MAJOR ARTICLE

Linezolid versus Vancomycin for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections

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Linezolid, the first available member of a new antibiotic class, the oxazolidinones, is broadly active against gram-positive bacteria, including drug-resistant strains. In this randomized, open-label trial, hospitalized adults with known or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) infections were treated with linezolid (600 mg twice daily; $n = 240$) or vancomycin (1 g twice daily; $n = 220$) for 7–28 days. *S. aureus* was isolated from 53% of patients; 93% of these isolates were MRSA. Skin and soft-tissue infection was the most common diagnosis, followed by pneumonia and urinary tract infection. At the test-of-cure visit (15–21 days after the end of therapy), among evaluable patients with MRSA, there was no statistical difference between the 2 treatment groups with respect to clinical cure rates (73.2% of patients in the linezolid group and 73.1% in the vancomycin group) or microbiological success rates (58.9% in the linezolid group and 63.2% in the vancomycin group). Both regimens were well tolerated, with similar rates of adverse events.

Gram-positive bacteria have emerged as important causes of hospital-acquired and community-acquired infections [1–11]. Recent data from the National Nosocomial Infection Surveillance System indicate that *Staphylococcus aureus* is the most common cause of nosocomial pneumonia and the second most common cause of bloodstream infections in the United States [12]. This trend is complicated by the increasing prevalence (from 2% in 1974 to as high as 64% in recent surveys) of methicillin-resistant *S. aureus* (MRSA) among nosocomial isolates [1, 13–16].

Some investigations suggest that MRSA infections are associated with prolonged hospitalizations, increased mortality, and increased costs, compared with infections due to methicillin-susceptible *S. aureus;* however, such comparisons may be confounded by an increased incidence of comorbid conditions among patients with MRSA infection [17–19, 20]. Unfortunately, therapeutic options for patients with MRSA infections are limited. The primary option is intravenous vancomycin therapy, because other antimicrobials, including the fluoroquinolones and third-generation cephalosporins, are ineffective against MRSA [13, 21]. The recent emergence of *S. aureus* with intermediate resistance to glycopeptides and heteroresistant MRSA [20, 22–25] suggests that full glycopeptide resistance may soon develop and limit the usefulness of vancomycin [26, 27], which underscores the need for new antibiotics.

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Linezolid, the first available oxazolidinone antibiotic, has broad in vitro activity against antibiotic-susceptible and antibiotic-resistant gram-positive bacteria [28–35], including activity against MRSA and against *S. aureus* with intermediate resistance to glycopeptides [2, 3, 28, 36]. Linezolid uniquely inhibits bacterial protein synthesis by preventing formation of the 70S initiation complex [29, 35–39]. Plasma concentrations of intravenous and oral linezolid are equivalent [40], with average concentrations exceeding the MICs for susceptible pathogens throughout the 12-h dosing interval [41, 42]. Clinical trials demonstrate that linezolid is well tolerated and that it is as effective as standard therapies [43, 44]. We report the results of the largest randomized, comparator-controlled, open-label clinical trial to date comparing the safety and efficacy of linezolid with that of vancomycin in treating patients with presumed MRSA infections.

METHODS

Study design. This randomized, open-label trial evaluated patients with presumed MRSA infections and was conducted at 104 sites in North America, Europe, Latin America, and Asia from July 1998 to July 1999. General and infection-specific inclusion and exclusion criteria are listed in table 1. Study sites obtained approval from local independent ethics committees or institutional review boards, and each patient provided written informed consent.

Hospitalized patients were randomized to receive either linezolid (600 mg iv twice daily) or vancomycin (1 g iv twice daily) for at least 7 days. When they had shown clinical improvement, linezolid-treated patients could have their treatment changed to oral linezolid (600 mg twice daily) at the discretion of the investigator. Concomitant administration of aztreonam or gentamicin was allowed. Use of topical antiseptics and topical steroids (not in direct contact with the skin and soft-tissue infection [SSTI] site) was permitted. The recommended infection-specific durations of treatment were as follows: for SSTI or urinary tract infection, 7–14 days; for pneumonia, 10–14 days; and for bacteremia of unknown source, 14–28 days. Medical histories were obtained, and physical examinations, routine hematologic and serum chemical assays, electrocardiography, and chest radiography (for patients with pneumonia) were performed for each patient at baseline (at study entry) and periodically during the study. Baseline comorbid conditions (as judged by the investigator) were reported.

