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Multicenter Prospective Observational Study of the Comparative Efficacy and Safety of Vancomycin versus Teicoplanin in Patients with Health Care-Associated Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Young Kyung Yoon,[a] Dae Won Park,[a] Jang Wook Sohn,[a] Hyo Youl Kim,[b] Yeon-Sook Kim,[c] Chang-Seop Lee,[d] Mi Suk Lee,[e] Seong-Yeol Ryu,[f] Hee-Chang Jang,[g] Young Ju Choi,[h] Cheol-In Kang,[i] Hee Jung Choi,[j] Seung Soon Lee,[k] Shin Woo Kim,[l] Sang Il Kim,[m] Eu Suk Kim,[n] Jeong Yeon Kim,[o] Kyung Sook Yang,[p] Kyong Ran Peck,[i] Min Ja Kim[a]

Division of Infectious Diseases, Department of Internal Medicine, Korea University, College of Medicine, Seoul, Republic of Korea[a]; Yonsei University Wonju College of Medicine, Wonju, Republic of Korea[b]; Chungnam National University Hospital, Daejon, Republic of Korea[c]; Chonbuk National University Medical School, Jeonju, Republic of Korea[d]; Kyung Hee University School of Medicine, Seoul, Republic of Korea[e]; Keimyung University Dongsan Hospital, Daegu, Republic of Korea[f]; Chonnam National University Medical School, Gwangju, Republic of Korea[g]; National Cancer Center, Seoul, Republic of Korea[h]; Sungkyunkwan University School of Medicine, Seoul, Republic of Korea[i]; Ewha Women's University School of Medicine, Seoul, Republic of Korea[j]; Hallym University Sacred Heart Hospital, Anyang, Republic of Korea[k]; Kyungpook National University Hospital, Daegu, Republic of Korea[l]; Catholic University of Korea, College of Medicine, Seoul, Republic of Korea[m]; Seoul National University Bundang Hospital, Seoul, Republic of Korea[n]; Samyook Medical Center, Seoul, Republic of Korea[o]; Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea[p]

The purpose of this study was to compare the clinical efficacy and safety of vancomycin to those of teicoplanin for the treatment of adult patients with health care-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) bacteremia. A multicenter observational study was prospectively conducted in 15 teaching hospitals in Korea between February 2010 and July 2011. Adult patients (≥18 years old) with HA-MRSA bacteremia who were initially treated with vancomycin (VAN) ($n = 134$) or teicoplanin (TEC) ($n = 56$) were enrolled. Clinical and microbiological responses and drug-related adverse events were compared between the two treatment groups using univariate and multivariate logistic regression analyses. The vancomycin and teicoplanin MICs were determined by Etest. The MRSA-related mortality, duration of fever, and duration of MRSA bacteremia in the treatment groups were not significantly different. There was no significant difference in the occurrence of drug-related adverse events. Among the 190 MRSA isolates, the VAN MICs ranged from 0.5 to 2 μg/ml (MIC_{50} and MIC_{90}, 1.5 μg/ml), and the TEC MIC ranged from 0.5 to 8 μg/ml (MIC_{50}, 3 μg/ml; MIC_{90}, 6 μg/ml). In multivariate analyses, the antibiotic type (vancomycin or teicoplanin) was not associated with treatment outcomes. This study indicates that teicoplanin is an effective and safe alternative to vancomycin for the treatment of HA-MRSA bacteremia.

Nosocomial bloodstream infections represent a major clinical challenge in many health care institutions worldwide, despite laborious and costly infection control efforts. Health care-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) bacteremia has imposed a distinctly high burden on medical expenses and has caused considerable morbidity and mortality (1, 2).

Vancomycin (VAN) has widely been used for the treatment of MRSA infection over the past decades. Increasingly, however, therapeutic failures with VAN have been reported (3). There is also growing evidence of bacteremia caused by MRSA isolates with an increased VAN MIC (4, 5). The VAN therapeutic monitoring guidelines in 2009 recommended more aggressive VAN dosing schemes, targeting VAN serum trough concentrations of 15 to 20 mg/liter for MRSA bacteremia (6). Similarly, optimizing the pharmacokinetics of VAN to achieve an area under the curve (AUC)/MIC ratio of ≥211 has been shown to predict more favorable treatment outcomes in cases of MRSA-associated complicated bacteremia (7). However, if the MRSA strains' MIC is ≥2 μg/ml, conventional intermittent dosing might not achieve this ratio. Rather, it may increase nephrotoxicity (8).

Teicoplanin (TEC) is a glycopeptide antibiotic with an antibacterial spectrum similar to that of VAN but is less toxic at daily doses of less than 800 mg (9, 10). It has a long half-life (45 to 70 h), permitting once-daily dosing (11), and may enhance the intracellular killing of bacteria by phagocytes (12). TEC is commonly used for MRSA infections in Europe, while its use has not yet been approved in the United States. TEC has been used as an alternative agent for MRSA infections; however, there is a limited number of studies that have evaluated the clinical efficacy of TEC in patients with HA-MRSA bacteremia (13, 14).

