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**Isavuconazole MICs distribution of 29 yeast species responsible for invasive infections
(2015-2017)**

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Abstract

Objectives

Isavuconazole is a recent extended-spectrum triazole with activity against yeasts. However, few data are available on the *in vitro* activity on rare yeast species. We report minimum inhibitory concentration (MIC) distribution of isavuconazole compared to fluconazole for a large collection of common or rare yeasts.

Methods

Isavuconazole and fluconazole MICs were determined using the EUCAST method for 1457 clinical isolates, mainly recovered from invasive infections, belonging to 29 species. They were sent to the National Reference Center for Invasive Mycoses & Antifungals between January 2015 and October 2017 and species identification was performed by polyphasic approach (MALDI-TOF and molecular method).

Results

Isavuconazole had effective *in vitro* activity against *Cryptococcus neoformans* (MIC₉₀<0.25mg/L), the five most common *Candida* spp. (MIC₉₀≤0.5mg/L for *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and, *Candida krusei*) and also against the majority of rare species, including *Candida kefyr* and *Candida lusitanae*. A few isolates of *C. albicans* (0.7%, 3/404), *C. glabrata* (2.7%, 5/184), *C. tropicalis* (1.0%, 1/96) and *C. parapsilosis* (0.8%, 1/127) exhibited MIC ≥4 mg/L. All were also resistant to fluconazole according to the EUCAST breakpoints. Some isolates with isavuconazole MIC ≥4 mg/L were also observed among rarer species: *Meyerozyma guilliermondii* (8.7%, 2/23), *Wickerhamomyces anomalus* (10.0%, 1/10). Other rare species *Saprochaete clavata*, *Magnusiomyces capitatus* and *Rhodotorula mucilaginosa* had high MIC₅₀ (≥1mg/L) and MIC₉₀ (≥4mg/L) and could be considered as resistant to isavuconazole.

Conclusions

47 We confirmed the good *in vitro* activity of isavuconazole against common *Candida*,
48 *Cryptococcus* species and majority of the rare yeast species studied.

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Introduction

Isavuconazole is part of the triazoles antifungal agents which exert antifungal activity through the inhibition of sterol 14- α -demethylase. It is currently approved as one of the first line therapy for human invasive aspergillosis and mucormycosis (1-4). *In vitro* activity of isavuconazole against *Cryptococcus* spp. is also reported (5) and a prospective clinical trial enrolling patients with candidemia or invasive candidiasis failed to demonstrate the non-inferiority with caspofungin (6). *In vitro*, isavuconazole is active against common *Candida* species with higher MIC value for *Candida glabrata* and *Candida krusei* than for *Candida albicans* (7-9). Few data are available for rare yeast species.

We here reported minimal inhibitory concentrations (MICs) of isavuconazole using EUCAST method for a large collection of yeast species recovered mainly from blood culture during a prospective multicenter surveillance program. We compared the results with those of fluconazole for which breakpoints (BP) exist for several *Candida* species and given that fluconazole is one of the first option for treating invasive yeast infections. The objective was to know whether isavuconazole could be proposed as an option for also treating yeast infection in case of concomitant mold infection, justifying using an extended spectrum azole.

Methods

Isolates and species identification

As part of its missions of expertise and surveillance, the National Reference Center for Invasive Mycoses & Antifungals (NRCMA) received clinical isolates involved in invasive infections from hospitals in France. Yeast isolates received between January 2015 and October 2017 were checked for purity on chromogenic medium BBL Chromagar™ *Candida* (BD) or Niger seed medium for *Cryptococcus* species and identified at the species level by phenotypic method and mass spectrometry (MALDI-TOF, Bruker Biotyper, Bruker Daltonic, Germany). For *C. albicans* and *Candida dubliniensis*, a duplex PCR was performed (10). For

rare species, D1D2 and ITS regions of ribosomal DNA were amplified and sequenced with panfungal primers (NL1/NL4 and V9D/LS266, respectively). In addition, actin gene (for *Candida lusitanae*), *RPBI* gene (for *Meyerozyma guilliermondii*, *Meyerozyma caribbica*, primer forward 5'-AGGGTTTGCGAGTGTGTTTGT-3', primer reverse 5'-CGTCAAGCTCCAATCTCTGC-3') and IGS1 region (for *Trichosporon* spp.) were sequenced (11). *Cryptococcus neoformans* serotypes were determined by amplification of *PAK1* and *GPA1* genes with serotype-specific primers and ploidy by flow cytometry (12).

