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2226. Impact of Prior and Concomitant Antibacterial Therapy on Outcomes in the ASPECT-NP Randomized, Controlled Trial of Ceftolozane/Tazobactam (C/T) vs. Meropenem (MEM) in Patients with Ventilated Nosocomial Pneumonia (NP)

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Background. NP is a frequent healthcare-acquired infection associated with high mortality; rising resistance rates among causative Gram-negative pathogens require new treatment options. In the randomized, controlled, double-blind, phase 3 ASPECT-NP trial, C/T (at double the initially approved dose) was noninferior to MEM for ventilated NP in both primary and key secondary endpoints. Here we evaluate the impact of prior and concomitant Gram-negative antibacterial therapy on outcomes in that trial.

Methods. Mechanically ventilated patients with ventilator-associated or hospital-acquired pneumonia were randomized 1:1 to 3 g C/T or 1 g MEM, both by 1-h IV infusion every 8 hours for 8–14 days. Patients could receive ≤24 hours of active antibacterial therapy within ≤72 hours prior to first dose; longer durations were permitted in case of prior treatment failure (i.e., signs and/or symptoms of the current episode of ventilated NP persisted/worsened despite ≥48 hours of treatment). At sites with MEM-resistant *Pseudomonas aeruginosa* rates ≥15%, patients could optionally receive up to 72 h of adjunctive empiric aminoglycoside (amikacin was recommended) until study drug susceptibility was confirmed. Primary and key secondary endpoints, respectively, were 28-d all-cause mortality and clinical response at test of cure (TOC; 7–14 days after the end of therapy) in the intent to treat (ITT) population (all randomized patients).

Results. In the C/T arm, 285/362 (79%) ITT patients received prior systemic Gram-negative therapy and 103/362 (28%) received adjunctive aminoglycoside, compared with 288/364 (79%) and 112/364 (31%) patients, respectively, in the MEM arm. In the microbiologic ITT population, causative pathogens in patients failing prior therapy at the time of enrollment (C/T 15%, MEM 11%) were mainly *Klebsiella* spp (33%), *P. aeruginosa* (17%), *Escherichia coli* (14%), and *Acinetobacter baumannii* (8%). Mortality and cure rates were comparable between C/T and MEM regardless of receipt of prior systemic or adjunctive Gram-negative therapy (table).

Conclusion. Prior and adjunctive Gram-negative antibacterial therapy did not affect the relative efficacy of C/T (at the 3-g dose) vs. MEM in these high-risk patients with Gram-negative ventilated NP.

Endpoint	C/T n/N (%)	MEM n/N (%)	% Treatment difference (95% CI)
28-day all-cause mortality (ITT)	87/362 (24.0%)	92/364 (25.3%)	1.1 (-5.13, 7.39)
Prior systemic therapy	67/285 (23.5%)	78/288 (27.1%)	3.6 (-3.55, 10.64)
Adjunctive therapy	31/103 (30.1%)	33/112 (29.5%)	-0.6 (-12.78, 11.42)
No prior & no adjunctive therapy	25/134 (18.7%)	20/126 (15.9%)	-2.8 (-11.95, 6.53)
Clinical cure at TOC (ITT)	197/362 (54.4%)	194/364 (53.3%)	1.1 (-6.17, 8.29)
Prior systemic therapy	152/285 (53.3%)	150/288 (52.1%)	1.3 (-6.88, 9.36)
Adjunctive therapy	47/103 (45.6%)	64/112 (57.1%)	-11.5 (-24.29, 1.82)
No prior & no adjunctive therapy	84/134 (62.7%)	71/126 (56.3%)	6.3 (-5.53, 17.99)
28-day all-cause mortality (mITT)	53/264 (20.1%)	63/247 (25.5%)	4.4 (-2.38, 11.75)
Prior systemic therapy	38/201 (18.9%)	54/197 (27.4%)	8.5 (0.21, 16.69)
Adjunctive therapy	21/72 (29.2%)	22/74 (29.7%)	0.6 (-14.04, 15.08)
No prior & no adjunctive therapy	17/110 (15.5%)	14/89 (15.7%)	0.3 (-9.72, 10.83)
Clinical cure at TOC (CE)	139/218 (63.8%)	143/221 (64.7%)	-1.3 (-10.21, 7.67)
Prior systemic therapy	106/173 (61.3%)	111/173 (64.2%)	-2.9 (-12.94, 7.24)
Adjunctive therapy	32/56 (57.1%)	50/71 (70.4%)	-13.3 (-29.29, 3.36)
No prior & no adjunctive therapy	62/86 (72.1%)	53/81 (65.4%)	6.7 (-7.29, 20.36)

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2227. Outcomes in Patients with Renal Impairment from a Phase 3 Clinical Trial for Ceftolozane–Tazobactam (C/T) Treatment of Nosocomial Pneumonia (ASPECT-NP)

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Background. ASPECT-NP, a phase 3, randomized, double-blind study, evaluated C/T (at double the approved dose for other indications) vs. meropenem (MEM) in adults with ventilated nosocomial pneumonia. We compared safety and efficacy outcomes from this trial among patients with and without renal impairment (RI).