The purpose of this prospective observational study was to compare the clinical efficacy and safety of VAN to those of TEC for the treatment of adult patients with HA-MRSA bacteremia.

MATERIALS AND METHODS

Study design and patients. A prospective, multicenter observational study was conducted in 15 teaching hospitals in the Republic of Korea over an 18-month period from February 2010 to July 2011. The subjects comprised hospitalized adult patients (≥18 years) with HA-MRSA bac-

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Address correspondence to Min Ja Kim, macropha@korea.ac.kr.

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teremia who were initially treated with VAN ($n = 134$) or TEC ($n = 56$) and who were followed until death or hospital discharge. Only the first episode of HA-MRSA bacteremia and the first blood isolate of MRSA per patient that was susceptible to both VAN and TEC were included for analysis. Patients with polymicrobial bacteremia were excluded in order for this study to evaluate the impact of antibiotic therapy for MRSA bacteremia specifically.

A loading dose of VAN (1 g every 12 h) or TEC (400 mg every 12 h) was administered for an initial 24 h or 36 h, respectively, and then followed by daily maintenance doses of each drug that were adjusted to the patient's renal function, if needed (15). In the 11 participating hospitals (73.3%) that ran the therapeutic drug monitoring (TDM) practices for VAN, the TDM-guided VAN dosing was performed, targeting serum trough levels between 15 and 20 μg/ml. None of the participating hospitals ran the TDM for TEC. During the study period, there were no other standardized interventions for the management of MRSA bacteremia, and physicians treated the patients according to routine medical practice.

The study protocol was approved prior to study initiation by the institutional review boards at each participating hospital. As this observational study required no deviation from routine medical practice, the boards waived the need for informed consent.

Definitions. MRSA bacteremia was considered present if one or more blood cultures had positive results and if the clinical signs and course were consistent with MRSA infection (16).

The primary source of infection, based on the organs affected, was classified as one of the following: lower respiratory tract, intra-abdominal area, genitourinary tract, skin and soft tissue, bone and joint, central nervous system, and catheter. The origin of infection was considered unknown in cases of positive blood cultures without primary infection at another body site (16).

MRSA bacteremia was categorized epidemiologically as health care associated or nosocomial. Community-onset MRSA bacteremia within ≤48 h of hospital admission was considered health care associated if, during the preceding 12 months, the patient had any of the following: admission to other hospitals or health care facilities for more than 2 days, surgery, dialysis, specialized home care, care received at day hospitals, or permanent indwelling catheters. Patients defined as having community-acquired infections were excluded from this study. Infections occurring in patients after 48 h of hospital admission were considered nosocomial.

The duration of bacteremia after VAN or TEC treatment was calculated as the number of days from the start of MRSA treatment to the day the first negative blood culture was drawn. Sepsis, severe sepsis, and septic shock were defined according to the standard criteria (17). The community-acquired phenotype for the MRSA isolates was defined as being susceptible to clindamycin, erythromycin, and ciprofloxacin (18, 19).

The primary endpoint was clinical failure, defined as a composite of mortality attributable to MRSA bacteremia, microbiological failure, and/or persistent fever, except drug fever. Mortality attributable to MRSA bacteremia was defined as positive blood cultures for MRSA, persistent fever, and no other definite causes of death. Microbiological failure was defined as positive blood cultures for MRSA ≥7 days from the index culture under VAN or TEC therapy. Persistent fever was defined as ≥38.0°C for ≥7 days after the commencement of VAN or TEC treatment.

Variables. Physicians or research coordinators of the participating hospitals entered the clinical data for each patient into a standardized web-based case report form. An infectious disease doctor at the coordinating center checked the entered data and supported the study sites by sending queries throughout the study period. The parameters collected for this analysis included demographic characteristics, comorbid medical conditions, including Charlson's comorbidity index (20), factors predisposing to infections, primary source of MRSA bacteremia, acute physiology and chronic health evaluation II (APACHE II) score (21) or Pitt's bacteremia score (22) at the onset of MRSA bacteremia, diagnosis of severe sepsis or septic shock, hospital mortality, and microbiological data.

Microbiological tests. Bacterial identification and antibiotic susceptibility were performed at each study site using a Vitek II (bioMérieux, Hazelwood, MO) or MicroScan Pos Combo panel type 6 system (Baxter Diagnostics, West Sacramento, CA). All MRSA isolates from participating hospitals were sent to the coordinating center. All isolates received were immediately stored at −70°C until August 2012, when microbiologic tests were performed all at once. The VAN and TEC MICs for all 190 MRSA isolates were further determined by the Etest (bioMérieux, Marcy l'Etoile, France) at the coordinating center according to the manufacturer's instructions.