Minimal Inhibitory Concentration (MIC) determination

Isavuconazole and fluconazole MICs were determined in parallel according to the EUCAST standardized broth microdilution method (13). The concentrations tested ranged between 0.007 mg/L to 4 mg/L and between 0.125 mg/L to 64 mg/L for isavuconazole and fluconazole, respectively. For MIC determination, tissue culture testplate with F-bottom, sterilized by radiation, were used (TPP®, Switzerland, Ref 92096). Quality control strains (ATCC22019, ATCC6258) were included in each set. The concentrations that inhibited 50% (MIC50) and 90% (MIC90) of the isolates were determined for isavuconazole and fluconazole for each species represented by at least 10 isolates. Results were analysed using EUCAST BP (resistance when MIC >4mg/L for *C. albicans*, *Candida tropicalis*, *Candida parapsilosis* >32mg/L for *C. glabrata*) (14). Rare species without defined BP and exhibiting fluconazole MIC50>4mg/L (non-species related BP determined by EUCAST is R>4mg/L) were considered as intrinsically resistant to fluconazole or at least less susceptible.

Results

The 1457 isolates analysed belonged to 29 species (23 ascomycetous and 6 basidiomycetous) including the five most frequent species involved in candidemia (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) and three serotypes of *Cryptococcus neoformans* (Table 1). Isolates were mostly (93%, 1351/1457) recovered from blood cultures (n=1133),

cerebrospinal fluids (n=89) or other site of invasive infections (n=129). Isolates were sent mainly (52.5%, 765/1457) in the context of the active surveillance of all yeasts fungemia in the Paris area (YEASTS program). Other isolates were sent in the context of the French Surveillance Network of Invasive Fungal Infections (RESSIF) but only in case of abnormal antifungal susceptibility profiles and/or rare species.

For 17 species among the 29 studied here, isavuconazole MIC₉₀ varied between <0.007 and 2 mg/L with 14/17 having an MIC₉₀ <0.5 mg/L. Of note, *C. neoformans* serotype D exhibited lower MIC₅₀ and MIC₉₀ for isavuconazole and fluconazole than serotype A and hybrid AD isolates. Three species exhibited an MIC₉₀ of 0.5 mg/L (*C. glabrata*, *Saccharomyces cerevisiae*) and 2 mg/L (*Meyerozyma guilliermondii*). Finally, *Saprochaete clavata*, *Magnusiomyces capitatus* and *Rhodotorula mucilaginosa* had high MIC₉₀ (≥ 4 mg/L).

MICs were also determined for 9 rare yeast species (7 Ascomycetous and 2 Basidiomycetous) (Table 1) for which less than ten isolates were studied. For four species, the MIC values were low (<0.25 mg/L) whereas MIC distribution was heterogeneous for the others (Table S1).

Analysis of the MIC distributions showed that for 11 species, some isolates (2.5%-10.0%) had a MIC above the MIC₉₀ (Table 1 and Table S1). Of those with MICs ≥ 4 mg/L were found isolates of *C. albicans* (n=3), *C. glabrata* (n=5), *C. tropicalis* (n=1), *C. parapsilosis* (n=1), *M. guilliermondii* (n=2), and *Wickerhamomyces anomalus* (n=1). All these isolates were considered resistant to fluconazole according to the EUCAST BP.

In the absence of BP and epidemiological cut-off values defined for isavuconazole, Astvad *et al* (17) categorized isolates as wild-type (wt) and non-wild-type (non-wt) based on a wild-type upper limit value (wtUL). The wtUL corresponds to two dilutions above the MIC₅₀, or to the lowest concentration tested in case all the isolates of a given species exhibit MICs less than or equal to the lowest concentration tested (*C. dubliniensis* in our study). In case of species exhibiting an MIC₅₀ equal to the highest concentration tested (*S. clavata* and *M. capitatus* in

our study), the wtUL is impossible to determine. Comparable to the published wtUL values, only minor differences (maximum two-fold dilutions) were detected here for some species. The percentage of isolates with MIC>wtUL ranged from 1.3% to 5.2% for common *Candida* species, a proportion similar to that of the fluconazole-resistant isolates (2.72% to 6.3%, Table 1). This proportion ranged between 0 and 13% for rare species, except for *S. cerevisiae* that reached almost 44% (7/16) of non-wt with a very heterogeneous MIC distribution (Table S1). Looking at cross-resistance (9), among the 12 non-wt isolates of *C. albicans*, 11 were resistant to fluconazole (MIC>4mg/L). For the 5 non-wt isolates of *C. tropicalis*, 3 were resistant to fluconazole (MIC>4mg/L). All the 6 non-wt isolates of *C. parapsilosis* and the 7 non-wt isolates of *C. glabrata* were also resistant to fluconazole (MIC>4mg/L and MIC>32mg/L, respectively). Similarly, all isolates of *C. albicans* (11/404, 2.7%) resistant to fluconazole were non-wt for isavuconazole. For *C. glabrata* (11/184, 5.9%), *C. tropicalis* (3/96, 3.1%) and *C. parapsilosis* (8/127, 6.3%) resistant to fluconazole, the majority (7/11, 2/3 and 6/8, respectively) were non-wt for isavuconazole.