Each patient was assessed at the end of therapy (EOT) and during an indication-specific test-of-cure (TOC) visit. The evaluation of clinical response was made on the basis of the resolution of clinical signs and symptoms, including fever, leukocytosis, reduction in the size of the lesion (for SSTI), and radiographically observed abnormalities (for pneumonia). Specimens of blood, sputum, and urine were obtained at baseline for Gram's staining, culture, and susceptibility testing, as appropriate. For skin lesions, performance of fine-needle aspiration or closed biopsy was required; for purulent lesions, swabs were obtained for culture. If bacteremia was suspected, $\geq$2 blood samples for culture were obtained from separate sites before the initiation of therapy, and 2 additional samples were obtained within 48–72 h. Culture was also done at the time of the switch from intravenous to oral therapy (in the linezolid group), at EOT, and at the TOC visit. Susceptibility testing was done in a central laboratory according to National Committee for Clinical Laboratory Standards guidelines [45].

Populations for analysis. Study populations were defined as follows. The intent-to-treat (ITT) population included all randomized patients who received $\geq$1 dose of study medication. The microbiological intent-to-treat (MITT) population included all ITT patients who had a culture-confirmed infection with a staphylococcal pathogen at baseline. The MRSA-ITT population was the subset of MITT patients with culture and susceptibility testing results that confirmed infection with an MRSA isolate at baseline. The evaluable MRSA population was the subset of MRSA-ITT patients who met enrollment criteria, received adequate study medication ($\geq$7 days and 13 doses), had received no prohibited antibiotics before or during study therapy, and returned for a follow-up assessment (unless clinical or microbiological outcome at EOT was "treatment failure").

Efficacy variables. Efficacy was assessed according to the clinical outcome at the TOC visit. There were 4 possible clinical outcomes: "cure," "treatment failure," "indeterminate," or "missing." "Cure" was defined as resolution of the baseline clinical signs and symptoms of infection after $\geq$5 days and $\geq$10 doses of treatment. The outcome "treatment failure" was assigned if there was persistence or progression of signs and symptoms of infection after $\geq$2 days and $\geq$4 doses of treatment or if there was no clinical assessment at EOT and TOC. "Indeterminate" was assigned if there was clinical improvement or cure at EOT and no assessment at TOC or if there was cure after receipt of <5 days or <10 doses of study medication. The outcome "missing" was assigned if <2 days or <4 doses of treatment were received.

There were 4 possible microbiological outcomes: "success," "treatment failure," "indeterminate," or "missing." "Success" was defined as documented or presumed eradication of all pathogens present at baseline or colonization. "Treatment failure" was defined as documented or presumed persistence of $\geq$1 pathogen present at baseline, superinfection, or reinfection. "Indeterminate" was assigned if the clinical outcome at

