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Posaconazole: a new option for invasive fungal infection management

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For most of the last 50 years, antifungal therapy has relied on amphotericin B deoxycholate. The emergence of lipid-based amphotericin B formulations rendered a significant advance in terms of reducing toxicity, although they are still associated with renal and hepatic damage. During the late 1980s fluconazole became available. It was the first antifungal drug with an excellent safety profile, but its activity spectrum is limited. A new era in antifungal therapy began in the early 2000s with the advent of a new class of antifungal drugs, the echinocandins, with a wide activity spectrum and excellent tolerability. At the same time voriconazole was introduced showing good efficacy against aspergillosis and fusariosis, as well as being the first successful treatment option for CNS aspergillosis. Its wide-spread use is currently being discussed as a predisposing factor for zygomycosis. Rare moulds are emerging infections and have led to a renaissance of lipid-based amphotericins, the only drug currently effective against mucormicosis.

The addition of posaconazole to the antifungal armamentarium is welcome because the drug's broad spectrum shows potent activity against a number of common and rare fungal patogens, expecially those refractory to standard antifungal therapy. Posaconazole, a new extended-spectrum triazole structurally similar to itraconazole, inhibits fungi by blocking ergosterol synthesis through inhibition of the enzyme lanosterol 14α-demethylase (CYP51). Ergosterol depletion couplet with the accumulation of methylated sterol precursors results in inhibition of fungal cell growth, fungal cell death, or both.

In vitro activity

Posaconzole's antifungal spectrum includes the main causative agents of fungal infections, such as *Candida* species, *Aspergillus* species, non-*Aspergillus* hyalohyphomycetes, phaeohyphomycetes, zygomycetes and endemic fungi. Posaconazole cross-resistance with fluconazole, itraconazole or both, has been shown in some *Candida* isolates.[2-3] A certain degree of cross-resistance between posaconazole and itraconazole has also been reported for *Aspergillus* fumigatus isolates. The clinical importance of this *in vitro* cross-resistance data has yet to be determined. In fact, in a study of more than 18.000 strains of clinically important yeasts and moulds obtained from over 200 centres worldwide over a period of 10 years, posaconazole retained activity against many *Candida* and *Aspergillus* isolates which show resistance to voriconazole, fluconazole and amphotericin B.[3] The *in vitro* activities of posaconazole against 3932 isolates of *Candida* species obtained from over 100 medical centres was relatively comparable to voriconazole in both spectrum and potency. Posaconazole showed fungistatic and fungicidal activity *in vitro* e *in vivo* for most *Candida* species isolates,[2] and inhibited 97% of them at concentration of 1 µg/mL or below.[4] Posaconazole is the most active triazole against filamentous fungi, inhibiting 95% of isolates at concentration of 1 µg/mL or below; by comparison, ravuconazole inhibits 91% of isolates and voriconazole inhibits 90%.[5] Posaconazole is four to 16 times as active as amphotericin B against *Aspergillus* species,[6] however, different species differ in their susceptibility to posaconazole. Posaconazole has been shown to have better *in vitro* activity than voriconazole or itraconazole against A. fumigatus and it also inhibits A *fumigatus* that is resistant to itraconazole, voriconazole and amphotericin B.[7] Posaconazole is active *in vitro* against Asoergillus terreus,[8] a species resistant to amphotericin B, and also against *Fusarium* species, with variable and species-dependent fungistatic activity.[9] Posaconazole has promising activity against the zygomycetes,[10] with the lowest MIC compared to voriconazole and itraconazole; it appears to be less active than amphotericin B, more active than voriconazole and and slightly more active than itraconazole against clinical agents of zygomycosis.

Pharmacology

Posaconazole is available for oral use in clinical trials; exposure is greater when it is administered as an oral suspension rather than when it is administered in tablet form;[11] no intravenous formulation has yet been used in clinical trials. Posaconazole is generally given at a dosage of 200 mg orally four times daily (loading dose) and then 400 mg twice daily (maintenance therapy). Absorption of posaconazole is not increased at doses above 800 mg/day[12] and it is enhanced by coadministration with food or nutritional supplements. After oral administration, posaconazole has a long terminal elimination half-life, which is dose-dependent.[13]

Since posaconazole is a substrate for the CYP450 enzymes, interactions are expected with drugs that are metabolised via CYP3A4. Posaconazole may have a similar drug interaction profile as itraconazole, and less wide interaction profile compared with voriconazole.[14] Either a dose reduction or monitoring of ciclosporin and tacrolimus is also recommended.[15]

