2 receptor antagonists and antacids had no effect on the AUC. In contrast to the oral suspension, the absorption profile of the DRO PCZtablet is not affected by gastric acidity or motility. To test, healthy volunteers were randomized to groups to receive a single 400-mg dose of the DRO PCZ tablet alone; with metoclopramide to affect gastric motility; or with an antacid (aluminum and magnesium hydroxide), ranitidine or esomeprazole to affect gastric acidity in a crossover trial (Kraft et al., 2014). Exposure, Tmax and $t_{1/2}$ were comparable whether PCZ was used alone or in combination with drugs that affect gastric pH and motility. Additional studies established increased plasma conc linked with the DRO tablet as leukemia patients transitioned from PCZoral suspension to tablets had considerably higher PCZconc (median, suspension 0.75 mg/l, tablet 1.91 mg/l without relevant hepatotoxicity) (Jung et al., 2014; Kraft et al., 2014).

1. 18. Clinical efficiency study

1. 18. 1. Phase II clinical trials

Two main Phase II trials were completed in the clinical advance agenda of Posaconazole (PCZ). For the indication of IFI prophylaxis, study P018893 was designed to set up the dose by testing the kinetic and dynamic activities of various PCZ dosing strategies (NDA 22-003–FDA, 2006; PK/PD, 2013). This study focuses on treating patients with azole-obstinate IFIs or patients experiencing febrile neutropenia and needing empiric antifungal drug therapy. Some patients were receiving PCZ as an oral suspension between 800 and 1600 mg per day divided into diverse dosing schedules. Patients continue to receive the drug for 6 months or until febrile neutropenia resolved. PCZ is well tolerated and comparably efficient at all dosing schedules in the action of the fungal infections. These results agreed with previous data, signifying that the

absorption of PCZ. Beyond an assured threshold, rising the dose does not affect PCZ exposure avoiding extra remedial benefit and worsen adverse effects. For the sign of oropharyngeal candidiasis (OPC) treatment, study C/I96-209 was used to explain the dose while evaluated the pharmacological profile. This trial involved about 450 HIV-infected patients with OPC. The goal of this trial was to compare behavior using various doses of PCZ with a recognized dose of fluconazole (FCZ), which is regularly used for this sign. Patients were receive either of the drugs with PCZ at the doses of attention and FCZ at 200 mg once followed by 100 mg per day and treatment was for 14 days. PCZ was well accepted and exhibited similar effectiveness at the dose levels and compared with FCZ. Based on these data, PCZ 100 mg per day dose was selected.

1. 18. 2. Phase III clinical trials:

IFI prophylaxis

The approval of Posaconazole (PCZ) by the FDA and the EMA was based on several crucial Phase III trials. Compared the efficacy of PCZ versus fluconazole (FCZ) in prevent IFIs in multicenter, randomized and double-blind trial (Ullmann et al., 2007). Various patients with HSCT and GVHD or patients who were being treated with highly immunosuppressive drugs were randomized to get either drug for 16 weeks. One group received PCZ as 200-mg oral suspension three times daily with placebo capsules per day. In contrast, the second group received FCZ as a 400-mg encapsulated tablet once daily with placebo oral suspension three-times per day. PCZ was shown to be non inferior to FCZ in the avoidance of IFIs (5.3 vs 9.0%) and shown superior in the treatment of invasive aspergillosis (2.3 vs 7.0%). Between both groups, adverse actions were similar (36 vs 38%) as was the rate of discontinuation due to adverse effects (34 vs 38%). A study comparing the effectiveness of PCZ with FCZ and Itraconazole (ICZ) for IFI prophylaxis in patients treated for cancer that were projected to neutropenia (Cornely et al., 2007). Various patients were received 200-mg PCZ three-times daily as an oral suspension or one of the alternate azole drugs for up to 12 weeks during their rounds of therapy; the choice of the alternate azole drug (400-mg FCZ once daily or ICZ 200 mg twice daily) was made by each researcher. Patients were observed for fungal infections. PCZ was shown to be better in stopping IFIs compared with the alternate azole drugs (2 vs 8%), the mean time to IFI was longer with PCZ (41 vs 25 days). Finally, the PCZ group practiced lower mortality during the treatment period (16 vs 22%).

