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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 lusitaniae*. 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

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

Introduction

Isavuconazole is part of the triazoles antifungal agents which exert antifungal activity through the inhibition of sterol 14-alpha-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 lusitaniae*), *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 MIC 90 <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 (≥4mg/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 (<0.25mg/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

147 our study), the wtUL is impossible to determine. Comparable to the published wtUL values,
148 only minor differences (maximum two-fold dilutions) were detected here for some species.
149 The percentage of isolates with MIC>wtUL ranged from 1.3% to 5.2% for common *Candida*
150 species, a proportion similar to that of the fluconazole-resistant isolates (2.72% to 6.3%, Table
151 1). This proportion ranged between 0 and 13% for rare species, except for *S. cerevisiae* that
152 reached almost 44% (7/16) of non-wt with a very heterogeneous MIC distribution (Table S1).

153 Looking at cross-resistance (9), among the 12 non-wt isolates of *C. albicans*, 11 were resistant
154 to fluconazole (MIC>4mg/L). For the 5 non-wt isolates of *C. tropicalis*, 3 were resistant to
155 fluconazole (MIC>4mg/L). All the 6 non-wt isolates of *C. parapsilosis* and the 7 non-wt
156 isolates of *C. glabrata* were also resistant to fluconazole (MIC>4mg/L and MIC>32mg/L,
157 respectively). Similarly, all isolates of *C. albicans* (11/404, 2.7%) resistant to fluconazole
158 were non-wt for isavuconazole. For *C. glabrata* (11/184, 5.9%), *C. tropicalis* (3/96, 3.1%)
159 and *C. parapsilosis* (8/127, 6.3%) resistant to fluconazole, the majority (7/11, 2/3 and 6/8,
160 respectively) were non-wt for isavuconazole.

161 **Discussion**

162 We here confirmed that isavuconazole is active *in vitro* against *C. neoformans* and the most
163 common *Candida* species (7, 8). Of note, *C. glabrata* and *C. krusei* which are considered as
164 less susceptible or intrinsically resistant to fluconazole, respectively, had isavuconazole
165 MIC90≤0.5 mg/L which is higher than for *C. albicans* but suggest a good *in vitro* activity (7,
166 9). We also observed a low percentage of isolates of common *Candida* species categorized as
167 fluconazole resistant or with high MIC for isavuconazole. But mainly, isolates resistant to
168 fluconazole were also nonwt for isavuconazole. The proportion of isavuconazole non-wt
169 isolates was comparable to that obtained by Marcos-Zambrano *et al.* for *C. albicans* [2.97%
170 (12/404) *vs.* 2.3%] but higher for *C. glabrata* [3.8% (7/184) *vs.* 1.1%], *C. parapsilosis* [4.7%
171 (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. .

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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)

			Isavuconazole						Fluconazole			
Species (current name)	**n**	**% of isolates from blood culture or CSF (nb of isolates)**	**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)**
Candida albicans	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)
Candida dubliniensis	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
Candida tropicalis	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)
Candida parapsilosis	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)
Candida orthopsilosis	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)
Candida metapsilosis	11	72.7% (8)	0.015	0.015	≤0.007-0.015	0 (0)	0.06	0	1	1	1 - 2	0
Candida glabrata	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)
Saccharomyces cerevisiae	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)
Candida lusitaniae (Clavispora lusitaniae)	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)
Candida guilliermondii (*Meyerozyma guilliermondii*)	23	91.3% (21)	0.25	2	0.03-≥4	8.7 (2)	1	13.04 (3)	4	16	1 -≥64	NA
Candida krusei (*Pichia kudriavzevii*)	76	90.8% (69)	0.125	0.25	0.015-1	6.58 (5)	0.5	1.32 (1)	32	64	16 -≥64	NA
Candida kefyr (Kluyveromyces marxianus)	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
Candida pelliculosa (*Wickerhamomyces anomalus*)	10	60% (6)	0.06	0.06	0.03-4	10 (1)	0.25	10.0 (1)	2	4	1-8	20 (2)
Pichia ohmeri (Kodamaea ohmeri)	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)
Geotrichum clavatum (*Saprochaete clavata*)	64	45.3%(29)	4	≥4	0.25-≥4	0 (0)	NA	NA	16	32	0.25-32	81.25 (52)
Geotrichum capitatum (Magnusiomyces capitatus)	25	48% (12)	4	≥4	0.125-≥4	0 (0)	NA	NA	4	16	0.25-32	48 (12)
Cryptococcus neoformans var. *grubii* (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)
Cryptococcus neoformans var. *neoformans* (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
Cryptococcus neoformans 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)
Rhodotorula mucilaginosa	16	93.8% (15)	1	4	0.125-4	0 (0)	4	25.0 (4)	≥64	≥64	1-≥64	93.75 (15)
Candida auris	2	50% (1)	NA	NA	0.015	NA	NA	NA	NA	NA	16-64	100 (2)
Candida inconspicua	8	75%(6)	0.06	NA	0.06-0.25	NA	NA	NA	16	NA	4-32	87.5 (7)
Candida nivariensis	3	100%(3)	NA	NA	≤0.007-0.5	NA	NA	NA	NA	NA	2-4	0
Candida utilis (Cyberlindnera jadinii)	5	80%(4)	0.03	NA	0.015-0.03	NA	NA	NA	1	NA	1-2	0
Geotrichum candidum (*Galactomyces candidus*)	7	0% (0)	0.25	NA	≤0.007-2	NA	NA	NA	16	NA	0.5-≥64	85.71 (6)
Candida fermentati (*Meyerozyma caribbica*)	3	66.7%(2)	NA	NA	0.06-≥ 4	NA	NA	NA	NA	NA	4-≥64	66.67 (2)
Yarrowia lipolytica	5	40% (2)	0.125	NA	0.125-0.25	NA	NA	NA	2	NA	≤0.124-16	20 (1)
Trichosporon asahii	9	66.7% (6)	0.25	NA	0.06-1	NA	NA	NA	2	NA	0.25-8	11.11 (1)
Trichosporon dermatis (*Cutaneotrichosporon dermatis*)	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.*