Evaluation of Isavuconazole Activity Against Non-fumigatus Aspergillus and Cryptic Aspergillus Species Causing Invasive Infections Worldwide

Cecilia G. Carvalhaes, Paul R. Rhomberg, Valerie Kantro, Beth A. Hatch, Mariana Castanheira Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA

Introduction

- While Aspergillus fumigatus is most commonly the cause of invasive aspergillosis (IA), cryptic and non-*fumigatus Aspergillus* spp. are a rising clinical concern.
- Isavuconazole, a second-generation broad-spectrum triazole, is a first-line therapy for the treatment of IA with favorable pharmacokinetic and safety profiles and few drugdrug interactions.
- There is limited data on antifungal susceptibility testing of clinically relevant non*fumigatus* and cryptic species of *Aspergillus* causing IA.
- The activity of isavuconazole and other azoles against non-fumigatus and cryptic species of Aspergillus causing IA worldwide was evaluated.

Methods

- A total of 390 non-fumigatus Aspergillus were collected in 2017–2021 from 41 medical centers located in Europe (EU; *n*=161; 17 centers), North America (NA; *n*=137; 16 centers), Asia-Pacific (AP; *n*=85; 7 centers), and Latin America (LA, *n*=7; 1 center).
- Only 1 isolate per patient was included.
- Isolates were identified by MALDI-TOF MS and/or ITS and β -tubulin sequencing and tested by CLSI broth microdilution.
- CLSI epidemiological cut-off values (ECV) for A. fumigatus, A. flavus, A. niger, and A. terreus were applied to the respective section, where available.
- Posaconazole ECVs of 0.5 mg/L was used against A. section *Fumigati*.

Results

Identification of non-fumigatus Aspergillus

- The distribution of isolates per *Aspergillus* section is displayed in Figure 1.
- 63 (16.2%) of non-fumigatus Aspergillus were considered cryptic Aspergillus isolates (Figure 2).
- A total of 222 isolates (56.9%) were identified to the species complex level only (Figure 2).
- A. terreus and A. niger corresponded to 19.7% (77 isolates) and 6.9% (27 isolates) of the non-fumigatus Aspergillus species, respectively (Figure 2).

Azole activity against non-fumigatus Aspergillus split by Aspergillus sections (Table 1)

- Isavuconazole showed activity against A. sections Flavi (n=122; 98.4% WT), Terrei (n=57; 98.2% WT), Nidulans (n=34; MIC_{50/90}, 0.12/0.25 mg/L), Versicolores (n=7; MIC₅₀, 1 mg/L), and Circumdati (n=2; MIC range, 0.12–2 mg/L; Table 1).
- Similar activity was displayed by other azoles against those Aspergillus sections (Table 1; Figure 3).
- Most of the isolates from A. section Fumigati (n=9), Nigri (n=146), and Usti (n=12) exhibited elevated MIC values to isavuconazole (MIC_{50/90}, 2/-, 2/4, and 2/8 mg/L), voriconazole (MIC_{50/90}, 2/-, 1/2, and 4/8 mg/L), and itraconazole (MIC_{50/90}, 2/-, 2/4, and 8/>8 mg/L), respectively (Table 1).
- Posaconazole exhibited lower MIC values than other azoles against A. section Fumigati (MIC_{50/90}, 0.5/- mg/L) and A. section Nigri (MIC_{50/90}, 0.5/1), but high MIC values against A. section Usti (MIC_{50/90}, >8/>8 mg/L; Table 1).

Azole activity against cryptic Aspergillus species (Table 2)

- for A. niger (Table 2).

Azole activity against other non-fumigatus Aspergillus (A. flavus species complex, A. terreus, and A. niger; Table 3)

Conclusions

- values overall.

Figure 1. Distribution of non-fumigatus Aspergillus collected from 2017–2021 worldwide by Aspergillus section

Nidulantes -



Isavuconazole was active (MIC values, ≤1 mg/L) against A. parasiticus, A. tamarii, A. nomius, A. nidulans, A. unguis, A. alabamensis, and A. hortai, while isavuconazole MIC values between 2–8 mg/L were observed against cryptic Aspergillus species from A. section Fumigati (Table 2).

Isavuconazole inhibited 80.0% of *A. tubingensis* at ≤4 mg/L, the CLSI WT cut-off value

• Voriconazole, itraconazole, and posaconazole showed similar activity to isavuconazole against most cryptic *Aspergillus* species (Table 2).

Isavuconazole was active against A. *flavus* species complex (98.3% WT), A. niger (96.1% WT), and A. terreus (100% WT; Table 3).

