Activity of F901318 against azole-resistant and difficult-to-treat *Aspergillus* species

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Background

- Invasive aspergillosis is a devastating disease mainly affecting immunocompromised patients
- Since 2002, voriconazole has been the mainstay of therapy for invasive aspergillosis as it was shown to achieve significant better survival compared with treatment with conventional amphotericin B
- The use of azole antifungal agents might be threatened by the emergence of azole resistance in *Aspergillus fumigatus*
- The clinical development of new antifungal drug classes is critical to overcome the current challenges in the management of invasive aspergillosis
- F901318 is a novel antifungal agent with activity against a broad spectrum of fungal pathogens
- It belongs to the new orotomide class targeting dihydroorotate dehydrogenase (DHODH), an important enzyme for pyrimidine biosynthesis

Objective

To investigate the activity of F901318 against a collection of *Aspergillus* isolates with elevated MICs/MECs for azoles, amphotericin B and/or anidulafungin

Table 1: Activity of F901318 against 213 azole-resistant and difficult-to-treat *Aspergillus* isolates with three comparator antifungal agents

			MIC50/MIC90 (Range) (mg/liter) #			
Species	**Mutation**	**Isolates**	**Voriconazole**	**Amphotericin B**	**Anidulafungin**	**F901318**
A. fumigatus	wild type	10	0.5/0.5 (0.25-1)	0.5/1 (0.5-1)	0.016/0.031 (0.016-0.031)	0.063/0.125 (0.031-0.125)
A. fumigatus	TR_{34}/L98H	25	4/16 (2-16)	0.5/1 (0.25-1)	0.016/0.031 (<0.016-0.063)	0.125/0.125 (0.031-0.125)
A. fumigatus	TR_{46}/Y121F/T128A	25	>16/>16 (>16)	0.5/1 (0.5-1)	0.016/0.063 (<0.016-0.063)	0.125/0.125 (0.062-0.25)
A. fumigatus	point mutations*	33	0.5/4 (0.125->16)	1/1 (0.25-2)	0.031/0.125 (<0.008-2)	0.031/0.063 (0.016-0.125)
A. fumigatus	unknown mechanism	50	2/>16 (1->16)	1/2 (0.25-2)	0.031/0.125 (<0.016-0.25)	0.063/0.125 (0.031-0.25)
A. calidoustus		25	8/16 (8-16)	1/2 (0.5-2)	1/4 (0.125-16)	0.25/0.5 (0.125-0.5)
A. flavus		10	4/>16 (1->16)	1/4 (1->16)	0.016/0.031 (0.016-0.031)	0.031/0.063 (0.016-0.063)
A. nidulans		10	0.5/0.5 (0.125-0.5)	1/2 (0.5-4)	0.031/0.063 (<0.016-0.125)	0.125/0.125 (0.063-0.25)
A. tubingensis		25	2/2 (1-4)	0.25/0.25 (0.125-0.5)	0.031/0.063 (<0.016-0.063)	0.031/0.063 (0.016-0.25)

** Isolates with CYP51A point mutations at position G54 (25) M220 (7) and G432 (1)*
 # For anidulafungin, the MECs are displayed

Methods

Susceptiblity testing

- 213 *Aspergillus* isolates, including both clinical and environmental strains
- The preparation of microtiter plates and the susceptibility testing of voriconazole, itraconazole, isavuconazole, posaconazole, amphothericin B and anidulafungin was performed according to the EUCAST broth microdilution reference method (E.Def 9.2)
- For F901318, EUCAST based method, with 100% growth inhibition after 48 hours as endpoint, was determined in duplicate

Statistics

- The mean F901318 MIC was used for analysis
- For comparing the mean MICs of *A. fumigatus* isolates, the Kruskal-Wallis Analysis of Variance was used on 2log transformed MIC values

Results

- F901318 completely inhibited the growth of *Aspergillus* in the tested range, therefore, 100% inhibition was used as endpoint

Activity of F901318

F901318 was active *in vitro* against all *Aspergillus* isolates. The highest MIC was determined for *A. calidoustus*, with 0.5 mg/L

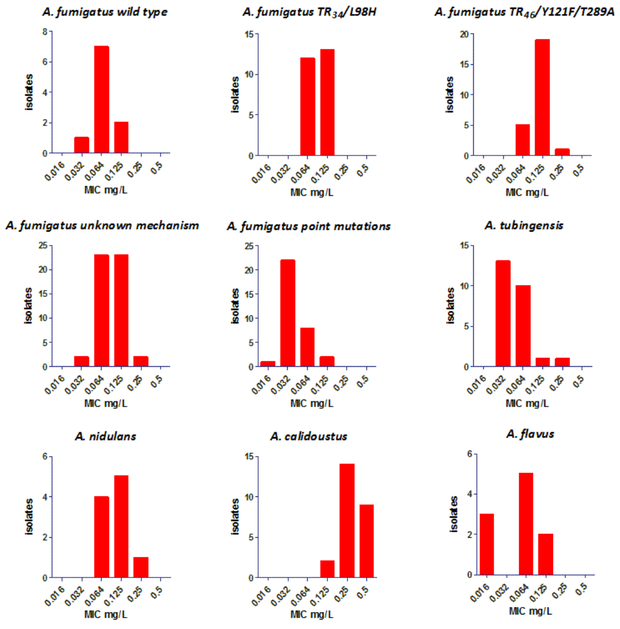
- The MIC of F901318 was in general lower than amphotericin B and the azoles
- The mean F901318 MIC of TR_{46}/Y121F/T128A isolates was one dilution higher than the wild type isolates
- The mean MIC of *A. fumigatus* isolates with *CYP51A* point mutations was one dilution lower than the wild type isolates
- MICs of voriconazole, itraconazole, isavuconazole and posaconazole were elevated for *A. calidoustus* and most *A. fumigatus* isolates

Conclusion

F901318 has potent activity against *Aspergillus fumigatus* isolates with acquired azole resistance due to various known and unknown resistance mechanisms

- F901318 is also active against *A. flavus, A. nidulans* and against the cryptic *Aspergillus* spp. *A. tubingensis* and *A. calidoustus*

Figure 1. F901318 MIC distribution of *Aspergillus* species



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