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In vitro combination of isavuconazole with echinocandins against Aspergillus spp.

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Background: Isavuconazole is an azole recently available in Europe as a first-line therapy for invasive aspergillosis. Nevertheless, azole resistance in *Aspergillus spp.* already exists and itraconazole and/or voriconazole-resistant isolates may be cross-resistant to isavuconazole. Therefore, we examined the *in vitro* combination of isavuconazole with caspofungin, micafungin and anidulafungin against azole-susceptible and –resistant *Aspergillus fumigatus, A. flavus, A. nidulans*, *A. terreus,* and *A. niger.*

Material/methods: 30 *Aspergillus spp.* (azole-susceptible *A. fumigatus* (n=5), azole-resistant *A. fumigatus* (n=5), *A. flavus* (n=5), *A. nidulans* (n=5), *A. terreus* (n=5), and *A. niger* (n=5)) were selected. The *in vitro* combinations (isavuconazole-caspofungin or micafungin or anidulafungin) were tested using two techniques: a two-dimensional checkerboard microdilution method (based on EUCAST reference method), and an agar based diffusion method (E-test). MICs were determined visually after 48h of incubation at 35°C. In the EUCAST method, a complete (100%) and a partial (50% or MEC) inhibition endpoint was used for isavuconazole, the echinocandins, and the combination. In the E-test method, a complete inhibition (100%) endpoint was determined for isavuconazole, a partial inhibition (50%) for the echinocandins, and a complete and a partial inhibition for the combination. Drug interactions were defined as synergistic (Fractional Inhibitory Concentration Index (FICI)≤0.5), indifferent (FICI]0.5-4[) or antagonistic (FICI≥4).

Results: Considering a complete inhibition endpoint, we found an indifference for all the strains with the EUCAST method: FICI range was [0,625-2,001] for the isavuconazole-caspofungin combinations, [1,001-2,001] for the isavuconazole-micafungin combinations, and [0,501-2,001] for the isavuconazole-anidulafungin combinations. With a less stringent partial inhibition endpoint, an indifferent effect was mainly observed but a synergy was noticed in 7/30 (23,3%) strains (1 azole-resistant *A. fumigatus*, 2 azole-susceptible *A. fumigatus*, 3 *A. niger*, 1 *A. terreus*) for the

isavuconazole-caspofungin combinations, in 11/30 (36,7%) (1 azole-susceptible *A. fumigatus*, 4 azole-resistant *A. fumigatus*, 4 *A. niger*, 1 *A. terreus*, 1 *A. flavus*) for the isavuconazole-micafungin combinations, in 5/30 (16,7%) (1 azole-susceptible *A. fumigatus*, 3 *A. niger*, 1 *A. terreus*) for the isavuconazole-anidulafungin combinations. Considering a complete inhibition endpoint, we found an indifference for all the strains with the E-test for the isavuconazole-micafungin combinations (FICI [0,917-1,349]) and the isavuconazole-anidulafungin combinations (FICI [0,508-1,502]). For the isavuconazole-caspofungin combinations, we highlighted an indifference in 24/30 strains (80%) (FICI [0,630-3,940]), a synergy in 4/30 strains (13,3%) (3 *A. terreus*, 1 azole-susceptible *A. fumigatus*) (FICI [0,084-0,424]), and an antagonism in 2/30 strains (6,7%) (2 *A. niger*) (FICI [4,149-5,601]). These results were similar using a partial endpoint.

Conclusions: These *in vitro* findings mainly showed that combination of isavuconazole and echinocandins is indifferent for azole-susceptible and –resistant *A. fumigatus*, *A. flavus, A. nidulans*, *A. terreus,* and *A. niger*. Antagonism was almost never observed. Further *in vivo* evaluation of these combinations are warranted.