

The Impact of Linezolid and Vancomycin Treatment on the Resolution of Signs and Symptoms of Nosocomial Pneumonia Caused by Culture Proven Methicillin-Resistant *Staphylococcus aureus* Among Ventilated Patients

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INTRODUCTION

- Nosocomial pneumonia (NP) is one of the most common hospital-acquired infections, and methicillin-resistant *Staphylococcus aureus* (MRSA) is a common pathogen.¹
- Patients who are responding to antimicrobial treatment typically have good clinical response within 48 to 72 hours of initiation of therapy.²
- We conducted a post hoc analysis that assessed the impact of antibiotic treatment on the resolution of signs and symptoms of NP caused by culture-proven MRSA among ventilated adult patients enrolled in a phase 4 prospective, double-blind, comparator-controlled, multicenter, international study comparing linezolid with vancomycin.

METHODS

Study Design and Patients

- Male and female patients ≥ 18 years old were enrolled if they had NP and isolation of MRSA from a respiratory specimen at baseline.
- Patients were randomized to intravenous treatment with either linezolid (600 mg twice a day) or vancomycin (15 mg/kg twice a day; with dose adjustment as necessary by an unblinded pharmacist based on trough levels and creatinine clearance).
- Pulmonary consolidation was defined as the presence of dullness on percussion, bronchial breath sounds, or egophony.
- Investigators at each site collected data on their patients' vital signs, laboratory parameters, and signs and symptoms of pneumonia (ie, purulent discharge, pulmonary consolidation, rales, decreased breath sounds, and hypoxemia) during the course of the study in a blinded fashion, and they recorded the signs and symptoms as present or absent.
- Post hoc analyses were conducted with patients with confirmed MRSA-NP in the per-protocol population who were ventilated at baseline to assess the impact of antibiotic treatment on the rate of resolution of signs and symptoms of NP.

Statistical Analysis

- All statistical tests were 2-sided. To assess statistical differences in the distribution of baseline characteristics between treatment

groups, one-way analysis of variance was used for continuous variables and Fisher exact test or chi-square test, as appropriate, was used for categorical variables.

- Patients who fell within the "unknown" (clinical) or "indeterminate" (microbiologic) categories were excluded from statistical analysis.
- P values < 0.05 were considered statistically significant.
- Statistical analyses were conducted using SAS, version 8.2.

RESULTS

Patient Characteristics

- At baseline, demographics, admission type, vital signs, Acute Physiology And Chronic Health Evaluation II scores, incidence of bacteremia, and duration of ventilation were similar between linezolid and vancomycin groups (Table 1).
- Although statistically not significant, more patients in the linezolid group had a modified Clinical Pulmonary Infection Score (modified to capture minute ventilation) higher than 6 (Table 1) and a bilateral lung involvement at baseline (Table 2).
- During the course of treatment, resolution of fever, purulent discharge, and normalization of white blood cell count were similar between linezolid and vancomycin treatment groups (Table 1).
- There was no difference in treatment effect on ventilation requirement between linezolid and vancomycin groups during the course of therapy (Table 1).
- At 72 hours, more patients treated with linezolid had resolution of rales, pulmonary consolidation, and hypoxemia compared with those treated with vancomycin (Figures 1, 2, and 3). These differences were not statistically significant.
- At the end of treatment and end of study, a greater number of patients treated with vancomycin had resolution of rales from baseline, although the difference was not statistically significant (Figure 1).
- At the end of study, percentage improvement from baseline for pulmonary consolidation and hypoxemia was greater for vancomycin-treated patients (Figures 2 and 3, respectively).
- At end of treatment, significantly more patients in the linezolid group had normalization of breath sounds (Figure 4) and chest X-ray (Table 2); however, there was no difference between treatment groups at the end of study.