Statistical analysis. For comparisons between groups of continuous independent variables that were normally distributed, the two-sample Student's *t* test was used. For comparisons of continuous independent variables that were not normally distributed, the Mann-Whitney U test was used. Summaries of the continuous variables were expressed as medians and interquartile ranges (IQR). Independent categorical variables were described using count (proportion), and comparisons between groups were made using the Pearson's chi-squared test or Fisher's exact test.

In the univariate analysis, the VAN and TEC MICs were evaluated as continuous variables as well as categorical variables. The cutoff values of the VAN MICs and the TEC MICs were determined with an analysis using the chi-squared automatic interaction detector (CHAID) decision tree algorithm, to predict treatment outcome in the respective treatment group. The cutoff values of the VAN MICs and the TEC MICs drawn from the CHAID algorithm were 1.5 μg/ml and 4.0 μg/ml, respectively.

Multivariate logistic regression analyses using the backward stepwise variable selection based on the LR statistic were used to examine the impact of multiple independent predictors on the clinical failure as a dependent variable. Trauma, renal diseases, hepatic diseases, pneumonia, Pitt's bacteremia score, C-reactive protein, acute renal injury, duration of fever or bacteremia after VAN or TEC treatment, and antibiotic type were evaluated as independent variables for multivariable logistic regression analysis if such independent variables were predictors of clinical failure at the 10% significance level. Hosmer-Lemeshow goodness-of-fit tests were performed to evaluate the models. Internal accuracy obtained by leave-one-out cross-validation was used to evaluate the performance of a predictive model. All tests were 2-tailed, and a P value <0.05 was considered statistically significant. All of the analyses were performed with IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY), R 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria), and SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patients and clinical characteristics. During the study period, 426 patients with HA-MRSA bacteremia were enrolled from the participating hospitals. Patients who were given antibiotics with no activity against MRSA isolates ($n = 81$) and 49 patients from whom MRSA isolates were not collected were excluded from the analysis. Patients who initially received other antibiotics before VAN or TEC ($n = 96$) and who received VAN or TEC for <3 days ($n = 10$) were also excluded. Eventually, 190 patients with HA-MRSA bacteremia who were initially treated with VAN ($n = 134$) or TEC ($n = 56$) for ≥3 days were included in this study.

The demographic and baseline characteristics of the 190 patients are listed in Table 1. Of these, 158 patients (83.2%) had nosocomial infections and 128 (67.4%) were male. The median age was 66 years (IQR, 51 to 74 years). The univariate analyses determined that there were no significant differences in sex, age, and category of infection between the VAN and TEC treatment groups (Table 1).

The most common source of MRSA bacteremia was catheter-related infections (47.9%), followed by pneumonia (14.7%), surgical wounds (10.0%), and bone and joint infections (5.8%). The

TABLE 1 Demographic and baseline characteristics of 190 patients with MRSA bacteremia according to treatment group and outcome[a]

