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Comparative Effectiveness of Linezolid and Vancomycin Among a National Veterans Affairs Cohort with Methicillin-Resistant *Staphylococcus aureus* Pneumonia

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Abstract

Study Objective: As variability in vancomycin dosing, susceptibility, and tolerability has driven the need to compare newer agents with vancomycin in real-world clinical settings, we sought to quantify the effectiveness of linezolid compared with vancomycin on clinical outcomes for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia.

Design: Retrospective cohort study.

Data Source: Veterans Health Administration national databases.

Patients: Adults admitted to Veterans Affairs hospitals between January 2002 and September 2010 with diagnosis codes for MRSA and pneumonia, and who initiated and received at least 3 days of continuous intravenous vancomycin therapy (4943 patients) or intravenous or oral linezolid therapy (328 patients) while in the hospital.

Measurements and Main Results: Propensity score–adjusted Cox proportional hazards regression models quantified the effect of linezolid compared with vancomycin on time to 30-day mortality (primary outcome), therapy change, hospital discharge, discharge from intensive care, intubation, 30-day readmission, and 30-day MRSA reinfection. In addition, a composite outcome of clinical success was defined as discharge from the hospital or intensive care unit by day 14 after treatment initiation, in the absence of death, therapy change, or intubation by day 14. Subgroup analyses were performed in a validated microbiology-confirmed MRSA subgroup and clinical subgroup meeting clinical criteria for infection. Although a number of baseline variables differed significantly between the vancomycin and linezolid treatment groups, balance was achieved within propensity score quintiles. A significantly lower rate of therapy change was observed in the linezolid group (adjusted hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.48–0.96). The clinical success rate was significantly higher among patients treated with linezolid (adjusted HR 1.25, 95% CI 1.07–1.47). Comparable findings were observed in the subgroup analyses.

Conclusion: Individual clinical outcomes were similar among patients treated for MRSA pneumonia with linezolid compared with vancomycin. A significantly higher rate of the composite outcome of clinical success was observed, however, among patients treated with linezolid compared with vancomycin.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of pneumonia, which is concerning because hospital-acquired pneumonia and ventilator-associated pneumonia (VAP) caused by MRSA are associated with significant morbidity and mortality.[1-3] For more than 50 years, the glycopetide antibiotic vancomycin has been considered the standard of care for MRSA infections.[4,5] Unfortunately, vancomycin may be a suboptimal therapeutic option because of increasing minimum inhibitory concentrations among MRSA strains, poor penetration into alveolar fluid, and high clinical failure rates.[6-12] These limitations have led to the need for additional therapeutic options.

Currently, vancomycin and linezolid are the only agents with activity against MRSA that are approved for the treatment of nosocomial pneumonia in the United States and Europe. Thus far, studies comparing the efficacy of these two drugs for the treatment of pneumonia have demonstrated conflicting results. Although some studies have shown benefits for linezolid treatment compared with vancomycin,[13,14] many have found that the two drugs to have equivalent efficacy.[15-19] A recent, prospective, randomized controlled trial of culture-confirmed MRSA nosocomial pneumonia showed benefits for linezolid over vancomycin for clinical success, but no significant differences in mortality.[20] Limitations of these studies, specifically their methodological and statistical approaches, have been noted in multiple commentaries.[21-28]

These randomized trials provide important comparative efficacy data; however, they may not reflect the effectiveness of these agents in real-world clinical practice. MRSA pneumonia is a complex disease with significant morbidity and mortality; therefore, evaluating real-world effectiveness in treating this disease is essential. Thus, we sought to quantify the effectiveness of linezolid compared with vancomycin on clinical outcomes for the treatment of MRSA pneumonia in a national Veterans Affairs (VA) cohort.

Methods

The study design and methods were defined a priori in the study protocol, which was reviewed and approved by the Institutional Review Board and Research and Development Committee of the Providence Veterans Affairs Medical Center (Providence, RI).

