

00176 Ceragenin CSA-131 proved *in vitro* antifungal activity against opportunistic yeasts and moulds showing reduced susceptibility to azoles or echinocandinsPilar Escribano*¹, Sara Lopez¹, Judith Diaz-Garcia¹, Patricia Muñoz¹, Emilio Bouza Santiago¹, Jesus Guinea Ortega¹¹ Gregorio Marañón Hospital, Madrid, Spain

Background: Antifungal resistance poses a problem in clinically relevant yeast and molds isolates making necessary the search of new antifungals. Ceragenins (cationic steroidal antimicrobial; CSAs) create transient pores in the membrane resulting in cell death of a broad spectrum of microorganisms, including fungi. However, little is known about the activity CSAs against fungal isolates showing resistance to antifungals. We studied the *in vitro* activity of three CSAs against yeasts and molds showing resistance to azoles and echinocandins.

Materials/methods: We studied 207 clinical isolates with reduced susceptibility to azoles or echinocandins: 79 *Candida* spp (fluconazole resistance, n=44; echinocandin FKS mutants, n=35), 20 non-*Candida* spp yeasts (*Rhodotorula* spp, n=6; *Trichosporon* spp, n=7; *C. neoformans*, n=7), 10 *cyp51A* mutant *Aspergillus fumigatus*, and 98 Mucorales. Antifungal susceptibility to CSAs [CSA44, CSA90, and CSA131] was obtained according to EUCAST EDef 9.3.1. The final concentration of CSAs in the plates ranged from 0.125 mg/L to 64 mg/L. MICs against molds were defined as the concentration of CSAs that completely inhibited fungal growth visually inspected after 24 hours (Mucorales) or 48 hours (*A. fumigatus*) of incubation. MICs against yeasts were defined as the lowest concentration of CSAs that resulted in inhibition of 50% of growth in comparison with a drug-free control growth.

Results: As shown in the table, CSAs showed systematically lower MICs against yeasts than against molds. MICs distributions of the three CSAs were non-truncated with the exception of Mucorales. Overall, the three compounds were very active against fluconazole-resistant *Candida* spp, with CSA-131 showing the highest activity (CSA-131 GM=1 vs. fluconazole GM=33; $P<0.05$). Furthermore, CSA-131 showed *in vitro* activity against echinocandin-resistant *Candida* spp (GM=1.1, range=1-2). Non-*Candida* spp presented reduced susceptibility to CSAs. CSA-131 inhibited the growth of *cyp51A* *A. fumigatus* mutant isolates; in contrast, the three CSAs showed limited *in vitro* activity against Mucorales although CSA-131 showed partial activity.

Species	Minimum Inhibitory Concentration (mg/L)					
	CSA-44		CSA-90		CSA-131	
	GM	Range	GM	Range	GM	Range
Fluconazole-resistant <i>Candida</i> spp	2.8	2-8	3.9	2-8	1	1-2
Echinocandin-resistant <i>Candida</i> spp	4	2-8	4.3	2-8	1.1	1-2
Non- <i>Candida</i> spp	2.2	2-4	2	0.25-4	1.1	0.5-4
<i>A. fumigatus</i>	16	16	28	16-32	2	2
Mucorales	9.1	2->64	18	4->64	4	1->64

GM: geometric mean. Fluconazole resistant *Candida* spp [*C. albicans* (n=4); *C. parapsilosis* (n=3); *C. guilliermondii* (n=3); *C. krusei* (n=18); *C. lusitanae* (n=2); *C. glabrata* (n=13) and *C. tropicalis* (n=1)]; echinocandin FKS mutants *Candida* spp [*C. krusei* (n=1); *C. glabrata* (n=32) and *C. tropicalis* (n=2)]. Mucorales [*Cunninghamella* spp (n=8); *Lichtheimia corymbifera* (n=8); *L. ramosa* (n=26); *Mucor circinelloides* (n=13); *Rhizomucor pusillus* (n=7); *Rhizopus arrhizus* (n=24); *R. microspores* (n=8); *Syncephalastrum* spp (n=4)].

Conclusions: CSA-131 showed *in vitro* activity against antifungal resistant *Candida*, non-*Candida*, and *A. fumigatus cyp51A* mutant isolates. In contrast, ceragenins showed marginal *in vitro* activity against Mucorales. Ceragenins are promising compounds for the treatment of patients with invasive fungal infections.

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