Linezolid vs. Vancomycin in the Treatment of Healthcare-Associated Pneumonia Caused by Culture-Proven Methicillin-Resistant *Staphylococcus aureus*

M. Bassetti,[1] D.H. Kett,[2] S. Puttagunta,[3] E.G. Scerpella,[3] P. Biswas,[3] D.B. Huang[3]

[1]*San Martino Hospital, University of Genoa School of Medicine, Genoa, Italy;* [2]*Jackson Memorial Hospital, Miller School of Medicine, University of Miami, Miami, FL, USA;*
[3]*Specialty Care Medicines Development Group, Pfizer Inc, Collegeville, PA, USA*

INTRODUCTION

- Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare-associated pneumonia (HCAP).[1,2]
- In a recently completed double-blind, randomized, multicenter, international, controlled trial, linezolid was shown to have a higher clinical response than vancomycin for its primary endpoint of clinical cure (57.6% vs 46.6%, respectively) at end of study (EOS) for the treatment of nosocomial pneumonia caused by culture-proven MRSA.[3]
- We describe clinical and microbiologic outcomes in the HCAP subgroup of patients enrolled in this trial.

METHODS

- We identified all patients with HCAP enrolled in this trial of linezolid (600 mg intravenously [IV] twice daily) compared with vancomycin (15 mg/kg IV twice daily, adjusted for creatinine clearance) for nosocomial pneumonia, including HCAP, caused by MRSA.
- We defined HCAP as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility; following a recent hospitalization (hospitalized for ≥48 hours and discharged within 90 days of current admission); or in a patient who received chronic dialysis care within the 30 days prior to study enrollment.
- In this subgroup analysis, our primary efficacy endpoints included clinical and microbiologic response at the EOS visit in patients with HCAP caused by culture-confirmed MRSA.
- Our secondary endpoints included clinical and microbiologic response at the end-of-treatment (EOT) visit.
- Continuous variables were compared using 2-sample *t* tests and categorical variables were compared via the Fisher exact test.
- Clinical and microbiologic response rates at EOS and EOT were compared across treatment using Fisher exact test. Odds ratios (OR) and 95% confidence intervals (CI) were computed. In all analyses, patients with missing or unknown responses were excluded.
- We recorded rates of treatment-related adverse events (TRAEs), serious adverse events (SAEs), AEs that led to study drug discontinuation, and 28-day all-cause mortality rates.

Definitions

Evaluation of Clinical and Microbiologic Response

- Clinical and microbiologic responses were evaluated at EOT and EOS visits.

Visit	Definition	Assessment of Clinical Response	Assessment of Bacterial Response
EOT	Within 72 hours after last dose of treatment is completed	• Cure • Improvement • Failure • Unknown	• Microbiologic success • Microbiologic failure
EOS	7–30 days after the end of therapy	• Cure • Failure • Unknown	

Response Categories

- Clinical success at EOT: cure or improvement
- Clinical success at EOS: cure
- Microbiologic success (EOT, EOS): defined as eradication (documented, presumed).
- Patients that fell within the "unknown" (clinical) or "indeterminate" (microbiologic) categories were excluded from statistical analysis of response.

RESULTS

- We identified 78 patients with MRSA HCAP in the modified intent-to-treat population (patients who received ≥1 dose of study drug and had a culture-proven MRSA at baseline).
- **Table 1** shows baseline demographics, severity of illness, and diagnosis characteristics for the HCAP study population. Patients randomized to linezolid (n=38) were similar to those treated with vancomycin (n=40) with respect to demographics, comorbidities (with the exception of chronic obstructive pulmonary disease and possibly chronic kidney disease), APACHE II (Acute Physiology And Chronic Health Evaluation) score, use of mechanical ventilator support at diagnosis, and chest X-ray findings.
- The treatment duration was similar in both groups. More than 60% of patients treated with vancomycin had a trough level ≥15 mg/L (**Table 2**).
- Rates of clinical success were 74% with linezolid compared with 76% with vancomycin at EOT (OR=0.9; 95% CI, 0.3 to 2.7), and 57% with linezolid compared with 44% with vancomycin at EOS (OR=1.7; 95% CI, 0.6 to 4.6) (**Figure 1**).
- Rates of microbiologic success were 81% with linezolid compared with 64% with vancomycin at EOT (OR=2.3; 95% CI, 0.8 to 7.1), and 66% with linezolid compared with 38% with vancomycin at EOS (OR=3.1; 95% CI, 1.1 to 8.6) (**Figure 2**).
- All-cause mortality within 28 days after randomization (linezolid = 5 vs vancomycin = 9) was comparable between patients treated with linezolid or vancomycin.

Table 1. Baseline Characteristics

Characteristic	Linezolid (n=38)	Vancomycin (n=40)	*P* Value[a]
Mean age (SD), y	72 (15)	72 (11)	0.86
Gender, n (%)			0.76
Male	25 (66)	25 (62)	
Female	13 (34)	15 (38)	
Race, n (%)			
White	31 (81)	27 (67)	0.20
African American	6 (16)	8 (20)	0.77
Asian	1 (3)	5 (13)	0.20
Region, n (%)[b]			
US	34 (89)	36 (90)	1
EU	3 (8)	1 (3)	0.35
Other	1 (3)	3 (8)	1
Mean weight (SD), kg	76 (20)	77 (20)	0.91
Comorbidities, n (%)			
Cardiac	33 (87)	30 (75)	0.18
Diabetes	18 (47)	25 (63)	0.18
Hepatobiliary	3 (8)	0	0.11
Neoplastic	3 (8)	6 (15)	0.48
Chronic kidney disease	18 (47)	27 (68)	0.07
COPD	36 (95)	31 (78)	0.03
Vascular	16 (40)	15 (39)	0.96
LTCF or SACF residence, n (%)	7 (18)	11 (28)	0.34
Chronic dialysis care, n (%)	1 (3)	4 (10)	0.36
Mean APACHE II score (SD)	17 (7)	18 (5)	0.69
Mechanical ventilation support at baseline, n (%)	19 (50)	25 (63)	0.27
Chest X-ray findings, n (%)			
Unilateral	8 (21)	10 (25)	0.79
Bilateral	29 (76)	30 (75)	1
Multilobar	31 (82)	32 (80)	0.86
Pleural effusions	20 (53)	17 (43)	0.5
Baseline respiratory culture, n (%)			
MRSA only	22 (58)	29 (72)	0.23
MRSA + other GPB	2 (5)	2 (5)	1
MRSA + GNB	11 (29)	7 (18)	0.29
MRSA + GPB + GNB	3 (8)	2 (5)	0.67