Data Sources

The Veterans Health Administration has used an electronic medical record system since 1999. Our study included national standardized databases capturing the following data relevant to patient care*: International Classification of Diseases, Ninth Revision* (ICD-9) diagnostic and procedure codes, pharmacy records (for prescriptions), laboratory tests and select laboratory results, mortality, and patients' vital signs.[29,30]

Patient Population and Study Design

We conducted a retrospective cohort study of adults (aged ≥ 18 years) admitted to VA hospitals between January 1, 2002, and September 30, 2010, with an ICD-9 code for MRSA (038.12, 041.12, 482.42, V09.0) and pneumonia (482.40-482.42, 482.49, 482.89, 482.9, 484.8, 485-486, 510.0, 510.9, 513.0-513.1). Those patients who initiated and received at least 3 days of continuous intravenous vancomycin or intravenous or oral linezolid therapy while in the hospital were included in the analysis. Initiation in the hospital setting was defined as the absence of linezolid or vancomycin therapy in the 7 days prior to starting therapy during the hospital admission. Patients who died or were discharged within 3 days of treatment initiation, were given vancomycin or linezolid in the nursing home, or were exposed to more than 2 consecutive days of another antibiotic therapy with anti-MRSA activity (clindamycin, daptomycin, doxycycline, linezolid, minocycline, tigecycline, trimethoprim-sulfamethoxazole, vancomycin) in the 3 days before treatment initiation or during treatment with linezolid or vancomycin were excluded. Only the first admission within the study period meeting all inclusion and exclusion criteria was included.

To validate our selection criteria for the study population, we conducted several subgroup analyses. From the overall cohort, we identified a validated microbiology-confirmed MRSA subgroup and clinical subgroup. To validate the MRSA and pneumonia diagnosis codes, a manual electronic chart review on a random sample of 10% of all patients was completed. The validated population included patients with an MRSA-positive culture from a suitable sputum culture (<10 squamous epithelial cells and ≥25 leukocytes, or taken by an invasive technique such as bronchoalveolar lavage) and patients from medical centers that achieved an average validation of 80%. The clinical subgroup included patients with one of the following clinical factors between admission day and treatment initiation: presence of a chest radiograph, elevated body temperature (≥100.4°F), or elevated white blood cell count (≥ 10 x 10^3/mm^3).

Definitions of Outcomes

The primary outcome measure was time to death (all-cause mortality) occurring within 30 days of treatment initiation. Secondary outcomes included time to each of the following events: therapy change, hospital discharge, intensive care unit (ICU) discharge, intubation, 30-day readmission, 30-day MRSA reinfection, and clinical success as defined below. Date of therapy initiation was used to define the index date of treatment. Time to therapy change, hospital discharge, ICU discharge, and intubation were calculated from the index date to the event date for each outcome. Postdischarge outcomes, including 30-day readmission and 30-day MRSA reinfection, were calculated in the 30 days after hospital discharge. Therapy change was defined as the discontinuation of linezolid or vancomycin and initiation of a different agent with activity against MRSA. As such, therapy change could have included switching from linezolid to vancomycin, switching from vancomycin to linezolid, or switching from either linezolid or vancomycin to another anti-MRSA antibiotic (listed above). Switching an antibiotic from intravenous to oral route was not considered a therapy change. Clinical rationale for therapy change was not ascertained. Transfer out of the ICU was assessed among patients initiating

linezolid or vancomycin therapy in the ICU. For all time-dependent variables, we censored patients on their date of death (if death occurred) or December 31, 2010, whichever occurred sooner.

Clinical success was a composite outcome defined as discharge from the hospital or ICU by day 14 after treatment initiation in the absence of death, therapy change, or intubation by day 14. Nonsuccess was defined as therapy change, intubation, ICU admission, discharge and readmission, or death between treatment initiation and day 14. Patients not meeting either definition were excluded. Day 14 was chosen to replicate the average end-of-treatment time frame from existing linezolid and vancomycin clinical trials.[15,16,20] Sensitivity analyses evaluated an alternate definition of clinical success excluding therapy change.

