Current status of *in vitro* and *in vivo* antifungal activities of posaconazole

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ABSTRACT

Posaconazole (POS) is a new triazole drug with broad-spectrum *in vitro* activity against most yeasts and molds such as *Candida*, *Cryptococcus neoformans*, *Aspergillus*, *Fusarium* and *Zygomycetes*, as well as certain species of dimorphic fungi and endemic fungi. In immunocompetent or immunocompromised animal models with invasive fungal infections, POS has demonstrated highly effective, broad-spectrum antifungal activities. *In vitro* and *in vivo* antifungal activities of POS were superior to those of other azoles against *Candida glabrata*, *Candida krusei*, *Aspergillus terreus*, *Fusarium* and *Zygomycetes*. *In vivo* susceptibility studies have shown promising efficacy of POS against life-threatening fungal infections in animal models with different immune status and infection sites.

Key words: animal model, antifungal activity, posaconazole, triazole antifungal

INTRODUCTION

Rapid progress has been made in recent 10 years in the development of antifungal drugs. One important progress of recently developed new drugs is posaconazole (POS) (Noxafil, POS), which has demonstrated potent *in vitro* activity against clinically common yeasts and filamentous fungi, less common fungi as well as some endemic fungi and reliable efficacy against infections induced by these fungi in various tissues and organs of animal models with different immune status. The present work has provided a systemic review of studies on the *in vivo* and *in vitro* susceptibility and antifungal activity of POS, in the hope of facilitating clinicians' better understanding of the antifungal spectrum and antibiotic activity of POS, as well as their management of clinical indications.

IN VITRO SUSCEPTIBILITY AND ANTIFUNGAL ACTIVITY

Candida species

The azole resistance of *Candida* species has attracted tremendous attentions clinically. The *in vitro* activity of POS against *Candida*

species is 2- to 4-fold higher than that of itraconazole.^[1] A study involving 3932 isolates of *Candida* species demonstrated that among all azole drugs, POS had the highest *in vitro* activity, with 97-98% of the isolates found to be susceptible at MIC₉₀ ≤1 mg/L, of which *Candida albicans* was the most susceptible (MIC₉₀, 0.015-0.030 mg/L) while *Candida glabrata* was the least susceptible (MIC₉₀, 1-2 mg/L). POS at a concentration of ≤1 mg/L resulted in 80% and 44% inhibition of *C. glabrata* and *Candida pelliculosa*, respectively and the MIC₉₀ of POS remained unchanged for *C. albicans*, *Candida krusei*, *Candida guilliermondii* and *Candida norvegensis* which are resistant to fluconazole.^[2] All 2000 isolates from the blood of candidemia patients were found susceptible to POS *in vitro* (MIC, 0.03-2 mg/L). MICs for different *Candida* are: 0.03-0.13 mg/L for *C. albicans*, *Candida parapsilosis* and *Candida lusitanae*, 1-2 mg/L for *Candida glabrata*, 0.06-1.00 mg/L for *Candida tropicalis*, 0.25-0.50 mg/L for *C. krusei* and 0.03-0.06 mg/L for *Candida dubliniensis*.^[3]

Cryptococcus species

No *Cryptococcus* has been found resistant to POS until now. A study of Yildiran *et al.*^[4] examined the *in vitro* activities of various azole drugs against 213 isolates

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of *Cryptococcus neoformans* from the cerebrospinal fluid of 192 patients during 1990-1999 and revealed MIC of 2-8 mg/L for fluconazole, ≤ 0.125 mg/L for voriconazole and ≤ 0.015 -0.06 mg/L for POS. The MIC of POS was the lowest and did not increase significantly over the 10-year period. Results from the susceptibility testing of 1811 clinical isolates of *C. neoformans* showed that POS (≤ 1 mg/L) could result in 99% inhibition of *C. neoformans*, including *C. neoformans* var *Cryptococcus gattii*, *C. neoformans* var. *neoformans* and strains with fluconazole resistance. The MIC of POS was even lower than those of amphotericin B and fluconazole.^[5]