1. 19. OPC treatment

The effectiveness of PCZ versus fluconazole (FCZ) for patients with HIV/AIDS in OPC therapy has been tested (Vazquez, 2007). Various patients were randomized and received 200-mg PCZ or FCZ oral suspension on the first day as the loading dose, followed by 100 mg per day of the same drug for a total of 14 days, each patient for clinical success, which was cure or improvement of OPC. Clinical success was seen in both groups at similar rates (91.7% for PCZ and 92.5% for FCZ). Of the patients clinically successful 42 days after trial completion, 31.5% of the PCZ patients decline compared with 38.2% of the FCZ patients. Also at the 42-day, mycological abolition was superior in patients of the PCZ arm (35.6 vs 24.2%). The role of PCZ

in azole-refractory OPC, patients infected with HIV with oropharyngeal or esophageal candidiasis resistant to standard azole treatments of FCZ and Itraconazole (ICZ) (Skiest et al., 2007). Patients received 400 mg twice daily for 3 days followed by 400 mg daily for 25 days or 400 mg twice daily for 28 days. 75% of patients showed clinical success, defined as cure or improvement. Treatment success was relatively invariable between the groups taking different regimens. Four weeks after the last dose, 74% of patients who had showed a clinical reaction had relapsed (80% of patients on the daily dosing therapy, 68% of patients on the twice daily dosing therapy).

1. 20. Treatment of other fungal infections

Support the approval of PCZ (PCZ) to treat a wide range of fungal infections in Europe (Noxafil: EPAR, 2005). Various patients with different fungal infections, which were resistant to or intolerant of standard drug therapy, including other azole drgs, echinocandins and amphotericin (AMB), were used PCZ 200 mg four-times per day while hospitalized and 400 mg twice daily on an outpatient basis for up to 1 year. About 50% of patients responded to PCZ. The clinical success rates for each fungal infection individually, showing the best efficacy with PCZ: aspergillosis (42%), fusariosis (39%), chromoblastomycosis or mycetoma (82%), coccidioidomycosis (69%). The role of PCZin treating patients with coccidioidomycosis (Catanzaro et al., 2007), in some patients with non meningeal disseminated or chronic pulmonary coccidioidomycosis, used 400 mg of PCZ daily, 85 % of the patients showed a response, defined as a 50% or greater decrease in the mycoses. Use of PCZin the treatment of treatment-resistant coccidioidomycosis (Stevens et al., 2007), some patients with refractory coccidioidomycosis were used for this trial. Patients were used 800 mg of PCZin divided doses daily for up to a year. At the end of the treatment period, 73% of the patients showed to treatment: few showed a complete abolition of disease and few showed a partial resolution. PCZ was well tolerated in both trials.

1. 21. Off-label indications

Posaconazole (PCZ) has been studied for rarer infections, often as rescue therapy in smaller, less restricted trials. While clinical practice with PCZ is limited with these indications. There is fact to support use of PCZ in mucormycosis (van Burik et al., 2006). Patients were treated with PCZ, 80% for at least 30 days, 60 % of patients responded to treatment. PCZ is usefulness as salvage treatment of histoplasmosis (Restrepo et al., 2007). Few patients who had failed other treatments were placed on PCZ 800 mg per day in divided doses. All patients reacted to treatment within a month as clinical improvement. PCZ has also shown good activity against the CNS's fungal infection (Pitisuttithum et al., 2005). Most of these patients had obstinate disease (95%) or an HIV infection (74%). A various fungi like Cryptococcus caused the infections, Aspergillus and various rarer fungi (*Pseudallescheria boydii*, *C. immitis, Histoplasma capsulatum, Ramichloridium mackenziei, Apophysomyces elegans* and Basidiomycetes sp.). Patients were used the PCZ oral suspension at 800 mg per day in divided doses for at least a month and up to 1 year. This trial provides facts that PCZ can be useful as retrieve therapy for a various fungal infections in the CNS.