Statistical Analysis

Between-group differences were assessed using χ^2 or Fisher exact tests for categorical variables and the *t*-test or Wilcoxon rank sum test for continuous variables as appropriate. Propensity scores were derived from unconditional logistic regression models. Time-to-event analyses were conducted with Cox proportional hazards regression models. Adjustment was achieved by controlling for propensity score quintiles. The propensity adjusted–Cox proportional hazards regression models were used to quantify the effect of linezolid compared with vancomycin treatment for MRSA pneumonia on the primary and secondary outcomes. A hazard ratio (HR) greater than 1 indicates a higher probability of the event occurring in the linezolid group compared with the reference vancomycin group. In terms of our study outcomes, HRs greater than 1 would represent a higher mortality rate, decreased length of stay (LOS), or higher readmission rate among patients treated with linezolid. All analyses were performed by using SAS statistical software, version 9.1.3 (SAS Institute Inc., Cary, NC).

Results

We identified 5271 patients who met our inclusion criteria, of whom 328 (6.2%) were treated with linezolid and 4943 (93.8%) with vancomycin. The mean patient age was 69 years in both treatment groups (Table 1). The majority of patients in both groups were white men. Several statistically significant differences in frequency of comorbidities, including renal disease, cancer, and dialysis, were observed between treatment groups. Geographic region of facility and infections in the year prior to admission were characteristics that varied significantly between the linezolid and vancomycin groups (Table 2). Although a number of baseline variables differed significantly between the treatment groups, balance was achieved within propensity score quintiles. The propensity score controlled for a number of patient demographics and comorbidities present during the MRSA pneumonia admission, as well as medical history in the year prior to the MRSA pneumonia admission. Several treatment-related characteristics were also controlled for, including time to treatment initiation, year of treatment initiation, hospital unit at treatment initiation, and treating specialty at initiation.

In the overall cohort, the 30-day mortality rate was 20.8% (19.5% linezolid vs 20.9% vancomycin, p=0.56). Time to 30-day mortality did not vary significantly between treatment groups (adjusted HR 0.91, 95% CI 0.70–1.17) (Table 3). A significantly lower rate of therapy change, specifically discontinuation of linezolid or vancomycin and initiation of a different anti-MRSA agent, among linezolid-treated patients was observed in the adjusted model (HR 0.68, 95% CI 0.48–0.96). Rates of hospital discharge, ICU discharge, intubation, 30-day MRSA reinfection, and 30-day readmission did not differ significantly in either the unadjusted or adjusted analyses. The mean ± SD time to discharge was 19.7 ± 24.4 days among linezolid-treated patients versus 20.3 ± 26.5 days among vancomycin-treated patients. Comparable findings were observed in the validated and clinical subgroups. The clinical success rate was significantly higher among patients treated with linezolid in the overall cohort, as well as in the validated and clinical subgroups, as shown in Table 4: overall cohort (adjusted HR 1.25, 95% CI

1.07–1.47), validated subgroup (adjusted HR 1.46, 95% CI 1.13–1.87), and clinical subgroup (adjusted HR 1.25, 95% CI 1.03–1.52).

In subgroup analyses of the overall cohort, no associations between treatment group and any of the study outcomes were observed among patients with renal insufficiency. Among obese patients in the overall cohort (123 patients in the linezolid group, 2068 patients in the vancomycin group), the rate of clinical success was significantly higher for linezolid-treated patients in the unadjusted (HR 1.57, 95% CI 1.07-2.31) and adjusted (HR 1.77, 95% CI 1.18–2.64) analyses. In sensitivity analyses of the overall cohort excluding therapy change from the definition of success, linezolid was still associated with a higher rate of clinical success (179 patients in the linezolid group, 2632 patients in the vancomycin group; unadjusted HR 1.19, 95% CI 1.02-1.38; adjusted HR 1.18, 95% CI 1.01-1.37).

