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2-hour Oral Session

New antibacterial agents - phase 2 and phase 3 clinical trials

Efficacy and safety of ceftolozane/tazobactam versus levofloxacin in the treatment of complicated urinary tract infections (cUTI): a European subgroup analysis

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Objective: Ceftolozane/tazobactam is a novel antibacterial with activity against Gram-negative pathogens, including most extended-spectrum β-lactamase-producing Enterobacteriaceae and drug-resistant *Pseudomonas aeruginosa*. Ceftolozane/tazobactam was compared to levofloxacin for the treatment of complicated lower urinary tract infection (cLUTI)/pyelonephritis in a pooled analysis of 2 identical global, randomised, double-blind Phase 3 trials (NCT01345929 and NCT01345955). Safety and efficacy were evaluated in the subgroup of patients enrolled in Europe. Analyses were conducted as per the European Medicines Agency's Guidelines for cUTI trials [1].

Methods: Hospitalised patients in Europe aged ≥18 years with pyuria and clinical symptoms of cUTI/pyelonephritis requiring intravenous therapy were randomised to ceftolozane/tazobactam 1.5g every 8 hours or levofloxacin 750mg/day for 7 days. The primary endpoint was microbiological eradication at the test-of-cure visit (5-9 days after end of therapy) in the microbiologically evaluable (ME) population. Other analyses included patient demographics, clinical response and per-pathogen microbiological eradication rates. Safety was evaluated in all treated patients.

Results: Of 812 patients enrolled in Europe, 608 (74.9%) had positive baseline urine cultures (mMITT population; n=304 per arm) and 544 (67.0%) qualified for the ME population (ceftolozane/tazobactam, n=269; levofloxacin, n=275). Baseline characteristics were similar between treatment groups (mean age, 47.6 years; 72.6% female; 81.1% pyelonephritis). *Escherichia coli* was the most predominant uropathogen (76.5%). In the primary analysis, ceftolozane/tazobactam demonstrated significantly higher microbiological eradication rates compared to levofloxacin in the ME population (84.8% vs 75.6% [99% CI, 0.3-17.8]). Ceftolozane/tazobactam also showed significantly higher microbiological eradication rates than levofloxacin in patients with Enterobacteriaceae (Table). Clinical cure rates in the ME population for ceftolozane/tazobactam versus levofloxacin were 95.2% versus 92.4%.

Analysis endpoints (Test-of-Cure)	Population	Ceftolozane/tazobactam% (n/N)	Levofloxacin % (n/N)	Difference % (95%CI)
Per-pathogen microbiological eradication rate	ME			
Enterobacteriaceae		88.2 (217/246)	76.7 (194/253)	11.5 (4.9,18.1)
Escherichia coli		90.0 (181/201)	78.6 (169/215)	11.4 (4.5,18.3)
Klebsiella pneumoniae		81.0 (17/21)	55.0 (11/20)	26.0 (-2.5,49.7)
Pseudomonas aeruginosa		83.3 (5/6)	45.5 (5/11)	37.9 (-9.9,65.7)

Drug-related adverse events (AEs) occurred in 8.8% and 11.4% of the ceftolozane/tazobactam and levofloxacin groups, respectively. The most common AEs in patients receiving ceftolozane/tazobactam were headache (5.0%) and nausea (2.3%). There was 1 death in the ceftolozane/tazobactam group (due to bladder cancer) unrelated to treatment and 2 drug-related serious AEs (both *Clostridium difficile* infection that resolved).

Conclusions: Ceftolozane/tazobactam demonstrated higher clinical and microbiological response rates compared to levofloxacin in the European subgroup. For the primary endpoint, ceftolozane/tazobactam showed statistical superiority over levofloxacin. In addition, ceftolozane/tazobactam showed high microbiological eradication for uropathogens *E. coli*, *Klebsiella pneumoniae* and *P. aeruginosa*. Ceftolozane/tazobactam was generally safe and well-tolerated. These data suggest that ceftolozane/tazobactam has the potential to be an efficacious and well-tolerated treatment for European patients with cUTI, including pyelonephritis.

1. Committee for Medicinal Products for Human Use. (CPMP/EWP/558/95 REV 2). EMA/CHMP/351889/2013. 24 October 2013.