Variable	All ($n = 190$)	Treatment group			Treatment outcome		
		Vancomycin ($n = 134$)	Teicoplanin ($n = 56$)	P	Success ($n = 112$, 58.9%)	Failure ($n = 78$, 41.1%)	P
No. (%) receiving vancomycin	134 (70.5)	134 (100)	0	<0.001	85 (75.9)	49 (62.8)	0.052
No. (%) of males	128 (67.4)	92 (68.7)	36 (64.3)	0.558	78 (69.6)	50 (64.1)	0.423
Median age, yrs (IQR)	66 (51–73)	64.5 (51–73)	68 (51.5–74)	0.521	65 (52–72)	67.5 (50–76)	0.508
No. (%) with time of bacteremia							
≤48 h	42 (25.6)	35 (26.1)	7 (23.3)	0.752	28 (26.9)	14 (23.3)	0.612
>48 h	122 (74.4)	99 (73.9)	23 (76.7)		76 (73.1)	46 (76.7)	
No. (%) with category of infection							
Health care associated	32 (16.8)	23 (17.2)	9 (16.1)	0.854	20 (17.9)	12 (15.4)	0.654
Nosocomial	158 (83.2)	111 (82.8)	47 (83.9)		92 (82.1)	66 (84.6)	
Comorbid illness							
No. (%) with cardiovascular disease	97 (51.1)	65 (48.5)	32 (57.1)	0.278	54 (48.2)	43 (55.1)	0.348
No. (%) with central nervous system disease	47 (24.7)	33 (24.6)	14 (25.0)	0.957	31 (27.7)	16 (20.5)	0.260
No. (%) with malignancy	57 (30.0)	47 (35.1)	10 (17.9)	0.018	36 (32.1)	21 (26.9)	0.440
No. (%) with trauma	18 (9.5)	12 (9.0)	6 (10.7)	0.706	5 (4.5)	13 (16.7)	0.005
No. (%) with renal disease	39 (20.5)	28 (20.9)	11 (19.6)	0.845	18 (16.1)	21 (26.9)	0.068
No. (%) with hepatic disease	20 (10.5)	17 (12.7)	3 (5.4)	0.133	16 (14.3)	4 (5.1)	0.043
No. (%) with respiratory disease	23 (12.1)	16 (11.9)	7 (12.5)	0.914	10 (8.9)	13 (16.7)	0.108
No. (%) with solid organ or bone marrow transplant	4 (2.1)	3 (2.2)	1 (1.8)	1.000	3 (2.7)	1 (1.3)	0.645
No. (%) with metabolic disease	66 (34.7)	48 (35.8)	18 (32.1)	0.627	34 (30.4)	32 (41.0)	0.129
No. (%) with HIV infection	2 (1.1)	2 (1.5)	0	1.000	1 (0.9)	1 (1.3)	1.000
No. (%) with hematologic disease	30 (15.8)	26 (19.4)	4 (7.1)	0.035	19 (17.0)	11 (14.1)	0.595
No. (%) with gastrointestinal bleeding	8 (4.2)	5 (3.7)	3 (5.4)	0.695	3 (2.7)	5 (6.4)	0.276
Charlson's comorbidity index, median (IQR)	2 (1–4)	3 (1–4)	1 (0–3)	0.008	2 (0–4)	2 (1–4)	0.693
No. (%) with primary source of bacteremia							
Catheter-related infection	91 (47.9)	70 (52.2)	21 (37.5)	0.064	59 (52.7)	32 (41.0)	0.114
Pneumonia	28 (14.7)	19 (14.2)	9 (16.1)	0.737	10 (8.9)	18 (23.1)	0.007
Surgical wound infection	19 (10.0)	13 (10.4)	5 (8.9)	0.750	13 (11.6)	6 (7.7)	0.376
Bone and joint infection	11 (5.8)	10 (7.5)	1 (1.8)	0.179	5 (4.5)	2 (2.6)	0.702
Intra-abdominal infection	10 (5.3)	3 (2.2)	7 (12.5)	0.008	3 (2.7)	4 (5.1)	0.448
Urinary tract infection	7 (3.7)	3 (2.2)	4 (7.1)	0.198	7 (6.2)	4 (5.1)	1.000
Skin and soft tissue infection	7 (3.7)	5 (3.7)	2 (3.6)	1.000	1 (0.9)	3 (3.8)	0.307
Cardiovascular infection	4 (2.1)	2 (1.5)	2 (3.6)	0.583	5 (4.5)	5 (6.4)	0.743
Central nervous system infection	1 (0.5)	1 (0.7)	0	1.000	0	1 (1.3)	0.411
Head and neck infection	1 (0.5)	0	1 (1.8)	0.295	1 (0.9)	0	1.000
Unknown	11 (5.8)	7 (5.2)	4 (7.1)	0.734	8 (7.1)	3 (3.8)	0.530
Clinical severity at the onset of MRSA bacteremia							
No. (%) with fever (≥38.0°C)	142 (74.7)	104 (77.6)	38 (67.9)	0.158	90 (80.4)	52 (66.7)	0.033
No. (%) with SIRS	189 (99.5)	133 (99.3)	56 (100)	1.000	111 (99.1)	78 (100)	1.000
No. (%) with development of severe sepsis or septic shock	66 (34.7)	43 (32.1)	23 (41.1)	0.236	31 (27.7)	35 (44.9)	0.014
Pitt's bacteremia score [median (IQR)]	1 (0–3)	1 (0–3)	1 (0–4)	0.542	1 (0–3)	2 (0–3)	0.286
APACHE II score [median (IQR)]	17 (12–21)	15 (12–21)	19 (13–23)	0.211	17 (11–21)	17 (13–21)	0.667
No. (%) with APACHE II score of ≥20	42 (33.3)	23 (32.9)	19 (33.9)	0.899	22 (30.6)	20 (37.0)	0.445
No. (%) with complicated condition							
Foreign body retention	8 (4.2)	7 (5.2)	1 (1.8)	0.440	7 (6.2)	1 (1.3)	0.144
Infective endocarditis	5 (2.6)	4 (3.0)	1 (1.8)	1.000	3 (2.7)	2 (2.6)	1.000
Metastatic infections[b]	11 (5.8)	9 (6.7)	2 (3.6)	0.512	8 (7.1)	3 (3.8)	0.530
Laboratory findings at the onset of MRSA bacteremia							
C-reactive protein (mg/liter)	10.8 (4.8–22.1)	11.1 (5.2–20.2)	9.9 (4.1–23.0)	0.914	9.2 (3.9–17.4)	14.3 (6.8–24.4)	0.039
No. (%) with hematocrit of <30%	98 (51.6)	66 (49.3)	32 (57.1)	0.321	53 (47.3)	45 (57.7)	0.159
No. (%) with platelet count of <100,000/μl	41 (21.6)	30 (22.4)	11 (19.6)	0.675	22 (19.6)	19 (24.4)	0.437