Voriconazole, itraconazole, and posaconazole showed similar activity to isavuconazole against A. flavus species complex, A. terreus, and A. niger isolates (Table 3).

Isavuconazole exhibited potent *in vitro* activity against most non-fumigatus Aspergillus, including cryptic Aspergillus species.

However, the activity of isavuconazole and other azoles vary among cryptic Aspergillus species: A. lentulus, A. thermomutatus, and A. ustus showed elevated azole MIC

Species identification of non-*fumigatus Aspergillus* isolates and susceptibility testing is critical to guide treatment of cryptic *Aspergillus* species causing IA.

Table 1. Activity of isavuconazole and other azoles against non-fumigatus Aspergillus split by sections

Aspergillus section	Aspergillus species included	No. of isolates	MIC _{50/90} ^a (MIC range; %WT ^b); mg/L				
			Isavuconazole	Voriconazole	Itraconazole	Posaconazole	
Circumdati	A. sclerotiorum	2	0.12/- (0.12-2; NA)	0.12/- (0.12-0.5; NA)	1/- (1; NA)	0.25/-(0.25-0.5; NA)	
Flavi	A. parasiticus, A. tamarii, A. nomius, A. flavus species complex	122	0.5/1 (0.12-2; 98.4%)	0.5/1 (0.25-2; 100%)	0.5/1 (0.12-1; 100%)	0.5/0.5 (0.12-1; 99.2%)	
Fumigati	A. lentulus, A. thermomutatus, A. udagawae	9	2/-(2-8;0%)	2/-(2-8;0%)	2/-(1-4;33.3%)	0.5/-(0.5-1;66.7%)	
Nidulantes	A. nidulans, A. unguis, A. nidulans species complex	34	0.12/0.25 (0.015-0.5; NA)	0.12/0.25 (0.03-0.5; NA)	0.5/1 (0.12-4; NA)	0.25/0.5 (0.06-1; NA)	
Nigri	A. niger, A. tubingensis, A. niger species complex	146	2/4 (0.06->8; 95.2%)	1/2 (0.06-4; 97.9%)	2/4 (0.12->8; 92.4%)	0.5/1 (0.12-2; 100%)	
Terrei	A. alabamensis, A. hortai, A. terreus, A. terreus species complex	57	0.5/0.5 (0.06-2; 98.2%)	0.25/0.5 (0.06-1; 100%)	0.5/1 (0.12-1; 100%)	0.25/0.5 (0.12-0.5; 100%)	
Usti	A. ustus, A. ustus species complex	12	2/8 (0.12-8; NA)	4/8 (0.25->8; NA)	8/>8 (0.25->8; NA)	>8/>8 (0.5->8; NA)	
Versicolores	A. versicolor, A. sydowii	7	1/- (0.5-2; NA)	1/- (0.25-1; NA)	1/- (0.5-2; NA)	1/- (0.25-1; NA)	
Abbreviations: WT, wildtype; NA, not available							

^b CLSI M57 (2022) ECV criteria for A. fumigatus, A. flavus, A. niger, and A. terreus applied to corresponding Aspergillus section isolates

Table 2. Activity of isavuconazole and other azoles against cryptic Aspergillus species

Acronation	Aspergillus species	No. of isolates	MIC range (%WT ^a) mg/L				
Asperginus section			Isavuconazole	Voriconazole	Itraconazole	Posaconazole	
Circumdati	A. sclerotiorum	2	0.12-2 (NA)	0.12-0.5 (NA)	1 (NA)	0.25-0.5 (NA)	
	A. parasiticus	2	0.5 (100%)	0.5-1 (100%)	0.5-1 (100%)	0.25-0.5(100%)	
Flavi	A. tamarii	2	0.12-0.25 (100%)	0.25-0.5 (100%)	0.25-0.5 (100%)	0.12-0.25 (100%)	
	A. nomius	1	0.5 (100%)	0.5 (100%)	0.5 (100%)	0.5 (100%)	
	A. lentulus	6	2-4 (0.0%)	2 (0.0%)	1-2 (50.0%)	0.5 (100.0%)	
Fumigati	A. thermomutatus	2	2-8 (0.0%)	4-8 (0.0%)	4 (0.0%)	1 (0.0%)	
	A. udagawae	1	2 (0.0%)	2 (0.0%)	2 (0.0%)	1 (0.0%)	
Nidulantas	A. nidulans	24	0.015-0.25 (NA)	0.03-0.5 (NA)	0.12-1 (NA)	0.06-0.5 (NA)	
Muulantes	A. unguis	3	0.25-0.5 (NA)	0.06-0.25 (NA)	0.5-4 (NA)	0.25-1 (NA)	
Nigri	A. tubingensis	5	2-8 (80.0%)	1-4 (80.0%)	2->8 (80.0%)	0.5-2 (100.0%)	
Torroi	A. alabamensis	2	0.25 (100%)	0.25-0.5 (100%)	0.5 (100%)	0.25 (100%)	
Тепе	A. hortai	1	0.25 (100%)	0.12 (100%)	0.5 (100%)	0.12 (100%)	
Usti	A. ustus	5	2-8 (NA)	4->8 (NA)	4-8 (NA)	4->8 (NA)	
Varcicalaras	A. versicolor	6	0.5-2 (NA)	0.25-1 (NA)	0.5-2 (NA)	0.25-1 (NA)	
versicolores	A. sydowii	1	2 (NA)	1 (NA)	2 (NA)	1 (NA)	
Abbreviations: WT, wildtype; NA, not available	A flavour A night and A tarrous applied to cruptic a	pacies from the same Aspersillus section					