Filamentous fungi

POS is the most active azole drug against filamentous fungi, inhibiting over 95% of the isolates of filamentous fungi at concentrations of ≤ 1 mg/L, while the inhibition rate for voriconazole was 90%. *In vitro* susceptibility testing involving 1423 isolates of *Aspergillus* from more than 200 medical centers found that POS was 16 times more active than amphotericin B.^[6] POS at 0.03 mg/L was already able to cause inhibition of *Aspergillus*, however, the inhibitory effect varied among *Aspergillus* species. The *in vitro* activity of POS against *Aspergillus fumigatus* was greater than those of voriconazole and itraconazole and POS was also found active against *A. fumigatus* that was resistant to voriconazole, itraconazole and amphotericin B. Although POS exhibited excellent *in vitro* activity against *Aspergillus terreus* which was resistant to amphotericin B, *Aspergillus niger* was not susceptible to POS *in vitro*. The *in vitro* activity of POS against *Zygomycetes* has greatly enhanced our confidence of clinical medication. Study on the *in vitro* activity against 86 isolates of *Zygomycetes* demonstrated that POS was more active than itraconazole and voriconazole, with MIC of 128 mg/L for voriconazole, 32 mg/L for itraconazole and 4 mg/L for POS. The susceptibility to POS varied among different strains of *Zygomycetes* and the MIC was 0.25-8.00 mg/L against *Rhizopus*, 0.125-8 mg/L against *Mucor*, 0.03-0.25 mg/L against *Absidia* and 0.03-1.00 mg/L against *Cunninghamella*.^[7] A study by Sun *et al.*^[8] showed that the MIC of POS against 37 isolates of *Zygomycetes* was 0.25-4 mg/L, with lower *in vitro* activity than amphotericin B but higher activity than other azole drugs.

Other rare fungi

POS is active against most dimorphic fungi and endemic fungi. The MIC₉₀ against dermatophyte is 1 mg/L, slightly higher than that of itraconazole.^[9] POS is highly effective against *Blastomyces dermatitidis*, *Histoplasma capsulatum* (MIC < 0.01 -2.00 mg/L for both) and *Coccidioides immitis* (MIC, 0.25-1.00 mg/L) and less active against *Sporothrix schenckii*. It has also exhibited antibiotic activity against several black yeasts (*Exophiala jeanselmei*, *Rhinochadiella*).^[10] There are still controversies about the *in vitro* activity against *Scedosporium*

apiospermum.^[7] The comparison of *in vitro* activities among various azole drugs and amphotericin B was shown in Table 1.^[11]

IN VIVO EXPERIMENTS

POS exhibits excellent tissue penetration and remarkable effects in the prevention and treatment against most fungal pathogens in animal models with different immune status and infection sites, which has provided adequate data for the clinical medication.

Saccharomyces

POS is highly active against *Saccharomyces in vivo* and highly effective in animal models of infection. POS had positive effects in the prevention and treatment of disseminated infection caused by inoculation with *C. albicans* which were susceptible, intermediate or resistant to fluconazole in immunocompetent and irradiated CF1 mice. The 50% protective doses (PD50S) were 1.5-19.4 mg/(kg•d) for preventive medication and 0.04-15.6 mg/(kg•d) for therapeutic medication. POS was superior to fluconazole in the prevention and treatment of disseminated infection induced by *C. albicans* that were intermediate and resistant to fluconazole in mice. Although POS was not detected in the cerebrospinal fluid of immunosuppressive rabbits, it was found equally active as fluconazole in the cerebrospinal fluid of rabbits with cryptococcal meningitis. For the treatment of disseminated cryptococcal infection in CD1 mice, POS (3 mg/(kg•d) and oral administration of 10 mg/(kg•d), for 10 successive days) extended the survival time of the mice and reduced the fungal load in the brain and lung tissues. Its efficacy was positively correlated with the dosage and was superior to that of amphotericin B (0.3 mg/(kg•d) for intravenous injection).^[12] These *in vivo* studies further demonstrated the strong antifungal activity of POS against *Saccharomyces*.

Filamentous fungi

POS is highly active against *Aspergillus* and reliably potent in animal models. For immunosuppressive rabbits suffering from disseminated *A. fumigatus* infection, POS (2.5 mg/(kg•d) and 10 mg/(kg•d)) could improve the survival rate of rabbits and reduce the fungal load in the brain and lung tissues, with an equal efficacy to amphotericin B and superior efficacy to itraconazole. For immunosuppressive mice with *A. fumigatus* and *Aspergillus flavus* infection in their lungs, both preventive and therapeutic medication of POS remarkably improved the survival rate of the mice and reduced the fungal load in lung tissues, with respective PD50S of 3.6-29.9 mg/kg and 4.8-6.5 mg/kg for therapeutic medication against *A. fumigatus* and *A. flavus* and a PD50S of 0.9-9.0 mg/kg for preventive medication, while a preventive effect of itraconazole

Table 1: In vitro antifungal activity of POS and other antifungal agents (MIC₉₀, mg/L)

