The Investigational Echinocandin Rezafungin (CD101) Demonstrates Potent In vitro Activity against *Aspergillus fumigatus*, including Azole-Resistant Isolates

N.P. Wiederhold, B.H. Tran, J.B. Locke, P.Daruwala, K. Bartizal
UT Health San Antonio Fungus Testing Laboratory, Cidara Therapeutics, Inc.
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UT Health San Antonio

Contact Information:
Nathan P. Wiederhold, PharmD
wiederholdn@uthscsa.edu

BACKGROUND & OBJECTIVE

- Invasive aspergillosis remains a significant cause of morbidity and mortality in at-risk patients populations
- There is increased concern for infections caused by azole-resistant isolates due to either prolonged clinical use of azoles or environmental exposure to these agents
- Rezafungin (previously CD101) is an investigational echinocandin with a long half-life in humans (>130 hrs) and potent in vitro activity vs. *Candida* and *Aspergillus* species
- Our objective was to further evaluate the in vitro activity of rezafungin against a panel of *Aspergillus fumigatus* isolates, including those with *CYP51A* mutations

MATERIALS & METHODS

- Clinical isolates of *A. fumigatus* received by the Fungus Testing Laboratory were included (15 wild-type and 31 with reduced posaconazole & voriconazole susceptibility)
- Isolates were confirmed to be *A. fumigatus sensu stricto* by DNA sequence analysis of β-tubulin and calmodulin genes as well as morphologic/phenotypic characteristics
- Antifungal susceptibility testing was conducted according to the CLSI M38-A2 standard for rezafungin, caspofungin, micafungin, posaconazole, and voriconazole
- The MEC/MIC$_{50}$, MEC/MIC$_{90}$, and geometric mean (GM) MEC/MIC values were determined

RESULTS (continued)

- Rezafungin demonstrated potent in vitro activity against *A. fumigatus*,
- Activity was maintained against both wild-type and azole-resistant isolates
- The rezafungin GM MEC was 0.024 mg/L against wild-type isolates and 0.043 mg/L against azole-resistant isolates
- Similar values were also observed for caspofungin and micafungin, and the differences in GM MEC values between the echinocandins was not significant
- This activity was maintained regardless of the known *CYP51A* mutations within the azole-resistant isolates
- GM MICs for posaconazole and voriconazole were significantly higher for azole-resistant isolates vs. wild-type isolates ($p < 0.001$ for all comparisons)

CONCLUSIONS

Rezafungin maintained potent in vitro activity against *A. fumigatus* isolates that were resistant to posaconazole or voriconazole, and this activity was similar to what was observed against wild-type isolates. Given the high, front-loaded exposures and long half-life of rezafungin observed in humans as well as the in vitro activity observed in this study, this agent may achieve and maintain pharmacokinetic/ pharmacodynamics targets that could positively influence clinical outcomes in patients with infections due to azole-resistant *A. fumigatus*. Further studies are warranted to determine if the potent in vitro susceptibility profile of rezafungin translates into enhanced efficacy against infections caused by resistant *A. fumigatus* isolates.

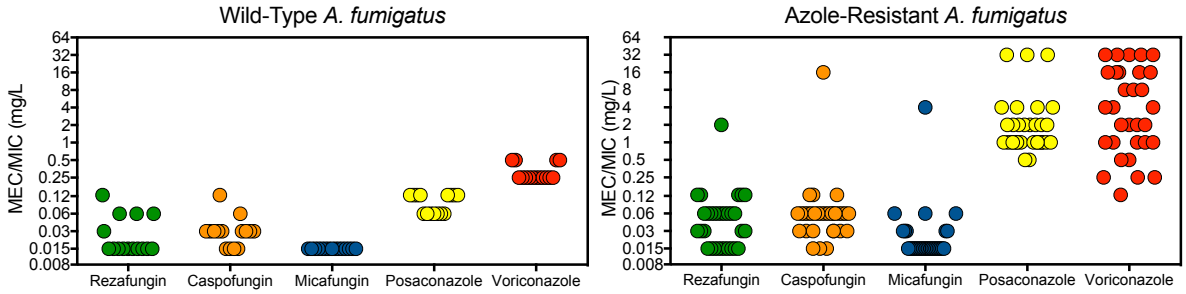

Figure 1. MEC/MIC distributions against wild-type and azole-resistant *A. fumigatus*

Table 1. Antifungal activities (MEC / MIC; mg/L) of CD101 and other agents against *A. fumigatus* clinical isolates.

Parameter	Rezafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole
All *A. fumigatus* 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
Azole Wild-Type *A. fumigatus* (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
Azole-Resistant *A. fumigatus* (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