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### In-vitro activity of F901318 and comparators against clinical isolates of cryptic species of *Aspergillus*

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**Background:** F901318 is a novel antifungal agent of the novel class orotomide that inhibits DHODH, a key enzyme in the pyrimidine biosynthesis. It has excellent activity against *Aspergillus* showing also good results against strains with acquired triazole resistance. The aim of this study was to evaluate the activity of F901318 and other antifungals against clinical isolates of cryptic *Aspergillus* species.

**Material/methods:** 150 strains were tested for antifungal susceptibility following EUCAST and CLSI methodologies. All strains were obtained from clinical samples and identified to species level by sequencing informative targets. Species included in the study were: *A.lentulus* (20), *A.hiratsukae* (7), *A. pseudofischerii* (10), *A.fumigatiaffinis* (10), *A. udagawae* (10), *A.tubingensis* (20), *A. calidoustus* (20), *A.insuetus* (3), *A.keveii* (2), *A.alliaceus* (20), *A.citrinoterreus* (5), *A. aureoterreus* (3), *A.hortai* (2), *A.carneus* (3), *A. ochraceus* (10), *A. sclerotiorum* (5). The antifungals included amphotericin B (range 0.03-16mg/L), voriconazole (0.015-8mg/L), posaconazole (0.015-8mg/L), micafungin (0.004-2mg/L) and F901318 (0.015-8mg/L). *A. flavus* ATCC204304 and *A. fumigatus* ATCC204305 were used as quality control strains. Minimal Inhibitory Concentrations (MICs) for amphotericin B, voriconazole, posaconazole and F901318 and Minimum Effective Concentration (MECs) for micafungin were read after 24 and 48h hours.

**Results:** F901318 showed excellent activity against all species tested (table) with the majority of the isolates inhibited at the lowest dilution (0.015mg/L), MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC<sub>100</sub>, for all strains were 0.015, 0.12 and 0.5mg/L, respectively. Species showing intrinsic resistance to amphotericin B (MIC<sub>90</sub>>16mg/L) such as *A. alliaceus*, *A. ochraceus* or *A. fumigatiaffinis*, were inhibited by F901318 (MIC<sub>90</sub><0.06mg/L). Similarly, species of *A. terreus* complex (amphotericin B MIC<sub>90</sub> = 8mg/L) showed low MICs to F901318 (MIC<sub>90</sub>=0.015). Cryptic species of *A. fumigatus* complex (*A. lentulus*, *A. udagawae*, *A. hiratsukae*, *A. fumigatiaffinis*, *A. pseudofischerii*) with different patterns of resistance to azoles and/or amphotericin B were also inhibited with this new drug (MIC<sub>90s</sub><0,03mg/L). Species of *A.*

*ustus* complex with high MICs to azoles, amphotericin B and echinocandins, showed MICs for F901318  $\leq 0.5$ mg/L.

**Conclusions:** F901318 was active against all cryptic species of *Aspergillus*. F901318 showed good activity against species with intrinsic resistance to amphotericin B and/or azoles. F901318 was the only active drug against all strains tested. More studies are warranted in order to confirm the activity of this promising antifungal drug

		EUCAST (mg/L)					CLSI (mg/L)
		AMB	VCZ	PCZ	MCF (MEC)	F901318	F901318
<i>A. fumigatus</i> complex (57)	MIC <sub>50</sub>	2	2	0.25	0.007	0.015	0.015
	Range	0.03-32	0.5-8	0.03-1	0.004-0.25	0.015-0.03	0.015-0.015
<i>A. ustus</i> complex (25)	MIC <sub>50</sub>	0.5	8	16	0.12	0.12	0.06
	Range	0.12-2	4-8	4-16	0.004-0.5	0.03-0.5	0.015-0.12
<i>A. terreus</i> complex (13)	MIC <sub>50</sub>	8	1	0.12	0.015	0.015	0.015
	Range	1-8	0.5-2	0.03-0.25	0.007-0.03	0.015-0.03	0.015-0.015
Other <i>Aspergillus</i> spp. (35)	MIC <sub>50</sub>	4	1	0.25	0.03	0.03	0.015
	Range	0.06-32	0.25-4	0.03-1	0.007-16	0.015-0.12	0.015-0.12