1. 22. Post marketing remark

The FDA requisite pediatric studies to be finished secondary to the approval of Posaconazole (PCZ). Finishing one study that tackled the use of PCZ in population, Itraconazole (ICZ), voriconazole (VCZ) and PCZ in pediatric patients with allogenic HSCT as an oral antifungal prophylactic drugs (Doring et al., 2014). Various patients between the age of 7 months and 18 years were divided evenly into three groups to receive 5 mg/kg twice daily ICZ, 100 mg twice daily (or 200 mg twice daily if body weight >40 kg) VCZ or 200 mg thrice daily PCZ. Patients also had taken antiviral and antibacterial prophylaxis for other possible infections. At the end of the inspection period (220 days after HSCT), there were no deaths due to IFIs. There were some 'possible' infections: two in the ICZ group, three in the VCZ group and none in the PCZ group. The three drugs were considered non inferior to each other in terms of effectiveness. Comparing the safety reports, the adverse effect ratio was comparable between all three groups, with improved liver enzymes representing one of the most frequent actions.

1. 23. Regulatory affairs

Posaconazole (PCZ) is approved as antifungal drug in the USA and EU with the trade name Noxafil® and marketed as Posanol in Canada (Product monograph–Noxafil, 2014). The FDA approved PCZ for prophylaxis of the Aspergillus and Candida IFIs in immuno-compromised patients of at least 13 years of age in September 2006 and approved for the OPC treatment, including those cases obstinate to other azole antifungal drugs, in October 2006. For both signs, PCZ was approved as a 40 mg/ml oral suspension. PCZ was then approved as a delayed-release oral (DRO) tablet in addition to an i.v solution for the invasive Aspergillus and Candida infection prophylaxis in November 2013 and March 2014. PCZ's patent is planned to expire in the USA in 2019 (NDA 205596 Approval. FDA 2014). The EMA has approved PCZ as an oral suspension and as a gastro-resistant tablet for treatment of IFIs (aspergillosis, chromoblastomycosis, fusariosis, and mycetoma, coccidioidomycosis, and OPC) together with those cases obstinate to standard antifungal treatment. PCZ is also approved to avoid IFIs in patients who receive immunosuppressive therapy after getting HSCT or chemotherapy for AML or any other myelodysplastic syndrome (Summary of Product Characteristics, 2010). For all of these signs, PCZ was approved as an oral suspension and as a gastro-resistant tablet in October 2005. For the IFI indication, the FDA required a pediatric study in patients aged 0 months to 12 years, for the OPC indication, a pediatric study is also necessary but in patients aged 0 months to 16 years. In addition, the FDA request a study among patients getting IFI prophylaxis at risk for low absorption to explore alternate dosing plans and the efficacy of therapeutic drug monitoring (TDM) (Postmarket Requirements and Commitments. FDA, 2014). For the new doses form, pediatric studies are also necessary and will require to be finished within the next 10 years (NDA 205596 Approval. FDA, 2014).

1. 24. Five-year analysis

Unlike in the USA, Posaconazole (PCZ) has not approved in the Europe (EU) as a delayed-release oral (DRO) tablet or as a solution for i.vuse (CHMP 2014). PCZ has been studied for other fungal infections ahead of those infections for which the major regulatory bodies approved it. PCZ in treating toenail onychomycosis and showed improved cure rates compared