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TABLE 1 (Continued)

Variable	All ($n = 190$)	Treatment group			Treatment outcome		
		Vancomycin ($n = 134$)	Teicoplanin ($n = 56$)	P	Success ($n = 112$, 58.9%)	Failure ($n = 78$, 41.1%)	P
No. (%) with albumin of <3.0 g/dl	84 (44.2)	56 (41.8)	28 (50.0)	0.299	49 (43.8)	35 (44.9)	0.878
No. (%) with total bilirubin of ≥2.0 mg/dl	37 (19.5)	27 (20.1)	10 (17.9)	0.716	20 (17.9)	17 (21.8)	0.500
No. (%) with creatinine of ≥2.0 mg/dl	52 (27.4)	37 (27.6)	15 (26.8)	0.907	33 (29.5)	19 (24.4)	0.272
No. (%) with serum sodium of <130.0 mmol/liter	17 (8.9)	15 (11.2)	2 (3.6)	0.093	13 (11.6)	4 (5.1)	0.124

[a] HIV, human immunodeficiency virus; SIRS, systemic inflammatory response syndrome; IQR, interquartile range; APACHE II, acute physiology and chronic health evaluation II; SD, standard deviation; MRSA, methicillin-resistant *Staphylococcus aureus*.
[b] Sites of metastatic infections include bones and joints, the epidural space, intervertebral disks, heart valves, and intra-abdominal organs.

univariate analyses revealed no significant differences in the primary source of infection between the 2 treatment groups, except for intra-abdominal infections (Table 1).

The median Charlson comorbidity index was 2 (IQR, 1 to 4), and univariate analyses determined that the VAN group had a significantly higher Charlson comorbidity index than the TEC group. In particular, underlying malignancy and hematologic diseases were significantly more common in the VAN group than the TEC group (Table 1). Sixty-six patients (34.7%) had severe sepsis or septic shock, and the median APACHE II score at the onset of HA-MRSA bacteremia was 17 (IQR, 12 to 21). There was no significant difference in the APACHE II score of HA-MRSA bacteremia between the two treatment groups (Table 1).

Microbiological characteristics. All 190 MRSA isolates underwent microbiological analysis. The VAN MIC range was 0.5 to 2 μg/ml, and the VAN MIC_{50} and MIC_{90} were both 1.5 μg/ml. The TEC MIC range was 0.5 to 8 μg/ml, and the TEC MIC_{50} and MIC_{90} were 3 μg/ml and 6 μg/ml, respectively. Distribution of the VAN and TEC MICs and the antibiotic phenotype among the MRSA isolates, categorized by treatment group and treatment outcome, are shown in Table 2. In a total of 190 patients analyzed, the VAN or TEC MICs were not associated with clinical failure.

When the influences of the VAN MICs on clinical outcomes in the VAN-treated group were evaluated, a VAN MIC of ≥1.5 μg/ml was the significant risk factor for in-hospital mortality (VAN MIC, <1.5 μg/ml versus ≥1.5 μg/ml; 19.1% [9/47] versus 41.4% [36/87]; $P = 0.009$) but not for clinical failure (40.4% [19/47] versus 34.5% [30/87]; $P = 0.495$). In the TEC-treated group, a TEC MIC of ≥4 μg/ml in the TEC group was not significantly associated with treatment failure (TEC MIC, <4 μg/ml versus ≥4 μg/ml; 53.3% [24/45] versus 45.5% [5/11]; $P = 0.639$) or in-hospital mortality (40.0% [18/45] versus 27.3% [3/11]; $P = 0.508$).

The proportion of MRSA isolates with phenotypic expression of community-acquired MRSA was 16.3% (31/190) and was not significantly different between the 2 treatment groups (Table 2).

Treatment outcomes. The overall all-cause in-hospital mortality and MRSA-related mortality were 34.7% (66/190) and 14.7% (28/190), respectively. There were no significant differences in the all-cause in-hospital mortality and MRSA-related mortality between the treatment groups. After the commencement of VAN or TEC therapy, a significant difference was not exhibited for the duration of fever and MRSA bacteremia between the treatment groups (Table 3). The median durations of VAN and TEC treatment showed no significant differences (median, [IQR], 14 days [IQR, 9 to 23 days] versus 13 days [IQR, 8 to 21 days]; $P = 0.239$).