Table 1. Baseline Demographics of Ventilated Patients With MRSA-NP Treated With Linezolid Versus Vancomycin in the Per-Protocol Population

Characteristic	Linezolid (N=126)	Vancomycin (N=141)	P Value
Mean age \pm SD, y	59.0 \pm 19.2	60.6 \pm 18.6	0.47
Sex, n (%)			0.89
Male	81 (64.3)	92 (65.2)	
Female	45 (35.7)	49 (34.8)	
Race, n (%)			0.25
White	93 (73.8)	98 (69.5)	
Black	12 (9.5)	22 (15.6)	
Asian	13 (10.3)	17 (12.1)	
Other	8 (6.3)	4 (2.8)	
Bacteremic at baseline, n (%)			0.39
Yes	9 (7.1)	15 (10.6)	
No	109 (86.5)	121 (85.8)	
Unknown	8 (6.3)	5 (3.5)	
APACHE II score at baseline, n (%)			0.90
≥ 20	57 (45.2)	63 (44.7)	
< 20	67 (53.2)	77 (54.6)	
Unknown	2 (1.6)	1 (0.7)	
mCPIS at baseline, n (%)			0.04
> 6	113 (89.7)	114 (80.9)	
≤ 6	7 (5.6)	19 (13.5)	
Unknown	6 (4.8)	8 (5.7)	
Mean days ventilated at baseline \pm SD	1.8 \pm 0.5	1.9 \pm 0.6	0.35
Pleural effusion at baseline, n (%)			0.14
Yes	61 (48.4)	55 (39.0)	
No	65 (51.6)	86 (61.0)	
Type of admission, n (%)			0.18
Medical	64 (50.8)	78 (55.3)	
Surgical	32 (25.4)	23 (16.3)	
Trauma	30 (23.8)	40 (28.4)	
On vasopressor support, n (%)			0.65
Baseline	23 (18.3)	29 (20.6)	
Day 3	15 (11.9)	18 (12.8)	0.86
Fever, n (%)			0.21
Baseline	46 (36.8)	63 (44.7)	
Day 3	33 (26.4)	47 (34.8)	0.18
WBC $> 10,000/\text{mm}^3$, n (%)			0.87
Baseline	107 (84.9)	118 (83.7)	
Day 3	89 (71.2)	99 (73.3)	0.78
Ventilated on day 3, n (%)			1.00
Unknown	1	3	
Purulent discharge, n (%)			0.38
Baseline	121 (96.8)	129 (94.2)	
Day 3	97 (80.8)	112 (86.2)	0.31

SD, standard deviation; APACHE, Acute Physiology And Chronic Health Evaluation; mCPIS, modified Clinical Pulmonary Infection Score; WBC, white blood cell. Missing values were excluded from the analyses. Percentages may not add up to 100 because of rounding.

Table 2. Normalization of Chest X-ray Among Ventilated Patients With MRSA-NP Treated With Linezolid Versus Vancomycin in the Per-Protocol Population^a

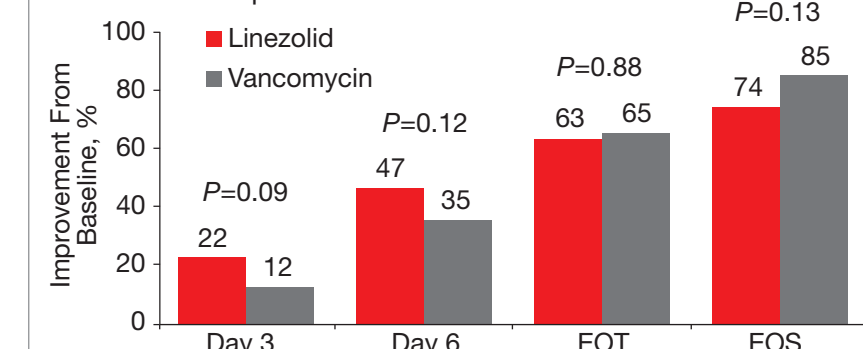
Chest X-ray, n/N (%)	Linezolid (N=126)	Vancomycin (N=141)	P Value
Baseline bilateral	93/125 (74.4)	88/141 (62.4)	0.05
Baseline unilateral	32/125 (25.6)	53/141 (37.6)	0.05
EOT resolved	108/122 (88.5)	89/127 (70.1)	0.0005
EOS resolved	73/89 (82.0)	80/91 (87.9)	0.30

EOT, end of treatment; EOS, end of study.

^a Number of patients having both baseline and visit observations.