with the generally used antifungal drug terbinafine (Elewski et al., 2012). PCZhas use in Chagas and chronic granulomatous disease (Molina et al., 2014; Welzen et al., 2011), both of these situation have limited therapeutic options. PCZ may be used for these signals in the future. The effect of PCZ in pediatric patients will become studies are completed in the next few years. Favorable results are expected given the positive safety data of the PCZ oral suspension in pediatric patients. The use of the PCZ doses form will likely increases over time in this subset of patients. PCZ oral suspension therapy, as interpatient conc variability is high, is the risk for underexposure. Prophylactic target PCZ conc ranges from at least 0.5 to 0.7 mg/l. A report the need for TDM because personal on-site education of low PCZplasma conc can lead to >40% raise in adequate plasma conc (Hoenigl et al., 2014). These results are consistent that found that cases of get through infections were all linked with low PCZplasma conc (Hoenigl et al., 2012; Bryant et al., 2011). In a study, greater than 7% of patients did not reach the lower target limit of 0.7 mg/l. PCZis liable to interact with various other agents. This may be useful in cases where PCZis used with an drug with whom it has a drug–drug interaction (DDI), which is ordinary, as various drugs used for cancer, HIV and transplants are CYP3A4 substrates, for example, tacrolimus and cyclosporine. With time, consent will be reached regarding TDM, the suitable conc goals for effective PCZ treatment. Isavuconazonium (IVZ) is a new triazole drug, which the FDA has approved for the treatment of aspergillosis and mucormycosis (NDA 207501 Approval. FDA, 2015). Preliminary data from Phase III studies proposed that it may have similar efficiency as voriconazole (VCZ) with less adverse effects in treating IFIs (Patterson et al., 2014). IVZ had a comparatively fast regulatory timeline because the prognosis of mucormycosis is so poor at the moment that the FDA labeled IVZ as an orphan drug (Isavuconazole, 2014). Following the approval of IVZ, it will present a good alternative for mucormycosis and may be used instead of PCZfor some patients suffering from persistent aspergillosis.

1. 25. Expert remarks

Posaconazole (PCZ) has recognized for quite a few therapeutic uses beyond its FDA approved indications. The Infectious Disease Society of America (IDSA) has included them for aspergillosis, candidiasis, cryptococcosis, skin and soft tissue infections and antimicrobial prophylaxis in neutropenia (Perfect et al., 2010; Stevens et al., 2014). The PCZ was recommended for the treatment of aspergillus, mucormycosis and fusariosis and also recommended for the general prophylaxis and treatment of IFIs for patients affected by HIV, hematopoietic cell transplantation and cancer (Masur et al., 2014; Tomblyn et al., 2009; National comprehensive care network, Abington PA: 2014). The usage of PCZ was mainly studied for the avoidance of IFIs secondary to febrile neutropenia or myelodysplastic syndrome. PCZ was the main alternative compared with standard antifungal therapy. PCZ has a unique place in therapy compared with the other azole antifungal drugs. It can be used in infections resistant to fluconazole (FCZ) and Itraconazole (ICZ). PCZ can also be used for prophylaxis of a large range of fungal infections than voriconazole (VCZ), one of the antifungals' new drug class. However, the adding of the delayed-release tablet and the i.v doses form, as choice will accelerate this development as it permit for more suitable doses (Al-Badriyeh et al., 2010; de la Camara et al., 2010; Heimann et al., 2014; Lyseng-Williamson, 2011; Jason et al., 2015).

