Journal de Mycologie Médicale xxx (2018) xxx–xxx

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General review/Revue générale

Isavuconazole: A new broad-spectrum azole. Part 1: In vitro activity

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ARTICLE INFO

Article history:
Received 22 November 2017
Received in revised form 4 February 2018
Accepted 6 February 2018
Available online xxx

Keywords:
Aspergillus
Mucorales
Candida
Isavuconazole
Voriconazole
Susceptibility test

ABSTRACT

Triazoles compounds are first-line agents for the treatment of invasive fungal diseases. Isavuconazole is the most recent triazole compound, approved in 2015 by the FDA and the EMA to treat invasive aspergillosis and mucormycosis. We reviewed here the in vitro activity of isavuconazole against a vast spectrum of species. Isavuconazole MICs were evaluated using CLSI, EUCAST or Etest methods, with no significant differences between the technics. Low MIC_{50} and MIC_{90} (< 1 μg/mL) were described for isavuconazole against the majority of *Candida* spp., except for *C. glabrata* and *C. krusei*. In vitro activity against *Aspergillus* spp. varied according to the species with an overall MIC_{90} of 1 μg/mL ranging from 0.125 μg/mL (*A. fumigatus*) to 16 μg/mL (*A. niger*, *A. tubingiensis*). As for *Aspergillus*, the activity of isavuconazole against agents of mucormycosis varies upon genus and species, with an overall MIC_{90} from 4 (*Rhizopus* spp.) to 16 μg/mL (*Rhizomucor* spp. and *Mucor* spp.). Recently, to help detecting non-wild-type isolates, EUCAST committee has proposed ECOFFs values for *C. albicans*, *C. parapsilosis* and *C. tropicalis* (0.03 μg/mL), for *Aspergillus fumigatus* (2 μg/mL), *A. nidulans* (0.25 μg/mL), *A. terreus* (1 μg/mL), *A. flavus* (2 μg/mL) and *A. niger* (4 μg/mL). Moreover, clinical breakpoints (susceptible/resistant) were defined for *Aspergillus fumigatus* (1 μg/mL), *A. nidulans* (0.25 μg/mL) and *A. terreus* (1 μg/mL). Using these breakpoints, isavuconazole showed activity against the vast majority of fungi.

1. Introduction

Isavuconazole (Cresemba®) is currently the most recent licensed triazole compound. It was approved in March 2015 by the Food and Drug Administration (FDA) for patients 18 years of age and older for the treatment of invasive aspergillosis and of invasive mucormycosis. The European Medicines Agency (EMA) has approved isavuconazole to treat adults with either of two life-threatening fungal infections: invasive aspergillosis and mucormycosis. For this later disease, isavuconazole is proposed when amphotericin B is inappropriate. The water-soluble prodrug, isavuconazonium sulfate (BAL8557), is administered orally or intravenously and is rapidly cleaved by plasma esterases into the active moiety, isavuconazole (BAL4815), and a cleavage product (BAL8728) (Fig. 1). The first part of this review summarizes the in vitro data while the second part is devoted to the preclinical and clinical data including efficacy, safety, pharmacodynamics and drug-to-drug interactions [1].

2. Mode of action

Triazoles exert their antimycotic action by inhibiting the 14-α-demethylase, a cytochrome P450 dependent membrane protein involved in ergosterol biosynthesis, resulting in an accumulation of toxic sterols [2]. Isavuconazole structure is close to voriconazole, but displays an added side arm, which widens its spectrum [3].

Triazoles compounds are first-line agents for the treatment of invasive fungal diseases. Activity of isavuconazole was tested in vitro against a broad spectrum of yeasts and molds and showed a good, albeit species-dependent, activity.