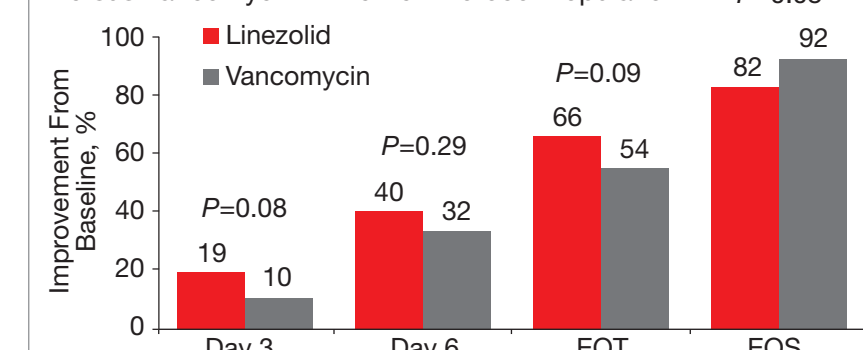
For categorical variables, Fisher exact test was used. Missing values are excluded from analyses.

Figure 1. Effect of Treatment on Rales Among Ventilated Patients With MRSA-NP Treated With Linezolid Versus Vancomycin in the Per-Protocol Population.



MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nosocomial pneumonia; EOT, end of treatment; EOS, end of study. Missing values were excluded from the analyses.

Figure 2. Effect of Treatment on Pulmonary Consolidation Among Ventilated Patients With MRSA-NP Treated With Linezolid Versus Vancomycin in the Per-Protocol Population.

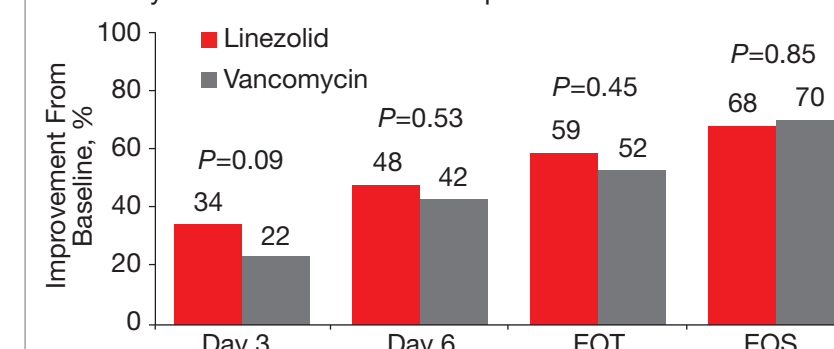


MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nosocomial pneumonia; EOT, end of treatment; EOS, end of study. Missing values were excluded from the analyses.

ACKNOWLEDGMENTS

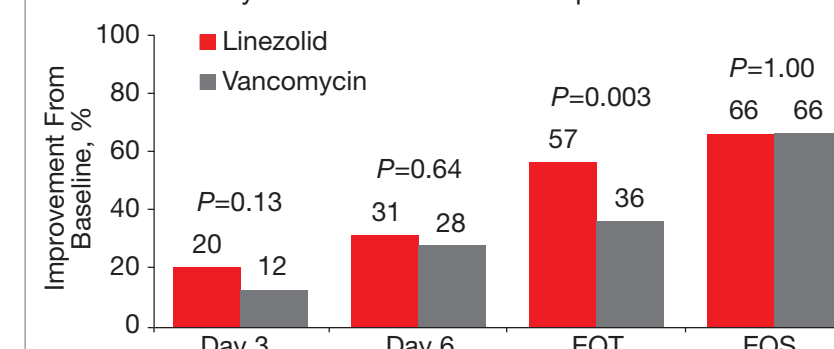
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Figure 3. Effect of Treatment on Hypoxemia Among Ventilated Patients With MRSA-NP Treated With Linezolid Versus Vancomycin in the Per-Protocol Population.



MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nosocomial pneumonia; EOT, end of treatment; EOS, end of study. Missing values were excluded from the analyses.

Figure 4. Effect of Treatment on Decreased Breath Sounds Among Ventilated Patients With MRSA-NP Treated With Linezolid Versus Vancomycin in the Per-Protocol Population.



MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nosocomial pneumonia; EOT, end of treatment; EOS, end of study.

CONCLUSIONS

- Compared with vancomycin-treated patients, those treated with linezolid had numerically greater rates of early resolution (day 3) of rales, pulmonary consolidation, and hypoxia, but comparable or numerically slightly lower rates at end of study. None of these differences were statistically significant.

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