Discussion

We here confirmed that isavuconazole is active *in vitro* against *C. neoformans* and the most common *Candida* species (7, 8). Of note, *C. glabrata* and *C. krusei* which are considered as less susceptible or intrinsically resistant to fluconazole, respectively, had isavuconazole MIC₉₀≤0.5 mg/L which is higher than for *C. albicans* but suggest a good *in vitro* activity (7, 9). We also observed a low percentage of isolates of common *Candida* species categorized as fluconazole resistant or with high MIC for isavuconazole. But mainly, isolates resistant to fluconazole were also nonwt for isavuconazole. The proportion of isavuconazole non-wt isolates was comparable to that obtained by Marcos-Zambrano *et al.* for *C. albicans* [2.97% (12/404) vs. 2.3%] but higher for *C. glabrata* [3.8% (7/184) vs. 1.1%], *C. parapsilosis* [4.7% (6/127) vs. 1.5%] and *C. tropicalis* [5.2% (5/96) vs. 0%] (19). Our data suggest that

isavuconazole is also active *in vitro* against the majority of rare yeast species studied, except for species already considered as intrinsically resistant to fluconazole such as *S. cerevisiae*, *M. guilliermondii*, *S. clavata*, *M. capitatus* and *R. mucilaginosa* (11, 15, 16). These results are in accordance with data reviewed by Miceli *et al.* and Astvad *et al.*, except for *M. capitatus* and *R. mucilaginosa* previously reported with low MICs (17, 18). In conclusion, except for *C. krusei*, MIC distributions of isavuconazole and fluconazole were comparable for common and rare yeast species. .

Preliminary results were presented at the 28th European Congress of Clinical Microbiology and Infectious Diseases, (21-24 April 2018, Madrid, Spain; abstract number 7965).

Conflict of interests

SB: consultancy (Gilead), honorarium for educational programs (Astellas), congress symposium (Gilead, Bio-Rad), and travel grants (Pfizer).

OL: member of speaker's bureau Merck, Pfizer, Astellas, Gilead; consultant for Gilead

MDO, AB, CG and FD: nothing to declare

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Table 1: Isavuconazole and Fluconazole susceptibility of the 20 yeast species with more than 10 isolates studied (France, 2015-2017)