In total, 36 patients (18.9%) received alternative drugs due to poor clinical response ($n = 23$), drug-related adverse events ($n = 12$), or other reasons ($n = 4$). In the VAN group, VAN was switched with alternative antibiotics in 20 patients (14.9%): TEC ($n = 11$), linezolid ($n = 6$), tigecycline ($n = 2$), or levofloxacin plus rifampin ($n = 1$). In the TEC group, 16 patients (28.6%) received alternative antibiotics: VAN ($n = 9$), linezolid ($n = 4$), an

TABLE 2 Microbiological characteristics of 190 patients with MRSA bacteremia according to treatment group and outcome

Variable	All ($n = 190$)	Treatment group			Treatment outcome		
		Vancomycin ($n = 134$)	Teicoplanin ($n = 56$)	P	Success ($n = 112$, 58.9%)	Failure ($n = 78$, 41.1%)	P
MIC, μg/ml [median (IQR)]							
Vancomycin	1.5 (1.0–1.5)	1.5 (1.0–1.5)	1.0 (1.0–1.5)	<0.001	1.5 (1.0–1.5)	1.5 (1.0–1.5)	0.324
Teicoplanin	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–3.0)	0.039	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.476
No. (%) with vancomycin MIC of ≥1.5 μg/ml	106 (55.8)	87 (64.9)	19 (33.9)	0.001	67 (59.8)	39 (50.0)	0.180
No. (%) with teicoplanin MIC of MIC ≥ 4 μg/ml	64 (33.7)	53 (39.6)	11 (19.6)	0.008	42 (37.5)	22 (28.2)	0.182
No. (%) with CA-MRSA[a] phenotype (18, 19)	31 (16.3)	25 (18.7)	6 (10.7)	0.101	21 (18.8)	10 (12.8)	0.199

[a] CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*.

TABLE 3 Antibiotic treatment outcomes and related adverse events for 190 patients with health care-associated MRSA bacteremia[a]

Variable	Treatment group				Treatment outcome		
	All (n = 190)	Vancomycin (n = 134)	Teicoplanin (n = 56)	P	Success (n = 112, 58.9%)	Failure (n = 78, 41.1%)	P
Antibiotic treatment							
No. (%) with interval from culture to VAN or TEC treatment of ≥48 h	64 (41.8)	42 (39.3)	22 (47.8)	0.324	38 (40.9)	26 (43.3)	0.762
Duration of VAN or TEC treatment (days), median (IQR)	14 (3–23)	14 (9–23)	13 (8–21)	0.239	14 (9–21)	13 (8–24)	0.995
Clinical response							
Duration of bacteremia after VAN or TEC treatment (days), median (IQR)	1 (0–2)	1 (0–2)	0 (0–1)	0.254	0 (1–0)	1 (0–7)	<0.001
No. (%) with bacteremia ≥7 days after VAN or TEC treatment	20 (10.9)	15 (11.7)	5 (9.1)	0.601	0	20 (25.6)	<0.001
Duration of fever after VAN or TEC treatment (days), median (IQR)	4 (2–7)	4 (2–6)	5 (2–11)	0.084	3 (2–5)	8 (4–17)	<0.001
No. (%) with fever ≥7 days after VAN or TEC treatment	51 (29.5)	29 (24.0)	22 (42.3)	0.015	0	51 (67.1)	<0.001
No. (%) with drug-related adverse events during treatment)	36 (18.9)	28 (20.9)	8 (14.3)	0.289	19 (17.0)	17 (21.8)	0.403
No. (%) with acute renal injury	17 (8.9)	14 (10.4)	3 (5.4)	0.262	6 (5.4)	11 (14.1)	0.038
No. (%) with hepatotoxicity	3 (1.6)	1 (0.7)	2 (3.6)	0.208	3 (2.7)	0	0.270
No. (%) with bone marrow toxicity	10 (5.3)	8 (6.0)	2 (3.6)	0.726	8 (7.1)	2 (2.6)	0.202
No. (%) with fever	8 (4.2)	6 (4.5)	2 (3.6)	1.000	5 (4.5)	3 (3.8)	1.000
No. (%) with rash	1 (0.5)	1 (0.7)	0	1.000	0	1 (1.3)	0.411
No. (%) with change of initial antibiotics	36 (18.9)	20 (14.9)	16 (28.6)	0.029	17 (15.2)	19 (24.4)	0.112
Outcome							
No. of days of hospital stay after bacteremia, median (IQR)	23 (11–49)	23 (12–49)	25 (9–52)	0.706	23 (10–47)	24 (12–53)	0.867
No. (%) with in-hospital mortality	66 (34.7)	45 (33.6)	21 (37.5)	0.605	27 (24.1)	39 (50.0)	<0.001
No. (%) with mortality attributable to MRSA	28 (14.7)	18 (13.4)	10 (17.4)	0.433	0	28 (35.9)	<0.001

[a] IQR, interquartile range; VAN, vancomycin; TEC, teicoplanin; MRSA, methicillin-resistant *Staphylococcus aureus*.

aminoglycoside (n = 1), clindamycin (n = 1), or trimethoprim-sulfamethoxazole plus rifampin (n = 1).

The median duration of VAN in alternation from VAN to TEC (n = 11) and vice versa (n = 9) was 9 days (IQR, 6 to 17 days) and 10 days (IQR, 7 to 13 days), respectively.

