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Activity of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults Enrolled in a Clinical Trial

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Introduction

- Invasive aspergillosis (IA) is a life-threatening disease with limited treatment options. IA is associated with delays in effective treatment and significant early mortality.
- Posaconazole is a broad-spectrum triazole antifungal that exhibits potent antifungal activity against a variety of yeasts and moulds.
- Posaconazole is approved by US-FDA for prophylaxis of invasive *Aspergillus* and *Candida* infections and for treatment of oropharyngeal candidiasis, including those infections refractory to itraconazole and/or fluconazole.
- We evaluated the antifungal susceptibility profiles of isolates collected during a randomized, prospective, phase 3, double-blind, double-dummy study comparing posaconazole with voriconazole given for ≤12 weeks in the primary treatment of IA (ClinicalTrials.gov, NCT01782131; EudraCT, 2011-003938-14) using CLSI and EUCAST reference testing methodologies.

Materials and Methods

- A total of 127 isolates were recovered from documented infections during 2013 through 2019 from more than 90 medical centers located in 23 countries.
- Isolates were identified by DNA sequencing of *28S* (all isolates) and 1 of the following genes: β-tubulin for *Aspergillus* spp., translation elongation factor (*TEF*) for *Fusarium* spp., or *ITS* for all other species of filamentous fungi and yeasts according to the CLSI MM18-A document.
- Susceptibility tests were conducted for posaconazole, itraconazole, voriconazole, caspofungin, and amphotericin B according to CLSI documents M27 (2017) and M38 (2018), as well as EUCAST document EDef 9.1.
- EUCAST clinical breakpoints (2018), CLSI breakpoints (M60, 2017), and epidemiological cutoff values (ECV; M59, 2018) were applied as interpretative criteria.
- Quality control (QC) was performed as recommended by CLSI and EUCAST guidelines using the following strains: *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258, *Aspergillus flavus* ATCC 204304, *Aspergillus fumigatus* ATCC 204305, and *Aspergillus fumigatus* ATCC MYA-3626.

Results

- Of the 127 samples tested, 119 were identified as *Aspergillus* species (Figure 1).
- *Aspergillus fumigatus* (N=76) was the most prevalent species, followed by *A. flavus* species complex (N=19), *A.* section *Nigri* (N=10), and *A.* section *Terrei* (N=7; Figure 1).
- Overall, posaconazole ($MIC_{50/90}$, 0.5/1 mg/L) displayed similar activity to voriconazole ($MIC_{50/90}$, 0.5/1 mg/L) and itraconazole ($MIC_{50/90}$, 1/2 mg/L) against 119 *Aspergillus* species isolates by both CLSI and EUCAST methods (Table 1).
- Posaconazole ($MIC_{50/90}$, 0.5/0.5 mg/L) and voriconazole ($MIC_{50/90}$, 0.25/0.5 mg/L) inhibited all 76 *A. fumigatus* isolates at an MIC of 1 mg/L (Figure 2).
- Among 19 *A. flavus* species complex isolates recovered from this study, posaconazole ($MIC_{50/90}$, 0.5/1 mg/L), voriconazole ($MIC_{50/90}$, 1/1 mg/L), and itraconazole ($MIC_{50/90}$, 0.5/1 mg/L) displayed equivalent activity (Table 1 and Figure 2).
- Posaconazole ($MIC_{50/90}$, 1/1 mg/L) also exhibited activity against 10 *A.* section *Nigri* and 7 *A.* section *Terrei* isolates (MIC_{50}, 0.5 mg/L). Posaconazole activity was similar to the activity displayed by voriconazole and itraconazole (Table 1 and Figure 2).
- Azole activity against other moulds, such as Mucorales group isolates and *Fusarium incarnatum-equiseti* species complex, was limited (Table 2).