Clinical uses

Preliminary data on efficacy studies have been presented above all on abstract forms in international meetings. The efficacy of oral posaconazole suspension in patients with proven or probabile invasive fungal infections who were intolerant of, or refractory to, other antifungal therapy has been examined in a large, open-label, multicentre, phase III study.[16] In this study 330 patients received posaconazole 800 mg/day in divided doses for an initial period of up to 12 months, with an additional 279 patients serving as the external control group; the majority of patients (86%) were refractory to previous antifungal therapies, above all amphotericin B and itraconazole. All study data were reviewed by an external blinded Review Committee who determined eligibility and global response (primary end point) based on clinical, microbiological, radiological data. Among patients receiving posaconazole and the control group, 45% and 40% were infected with *Aspergillus*,10% and 14% were infected with *Candida*, 8% and 2% were infected with *Fusarium*, 13% and 29% were infected with *Cryptococcus*, 5% and 4% were infected with *Zygomycetes*. Oral posaconazole 800 mg/day demonstrated clinically relevant activity against a range of fungi in patients with invasive fungal infections. In patients with aspergillosis (106 posaconazole recipients and 86 patients in control group) the global response success rate was significantly higher in posaconazole recipients than in control group (42% versus 26%; p=0.006). Kaplan-Meyer analysis showed a significant survival benefit in posaconazole recipients (p<0.001 vs controls). Of six posaconazole recipients resistant to voriconazole, three had successful outcome.

Posaconazole was associated with overall success rate of 54% in patients with zygomycosis, 46% in patients with fusariosis, 43% in patients with *Pseudallescheria* (3 of seven patients) 80% in patients with phaeohyphomycosis (4 of5 patients) and 100% with histoplasmosis (7 of 7 patients).[16]

Success rates with posaconazole 800 mg/day were 48% in patients with refractory candidiasis (11 of 23 patients) 69% in patients with refractory coccidioidomycosis (11 of 16 patients), 48% in patients with refractory *Cryptococcus* infection (15 of 31 patients) and 82% in patients with refractory chromoblastomycosis or mycetoma (9 of 11 patients) (16).

At the same dosage Posaconazole has potential in the treatment of fungal CNS infections, showing success rate of 59% (23 of 39 patients) in HIV-related cryptococcal meningitis and 50% (5 of 10 patients) in other fungi.[17]

Regarding prophylaxis with posaconazole in high risk patients, two studies were recently presented at international meetings. The first study is a double-blinded, multicentre clinical trial,[18] in which posaconazole was compared with fluconazole in transplant recipients with GVHD. Six hundred patients were enrolled, 301 received posaconazole (200 mg every 8 hours) and 299 fluconazole (400 mg once a day) for up to 16 weeks. Posaconazole was significantly superior (p<0.01) to fluconazole in preventing aspergillosis and comparable to fluconazole in preventing other breakthrough invasive fungal infections. Similar results were found in the second study,[19] comparing in high risk acute myeloid leukemia patients (in induction or salvage therapy) the same dose of posaconazole with the usual prophylaxis regimen (fluconazole or itraconazole) of each participating hematologic centre. The incidence of proven or probabile invasive fungal infections was 2% (7/304 subjects) in the posaconazole group and 8% (25/298) in the fluconazole/itraconazole group (p=0.0009) with established superiority of posaconazole. This superiority was demonstrated also with respect to the incidence of mycoses in the 100-day phase (5% posaconazole versus 11% comparators; p=0.0031).

Data concerning the tolerability of oral posaconazole suspension are available from the phase III trial[16] and related tolerability analysis[20] and from another recent paper.[21] Oral posaconazole was generally well tolerated. In the phase III trial, the most commonly adverse events included nausea (9%), vomiting (6%), abdominal pain (5%), headache (5%), and diarrhoea, elevated ALT or AST levels and rash (3% each). Among patients treated for > 6 months, 19 serious adverse events were reported in 12 of 102 posaconazole recipients,[20] including adrenal insufficiency, nausea/vomiting, nephrotoxicity and QTc-interval prolongation.

Altered drug concentrations (e.g. increased tacrolimus, ciclosporin or digitalis concentrations) were reported in 4 posaconazole recipients and needed interruption of posaconazole therapy in two cases. However, discontinuation because of a serious treatment-related adverse event occurred in only one patient.

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