Fungi (strains)	POS	Itraconazole	Voriconazole	Fluconazole	Amphotericin B
<i>Candida</i>					
<i>Candida albicans</i> (3535)	0.063	0.25	0.063	2.0	1.0
<i>Candida glabrata</i> (1218)	2.0	4.0	2.0	64.0	1.0
<i>Candida parapsilosis</i> (970)	0.25	0.5	0.125	4.0	1.0
<i>Candida tropicalis</i> (719)	0.25	0.5	0.5	4.0	1.0
<i>Candida krusei</i> (189)	1.0	1.0	0.5	64.0	1.0
<i>Candida lusitanae</i> (84)	0.25	2.0	0.06	34.0	2.0
<i>Aspergillus</i>					
<i>Aspergillus fumigatus</i> (1119)	0.5	1.0	0.5	—	1.0
<i>Aspergillus niger</i> (101)	0.5	2.0	2.0	—	1.0
<i>Aspergillus flavus</i> (89)	0.5	1.0	1.0	—	2.0
<i>Aspergillus terreus</i> (22)	0.25	0.5	0.5	—	2.0
<i>Zygomycetes</i>					
<i>Rhizopus</i> (32)	8.0	32.0	128.0	—	2.0
<i>Mucor</i> (18)	16.0	32.0	128.0	—	1.0
<i>Absidia</i> (16)	0.25	0.5	128.0	—	0.125-2.0
<i>Cunninghamella</i> (6)	0.031-1.0	0.125-2.0	8.0-128.0	—	0.125-2.0
<i>Apophysomyces</i> (5)	0.031-4.0	0.031-8.0	16.0-128.0	—	0.031-4.0
<i>Phialophora</i> (4)	0.016-2.0	0.016-0.125	0.5-4.0	—	0.063-0.5
<i>Rhizomucor</i> (3)	0.016-0.25	0.016-0.25	2.0-16	—	0.063-0.125
<i>Cokeromyces</i> (2)	0.25-4.0	0.25-8.0	16.0-64.0	—	0.125-0.5
<i>Fusarium</i>					
<i>Fusarium solani</i> (39)	32.0	—	32.0	—	32.0
<i>Fusarium oxysporum</i> (12)	4.0	—	32.0	—	16.0
Other species					
<i>Cryptococcus</i> (271)	0.25	0.5	0.125	8.0	1.0
<i>Actinomyces</i> (80)	32.0	64.0	—	—	32.0
<i>Histoplasma capsulatum</i> (53)	0.25	0.063	—	—	0.5
<i>Pseudallescheria</i> (41)	1.0	0	—	—	4.0
<i>Scedosporium</i> (26)	1.0	32.0	—	—	8.0
<i>Coccidioides</i> (25)	0.25	0.25	—	—	0.5

POS: Posaconazole, MIC: Minimum inhibitory concentrations

could hardly been found on the pulmonary infection induced by these two strains (PD50S >75 mg/kg). POS (10 mg/kg and 25 mg/kg) could completely eliminate 60% of *A. fumigatus* but only 3% of *A. flavus* in mice lungs, suggesting a higher *in vivo* activity against *A. fumigatus* than that against *A. flavus*. For immunosuppressive rats with *A. fumigatus* in their lungs, the efficacy of POS (2-10 mg/kg) was dependent on its dosage and was similar to that of amphotericin B. However, 20 mg/kg POS was more potent than the maximum dosage of amphotericin B (4 mg/kg for intravenous injection) and eliminated pulmonary infection more effectively.^[13] For persistently neutropenic rabbits with *A. fumigatus* infection in lungs, the preventive medication of POS with a dosage range of 2-20 mg/(kg•d) significantly extended the survival time of rabbits and reduced the fungal load in lungs, whereas the therapeutic medication almost completely eliminated the focus of infection in pulmonary and achieved a 72% survival rate of the rabbits. The efficacy of POS was superior to that of itraconazole and comparable to that of amphotericin B.^[14] For transient neutropenic mice with disseminated infection by itraconazole-resistant

stains of *A. fumigatus*, the efficacy of POS (5-25 mg/kg for oral administration once a day) was positively correlated with its dosage. It could significantly extend the survival time of mice with infections and reduce the fungal load in lung and renal tissues. For persistently neutropenic rabbits and mice with disseminated *A. terreus* infection in lungs, POS could prolong the survival time of both infected animals and reduce the fungal load in lungs, while caspofungin only prolonged the survival time of mice and no indication of effect was found for amphotericin B (1 mg/kg) or liposomal amphotericin B (1 mg/kg).^[15] For neutropenic mice with disseminated *Mucor* infection, POS (≥15 mg/kg, twice a day) could increase the survival rate of infected mice and reduce the fungal load in tissues, while the equivalent dosage of itraconazole (30 mg/kg, twice a day) had no effect. The efficacy of POS (30 mg/kg, twice a day) was comparable to that of amphotericin B.^[16] For mice with disseminated *Rhizopus* and *Absidia corymbifera* infection, POS behaved differently among various species, ineffective against *Rhizopus oryzae*, partially effective against *Absidia corymbifera* and effective against *Rhizopus microsporus*

in a dose-dependent manner, while all strains were found susceptible to amphotericin B which significantly prolonged the survival time of the infected mice.^[17]