Methods. Patients were stratified by age and diagnosis and were randomized 1:1 to intravenous (IV) C/T 3 g every 8 h or IV MEM 1 g every 8 h. Study drug was administered for 8–14 days; doses were adjusted for moderate and severe RI. Eligible patients were mechanically ventilated; those on renal replacement therapy or with creatinine clearance (CrCL) < 15 mL/minute were excluded. Key efficacy endpoints included clinical cure rates at the test of cure (TOC) visit in the intent-to-treat (ITT) and clinically evaluable (CE) populations and Day 28 all-cause mortality (ACM) in the ITT population. In this analysis, patients were stratified based on renal function for outcome comparisons: normal renal function (CrCL ≥ 80 mL/minute); mild RI (CrCL > 50 to < 80 mL/minute); moderate RI (CrCL ≥ 30 to ≤ 50 mL/minute); and severe RI (CrCL ≥ 15 to < 30 mL/minute).

Results. A total of 726 patients were enrolled (C/T, *N* = 362; MEM, *N* = 364). Clinical cure rates at the TOC visit (CE and ITT populations) were robust across CrCL subgroups in both treatment arms and were similar based on 95% confidence intervals for treatment differences that included 0 (table). Day 28 ACM rates for patients with moderate and severe RI were numerically higher than those with mild RI in the MEM treatment arm. Rates of treatment-emergent adverse events (TEAEs) were similar in both treatment arms and across CrCL subgroups, with rates generally increasing with increasing RI severity. Rates of treatment-related TEAEs were low across treatment arms and CrCL subgroups with no treatment-related deaths reported.

Conclusion. Similar clinical cure and Day 28 ACM rates at the TOC visit were found across treatment groups for all CrCL subgroups, consistent with the overall primary and key secondary efficacy results for the ASPECT-NP study. Both drugs were well-tolerated. The results of this analysis indicate that the use of dose-adjusted C/T is appropriate in patients with nosocomial pneumonia and moderate or severe RI.

Table. Efficacy Outcomes by Treatment Arm and Renal Function Subgroup[a]

Outcome	C/T n/N1 (%)	MEM n/N1 (%)	Between Treatment Arm Difference, % (95% CI)[b]
Clinical cure at TOC (ITT population), N	362	364	
Normal renal function	132/227 (58.1)	138/236 (58.5)	-0.3 (-9.2, 8.6)
Mild RI	45/82 (54.9)	35/77 (45.5)	9.4 (-6.0, 24.2)
Moderate RI	13/35 (37.1)	11/26 (42.3)	-5.2 (-28.6, 18.4)
Severe RI	7/17 (41.2)	10/21 (47.6)	-6.4 (-34.4, 23.4)
Clinical cure at TOC (CE population), N	218	221	
Normal renal function	95/150 (63.3)	98/146 (67.1)	-3.8 (-14.5, 7.0)
Mild RI	31/44 (70.5)	27/46 (58.7)	11.8 (-7.9, 30.1)
Moderate RI	8/16 (50.0)	10/18 (55.6)	-5.6 (-35.2, 25.4)
Severe RI	5/8 (62.5)	8/11 (72.7)	-10.2 (-46.7, 27.5)
28-day all-cause mortality (ITT population), N	362	364	
Normal renal function	40/227 (17.6)	45/236 (19.1)	1.4 (-5.7, 8.5)
Mild RI	30/82 (36.6)	22/77 (28.6)	-8.0 (-22.0, 6.5)
Moderate RI	11/35 (31.4)	10/26 (38.5)	7.0 (-16.0, 30.0)
Severe RI	6/17 (35.3)	13/21 (61.9)	26.6 (-4.9, 51.6)

CE, clinically evaluable; CI, confidence interval; CrCL, creatinine clearance; C/T, ceftolozane-tazobactam; ITT, intent-to-treat; MEM, meropenem; N, number of patients in the analysis population; n, number of patients achieving a specified outcome; N1, number of patients in a specific subgroup; RI, renal impairment; TOC, test of cure.

[a]Renal function subgroups: normal renal function (CrCL ≥80 mL/min); mild RI (CrCL >50 to <80 mL/min); moderate RI (CrCL ≥30 to ≤50 mL/min); severe RI (CrCL ≥15 to <30 mL/min).

[b]The difference was calculated as C/T minus MEM for clinical cure and as MEM minus C/T for day-28 all-cause mortality; the 95% CI was calculated using the unstratified Newcombe method.

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