O423
1-hour Oral Session
Challenges in antifungal treatment

Isavuconazole versus caspofungin in the treatment of candidaemia and other invasive Candida infections: the ACTIVE trial

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Background: Isavuconazole, a new triazole with broad-spectrum antifungal activity, was compared to caspofungin followed by oral voriconazole in a Phase 3, randomized, double-blind, multinational clinical trial (ACTIVE; NCT00413218) for safety and efficacy in patients with proven candidemia or invasive candidiasis (IC).

Material/methods: Adults were randomized 1:1 to isavuconazole (200mg IV TID for two days, followed by 200mg IV QD) or caspofungin (70 mg IV QD on Day 1, followed by 50 mg IV QD) for a maximum of 56 days. After day 10, qualified patients could switch to oral isavuconazole (isavuconazole-arm) or voriconazole (caspofungin-arm). Documentation of infection and outcomes were assessed by an independent Data-Review Committee. Daily blood cultures were collected through Day 9. Primary efficacy endpoint was successful overall response (based on successful clinical and mycological responses, and no use of alternative systemic antifungal therapy post end of treatment) at the end of IV therapy (EOIV) in patients with proven infection who received ≥1 dose of study drug (modified intent-to-treat [mITT] population). The pre-specified non-inferiority margin was 15%. The key secondary outcome (mITT) was successful overall response at end of treatment + 2 weeks (FU1). All-cause mortality (ACM) at Day 14 and 56 and safety were also assessed.

Results: 450 patients were randomized; 400 patients comprised the mITT population. Baseline characteristics were balanced between the groups. The primary endpoint of successful overall response at EOIV (isavuconazole, n/N=120/199 [60.3%]; caspofungin, n/N=143/201 [71.1%]; adjusted difference [95%CI]: -10.8 [-19.9, -1.8]) did not meet the noninferiority margin. The key secondary endpoint, all-cause mortality and other outcomes were similar in both arms (Table). Safety results were comparable between the groups (Table).

Conclusions: The primary endpoint was not met; however, the key secondary endpoint was similar between the two groups. Both drugs were safe and well tolerated.

Table. Patient characteristics and outcomes

Parameter **mITT**	**Isavuconazole (n=199)**	**Caspofungin (n=201)**	**Adjusted difference* % (95% CI)**
Mean APACHE II score	14	14	
Baseline neutropenia, n (%)	24 (12.1)	24 (11.9%)	
Infecting pathogen, n (%)			
C. albicans	84 (42.2)	74 (36.8)	
C. tropicalis	41 (20.6)	38 (18.9)	
C. parapsilosis	26 (13.1)	27 (13.4)	
C. glabrata	22 (11.1)	21 (10.4)	
IV duration [days], mean (SD)	12.8 (7.6)	14 (8.7)	
Successful overall response, n (%)			
FU1	109 (54.8)	115 (57.2)	-2.7 (-12.2, 6.8)
All-cause mortality, n (%)			
Day 14	29 (14.6)	25 (12.4)	2.5 (-3.8, 8.9)
Day 56	61 (30.7)	60 (29.9)	1.4 (-7.1, 10)
Breakthrough fungal infections	5 (2.5)	15 (7.5)	
Safety	**(n=220)**	**(n=220)**	

Safety			
TEAEs	209 (95.0)	208 (94.5)	
Study-drug related TEAEs	78 (35.5)	71 (32.3)	

APACHE II, Acute Physiology and Chronic Health Evaluation II; TEAEs, Treatment-emergent adverse events