#P1712

In vitro combination of Isavuconazole with Echinocandins against Azole-Susceptible and –Resistant *Aspergillus spp.*

Courbin V. (1,4), Raffetin A. (1,3), Jullien V. (1,2), Dannaoui E.(1,2)

(1)Hôpital Européen Georges Pompidou, Paris, France ; (2)Université René Descartes, Paris V ; (3)Université Pierre et Marie Curie, Paris VI ; (4)Université Paris-Sud, Paris XI, Chatenay-Malabry

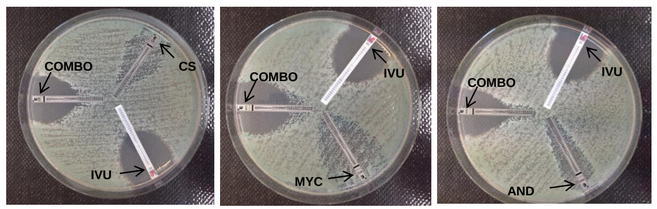
27th ECCMID
Vienna, Austria
22 – 25 April 2017

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.* were selected : azole-susceptible *A. fumigatus* (n=5), azole-resistant *A. fumigatus* (n=5 : 2 Isavuconazole-susceptible and 3 Isavuconazole-resistant), *A. flavus* (n=5), *A. nidulans* (n=5), *A. terreus* (n=5) and *A. niger* (n=5).
- 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 visually determined 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).
- Example (E-test) : combination of Isavuconazole with Echinocandins against azole-susceptible *Aspergillus fumigatus* :



CS = caspofungin ; MYC = micafungin ; AND = anidulafungin ; IVU = isavuconazole.
COMBO = for the combination study, an isavuconazole E-test strip was placed on the RPMI agar and then removed after 1h of incubation at 35°C. An echinocandin E-test strip was placed over demarcation left from the previous strip (on the minimal value) .

Results

- **E-test** : These results are similar using a complete or a partial inhibition endpoint.

	Synergy (FICI ≤ 0,5)	Indifference (FICI]0,5 - 4[)	Antagonism (FICI ≥ 4)
		Combination isavuconazole-micafungin :	
Aspergillus spp. (n=30)	0	**30 (100%)** FICI [0,917 – 1,349]	0
		Combination isavuconazole-anidulafungin :	
Aspergillus spp. (n=30)	0	**30 (100%)** FICI [0,508 – 1,502]	0
		Combination isavuconazole-caspofungin :	
Aspergillus spp. (n=30)	4 (13,3%) FICI [0,084 – 0,424]	**24 (80%)** FICI [0,630 – 3,940]	2 (6,7%) FICI [4,149 – 5,601]

- **EUCAST reference method** :
  - Considering a complete inhibition endpoint : **indifference** for all the strains.
  - Considering a partial inhibition endpoint :

	Synergy (FICI ≤ 0,5)	Indifference (FICI]0,5 - 4[)	Antagonism (FICI ≥ 4)
		Combination isavuconazole-micafungin :	
Aspergillus spp. (n=30)	11 (36,7%)	**19 (63,3%)**	0
		Combination isavuconazole-anidulafungin :	
Aspergillus spp. (n=30)	5 (16,7%)	**25 (83,3%)**	0
		Combination isavuconazole-caspofungin :	
Aspergillus spp. (n=30)	7 (23,3%)	**23 (76,7%)**	0

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.

Contact : Eric DANNAOUI, HEGP, Unité de Parasitologie-Mycologie, Service de Microbiologie, Paris, France Email: eric.dannaoui@aphp.fr