

Rezafungin (CD101) Demonstrates Potent In vitro Activity against *Aspergillus*, including Azole-Resistant *A. fumigatus* Isolates and Cryptic Species

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Disclosures

Funding

- Astellas
- bioMerieux
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Speakers Bureaus

- Gilead

Member, CLSI Antifungal
Susceptibility Subcommittee

Aspergillosis

- Acute invasive aspergillosis

- Estimated ~200,000 cases/year
- Leading cause of invasive mould infections
 - SOT recipients (TRANSNET)
 - Lung transplant recipients (TRANSNET)
 - HSCT recipients (TRANSNET & PATH Alliance)
 - Leading cause IFI in HSCT recipients

- Chronic pulmonary aspergillosis

- Estimated >3 million people infected worldwide
- Common with underlying lung disease
 - Tuberculosis, sarcoidosis

- Azole Resistance

- Point mutations in *CYP51A* (gene encoding for 14 α -demethylase – azole target) observed in *A. fumigatus* clinical and laboratory isolates with azole resistance
 - Position of point mutation determines azole resistance
 - Some cause pan-resistance, others specific for voriconazole/isavuconazole or posaconazole/itraconazole
- Historically observed with chronic azole exposure

Denning et al. *Bull World Health Organ* 2011;89:864-872.

Denning et al. *Eur Respir J* 2013;41:621-626.

Denning et al. *Med Mycol* 2013;51:361-370.

Seyedmousavi et al. *Drug Resist Updat* 2014;17:37-50.

Cryptic *Aspergillus* Species

- Leading causes of Invasive aspergillosis:
 - *A. fumigatus* (45% – 60%)
 - *A. flavus* (6% – 10%)
 - *A. terreus* (4% – 10%)
 - *A. niger* (2% - 9%)
- TRANSNET (U.S.: 2001 – 2006) - 11% cryptic species among 218 *Aspergillus* isolates
 - *A. lentulus* (1.8%), *A. udagawae* (1.4%), *A. tubingensis* (2.8%), *A. calidoustus* (2.8%)
- FILPOP (Spain: Oct. 2010 & May 2011) – 14.5% cryptic species among 323 *Aspergillus* isolates
 - *A. lentulus* (1.1%), *A. alliaceus* (1.1%), *A. tubingensis* (7.9%), *A. calidoustus* (1.4%)

Aspergillus Section *Fumigati*

(aka *A. fumigatus* Species Complex)

At least 15 reported to have caused disease in humans

Several with reduced azole susceptibility

Aspergillus species

A. felis, *A. fumigatiaffinis*, *A. fumigatus*, *A. fumisynnematus*, *A. lentulus*, *A. novofumigatus*, *A. parafelis*, *A. pseudofelis*, *A. pseudoviridinutans*, *A. viridinutans*

Previously *Neosartorya* species

A. fischeri (*N. fischeri*), *A. hiratsukae* (*N. hiratsukae*), *A. thermomutatus* (*N. pseudofischeri*), and *A. udagawae* (*N. udagawae*)

Species	AMB	ITR	VOR
<i>A. fumigatus</i>	1	2	2
<i>A. lentulus</i>	1	1	4
<i>A. viridinutans</i>	0.25	1	1
<i>A. felis</i>	1	8	8
<i>A. parafelis</i>	2	>16	8
<i>A. pseudofelis</i>	2	>16	8
<i>A. pseudoviridinutans</i>	2	>16	8

Infections include: IPA, osteomyelitis, peritonitis, cerebral aspergillosis, etc.

Other *Aspergillus* Sections/Species

Section	Species	Antifungal Susceptibility
<i>Flavi</i>	<i>A. flavus</i> <i>A. alliaceus</i>	Reduced susceptibility to amphotericin B and echinocandins
<i>Nidulantes</i>	<i>A. nidulans</i> <i>A. delacroixii</i> <i>A. quadrilineatus</i>	Variable amphotericin B susceptibility Azole susceptible
<i>Nigri</i>	<i>A. niger</i> <i>A. tubingensis</i>	Variable azole susceptibility
<i>Terrei</i>	<i>A. terrei</i> <i>A. alabamensis</i> <i>A. citrinoterreus</i>	Reduced amphotericin B susceptibility
<i>Usti</i>	<i>A. calidoustus</i>	Reduced amphotericin B and azole susceptibility
<i>Versicolores</i>	<i>A. sydowii</i> <i>A. versicolor</i>	Variable amphotericin B susceptibility & reduced azole susceptibility

NOT A COMPREHENSIVE LIST!