Table 1. Summary of general and infection-specific inclusion and exclusion criteria for patients in a study of linezolid versus vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Category or diagnosis, type of criteria	Criterion or criteria
General	
Inclusion	Patient hospitalized or institutionalized, ⩾13 years of age, weight ⩾40 kg, with presumed MRSA infection
	Laboratory findings (e.g., Gram staining or culture results) consistent with *S. aureus* infection and signs and symptoms consistent with pneumonia, skin and soft-tissue infection, urinary tract infection, right-side endocarditis, "other" infection, or bacteremia of unknown source
	Patient expected to survive for duration of study
Exclusion	Left-side endocarditis, osteomyelitis, or infections of the CNS; presence of infected devices that could not be removed; absolute neutrophil count of <500 cells/mm^3; known liver disease with total bilirubin level of >5.0 mg/dL
	Pregnancy, breast-feeding, inability or unwillingness to practice contraception
	Hypersensitivity to study medications, receipt of ⩾24 h of potentially effective antibiotic within 48 h of study entry (unless that therapy had failed or the isolated pathogen was drug-resistant)
	History of pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension
Pneumonia	
Inclusion	Baseline chest radiograph demonstrated new or progressive infiltrates, consolidation with or without effusion, and ⩾2 of the following signs and symptoms: cough, new or worsened purulent sputum production, rales and/or signs of pulmonary consolidation, dyspnea, tachypnea, and/or hypoxemia
	At least 2 of the following findings: fever (temperature, ⩾38°C [⩾100.4°F] taken orally, ⩾38.5°C [⩾101.2°F] tympanically, or ⩾39°C [⩾102.2°F] rectally); respiratory rate of >30 breaths per minute; systolic hypotension; heart rate of ⩾120 beats per minute; altered mental status; requirement for mechanical ventilation; elevated total peripheral WBC count of >10,000 cells/mm^3, with >15% immature neutrophils (band forms), or leukopenia (WBC count of <4500 cells/mm^3)
	If patient is HIV-infected, CD4 cell count of >200 cells/mm^3
Exclusion	Chronic granulomatous disease, lung cancer or malignancy that had metastasized to the lungs, cystic fibrosis or known or suspected active tuberculosis
Skin and soft-tissue infection	
Inclusion	Accessible infection site for obtaining specimens for Gram staining and culture
	At least 2 of following findings: drainage or discharge, erythema, fluctuance, heat or localized warmth, pain or tenderness to palpation, swelling or induration
Exclusion	Presence of infection that has a high cure rate with surgical intervention alone (e.g., furunculosis or folliculitis); superinfected eczema; concomitant systemic corticosteroid therapy; foot, ischemic, or decubitus ulcers associated with diabetes; necrotizing fasciitis; gas gangrene; burns on >20% of the body surface
Urinary tract infection, inclusion	At least 1 of following findings: dysuria, frequency, urgency, suprapubic pain
	Culture of a pretreatment (obtained within 48 h of baseline), clean-catch, midstream urine specimen (or catheter-collected urine sample) that yielded >10^5 cfu/mL MRSA with ⩾10 WBCs per high-power field
Bacteremia of unknown origin, inclusion	Culture of ⩾1 blood sample that yielded *S. aureus* and 1 of the following findings: fever, chills, leukocytosis with prominent left shift, changes in vital signs

the TOC visit was indeterminate or missing. The outcome "missing" was assigned if there was no microbiological data from the TOC visit. Specific pathogen eradication rates were determined.

Safety variables. All patients who received ⩾1 dose of study medication were included in the safety analyses. Evaluations included periodic assessment of adverse events; performance of laboratory tests (including hematologic and serum chemical analyses), urinalysis, and physical examination; measurement of vital signs; and monitoring of concomitant nonstudy medications.

Statistical analyses. Assuming a 90% treatment success rate, 142 evaluable patients were required per treatment group for an equivalence determination within 10%, with a 2-sided

Table 2. Populations for analysis in a study of linezolid versus vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Study population	No. of patients, by treatment group	
	Linezolid group	Vancomycin group
ITT	240	220
MITT		
Total	157	144
S. aureus isolated	124	118
MRSA-ITT	117	107
Evaluable MRSA	56	60

NOTE. ITT, intent-to-treat (i.e., all treated patients); MITT, microbiological ITT (i.e., patients with culture-proven infection with a staphylococcal pathogen at baseline); MRSA-ITT, ITT patients with confirmed MRSA infection at baseline; evaluable MRSA, patients infected with MRSA who met clinical and microbiological evaluability criteria.

test level of 5% and a desired statistical power of 80%. Ninety-five percent confidence intervals were calculated for differences between treatment groups in the rates of clinical cure, microbiological success, and pathogen eradication. Categorical variables were compared by the χ^2 test. All statistical tests were 2-sided; $P \leqslant .05$ was considered statistically significant. Analyses were done with SAS, version 6.0 (SAS Institute). Stepwise logistic regression analysis was used to evaluate differences between treatment groups in the rate of clinical outcomes for the ITT population and for subsets of ITT patients with pneumonia or SSTI at the follow-up visit. Odds ratios and the level of significance were also calculated.