Other rare fungi

POS was superior to the other azole drugs in the antibiotic activity against infections caused by rare fungi. For transient neutropenic mice with disseminated *Pseudallescheria* infection, POS could significantly reduce the fungal load *in vivo*, with overall efficacy superior to itraconazole and comparable efficacy to fluconazole in improving the survival rate of the infected mice.^[18] The therapeutic efficacy of POS in treating immunocompetent mice with disseminated *Fusarium* infection was positively correlated with the dosage and high-dosage of POS (50 mg/kg and 100 mg/kg) exhibited comparable efficacy to amphotericin B (1 mg/kg). For immunocompetent and athymic mice with disseminated dematiaceous fungal infection, the efficacy of POS was dependent on its dosage in both cases. It could significantly reduce the fungal load in tissues and increase the survival rate of the mice.^[19] For immunocompetent mice with pulmonary blastomycosis, POS (25 mg/kg) could achieve complete removal of fungi from lung tissues and significantly prolong the survival time of mice, with a comparable efficacy to the standard dosage of amphotericin B (1 mg/kg, intravenous injection) and markedly superior efficacy to itraconazole (150 mg/kg). For the treatment of immunosuppressive mice with disseminated coccidioidomycosis, POS also completely eliminated fungi in lung tissues, 200 times more effective than fluconazole (100 mg/kg) and 50 times more effective than itraconazole (100 mg/kg).^[13] For immunocompetent and CD4⁺/CD8⁺-deficient mice with disseminated histoplasmosis, POS was effective in both cases and POS treatment (≥ 0.25 mg/kg) could achieve 100% survival rate in the infected immunocompetent mice. However, for mice with disseminated infection due to pan-resistant *S. apiospermum*, no indication of effect was found by either POS alone or in combination with granulocyte colony-stimulating factor (G-CSF).^[13] Overall, the effect of POS on infections caused by rare fungi is superior to that of itraconazole and comparable to that of amphotericin B.

IN VIVO AND IN VITRO STUDIES OF COMBINATION THERAPY

Combination therapy is not the first choice for the initial treatment of invasive fungal infections, but it can improve the success rate of treating drug-resistant, refractory and mixed fungal infections. *In vivo* and *in vitro* drug susceptibility testing has provided solid evidence for clinical treatment. For example, according to an

in vitro drug susceptibility testing of *C. glabrata* that was resistant or intermediate to azoles, the combination of POS and terbinafine showed synergistic effect against 12% of the isolates.^[20] The combination of POS and caspofungin was found to be synergistic against 18% of the 119 isolates (including 4% fluconazole-resistant strains) of *C. glabrata*.^[21] For the treatment of mice with systemic *Candida* infections, POS and amphotericin B at four dose levels each were tested in all possible combinations and 65.3% of the combination therapies further prolonged the survival time of the mice, superior to the monotherapies ($P < 0.05$).^[22] However, for the treatment of mice with systemic *C. neoformans* infection, the combination of amphotericin B and POS was not superior to amphotericin B alone in extending the survival time of mice and reducing the fungal load *in vivo*.^[23] POS in combination with 5-fluorocytosine exhibited higher *in vitro* activity against *C. neoformans* than using each drug alone and for the treatment of BALB/V mice with disseminated *Cryptococcus* infection and ICR mice with cryptococcal meningitis, POS (2 mg/(kg•d) and 20 mg/(kg•d), oral administration for 10 d) in combination with 5-fluorocytosine (10-60 mg/(kg•d), oral administration for 10 d) could lead to a further reduction of the fungal load in brain tissues but not the extension of survival time of the mice.^[12] For the treatment of mice with disseminated *A. fumigatus* and *A. flavus* infections, POS (0.1-25 mg/kg) and caspofungin (0.05-10 mg/kg) at three dosage levels each were examined in all possible combinations and 74% of the combination therapies further prolonged the survival time of the mice, superior to the monotherapies. Moreover, there was no indication of resistance in any of the combination therapies.^[16] However, when the combination of POS with G-CSF was used for the treatment of immunosuppressive mice with disseminated *Zygomycetes* infection, the combination therapy was not found superior to POS alone.^[24] Intensive studies on the mechanisms of combination therapy remain to be conducted in standard animal models to facilitate more effective and reliable combination treatment.

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