2 Discussions

Posaconazole **(**PCZ) is a wide-spectrum antifungal drug against yeasts, filamentous fungi and azole resistant *Candida* species. PCZ uses its antifungal activity by fungal cell wall synthesis inhibitor. It is orally bioavailable and is absorbed by the gastrointestinal tract (GIT) independent of pH. The PCZ is optimized when it is taken with food or a nutritional supplement. However, this only applies to the suspension doses form since the bioavailability of PCZ tablet and injection forms is unaffected by the existence of food. PCZ has a bulky volume of allocation and is highly protein bound. The antifungal drug is metabolized in the liver to several inactive glucuronide metabolites by the UGT enzyme pathway. The main excretion route of PCZ and its metabolites is fecal (about 77%) and only small parts are detected in the urine (about 14%). The half-life of PCZ is long ($t_{1/2}$>24 hr) which permits this drug to be used once daily. Due to its exceptional oral absorption profile, PCZ is best used as divided doses with a maximum dose of 800 mg daily. Age, gender, race and diseases, like continual febrile neutropenia and refractory IFIs, do not come out to change the kinetics of PCZ. Dose modifications are not desired in patients with renal failure and patients who are on hemodialysis (Leung et al., 2015). Furthermore, unreliable pharmacokinetic, effectiveness and safety data support the use of PCZ as save therapy in child patients with IFIs. The use of PCZ is contraindicated in lactation and pregnancy. PCZ is efficacious, safe and well tolerated in the area of oropharyngeal candidiasis linked with HIV/AIDS infection, prophylaxis in neutropenia secondary to chemotherapy or in severe graft-*versus*-host disease related with hematopoietic stem-cell transplantation in adults. The main adverse effects of PCZ like headache, nausea, fatigue and dry mouth. Probable drug-drug interactions (DDIs) exist between PCZ and other therapeutic drugs like cimetidine, proton pump inhibitors (PPIs), cyclosporine, phenytoin, tacrolimus and rifabutin via either hepatic enzyme inhibition (CYP3A4) or induction. The action for drug interactions is very much dependent on the doses form of PCZ, mainly when co administered with drugs that affect gastric pH and motility, as the tablet and injections have shown to be unaffected. Drug interactions also exist between PCZ and antiretroviral drugs used for the HIV treatment, like atazanavir, efavirenz, ritonavir, and fosamprenavir. Restriction warrants PCZ oral use in immuno-compromised patients with functional GIT who fail usual antifungal drug therapies or who are supposed to have a advance fungal infections. A comparative study showed that most patients with compromised GIT function can still achieve a therapeutic serum concentration of PCZ. However, the new i.v injection is a smart option for this patient population and will play a critical role when patients cannot accept oral doses form of PCZ. These grants plenty of scope for future research with better-controlled clinical trials in order to launch the role of PCZ in the treatment and avoidance of several fungal infections, and potentially enlarge its FDA signals and function in clinical practice.

3 Conclusion

Antifungal therapy has evolved extensively since the 1960's. Amphotericin-B (AMB) was the core of treatment for fungal infections for decades until the beginning of the azole antifungal drugs in the 1980's. Successive optimization of azole antifungal drugs and latest doses form of AMB has significantly superior fungal morbidity and mortality. The opening of echinocandins has added to the advance in result related to fungal infections. Posaconazole (PCZ) is an antifungal drug. PCZhas a favorable safety and tolerability profile and has efficacy in the role of IFI prophylaxis, the therapy of OPC and salvage treatment for obstinate fungal infections. Initially approved oral suspension doses form has a wide interpatient inconsistency with respect to absorption. The systemic accessibility of the oral suspension can be enhanced by use with a high-fat food, nutritional complement or acidic beverage in daily doses. The PCZ suspension has shown a drop in systemic accessibility when used with Proton Pump Inhibitors (PPIs) that increase gastric motility. Both diarrhea and mucositis have been shown to decrease the bioavailability of PCZ. The use of multiple daily doses with a full food or nutritional supplement can be complicated for patients who have troubles in swallowing. The recent authorization of a delayed-release tablet that needs use only once daily and does not show to be clinically affected by food, changes in gastric pH or motility characterizes a new alternative for the prophylaxis of IFI. The delayed-release tablet is a better alternative than suspension for both prophylaxis and treatment of IFI. An i.v doses form has been newly developed and approved, offering even better patient access. Invasive fungal-related mortality remains high and resistance to accessible drugs is concerning. The recognition of both novel drugs (SYC-078 and T-2307) and new fungal targets (mitochondrial membrane potential) is of supreme significance to successful therapy of fungal infections in the population ages and the immune-compromised patients rises.

4 Key issues

Invasive fungal infections (IFIs) are a considerable cause of morbidity and mortality for immuno compromised patients; unfortunately, the clinical usefulness of many antifungal drugs is limited by safety and tolerability. Posaconazole (PCZ) is a relatively safe and well-tolerated broad-spectrum azole antifungal drug. PCZ is a cost–-effective and dominant option compared with standard antifungal therapy in many markets. New PCZ formulations, oral tablet and intravenous, increase its availability to a larger patient population. PCZ continues to be studied for additional fungal infections beyond original approval, including toenail onychomycosis, Chagas disease and chronic granulomatous disease.

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Conflict of interests

The authors declared that there is no conflict of interests regarding publication of this paper.

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