RESULTS

Study population. Table 2 shows the distribution of patients in each study population. Sixty-five percent of the ITT population had culture-confirmed infection with a staphylococcal organism at baseline. *S. aureus* was identified in 80% of the MITT population, and 93% of these isolates were methicillin resistant. Demographic characteristics (for the ITT population) were similar at baseline for the 2 treatment groups with respect to weight, sex, race, region, and diagnosis (table 3). The treatment groups were similar with respect to medical history, physical examination findings, clinical signs and symptoms, vital signs, and clinical laboratory values. The size of skin lesions of patients with SSTI, the degree of lobar involvement in patients with pneumonia, and the number of bacteremic patients were similar between the 2 groups. The mean age was higher in the linezolid group than in the vancomycin group. Among ITT patients, 154 (64.2%) of 240 patients in the linezolid group

Table 3. Summary of baseline demographic and clinical characteristics of the intent-to-treat population in a study of linezolid versus vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* infections.

Characteristic	Linezolid group (n = 240)	Vancomycin group (n = 220)	P
Sex			.993
Male	143 (59.6)	131 (59.5)	
Female	97 (40.4)	89 (40.5)	
Race			.161
White	195 (81.3)	168 (76.4)	
Black	18 (7.5)	30 (13.6)	
Other	27 (11.3)	22 (10.0)	
Age, mean years ± SD	63.9 ± 16.1	59.8 ± 20.2	.016
Weight, mean kg ± SD	73.33 ± 20.31	73.10 ± 20.31	.907
Other conditions			
Bacteremia	45/240 (18.8)	40/220 (18.2)	.875
Pneumonia			
Multilobar pneumonia	19/50 (38.0)	26/49 (53.1)	.132
Pleural effusion	19/50 (38.0)	16/49 (32.7)	.578
SSTI			
Infected surgical incision or wound	49/92 (53.3)	45/83 (54.2)	.899
Skin ulcer, abscess, or other lesion	31/92 (33.7)	28/83 (33.7)	.996
Cellulitis	12/92 (13.0)	10/83 (12.0)	.843
Area of skin lesion >28 cm^2	44/86 (51.2)	37/76 (48.7)	.753

NOTE. Data are no. (%) of patients or no. of patients with specific diagnosis/no. of patients with general diagnosis (%), unless noted otherwise. SSTI, skin and soft-tissue infection.

Table 4. Clinical diagnosis at baseline (ITT and MRSA-ITT populations) in a study of linezolid versus vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

	No. (%) of patients, by treatment group and population			
	Linezolid group		Vancomycin group	
Diagnosis[a]	ITT (n = 240)	MRSA-ITT (n = 117)	ITT (n = 220)	MRSA-ITT (n = 107)
Skin infection				
Total	122 (50.8)	60 (51.3)	108 (49.1)	51 (47.7)
With bacteremia	8 (3.3)	8 (6.8)	5 (2.3)	3 (2.8)
Pneumonia				
Total	50 (20.8)	31 (26.5)	49 (22.3)	33 (30.8)
With bacteremia	8 (3.3)	8 (6.8)	7 (3.2)	7 (6.5)
Urinary tract infection				
Total	12 (5.0)	6 (5.1)	15 (6.8)	6 (5.6)
With bacteremia	1 (0.4)	1 (0.9)	1 (0.5)	1 (0.9)
Other[a]				
Total	30 (12.5)	14 (12.0)	23 (10.5)	9 (8.4)
With bacteremia	11 (4.6)	6 (5.1)	15 (6.8)	6 (5.6)
Bacteremia of unknown source	26 (10.8)	6 (5.1)	24 (10.9)	7 (6.5)

NOTE. ITT, intent-to-treat (i.e., all treated patients); MRSA-ITT, ITT patients with confirmed MRSA infection at baseline.

[a] Includes catheter-associated infection, intra-abdominal or pelvic infection, laryngotracheobronchitis, mediastinitis, infected device, bacteremia secondary to parotitis, empyema, lumbar fistula, sinusitis, and subgaleal empyema. One patient with right-side endocarditis was also included in this category.

and 134 (60.9%) of 220 in the vancomycin group had ⩾1 comorbid condition; 34 (14.2%) of 240 and 21 (9.5%) of 220, respectively, had ⩾3 comorbid conditions. The most common diagnoses were SSTI and pneumonia, and proportions of diagnoses were similar for the 2 treatment groups (table 4).

