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O0939 Rezafungin (CD101) demonstrates potent in vitro activity against Aspergillus, including azole-resistant A. fumigatus isolates and cryptic species

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Background: Rezafungin (CD101) is an investigational echinocandin being developed for treatment and prevention of invasive fungal infections, with a long half-life in humans (>100 hours) and potent *in vitro* activity against *Aspergillus* species. Our objective was to further evaluate the *in vitro* activity of rezafungin against *A. fumigatus* isolates, including azole-resistant isolates, and cryptic *Aspergillus* species.

Materials/methods: Clinical isolates of *Aspergillus* received by the Fungus Testing Laboratory at UT Health San Antonio were studied, including 15 wild-type *A. fumigatus*, 31 azole-resistant *A. fumigatus*, 11 *A. lentulus*, 5 each *A. thermomutatus* and *A. udagawae*, and 11 *A. calidoustus* isolates confirmed to the species level by DNA sequence analysis. MECs and MICs were determined by CLSI M38-A2 broth microdilution methods for rezafungin, caspofungin, micafungin, posaconazole, and voriconazole. Differences in geometric mean (GM) MEC/MIC values were assessed for significance by ANOVA with Tukey's post-test for multiple comparisons.

Results: Rezafungin demonstrated potent activity against each *Aspergillus* species tested. GM MECs against *A. fumigatus* isolates were 0.024 and 0.043 mg/L against wild-type and azole-resistant isolates, respectively, and were similar to that of caspofungin (0.026 & 0.058 mg/L) and micafungin (≤0.015 & 0.023 mg/L). Rezafungin was also active against cryptic species, including *A. lentulus* (0.016 mg/L), *A. calidoustus* (0.044 mg/L), *A. thermomutatus* (MEC range ≤0.015-0.25 mg/L) and *A. udagawae* (≤0.015-0.03 mg/L). This was similar to that of caspofungin and micafungin with the exception of *A. calidoustus*, against which rezafungin was significantly more potent than caspofungin (GM MEC 0.044 vs. 0.468 mg/L; p<0.0001). Posaconazole and voriconazole demonstrated limited activity against azole-resistant *A. fumigatus* and the cryptic *Aspergillus* species (GM MIC ranges: posaconazole 0.219-3.53 mg/L; voriconazole 2-3.76 mg/L).

Conclusions: Rezafungin demonstrated potent *in vitro* activity against *Aspergillus* species, including azole-resistant *A. fumigatus* isolates and cryptic species with elevated posaconazole and voriconazole MICs. Given the long half-life of rezafungin in humans and potent *in vitro* activity, rezafungin may achieve and maintain pharmacokinetic/pharmacodynamic targets that may positively influence outcomes in patients with infections due to azole-resistant *Aspergillus*. Additional studies are warranted to determine if this potent *in vitro* activity translates into enhanced efficacy against infections caused by resistant *Aspergillus* isolates.