There was no significant difference in the occurrence of drug-related adverse events between the 2 treatment groups (20.9% [28/134] versus 14.3% [8/56], P = 0.289) (Table 3). Among the 8 patients who received alternative glycopeptides due to drug-related adverse events, cross-reactivity was not observed between VAN and TEC. One patient with VAN-induced acute kidney injury developed TEC-induced neutropenia.

In the multiple logistic regression modeling, the antibiotic type (VAN or TEC) was not an independent risk factor for clinical failure in the patients with HA-MRSA bacteremia, regardless of variable selection (Table 4). The statistically significant factors as-

TABLE 4 Multivariable logistic regression analysis of risk factors associated with clinical failure in the 190 patients with MRSA bacteremia[a]

Independent variable	Multivariate logistic regression analysis without variable selection		Multivariate logistic regression with backward variable selection based on LR	
	OR (95% CI for OR)	P	OR (95% CI for OR)	P
Antibiotic type (vancomycin)	0.73 (0.18, 2.98)	0.666		
Trauma (yes)	7.38 (0.85, 63.77)	0.069		
Renal disease (yes)	1.62 (0.39, 6.76)	0.509		
Hepatic disease (yes)	1.09 (0.12, 10.21)	0.939		
Pneumonia (yes)	1.94 (0.43, 8.78)	0.391		
Pitt's bacteremia score	1.60 (1.13, 2.26)	0.008	1.51 (1.10, 2.06)	0.010
C-reactive protein	1.00 (0.99, 1.02)	0.740		
Acute renal injury (yes)	18.41 (1.76, 192.26)	0.015	15.99 (1.81, 141.16)	0.013
Duration of fever (days)	1.78 (1.34, 2.37)	<0.001	1.77 (1.36, 2.32)	<0.001
Duration of bacteremia (days)	1.83 (1.34, 2.48)	<0.001	1.76 (1.34, 2.31)	<0.001

[a] LR, Logistic regression analysis; OR, odds ratio; 95% CI, 95% confidence interval.

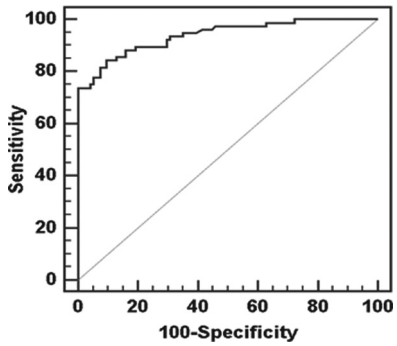

FIG 1 Receiver operating characteristic curve for clinical failure obtained using the predictive probability of multivariate logistic regression model and validation results.

sociated with clinical failure included Pitt's bacteremia score (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.10 to 2.06), acute renal injury (OR, 15.99; 95% CI, 1.81 to 141.16), duration of fever (OR, 1.77; 95% CI, 1.36 to 2.32), and duration of bacteremia (OR, 1.76; 95% CI, 1.34 to 2.31) (Table 4). The *P* values for the Hosmer-Lemeshow goodness-of-fit test were greater than 0.05. Hence, there is no significant evidence of lack of fit for any of the final models.

Leave-one-out cross-validation was performed to assess the predictive accuracy of each final model. The AUCs for the clinical failure model were greater than 0.90 for both the raw data set and leave-one-out cross-validation. For this mode, the sensitivity, specificity, positive predictive value, and negative predictive value obtained with an optimal cutoff point were greater than 0.80 (Fig. 1; Table 5).

DISCUSSION

This multicenter prospective study compared the clinical efficacy and safety of VAN versus TEC for the treatment of adult patients with HA-MRSA bacteremia in hospital settings where MRSA prevalence was about 70% (23). This study found that TEC has efficacy and safety comparable to those of VAN for the treatment of HA-MRSA bacteremia.

The in-hospital mortality rate of HA-MRSA bacteremia in the VAN and TEC treatment groups of this study were 33.6% and 37.5%, respectively, which is comparable to the range of 14% to 60% reported previously in other studies (3, 24–26). Based on the Charlson comorbidity index or Pitt's bacteremia score, the clinical severity of the infections of the patients in our study was comparable to that of health care-associated and community-acquired MRSA infections (14, 26). In addition, 4 risk factors for clinical failure of HA-MRSA bacteremia, namely, Pitt's bacteremia score, acute renal injury, duration of fever, and bacteremia, were not different from those reported previously (26–29).

