P0266a

Poster Session I

Antibiotic choices: clinical studies

Efficacy and safety of ceftolozane/tazobactam versus meropenem in the treatment of complicated intra-abdominal infections (cIAI) in hospitalised adults: results from the phase 3 aspect-cIAI trial

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Objective: Ceftolozane/tazobactam (C/T) is a novel antibacterial agent with activity against common Gram-negative pathogens, including extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and drug-resistant *Pseudomonas aeruginosa*. The objective was to compare the efficacy and safety of intravenous (IV) ceftolozane/tazobactam plus metronidazole (C/T+MTZ) to meropenem (MER) for the treatment of cIAI in a large phase 3 global, randomised, double-blind trial (NCT01445665 and NCT01445678).

Methods: Hospitalised adult patients with cIAI who required surgical intervention were randomised to receive C/T 1.5 g (containing 1000 mg ceftolozane and 500 mg tazobactam) every 8 hours (q8h) + MTZ (500 mg q8h) or MER (1 g q8h) + placebo for 4-10 days. The primary and key secondary objectives were to demonstrate non-inferiority (NI) of C/T+MTZ to MER based on the clinical cure rate at the test-of-cure (TOC) visit (26-30 days after initiation of therapy). For the European Medicines Agency (EMA), this was tested using a NI margin of 12.5% at a 1-sided alpha of 0.005 in the clinically evaluable (CE) and intent-to-treat (ITT) populations. For the US Food and Drug Administration (FDA), this was tested using a NI margin of 10% at a 1-sided alpha of 0.025 in the microbiological ITT (MITT) and microbiologically evaluable (ME) populations. Per-pathogen responses and safety were also evaluated.

Results: Overall, 993 patients were randomised to receive C/T+MTZ (n = 487) or MER (n = 506); 774 (77.9%) were included in the CE population. The clinical cure rates at the TOC visit with C/T+MTZ were non-inferior to those with MER for the CE, ITT, MITT and ME populations (**Table**).

Enterobacteriaceae were the most common pathogens, with a C/T MIC_{90} of 1 mg/L; the overall ESBL rate was 7.2%. Per-pathogen microbiological eradication rates were comparable between groups (**Table**). Clinical cure for ESBL-producing Enterobacteriaceae was achieved in 25/29 (86.2%) and 24/29 (82.8%) patients in the C/T+MTZ and MER treatment groups, respectively.

The most commonly reported AEs in the C/T+MTZ and MER groups were nausea (7.9% vs 5.8%), diarrhoea (6.2% vs 5.0%), and pyrexia (5.2% vs 4.0%). Drug-related serious AEs were rare, occurring in only 1 subject in each treatment group (both *Clostridium difficile* infection that resolved). There were 11 deaths in the C/T+MTZ group and 8 deaths in the MER group; none were considered drug-related.

Conclusions: C/T+MTZ demonstrated comparable clinical cure rates to MER for the treatment of cIAI at the TOC visit, achieving non-inferiority in multiple populations with pre-specified statistical criteria. C/T+MTZ was generally safe and well tolerated. These data suggest that C/T+MTZ is a useful treatment regimen for patients

with cIAI.

Analysis at the TOC visit	Population	C/T+MTZ % (n/N)	MER % (n/N)	Difference % (confidence interval [CI])
Overall clinical cure	CE	94.1 (353/375)	94.0 (375/399)	0 (-4.2 to 4.3)[a]
	ITT	83.8 (399/476)	85.8 (424/494)	-2.2 (-8.0 to 3.4)[a]
	MITT	83.0 (323/389)	87.3 (364/417)	-4.2 (-8.9 to 0.5)[b]
	ME	94.2 (259/275)	94.7 (304/321)	-1.0 (-4.5 to 2.6)[b]
Microbiological eradication[b]				
Gram-negative aerobes	ME	96.3 (234/243)	95.4 (269/282)	0.9 (-2.8 to 4.5)
Escherichia coli		96.0 (193/201)	95.1 (214/225)	0.9 (-3.3 to 5.1)
Klebsiella pneumoniae		100 (28/28)	88.0 (22/25)	12.0 (-2.4 to 30.0)
P. aeruginosa		100 (25/25)	100 (28/28)	0 (-13.3 to 12.1)
Gram-negative anaerobes		98.2 (107/109)	97.8 (134/137)	0.4 (-4.5 to 4.6)
Gram-positive aerobes		92.9 (131/141)	94.6 (158/167)	-1.7 (-7.7 to 3.8)
Gram-positive anaerobes		100 (34/34)	93.9 (46/49)	6.1 (-4.8 to 16.5)

[a] EMA requirement for demonstration of non-inferiority (99% CI)

[b] US FDA requirement for demonstration of non-inferiority (95% CI)