Objective & Methods

Objective: evaluate the *in vitro* activity of rezafungin against *A. fumigatus* isolates, including azole-resistant isolates, and cryptic *Aspergillus* species with reduced azole susceptibility

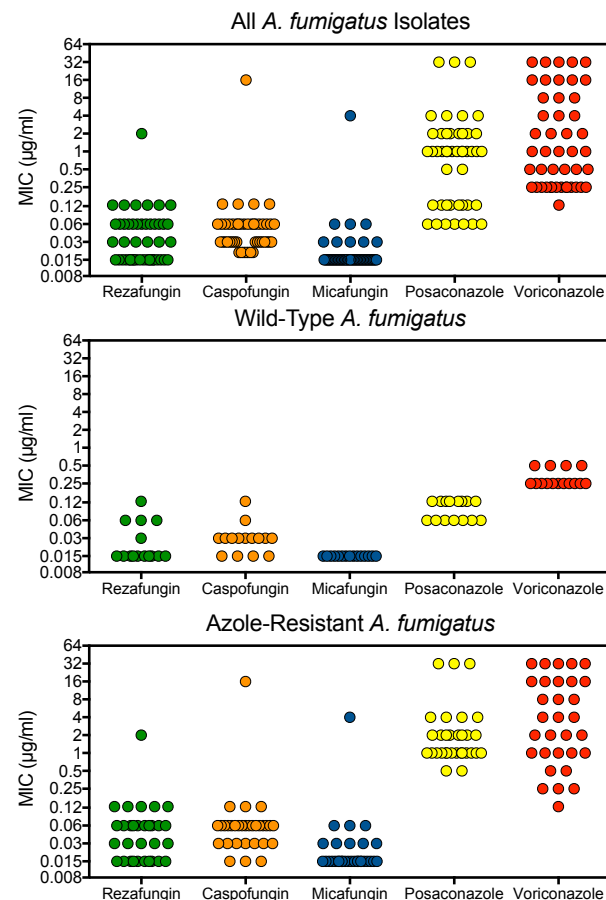
Methods:

- Clinical *Aspergillus* isolates from U.S. institutions
 - Wild-type (n = 15) and azole-resistant (n = 31) *A. fumigatus*
 - Cryptic species: *A. lentulus* (n = 11), *A. udagawae* (n = 5), *A. thermomutatus* (n = 5), *A. calidoustus* (n = 11)
 - Isolates confirmed to the species level by DNA sequence analysis
 - β -tubulin & calmodulin genes and
 - morphologic/phenotypic characteristics (temperature studies)
 - *CYP51A* sequence known for 16 azole-resistant *A. fumigatus* isolates
- Susceptibility testing performed by CLSI M38-A2 broth microdilution methods
 - Rezafungin, caspofungin, & micafungin MECs read at 24 hours
 - Posaconazole & voriconazole MICs read at 48 hours
 - 100% inhibition of growth

Results – *A. fumigatus*

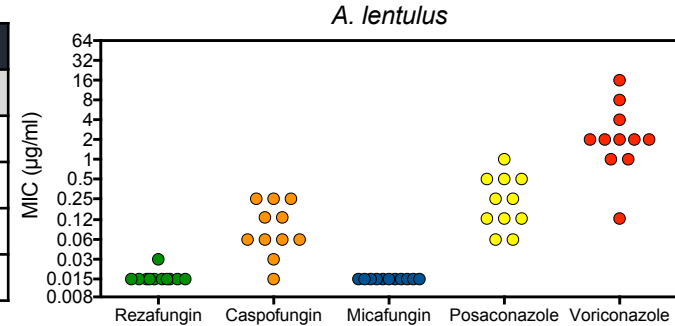
Parameter	Rezafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole
All <i>A. fumigatus</i> isolates (n = 46)					
MEC/MIC Range	≤0.015-2	≤0.015->8	≤0.015-4	0.06->16	0.125->16
MEC/MIC ₅₀	0.03	0.03	≤0.015	1	1
MEC/MIC ₉₀	0.12	0.06	0.03	4	>16
GM MEC/MIC	0.036	0.046	0.020	0.703	1.502
<i>A. fumigatus</i> wild-type isolates (n = 15)					
MEC/MIC Range	≤0.015-0.12	≤0.015-0.06	≤ 0.015	0.06-0.12	0.25-0.5
MEC/MIC ₅₀	≤0.015	0.03	≤0.015	0.12	0.25
MEC/MIC ₉₀	0.06	0.03	≤0.015	0.12	0.5
GM MEC/MIC	0.024	0.029	≤0.015	0.089	0.301
<i>A. fumigatus</i> azole-resistant isolates (n = 31)					
MEC/MIC Range	≤0.015-2	≤0.015->8	≤0.015-4	0.5->16	0.12->16
MEC/MIC ₅₀	0.06	0.06	≤0.015	1	4
MEC/MIC ₉₀	0.12	0.06	0.06	4	>16
GM MEC/MIC	0.043	0.058	0.023	1.91	3.27

1 isolate with elevated echinocandin MICs (unknown *FKS* status)