In this study, the type of glycopeptide, i.e., VAN or TEC, was not the risk factor associated with clinical failure. Meta-analysis studies have reported that there were no differences in clinical cure, microbiological cure, and mortality between VAN and TEC treatments for Gram-positive infections, including bacteremia, pneumonia, febrile neutropenia, and skin and soft tissue infections (10, 30, 31). However, studies on the comparative efficacy of VAN versus TEC against MRSA bacteremia (13, 32, 33) are still limited. Liu et al. (33) demonstrated that TEC was as efficacious as VAN in terms of treatment success rate for MRSA bacteremia (TEC group, 85% [17/20], versus VAN group, 75% [15/20]; $P = 0.69$). On the other hand, Huang and Hsu (32) reported that there was no statistically significant difference in the hospital mortality rate (42% versus 47%) and microbiological failure rate (34% versus 40%) between the VAN group ($n = 36$) and the TEC group ($n = 15$) among patients with MRSA infective endocarditis.

In this study, there was no significant difference in the occurrence of drug-related adverse events between the VAN and TEC treatment groups. In meta-analysis studies, the incidence of total drug-related adverse events, including nephrotoxicity and red man syndrome, was lower with TEC (10, 30, 31). This discrepancy might have resulted from the closed TDM of VAN in our study, carried out according to recent clinical practice guidelines (34). On the other hand, TEC was administered as directed in the package insert because TDM of TEC is not routinely available.

In this study, the use of an alternative agent, i.e., switching from VAN to TEC or vice versa, was common in the patients with HA-MRSA bacteremia due to the reimbursement system in Korea. VAN was replaced with TEC as an alternative agent, or vice versa, in 20 (14.9%) and 16 patients (28.6%), respectively. Lin et al. (13) reported no significant difference in 30-day mortality among 3 treatment groups of elderly patients with persistent MRSA bacteremia (VAN versus TEC versus VAN/TEC alternately, 59.6% [65/109] versus 50.0% [7/14] versus 65.5% [19/29]). They also reported that alternation between VAN and TEC treatment was not more effective than either VAN or TEC treatment alone (13). However, the appropriateness of this alternative therapy needs to be evaluated in prospective randomized controlled trials. Antibiotics such as linezolid or daptomycin as promising salvage agents or a novel strategy of combined antibiotic treatment should be considered for better treatment outcomes of HA-MRSA bacteremia (27, 35).

In our study, the adverse cross-reactions between VAN and TEC were not remarkable, although a limited number of cases were evaluated. Previous studies have reported that the alternate use of TEC in cases of VAN intolerance was associated with a high incidence of drug-related adverse events, most notably neutropenia (36, 37). Therefore, the potential cross-reactivity between these 2 glycopeptides remains to be clarified in future studies.

In recent meta-analysis studies, VAN MICs of ≥1.5 μg/ml or ≥2.0 μg/ml are associated with increased mortality as well as clinical failure among patients with MRSA infections (4, 5). In this

TABLE 5 Validation results for the clinical failure variable[a]

Validation	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Validation for raw data set	0.939 (0.903–0.974)	84.2 (74.0–91.6)	90.4 (82.6–95.5)	87.7 (78.1–93.5)	87.6 (79.1–94.1)
Leave-one-out cross-validation	0.926 (0.876–0.961)	80.3 (69.5–88.5)	91.5 (83.9–96.3)	88.4 (78.4–94.9)	85.1 (76.6–91.5)

[a] All values except AUC are optimal values in each final model. AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; MRSA, methicillin-resistant *Staphylococcus aureus*.

study, the VAN MICs of ≥1.5 μg/ml from the VAN-treated group and the TEC MICs of ≥4.0 μg/ml from TEC-treated group were more common in the nonsurvivors than the survivors but were not a significant factor for clinical failure. These findings indicate that the threshold VAN or TEC MICs for clinical outcomes might be different among the study populations.

This study has some limitations. First, this prospective study was not designed to include the detailed complications associated with MRSA bacteremia. This may have resulted in a falsely low complication rate. However, catheter-related infections accounted for 47.9% of the HA-MRSA bacteremia cases in this study, which were easily controlled with catheter removal and antibiotic therapy. Thus, the related confounding factors might be minimal. Second, this was not a randomized clinical trial: the doctors chose VAN to initiate treatment due to the reimbursement system in Korea. Therefore, the patients who received TEC therapy may not be representative of the larger population with HA-MRSA bacteremia. Third, individualized dosing regimens of VAN or TEC relative to the MICs were not undertaken in this study. Implementation of the individualized VAN dosing approach targeting an AUC/MIC ratio of 400 μg · h/ml or greater, rather than a trough serum concentration, may lead to improved clinical outcomes in critically ill patients (38). Lastly, other antibiotics switched from VAN or TEC or concomitant antibiotics with VAN or TEC might have influenced the treatment outcome. The clinical effect of these antibiotics were not evaluated owing to the small number of study cases.

In conclusion, this multicenter prospective study indicates that TEC is an effective and safe alternative to VAN for the treatment of HA-MRSA bacteremia. Further studies that take the AUC/MIC ratio of VAN and TEC into account may be required for better clinical outcomes in treating patients with HA-MRSA bacteremia.

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