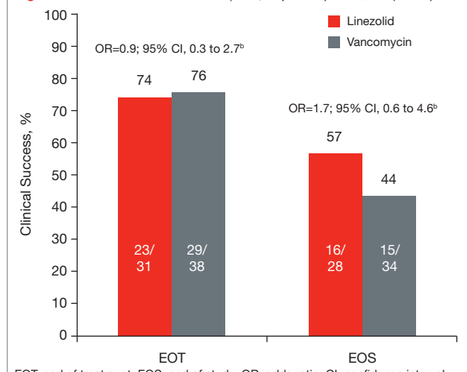
SD, standard deviation; COPD, chronic obstructive pulmonary disease; LTCF, long-term care facility; SACF, subacute/intermediate healthcare facility; APACHE II, Acute Physiology And Chronic Health Evaluation; MRSA, methicillin-resistant *Staphylococcus aureus*; GPB, gram-positive bacteria; GNB, gram-negative bacteria.
[a] Continuous variables were compared using 2-sample *t* test while categorical variables were compared using Fisher exact test.
[b] Because of rounding, values may not add up to 100%.

Table 2. Treatment Characteristics

Characteristic	Linezolid (n=38)	Vancomycin (n=40)	*P* Value[a]
Mean treatment duration (SD), d	8.4 (3.6)	9.0 (4.9)	0.56
Median vancomycin trough (range) day 3, mg/L	ND	14.1 (4.1–36.1)[b]	ND
Highest vancomycin trough level, n (%)[b]			
<15 mg/L	ND	12 (37.5)	ND
15–20 mg/L	ND	8 (25.0)	ND
>20 mg/L	ND	12 (37.5)	ND

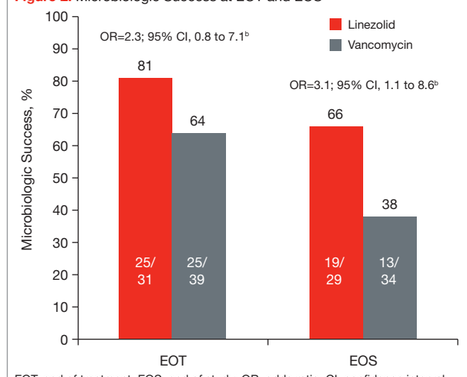
SD, standard deviation; ND, not done.
[a] Based on 2-sample *t* test.
[b] Based on 32 cases (data not available in 8 cases).

Figure 1. Clinical Success at EOT (cure, improved) and EOS (cured)[a]



EOT, end of treatment; EOS, end of study; OR, odds ratio; CI, confidence interval.
[a] Unknown or indeterminate values were excluded from the analysis.
[b] OR and 95% CI are based on Fisher exact test.

Figure 2. Microbiologic Success at EOT and EOS[a]



EOT, end of treatment; EOS, end of study; OR, odds ratio; CI, confidence interval.
[a] Unknown or indeterminate values were excluded from the analysis.
[b] OR and 95% CI are based on Fisher exact test.

Table 3. Safety Outcomes

mITT Population	Linezolid (n=38)	Vancomycin (n=40)
All causalities		
Patients with ≥1 AE	34	36
Patients with ≥1 SAE	16	18
Patients with ≥1 AE leading to drug discontinuation	1	2
Treatment-related		
Patients with ≥1 AE	9	11
Patients with ≥1 SAE	0	0
Patients with ≥1 AE leading to drug discontinuation	0	2

mITT, modified intent-to-treat; AE, adverse event; SAE, serious adverse event.

- The number of patients with treatment-related AEs (linezolid = 9 vs vancomycin = 11) and study drug discontinuations (linezolid = 0 vs vancomycin = 2) were comparable (**Table 3**). No treatment-related SAEs were observed, and AE distribution was similar for both groups (**Table 4**).

Table 4. Treatment-Related Adverse Events

mITT Population	Linezolid (n=38)	Vancomycin (n=40)
Diarrhea	1	0
Nausea	0	2
Vomiting	1	0
Skin rash	2	4
Anemia	0	1
Decreased platelet count	1	0
Kidney failure (acute), renal impairment	0	3
Hypokalemia	0	1

mITT, modified intent-to-treat.

CONCLUSIONS

- The primary efficacy analysis at EOS demonstrates that linezolid resulted in numerically higher rates of clinical success and statistically significantly higher rates of microbiologic success in MRSA HCAP than weight-based vancomycin dosing.
- Secondary endpoint analysis at EOT showed that linezolid resulted in comparable rates of clinical success and numerically higher rates of microbiologic success in MRSA HCAP compared with vancomycin.
- Both linezolid and vancomycin had comparable 28-day all-cause mortality and frequencies of TRAEs, SAEs, and study drug discontinuations.

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