3. In vitro susceptibilities

In the armamentarium of azole antifungal drugs, isavuconazole main features are its activity against molds and its otherwise broad-spectrum activity against *Candida* and rare pathogenic yeasts such as *Saccharomyces cerevisiae* or *Trichosporon* spp. We reviewed here the results evaluating isavuconazole MICs against a vast spectrum of species. Different methods like the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) to determine

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https://doi.org/10.1016/j.mycmed.2018.02.005
1156-5233/

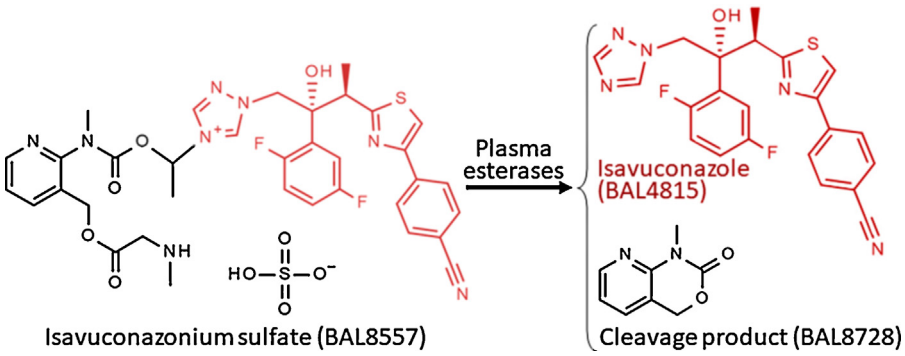

Fig. 1. Chemical structure of the prodrug (isavuconazium sulfate, BAL8557), the active drug (isavuconazole, BAL4815), and the cleavage product (BAL8728).

MICs were used across the studies. Thus, we presented here the overall comparison of MICs, MIC_{50} and MIC_{90} when available, no matter MIC determination methods used.

3.1. MIC determination methods

Some studies compared isavuconazole MIC using CLSI and EUCAST broth microdilution methods (BMD) [4–8]. MICs determined by EUCAST method were 1 to 2 dilutions higher than those obtained by CLSI method. Indeed, overall agreement was evaluated in a few studies and was 99.1% for *Candida* and 98.9% for *Aspergillus flavus* for both methods [7–9]. However, more discrepancies were observed in the mucorales group, particularly for *Rhizopus arrhizus* and *Rhizopus microsporus* [4,6]. For quality control assessment of isavuconazole MIC determination, ranges were established against *Candida krusei* ATCC6258: 0.015–0.06 μg/mL and *C. parapsilosis* ATCC 22019: ≤ 0.015–0.03 μg/mL [5]. It should be noted that, while they can help in determining MICs to test antimycotic compounds, broth microdilution techniques are not adapted for routine diagnosis. Consequently, some authors tested the concordance between Etest strip and BMD methods [2,10–13]. For *Candida* and *Cryptococcus*, a high level of agreement (93% and 100%, respectively) was noted in some studies, notably for *Candida albicans* (92.6%), *Candida parapsilosis* (95.2%) or *C. krusei* (100%) [11]. A study investigating Etest strip and BMD test methods directly on yeasts from blood samples detected the major discrepancies for *Candida glabrata* (10.6% of majors errors) or rare yeasts like *Rhodotorula mucilaginosa*, *Saccharomyces cerevisiae* or *Trichosporon* spp. [10]. Another study examining the level of agreement of these 2 methods found an excellent concordance of Etest and BMD for *Aspergillus* spp. (94 to 100%) but a more variable agreement for mucorales (80% for *Mucor* sp. to 100% for *Lichtheimia* sp.) [2]. Mostly the Etest strip tended to generate higher MICs values than BMD methods but can be adaptable to routine for the majority of species.

