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Activity of SCY-078 against *Candida* spp. obtained by EUCAST and CLSI procedures

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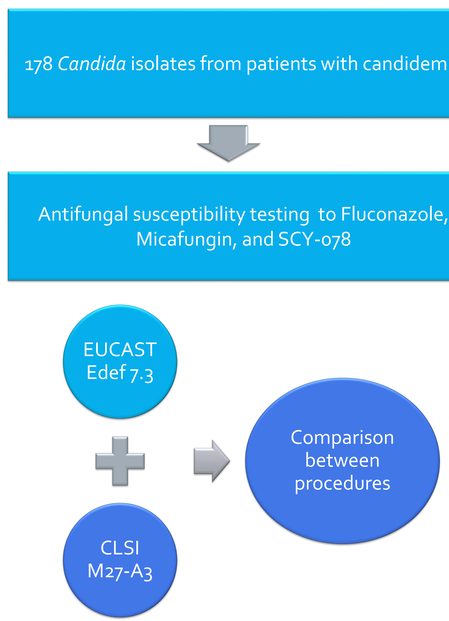
INTRODUCTION AND PURPOSE

We studied the antifungal activity of SCY-078 (an orally bioavailable 1,3-beta-D-glucan synthesis inhibitor), micafungin and fluconazole against 178 yeasts isolates causing fungemia in patients recently admitted to Gregorio Marañón hospital in Madrid, Spain, from Jan 2014 to Dec 2015.

MATERIAL AND METHODS



CONCLUSION

- SCY-078 is a promising drug with high *in vitro* antifungal activity against *Candida* and other yeast isolates causing fungemia.
- CLSI and EUCAST standard procedures were comparable and suitable for antifungal susceptibility testing of this compound.

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RESULTS

SCY-078 and micafungin showed potent *in vitro* activity against the isolates as shown by the low MIC values obtained by CLSI and EUCAST, respectively (Table 1). SYC-078 demonstrated significantly lower MIC values than micafungin against *C. parapsilosis* (GM values 0.206 mg/L vs 0.458 mg/L respectively) and non-*Candida* isolates (GM values 4.66 mg/L vs 9.33 mg/L, respectively) by EUCAST, and this phenomenon is also observed by CLSI methodology. By contrast, micafungin demonstrated significantly lower MIC values compared to SCY-078 for the remaining species (MIC range 0.008 – 0.053 mg/L vs 0.029 – 0.556 mg/L, respectively), regardless of the procedure used (Table 1). *C. albicans* and non-*Candida* isolates showed the highest and lowest susceptibility, respectively, to both SCY-078 and micafungin.

SCY-078 and micafungin showed attenuated activity against the *Candida* isolates with mutations in the *fks* genes compared to wild-type isolates (Table 2). However, differences were observed both in the overall susceptibility of the isolates and in the impact of *fks* mutations between both drugs. The MIC_{50} of micafungin against echinocandin-resistant isolates increased a mean of 15 fold (range 4 - 133) compared to the wild-type isolates. By contrast, the individual MICs of SCY-078 only increased by 2 fold (range 1 - 32).

Individual mutations in *fks* genes had different effects on the two compounds activity. While the F641S mutation in the one *C. albicans* isolate tested appeared to have a greater effect on the activity of SCY-078 compared to micafungin, among the *C. glabrata* isolates, mutations in *fks* genes had a greater impact on the activity of micafungin compared to SCY-078 (Table 2).

We did not find cross-resistance between SCY-078 and fluconazole in the panel of fluconazole-resistant isolates. The geometric mean MIC of SCY-078 against this set of isolates was higher than the overall MIC due to the high proportion of *C. krusei* (Table 1).

Table 1. Antifungal activity (GM) of fluconazole, micafungin, and SCY-078 against the 178 isolates studied by CLSI-M27A3 and EUCAST EDef 7.3 procedures.

CLSI M27-A3	Fluconazole		Micafungin		SCY-078	
	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST
C. albicans (55)	0.178	0.273	0.008	0.016	0.029	0.065
C. parapsilosis (33)	0.422	0.5	0.458	0.656	0.206	0.266
C. glabrata (31)	2.287	7.153	0.011	0.030	0.168	0.365
C. tropicalis (8)	0.25	0.353	0.035	0.051	0.066	0.353
C. krusei (12)	10.07	22.627	0.051	0.06	0.395	0.445
Other *Candida* spp. (26)	1.026	1.205	0.036	0.053	0.369	0.556
Non-*Candida* (13)	10.886	20.88	9.33	11.61	4.66	7.19
FLC-R *Candida* isolates (24)	19.5	24.6	0.043	0.049	0.291	0.423
fks-mutant *Candida* isolates (9)	0.925	1.714	0.169	0.734	0.338	0.793

Table 2. MICs of micafungin and SCY-078 against the *Candida* isolates with *fks* mutations.

Species	Mutation	Region	CLSI				EUCAST			
			Micafungin		SCY-078		Micafungin		SCY-078	
			MIC	Fold-Δ	MIC	Fold-Δ	MIC	Fold-Δ	MIC	Fold-Δ
C. albicans	F641S	HS1 *fks1*	0.125	17.8	1	32.2	1	66.6	2	32
C. glabrata	delF649	HS1 *fks2*	0.03	4.3	0.25	8	1	66.6	1	4
C. glabrata	delF658	HS1 *fks2*	0.125	17.8	2	16	2	133	4	16
C. glabrata	S663P / D666Y	HS1 *fks2*	0.125	17.8	0.125	1	2	133	0.5	2
C. glabrata	delF658	HS1 *fks2*	0.125	17.8	1	4	1	66.6	4	16
C. glabrata	S663Y	HS1 *fks2*	0.5	71.4	0.5	2	0.5	33.3	0.25	1
C. tropicalis	S645F	HS1 *fks1*	2	133.3	0.06	1	2	64.5	0.25	1
C. tropicalis	F641L	HS1 *fks1*	0.125	8.3	0.125	2	0.125	4	0.5	2
C. tropicalis	R647G	HS1 *fks1*	0.125	8.3	0.25	4	0.125	4	0.25	1

Fold-Δ= Ratio of each individual MIC/MIC_{50} of the overall wild-type isolates of each species.

The MIC for all the species were lower by CLSI than for EUCAST $P<0.001$. Overall essential agreement between CLSI and EUCAST was 90.3%. However, the agreement was higher for *C. albicans*, *C. parapsilosis* and non-*Candida* than for *C. tropicalis* and other *Candida* spp. The essential agreement is shown in Table 3.

Table 3. Essential agreement. Percentage of strains in which the MIC obtained by EUCAST differed ±1, and ±2 log_2 dilutions over the MIC obtained by CLSI

	C. albicans	*C. parapsilosis*	*C. glabrata*	*C. tropicalis*	*C. krusei*	*Candida* spp.	Other yeasts
Within ±1 log2	72.7	97	54.9	50	91.7	69.2	61.5
Within ±2 log2	94.5	97	87.2	50	91.7	84.5	69.2