Figure 1 Distribution of main species and organism groups of fungi isolates

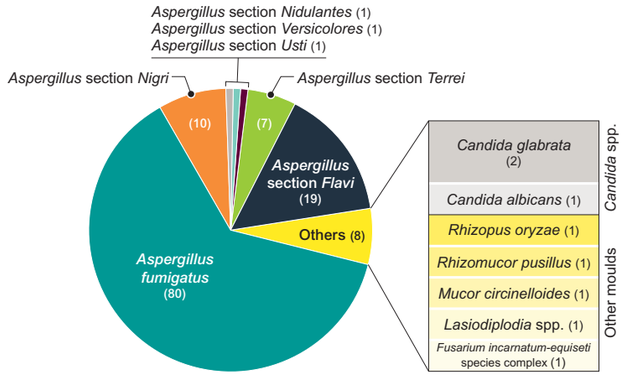
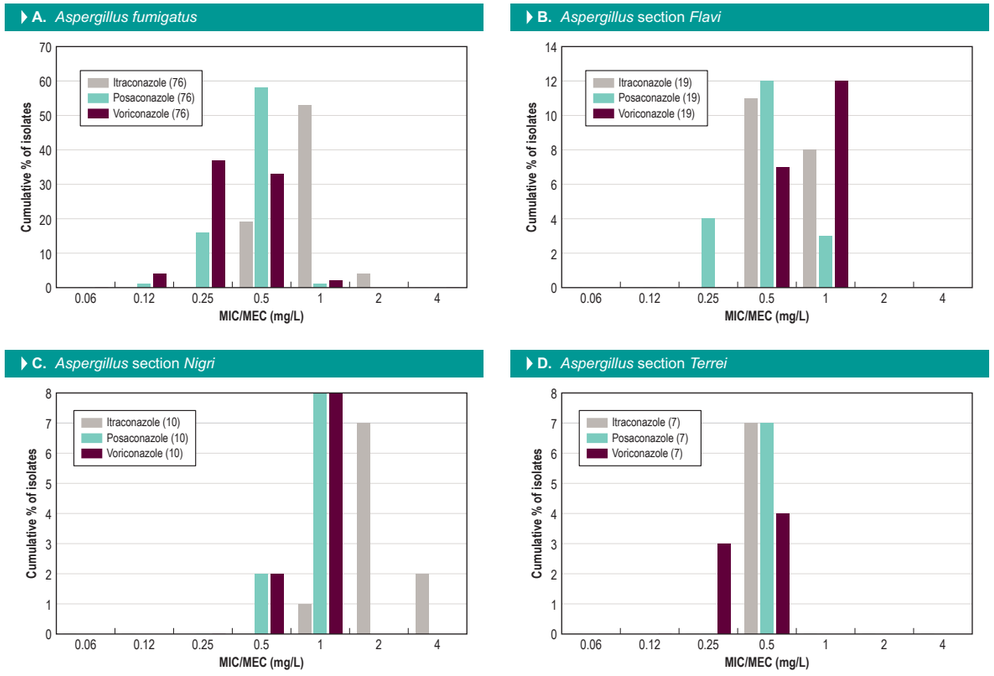


Figure 2 Posaconazole, voriconazole, and itraconazole MIC distributions against the main *Aspergillus* species



Conclusions

- Posaconazole displayed good activity against all *Aspergillus* species isolates.
- Posaconazole *in vitro* activity against *Aspergillus* species was similar to that activity observed by voriconazole and itraconazole.
- Azoles exhibited limited activity against *Fusarium* spp. and Mucorales group isolates.

Table 1 Antimicrobial activity of posaconazole and comparator agents tested against *Aspergillus* spp. isolates

Antimicrobial agent (No. of isolates)	CLSI[a]				EUCAST[b]				
	MIC/ MEC_{50}	MIC/ MEC_{90}	ECV %WT	ECV %NWT	MIC_{50}	MIC_{90}	%S	%I	%R
***Aspergillus* spp. (n=119)**									
Amphotericin B	2	2			0.5	2			
Caspofungin	0.03	0.06			0.06	0.12			
Itraconazole	1	2			0.5	1			
Posaconazole	0.5	1			0.12	0.25			
Voriconazole	0.5	1			0.5	2			
***A. fumigatus* (n=76)**									
Amphotericin B	2	2	100	0	0.5	1	98.7	1.3	0
Caspofungin	0.03	0.06	100	0	0.06	0.12			
Itraconazole	1	1	94.7	5.3	0.5	0.5	100	0	0
Posaconazole	0.5	0.5			0.12	0.12	93.4	6.6	0
Voriconazole	0.25	0.5	100	0	0.5	1	94.7	5.3	0
***A.* section *Flavi* (n=19)**									
Amphotericin B	2	2	100	0	1	1			
Caspofungin	0.015		100	0	0.03	0.12			
Itraconazole	0.5	1	100	0	0.5	0.5	100	0	0
Posaconazole	0.5	1	84.2	15.8	0.12	0.25			
Voriconazole	1	1	100	0	1	2			
***A.* section *Nigri* (n=10)**									
Amphotericin B	0.5	1	100	0	0.25	0.25	100	0	0
Caspofungin	0.015		100	0	0.03	0.25			
Itraconazole	2	4	100	0	1	1			
Posaconazole	1	1	100	0	0.25	0.25			
Voriconazole	1	1	100	0	1	1			
***A.* section *Terrei* (n=7)**									
Amphotericin B	2		100	0	2				
Caspofungin	0.03		100	0	0.06				
Itraconazole	0.5		100	0	0.25		100	0	0
Posaconazole	0.5		100	0	0.12		100	0	0
Voriconazole	0.5		100	0	0.5				

[a] ECV criteria published in CLSI M59 (2018)
[b] Clinical breakpoint criteria published by EUCAST (2019)
MIC = minimal inhibitory concentration, MEC = minimal effective concentration, WT = wild-type, NWT = non wild-type, S = susceptible, I = intermediate, R = resistant

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Table 2 Antimicrobial activity of posaconazole and comparator agents tested against 5 other mould isolates

Organism[a]	CLSI MIC/MEC (mg/L)				EUCAST MIC (mg/L)			
	Amp B	Itra	Posa	Vori	Amp B	Itra	Posa	Vori
Rhizomucor pusillus	1	0.5	0.5	0.25	0.25	0.25	0.06	0.5
Rhizopus oryzae	1	2	1	8	0.25	1	0.5	8
Mucor circinelloides	0.25	4	2	>8	0.06	>8	1	>8
Lasiodiplodia spp.	0.5	>8	8	2	2	>8	>8	2
Fusarium incarnatum-equiseti species complex	2	8	2	2	0.5	>8	2	2

[a] Clinical breakpoint criteria or ECV interpretation unavailable
Amp B = amphotericin B, Itra = itraconazole, Posa = posaconazole, Vori = voriconazole

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