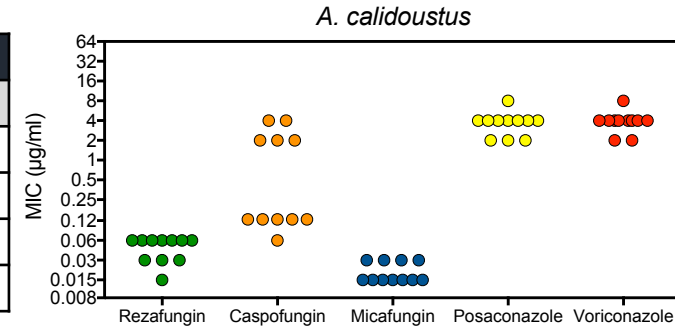


A. lentulus & *A. calidoustus*

Parameter	Rezafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole
<i>A. lentulus</i> isolates (n = 11)					
MEC/MIC Range	≤ 0.015-0.03	≤ 0.015-0.25	≤ 0.015	0.06-1	0.125-16
MEC/MIC ₅₀	≤ 0.015	0.06	≤ 0.015	0.25	2
MEC/MIC ₉₀	≤ 0.015	0.25	≤ 0.015	0.5	8
GM MEC/MIC	0.016	0.084	≤ 0.015	0.219	2



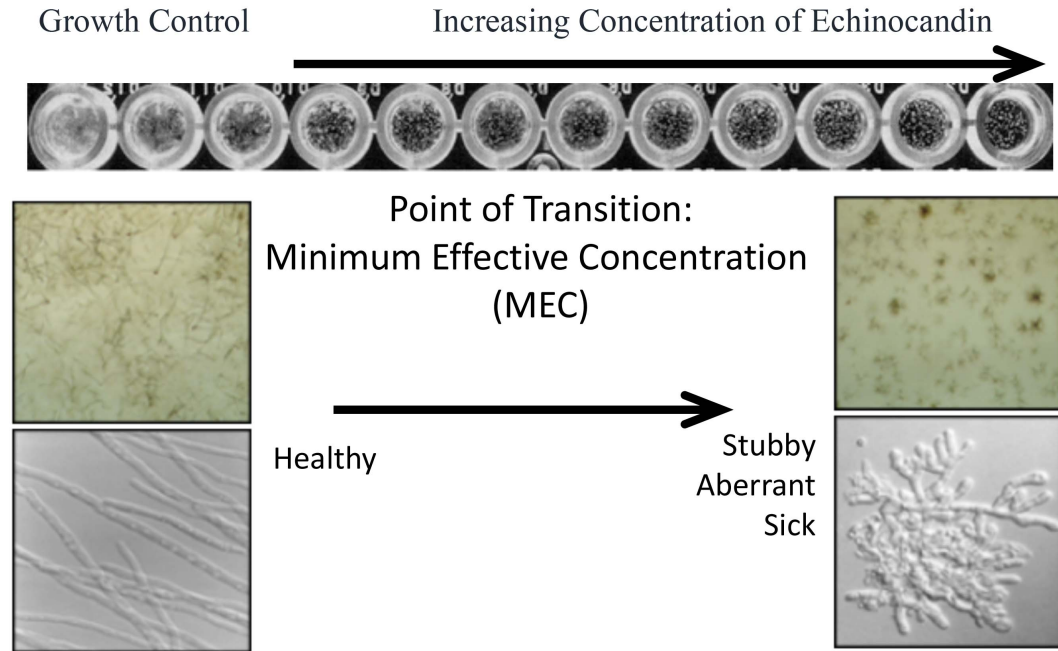
Parameter	Rezafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole
<i>A. calidoustus</i> isolates (n = 11)					
MEC/MIC Range	≤ 0.015-0.06	0.06-4	≤ 0.015-0.03	2-8	2-8
MEC/MIC ₅₀	0.06	0.12	≤ 0.015	4	4
MEC/MIC ₉₀	0.06	4	0.03	4	4
GM MEC/MIC	0.044	0.468	0.019	3.53	3.76



**GM MECs rezafungin and micafungin significant lower than caspofungin ($p < 0.0001$ for both comparisons)

Limitations & Next Steps

- Echinocandin MEC endpoint based on changes in morphology
- Relationship to clinical outcome unknown
- *In vivo* efficacy data needed
 - *CYP51A* mutations only
 - TR₃₄L98H
 - TR₄₆/Y121F/T289A
 - Unknown mechanisms of resistance



Summary

- Rezafungin demonstrated potent in vitro activity against *Aspergillus* species
 - Activity similar to that of caspofungin and micafungin
- Activity maintained against azole-resistant isolates
 - *CYP51A* mutations
 - TR₃₄/L98H & TR₄₆/Y121F/T289A isolates
 - Unknown mechanisms of resistance
- Activity maintained against cryptic *Aspergillus* species
 - Reduced susceptibility to posaconazole & voriconazole
- Further work needed to determine in vivo efficacy and potential clinical utility

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