Molecular identification of Scedosporium *species from CF patients and* in vitro *susceptibility of the novel antifungal compound F901318*

Steeg D[1], Hagen F[1], Chowdhary A[2], Verweij PE[1], Meis JF[1]

[1]Center of Expertise in Mycology, Radboudumc/Canisius Wilhelmina Hospital, NIJMEGEN, Netherlands; [2]Dept of Mycology, VP Chest Institute, DELHI, India

Introduction

Scedosporium spp. and relatives are among the fungi with resistance to many conventional antifungal compounds and which rank second among filamentous fungi colonizing cystic fibrosis (CF) patients. F901318[1], a leading representative of a novel class of drugs, the orotomides, is an antifungal drug in clinical development that demonstrates excellent potency against multidrug-resistant filamentous fungi[2] including *Scedosporium* spp.[3] We aimed to identify a large collection of *Scedosporium* isolates from CF patients and test *in vitro* activity of the novel antifungal drug F901318.

Materials and Methods

Two hundred and forty-one clinical isolates originating from CF-patients were genotyped using amplified fragment length polymorphism (AFLP) fingerprinting. Further identification of clusters was done using Sanger sequencing of the β-tubulin region. Based on these results a new assay was used for rapid molecular identification of Scedosporium isolates to species level using a qPCR melting curve analysis. To test the sensitivity and specificity of this newly developed assay, 281 samples were tested. Susceptibility patterns of 110 isolates were analysed using the Clinical & Laboratory Standards Institute (CLSI) guidelines M38-A2. The novel compound F901318 (F2G, Manchester, UK) in a range of 0.002–2 µg/ml, amphotericin B, itraconazole, voriconazole, posaconazole, and isavuconazole in a range of 0.016–16 µg/ml, and fluconazole in a range of 0.064–64 µg/ml were tested.

Results

AFLP fingerprinting analysis and Sanger sequencing identified six *Scedosporium* species: *Lomentospora prolificans* (*n*=19), *Pseudallescheria boydii* (*n*=71), *Pseudallescheria ellipsoidea* (*n*=34), *Pseudallescheria minutispora* (*n*=1), *Scedosporium apiospermum* (*n*=94), and *Scedosporium aurantiacum* (*n*=21). Susceptibility testing of 110 isolates against the novel drug F901318 showed excellent *in vitro* activity against *Scedosporium* spp. and *Lomentospora prolificans* (GM MIC 0.1 µg/ml). The low MICs were in contrast to conventional compounds that showed higher MIC values (GM MIC >24 µg /ml). Conventional compounds had no *in vitro* activity against *Lomentospora prolificans* (Table).

Scedosporium (no. of strains)		MIC (µg/ml)						
		F901318	AMB	FLC	ITC	VRC	POS	ISA
Total (*n*=110)	Range	0.008--0.5	0.25->16	32->64	16->16	0.25->16	0.5->16	4->16
	MIC_{50}	0.063	16	>64	>16	1	2	16
	MIC_{90}	0.25	>16	>64	>16	16	>16	>16
	GM	0.093	8.36	101	31	2	3	13
	Mode	0.125	16	>64	>16	1	1	16
S. apiospermum (*n*=41)	Range	0.016-0.5	0.25-16	32->64	16->16	0.25-4	0.5->16	4->16
	MIC_{50}	0.063	4	>64	>16	1	2	16
	MIC_{90}	0.25	16	>64	>16	2	4	>16
	GM	0.073	3	120	31	1	2	15
	Mode	0.125	16	>64	>16	1	2	16
P. boydii (*n*=35)	Range	0.008-0.25	1->16	32->64	16->16	0.5-4	0.5->16	4->16
	MIC_{50}	0.063	16	64	>16	0.5	1	8
	MIC_{90}	0.125	32	128	>16	1	2	16
	GM	0.062	11	74	30	0.728	1	8
	Mode	0.063	16	64	>16	0.5	1	8
P. ellipsoidea (*n*=8)	Range	0.016-0.125	2->16	64->64	>16	0.5->16	2->16	8->16
	MIC_{50}	0.063	16	>64	>16	1	>16	16
	MIC_{90}	0.125	>16	>64	>16	4	>16	>16
	GM	0.058	12	117	32	2	16	19
	Mode	0.125	16	>64	>16	1	>16	>16
S. aurantiacum (*n*=12)	Range	0.016-0.5	16->16	32->64	>16	0.5-2	1->16	8->16
	MIC_{50}	0.125	16	>64	>16	1	2	16
	MIC_{90}	0.5	>16	>64	>16	2	32	16
	GM	0.118	20	102	32	1	4	16
	Mode	0.031	16	>64	>16	1	2	16
L. prolificans (*n*=14)	Range	0.063-0.25	>16	>64	>16	>16	>16	>16
	MIC_{50}	0.125	>16	>64	>16	>16	>16	>16
	MIC_{90}	0.25	>16	>64	>16	>16	>16	>16
	GM	0.106	24	128	29	25	32	28
	Mode	0.063	>16	>64	>16	>16	>16	>16

Conclusion

F901318 demonstrated potent *in vitro* activity against *Scedosporium* species and *L. prolificans* confirming an earlier study.[3] Clinical studies are warranted to evaluate the efficacy of F901318 against difficult to treat *Scedosporium* infections.

References

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