Species (current name)	n	% of isolates from blood culture or CSF (nb of isolates)	Isavuconazole						Fluconazole			
			MIC50 (mg/L)	MIC90 (mg/L)	MIC range (mg/L)	% isolates with MIC > MIC90 (nb of isolates)	wtUL (mg/L)	% isolates with MIC>wtUL (nb of isolates)	MIC50 (mg/L)	MIC90 (mg/L)	MIC range (mg/L)	% of isolates Resistant*(nb of isolates)
<i>Candida albicans</i>	404	91.8% (371)	≤0.007	≤0.007	≤0.007-≥4	4.95 (20)	0.03	2.97 (12)	≤0.125	0.25	≤0.125 -≥64	2.72 (11)
<i>Candida dubliniensis</i>	34	97.1 (33)	≤0.007	≤0.007	≤0.007-≤0.007	0 (0)	≤0.007	0	≤0.125	0.25	≤0.125 -0.5	NA
<i>Candida tropicalis</i>	96	89.6% (86)	≤0.007	0.03	≤0.007-≥4	5.21 (5)	0.03	5.21 (5)	0.25	1	≤0.125 -≥64	3.16 (2)
<i>Candida parapsilosis</i>	127	85.8% (109)	0.015	0.03	≤0.007-≥4	5.51 (7)	0.06	4.72 (6)	0.5	2	≤0.125 -≥64	6.3 (8)
<i>Candida orthopsilosis</i>	10	100% (10)	0.015	0.06	≤0.007-0.25	10 (1)	0.06	10.0 (1)	0.5	16	0.25 - 16	20 (2)
<i>Candida metapsilosis</i>	11	72.7% (8)	0.015	0.015	≤0.007-0.015	0 (0)	0.06	0	1	1	1 - 2	0
<i>Candida glabrata</i>	184	91.3% (168)	0.25	0.5	0.03-≥4	7.07 (13)	1	3.80 (7)	8	16	1 - ≥64	5.98 (11)
<i>Saccharomyces cerevisiae</i>	16	100% (16)	≤0.007	0.5	0.03-0.5	0 (0)	0.03	43.75 (7)	8	32	≤0.125 -32	56.25 (9)
<i>Candida lusitanae</i> (<i>Clavispora lusitanae</i>)	55	96.4% (53)	≤0.007	0.015	≤0.007-0.5	5.45 (3)	0.03	3.64 (2)	0.25	0.5	≤0.125 -16	3.64 (2)
<i>Candida guilliermondii</i> (<i>Meyerozyma guilliermondii</i>)	23	91.3% (21)	0.25	2	0.03-≥4	8.7 (2)	1	13.04 (3)	4	16	1 -≥64	NA
<i>Candida krusei</i> (<i>Pichia kudriavzevii</i>)	76	90.8% (69)	0.125	0.25	0.015-1	6.58 (5)	0.5	1.32 (1)	32	64	16 -≥64	NA
<i>Candida kefyr</i> (<i>Kluyveromyces marxianus</i>)	41	80.5%(33)	≤0.007	≤0.007	≤0.007-0.015	4.88 (2)	0.03	0	0.25	0.5	≤0.125 -1	0
<i>Candida pelliculosa</i> (<i>Wickerhamomyces anomalus</i>)	10	60% (6)	0.06	0.06	0.03-4	10 (1)	0.25	10.0 (1)	2	4	1-8	20 (2)
<i>Pichia ohmeri</i> (<i>Kodamaea ohmeri</i>)	11	100%(11)	0.015	0.03	≤0.007-0.25	9.09 (1)	0.06	9.09 (1)	4	4	2-64	9.09 (1)
<i>Geotrichum clavatum</i> (<i>Saprochaete clavata</i>)	64	45.3%(29)	4	≥4	0.25-≥4	0 (0)	NA	NA	16	32	0.25-32	81.25 (52)
<i>Geotrichum capitatum</i> (<i>Magnusiomyces capitatus</i>)	25	48% (12)	4	≥4	0.125-≥4	0 (0)	NA	NA	4	16	0.25-32	48 (12)
<i>Cryptococcus neoformans</i> var. <i>grubii</i> (A)	158	70.9% (112)	0.06	0.25	≤0.007-0.5	2.53 (4)	0.25	2.53 (4)	2	8	≤0.125 -16	11.39 (18)
<i>Cryptococcus neoformans</i> var. <i>neoformans</i> (D)	25	60% (15)	0.015	0.03	≤0.007-0.125	8 (2)	0.06	4.0 (1)	1	2	0.25-2	0
<i>Cryptococcus neoformans</i> AD hybrid	26	73.1% (19)	0.03	0.125	≤0.007-0.25	7.69 (2)	0.125	7.69 (2)	2	8	≤0.125 -16	15.38 (4)
<i>Rhodotorula mucilaginosa</i>	16	93.8% (15)	1	4	0.125-4	0 (0)	4	25.0 (4)	≥64	≥64	1-≥64	93.75 (15)
<i>Candida auris</i>	2	50% (1)	NA	NA	0.015	NA	NA	NA	NA	NA	16-64	100 (2)
<i>Candida inconspicua</i>	8	75%(6)	0.06	NA	0.06-0.25	NA	NA	NA	16	NA	4-32	87.5 (7)
<i>Candida nivariensis</i>	3	100%(3)	NA	NA	≤0.007-0.5	NA	NA	NA	NA	NA	2-4	0
<i>Candida utilis</i> (<i>Cyberlindnera jadinii</i>)	5	80%(4)	0.03	NA	0.015-0.03	NA	NA	NA	1	NA	1-2	0
<i>Geotrichum candidum</i> (<i>Galactomyces candidus</i>)	7	0% (0)	0.25	NA	≤0.007-2	NA	NA	NA	16	NA	0.5-≥64	85.71 (6)
<i>Candida fermentati</i> (<i>Meyerozyma caribbica</i>)	3	66.7%(2)	NA	NA	0.06-≥ 4	NA	NA	NA	NA	NA	4-≥64	66.67 (2)
<i>Yarrowia lipolytica</i>	5	40% (2)	0.125	NA	0.125-0.25	NA	NA	NA	2	NA	≤0.124-16	20 (1)
<i>Trichosporon asahii</i>	9	66.7% (6)	0.25	NA	0.06-1	NA	NA	NA	2	NA	0.25-8	11.11 (1)
<i>Trichosporon dermatis</i> (<i>Cutaneotrichosporon dermatis</i>)	3	66.7%(2)	NA	NA	0.06-2	NA	NA	NA	NA	NA	2-4	0

*EUCAST BP were used for categorized isolates as resistant. Non-species related BP (R>4mg/L) was used for all species without any BP.