Table 3. Activity of isavuconazole and other azoles against worldwide A. flavus species complex, A. terreus, and A. niger from 2017–2021

<i>Aspergillus</i> section	Aspergillus species	No. of isolates	MIC _{50/90} (MIC range; %WT ^a); mg/L				
			Isavuconazole	Voriconazole	Itraconazole	Posac	
Flavi	A. flavus species complex	117	0.5/1 (0.12-2; 98.3%)	0.5/1 (0.25-2; 100%)	0.5/1 (0.12-1; 100%)	0.5/0.5 (0.	
Terrei	A. terreus	27	0.5/0.5 (0.06-1; 100%)	0.25/0.5 (0.12-0.5; 100%)	0.5/1 (0.25-1; 100%)	0.25/0.5 (0.	
Nigri	A. niger	77	2/4 (0.5->8; 96.1%)	1/1 (0.25-4; 98.7%)	2/4 (0.25->8; 97.4%)	0.5/4(0.2	
Abbreviations: WT, wildtype ^a Using CLSI M57 (2022) ECV c	riteria.						



Figure 3. Activity of isavuconazole and other azoles against non-fumigatus Aspergillus isolates split by Aspergillus sections (2017–2021)



A. ustus species complex (3.2%) A. *nidulans* species complex (3.2%)

Aspergillus section (no. of isolates)

12-1; 99.1%) 12-0.5; 100%) 25-1; 100%)



Abbreviations: WT, wildtype CLSI M57 (2022) ECV criteria for A. fumigatus, A. flavus, A. niger, and terreus applied to corresponding Aspergillus section isolates ollowing species: A. parasiticus (. A. tamarii (2), A. nomius (1), A. flavus species complex (11) spergillus section Fumigati ncludes the following species: A. lentulus (6), A. thermomutatus (2), . udagawae (

spergillus section Nigri includes he following species: A. niger (77),

spergillus section Terrei includes the ollowing species: A. alabamensis (2), A. hortai (1), A. terreus (27), A. terreus

Funding

This study was supported by Pfizer Inc. (New York, NY). CG Carvalhaes, PR Rhomberg, V Kantro, BA Hatch, and M Castanheira are employees of Element Materials Technology (JMI Laboratories) at the time of this study, which was paid consultant to Pfizer in connection with the development of this poster.

References

Bosetti D, Neofytos D. Invasive Aspergillosis and the Impact of Azole-resistance. Curr Fungal Infect Rep. 2023 Mar 18:1-10.

Jenks JD, Salzer HJ, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther. 2018 Apr 30;12:1033-1044.

CLSI (2017). M38Ed3. Reference method for broth dilution antifungal susceptibility testing of Filamentous Fungi. Wayne, PA.

CLSI (2022). M57SEd4. Epidemiological cutoff values for antifungal susceptibility testing. Wavne, PA

CLSI (2022). M38M51SEd3. Performance standards for antifungal susceptibility testing of filamentous fungi. Wayne, PA.

Acknowledgments

The authors thank all the participant centers for their work in providing isolates.

Contact



Cecilia Carvalhaes, MD, Ph.D., D(ABMM) Element Iowa City (JMI Laboratories) 345 Beaver Kreek Centre, Suite A North Liberty, IA 52317 Phone: (319) 665-3370 Fax: (319) 665-3371 Email: cecilia.carvalhaes@element.com



To obtain a PDF of this poster: Scan the QR code or visit https://www .jmilabs.com/data/posters/IDWeek2023 _23-PZR-06_P2_Cryptic_Aspergillus.pdf

Charges may apply. No personal information is stored.