Discussion

We assessed the real-world effectiveness of linezolid compared with vancomycin in the treatment of MRSA pneumonia in a large cohort of patients admitted to VA facilities nationally. No significant differences were observed in the primary outcome measure, time to 30-day mortality. These results regarding mortality are similar to findings from a pneumonia subset analysis in a large national cohort study of veterans with MRSA infections.[30] In addition, these results are congruent with a recent clinical trial comparing linezolid with vancomycin for the treatment of culture-confirmed MRSA pneumonia, in which no significant difference was observed in mortality at 60 days (linezolid 15.7% vs vancomycin 17.0%).[20]

In our study, linezolid was associated with greater clinical success, a composite outcome measure, compared with vancomycin. Our definition of clinical success was defined a priori based on recently published clinical trials.[15,16,20] Several clinical trials have demonstrated greater clinical success with linezolid; however, the definitions of success varied among trials and

compared with our study.[13,14,20] Further, clinical success was determined by clinical judgment in those trials rather than by objective criteria as in our study.

Previous retrospective infectious disease studies have developed definitions of clinical success or failure based on available data, such as clinical, pharmacological, microbiological, and laboratory measures.[31-34] However, there is no consensus in the literature regarding the definition of clinical success, particularly regarding the time of evaluation and specific parameters to include in the measure.[31-34] The clinical success definition we used in our study is an algorithm based on objective criteria derived from the individual outcomes collected (mortality, discharge, intubation, therapy change, readmission). Our sensitivity analyses of an alternate definition of success, which removed therapy change as a parameter, revealed similar findings, although to a lower magnitude (overall HR 1.25; excluding therapy change, HR 1.18), of an association between linezolid and clinical success. In addition to traditional outcome measures, such as mortality, length of stay, and pharmacoeconomics, it is useful to develop outcome measures that are clinically or microbiologically based to assess differences between groups and to assist in clinical decision making. As the prevalence of retrospective clinical studies increase, it is likely that these measures will evolve and be validated over time.[31]

We did not observe an association between linezolid treatment and a higher discharge rate for MRSA pneumonia, and thus mean LOS was comparable between treatment groups (linezolid 19.7 days, vancomycin 20.3 days). This finding differs from an earlier national MRSA cohort study, in which linezolid treatment was associated with a shorter LOS.[30] In general, evidence from randomized studies demonstrates a shorter LOS with linezolid treatment.[35,36] However, these studies included patients with other types of infections, such as complicated skin and soft tissue infections. MRSA pneumonia is a complicated infection with lengthy recommended treatment durations of up to 21 days, depending on the extent of the infection,[37] so it may have been less likely that we would observe differences in LOS and discharge rates in our study than in studies of other infection types.

In our retrospective cohort study, linezolid treatment was associated with a lower rate of therapy change compared with vancomycin treatment in the adjusted overall analysis. Limited data have been published on differences in therapy change with different agents. However, in randomized trials, rates of discontinuation of linezolid or vancomycin were comparable to our findings.[15,16,19] It is possible that patients receiving intravenous vancomycin may have been switched to a different antibiotic with an oral option as they were being prepared for discharge.

Comparable rates of time to ICU discharge, intubation, 30-day MRSA reinfection, and 30-day readmission were found between treatment groups in our study. In contrast, a prospective, open-label trial found a nonsignificant trend favoring decreased length of ICU stay with linezolid treatment; however, this trial limited inclusion to patients with MRSA VAP.[38] In retrospective studies, comparable rates of intubation and readmission rates have been found with linezolid compared with vancomycin treatment.[30,39] Few studies report readmission and reinfection rates due to short follow-up periods.