3.2. Candida *species*

Isavuconazole MIC ranges, MIC_{50} and MIC_{90} for clinical and environmental *Candida* species are detailed in Table 1. $MICs_{90}$ were low for *C. albicans* (MIC_{90}: 0.07 [range: 0.016 to 0.21] μg/mL), *C. cdubliniensis* (0.015 μg/mL), *C. lusitaniae* (0.06 μg/mL), *C. parapsilosis* (0.07 [0.016–0.12] μg/mL) and *C. tropicalis* (0.09 [0.02–0.25] μg/mL) but higher for *C. krusei* (0.5 [0.06–0.1] μg/mL), *C. glabrata* (1.10 [0.25–2] μg/mL), *C. auris* (0.5 μg/mL) and *C. guillermondii* (8 μg/mL) [2,7,9,14–18]. Similar low MIC_{90} (≤ 0.52 μg/mL) were observed for echinocandins for the most frequent *Candida* species. Based on clinical data showing improved survival, echinocandins remain indeed recommended as first-line treatment for invasive candidiasis [19]. Compared to others azole drugs, MICs for isavuconazole were generally similar or slightly higher than for voriconazole and lightly lower than for posaconazole but the differences are not significant. Few strains of *C. glabrata* which were less susceptible or resistant to classical azole drug presented also higher isavuconazole MIC_{90} (1–2 μg/mL), suggesting that isavuconazole would not be an appropriate second-line drug for these strains [14–17,20].

Since several years, an increased level of azole resistant was described especially for certain species like *C. glabrata.* Azole resistance mechanisms included the overexpression of CDR genes, MDR1 or FLU 1 transporters or ERG11 mutations. Increased isavuconazole MIC (from 2 to 32-fold) were observed for *Candida* strains harboring overexpressed *CDR* genes or ERG 11 mutations, but no MICs were affected by MDR1 or FLU1 alterations [21]. Possible cross resistances between isavuconazole and one or more triazole were detected for *C. albicans*, *C. tropicalis*, *C. guillermondii* [7]. The same result was described for *C. glabrata* strains with high isavuconazole MIC (> 1 μg/mL) associated to high fluconazole, voriconazole and posaconazole MICs (respectively > 128, 0.5 and 2 μg/mL) [14].

In vitro activity of isavuconazole combined with other antifungal drugs has also been assessed [22]. A synergistic activity between isavuconazole and micafungin was demonstrated for *C. albicans*, *C. parapsilosis* and *C. krusei*, as well as for a combination of isavuconazole and amphotericin B for *C. krusei*. On the contrary, an antagonistic activity between isavuconazole and amphotericin B was observed for *C. glabrata*. For now, these results must be confirmed, considering the small numbers of the strains (1 to 4 per species) tested in this study.

As yet, no clinical breakpoints were defined by EUCAST or CLSI for all *Candida* spp. to categorize isavuconazole MICs into susceptible intermediate or resistant strains. Recently, an ECOFF value of 0.03 μg/mL was proposed for isavuconazole against *C. albicans*, *C. parapsilosis* and *C. tropicalis* to help detecting non-wild-type isolates [15]. Using these ECOFF, the vast majority of strains tested showed isavuconazole MIC lower than the ECOFFs values.

3.3. *Non*-Candida *yeasts*

Like other azole drugs, low isavuconazole $MICs_{90}$ were observed for non-*Candida* yeasts like *Pichia* spp. (0.03 μg/mL), *S. cerevisiae* (0.4 μg/mL) or *Trichosporon* spp. (0.35 μg/mL) (Table 2) [10,16,17,23–26]. Isavuconazole showed low MIC_{90} to *R. mucilaginosa* (0.03 μg/mL) even for strains resistant to voriconazole and fluconazole but these results were not confirmed in another study (isavuconazole MIC_{90} 2 μg/mL) [10,16].

For *Cryptococcus* spp., isavuconazole $MICs_{90}$ (0.13 μg/mL) were equal or lower than for other azoles MICs [16,26–31]. However, some strains displayed resistance to all azole drugs, including

Please cite this article in press as: Denis J, et al. Isavuconazole: A new broad-spectrum azole. Part 1: In vitro activity. Journal De Mycologie Médicale (2018), https://doi.org/10.1016/j.mycmed.2018.02.005