Our study has several limitations. The retrospective design is associated with a number of limitations, including that ICD-9 coding practices may vary among institutions and affect the accuracy of our findings. In addition, there is discordance with ICD-9 coding and culture-confirmed MRSA pneumonia infection,[40] thereby leading to a potential misclassification. It is likely our study did not capture all MRSA pneumonia infections due to missing codes for MRSA. Because of the complexity of obtaining microbiologic data for this study, validation of ICD-9 codes of MRSA pneumonia was performed in a 10% patient sample. In addition, we had no control over culture collection. Of the patients randomly selected for validation, 29% were nonevaluable because no sputum samples were taken. This indicates treatment initiation for suspected MRSA pneumonia, based on clinical signs and symptoms, without ever collecting a sputum culture, which is why we also included a clinical subgroup in our analyses. In the clinical subgroup, results of the chest radiographs were not available in the databases used. However, patients in the clinical subgroup had to meet all inclusion criteria for the overall cohort

in addition to having a chest radiograph between admission and initiation of treatment or one of the other clinical symptoms (elevated body temperature or elevated white blood cell count).

Our study is further limited in that we did not evaluate success in all patients since we excluded those not meeting the definition of success or nonsuccess by day 14 after treatment initiation (linezolid 29.6%, vancomycin 29.2%). It is not known whether vancomycin dosing was optimized among patients included in this study because trough levels were not available for evaluation. Although balance was achieved within propensity score quintiles, there is the potential for residual confounding by unobserved covariates. Finally, the generalizability of our study may be limited to the VA population.

Conclusion

Our retrospective national cohort study demonstrated similar survival, LOS, readmission, and reinfection rates for patients with MRSA pneumonia treated with linezolid or vancomycin. Linezolid treatment was associated with a significantly higher rate of the composite outcome of clinical success than vancomycin. These real-world clinical data support the results of previous studies and further the understanding of MRSA pneumonia treatment.

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Table 1. Demographics and Comorbid Conditions by Treatment Group

Covariate	Linezolid Group (n = 328)	Vancomycin Group (n = 4943)
Age (years)	69.1 ± 12.5	69.1 ± 12.7
Male sex	323 (98.5)	4844 (98.0)
Race-		
White	266 (81.1)	3945 (79.8)
Other or unknown	62 (18.9)	998 (20.2)
Charlson comorbidity index	2.8 ± 2.3	2.7 ± 2.3
Comorbid conditions		
Chronic respiratory disease	140 (42.7)	2113 (42.7)
Renal disease[a]	83 (25.3)	728 (14.7)
Diabetes mellitus	93 (28.4)	1547 (31.3)
Heart failure	86 (26.2)	1201 (24.3)
Coronary heart disease	83 (25.3)	1120 (22.7)
Cancer[a]	45 (13.7)	945 (19.1)
Dialysis[a]	36 (11.0)	183 (3.7)
Obesity	15 (4.6)	141 (2.9)
Amputation	4 (1.2)	90 (1.8)
Para- or quadriplegia	21 (6.4)	291 (5.9)
Cerebrovascular disease	32 (9.8)	485 (9.8)
Peripheral vascular disease	20 (6.1)	336 (6.8)
Moderate or severe liver disease	6 (1.8)	93 (1.9)
HIV/AIDS	7 (2.1)	55 (1.1)
Bacteremia[a]	52 (15.9)	1037 (21.0)
Skin infection	88 (26.8)	1213 (24.5)
Surgical site infection	9 (2.7)	178 (3.6)

Data are mean ± SD or no. (%) of patients.
HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.
[a]$p<0.05$ for the comparison between treatment groups.

Table 2. Healthcare and Antibiotic Exposures and Hospitalization-Related Characteristics by Treatment Group

Variable	Linezolid Group (n = 328)	Vancomycin Group (n = 4943)
Previous hospitalization in the last year	227 (69.2)	3368 (68.1)
Previous hospitalization in the last 90 days	186 (56.7)	2530 (51.2)
Previous surgery in the last year	78 (23.8)	993 (20.1)
Previous anti-MRSA antibiotics in the last 90 days	154 (47.0)	2181 (44.1)
Previous immunosuppressants in the last 90 days	8 (2.4)	131 (2.7)
Infections during the previous year		
Pneumonia	143 (43.6)	1722 (34.8)
Chronic skin ulcer	73 (22.3)	909 (18.4)
Bacteremia[a]	36 (11.0)	303 (6.1)
MRSA	59 (18.0)	574 (11.6)
Pseudomonas aeruginosa	23 (7.0)	232 (4.7)
Admission source		
Home	121 (36.9)	1771 (35.8)
Hospital	30 (9.1)	303 (6.1)
Nursing home	32 (9.8)	612 (12.4)
Hospital unit at treatment initiation		
Intensive care	137 (41.8)	1998 (40.4)
Surgery	21 (6.4)	280 (5.7)
General medicine	170 (51.8)	2665 (53.9)
Treating specialty		
Intensive care	142 (43.3)	1878 (38.0)
Surgery	14 (4.3)	183 (3.7)
General medicine	172 (52.4)	2882 (58.3)
Region of facility		
North[a]	39 (11.9)	629 (12.7)
South	178 (54.3)	2278 (46.1)
Midwest	65 (19.8)	953 (19.3)
West	46 (14.0)	1083 (21.9)

Data are no. (%) of patients.
MRSA = methicillin-resistant *Staphylococcus aureus*.
[a]$p<0.05$ for the comparison between treatment groups.

Table 3. **Outcomes in Overall Cohort: Linezolid Compared with Vancomycin**

Outcome	Unadjusted Hazard Ratio (CI) (linezolid group [n=328] vs vancomycin group [n=4942])	Adjusted Hazard Ratio (CI) (linezolid group [n=328] vs vancomycin group [n=4942])
30-day mortality	0.93 (0.72–1.20)	0.91 (0.70–1.17)
Discharge	1.02 (0.90–1.15)	1.04 (0.92–1.18)
Therapy change	0.75 (0.53–1.05)	0.68 (0.48–0.96)
ICU discharge	1.03 (0.86–1.25)	1.03 (0.85–1.24)
ICU transfer	0.65 (0.39–1.09)	0.70 (0.42–1.18)
Intubation	0.96 (0.68–1.37)	0.97 (0.68–1.38)
30-day MRSA reinfection	0.89 (0.54–1.48)	0.93 (0.56–1.56)
30-day readmission	0.88 (0.68–1.13)	0.89 (0.69–1.15)

CI = confidence interval; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*.

The propensity score for the overall cohort was derived from an unconditional logistic regression model controlling for race, admission source, region of facility, hospital unit at treatment initiation, treating specialty, chronic renal disease, diabetes mellitus, cancer, metastatic cancer, myocardial infarction, cardiac arrhythmia, obesity, depression, bacteremia, endocarditis, gram-negative infection, *Escherichia coli* infection, *Streptococcus* infection, complication of implant or graft, complication of surgery or medical care, amputation procedure, dialysis, intravenous line, urinary catheter, number of inpatient procedures, time to therapy initiation, year, MRSA pneumonia diagnosis code, inpatient admission in the previous 30 days, procedure in the previous 180 days, previous metastatic cancer, previous coronary heart disease, previous congestive heart failure, previous human immunodeficiency virus infection, previous peripheral vascular disease, previous plegia, previous rheumatoid arthritis or connective tissue disease, previous peptic ulcer, previous weight loss, previous depression, previous drug abuse, previous *S. aureus* infection, previous pneumonia, previous bacteremia, previous surgical site infection, previous skin abscess, previous chronic ulcer, previous infective arthritis, previous vancomycin-resistant *Enterococcus* infection, previous *E. coli* infection, and previous intravenous line.

Table 4. **Clinical Success of Linezolid Compared with Vancomycin**

Cohort	Unadjusted Hazard Ratio (CI)	Adjusted Hazard Ratio (CI)
Overall cohort (linezolid group [n=231] vs vancomycin group [n=3500])	1.24 (1.06–1.45)	1.25 (1.07–1.47)
Validated subgroup (linezolid group [n= 97] vs vancomycin group [n=1411])	1.40 (1.10–1.78)	1.46 (1.13–1.87)
Clinical subgroup (linezolid group [n=165] vs vancomycin group [n=2536])	1.19 (0.98–1.44)	1.25 (1.03–1.52)

CI = confidence interval.