The duration of treatment (in the ITT population) was similar between the 2 treatment groups: 188 (78.3%) of 240 patients in the linezolid group and 166 (75.5%) of 220 in the vancomycin group received study medication for ⩾7 days. The mean duration of treatment (±SD) was 12.6 ± 7.1 days in the linezolid group and 11.3 ± 6.7 days in the vancomycin group. Sixty-one percent of patients in the linezolid group received oral linezolid. Overall, 78 (32.5%) of 240 patients in the linezolid group and 69 (31.4%) of 220 in the vancomycin group discontinued treatment. The most common reasons for discontinuation of study medication were as follows: no methicillin-resistant pathogen detected at baseline (13.3% of patients [32 of 240] in the linezolid group vs. 17.3% of patients [38 of 220] in the vancomycin group), death (6.7% [16 of 240] vs. 5.9% [13 of 220]), adverse events (3.8% [9 of 240] vs. 3.2% [7 of 220]), lack of treatment efficacy (2.9% [7 of 240] vs. 1.4% [3 of 220]), noncompliance (0.8% [2 of 240] vs. 0.9% [2 of 220]), personal request (0.8% [2 of 240] in the linezolid group), and unspecified (4.2% [10 of 240] vs 2.7% [6 of 220]).

Efficacy data. There were no statistically significant differences between the treatment groups in the rates of clinical cure or microbiological success; this was true for all 4 patient populations (table 5). In the evaluable MRSA population, the clinical outcome for 73.2% of patients in the linezolid group and 73.1% of patients in the vancomycin group was "cure"; the microbiological outcome for 58.9% and 63.2% of patients, respectively, was "success" at the time of the TOC visit. Resistance to linezolid or vancomycin was not detected at baseline or after the end of treatment in any patient. Concomitant aminoglycoside use in patients with suspected gram-negative pathogens was rare; for these patients, the clinical and microbiological outcomes were similar between treatment groups. Pathogen eradication rates for all staphylococcal species (regardless of resistance status) were 52.3% (68 of 130 isolates) in the linezolid group and 51.2% (64 of 125 isolates) in the vancomycin group. MRSA eradication rates in evaluable MRSA isolates were 60.7% (34 of 56 isolates) and 63.2% (36 of 57 isolates), respectively. At baseline, few patients were infected with isolates of other methicillin-susceptible or methicillin-resistant staphylococcal species (i.e., *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*).

Efficacy results were not different among patients with the same baseline diagnosis between the 2 treatment groups (table

Table 5. Clinical and microbiological outcomes at the test-of-cure visit in a study of linezolid versus vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Outcome, study population	Linezolid group, by outcome (n = 240)			Vancomycin group, by outcome (n = 220)			P	95% CI
	Cure or success	Indeterminate	Missing	Cure or success	Indeterminate	Missing		
Clinical cure								
ITT	109/192 (56.8)	27	21	93/169 (55.0)	27	24	.74	−8.5 to 12.0
MITT	75/125 (60.0)	22	10	69/117 (59.0)	19	8	.87	−11.4 to 13.4
MRSA-ITT	59/98 (60.2)	15	4	53/85 (62.4)	16	6	.77	−16.3 to 11.9
Evaluable MRSA	41/56 (73.2)	0	0	38/52 (73.1)	5	3	.99	−16.6 to 16.8
Microbiological success								
MITT	62/122 (50.8)	20	15	62/120 (51.7)	14	10	.90	−13.4 to 11.7
MRSA-ITT	49/99 (49.5)	14	4	47/91 (51.6)	12	4	.77	−16.3 to 12.1
Evaluable MRSA	33/56 (58.9)	0	0	36/57 (63.2)	1	2	.65	−22.2 to 13.7

NOTE. Data are no. of patients or no. with outcome/total no. of patients (%), based on the number of patients assessed and excluding those with indeterminate or missing outcomes. Possible outcomes were "cure/success," "treatment failure," "indeterminate," or "missing." ITT, intent-to-treat (i.e., all treated patients); MITT, microbiological ITT (i.e., patients with culture-proven infection with a staphylococcal pathogen); MRSA-ITT, ITT patients with confirmed MRSA infection at baseline; evaluable MRSA, patients infected with MRSA who met clinical and microbiological evaluability criteria.

6). Despite the small number of patients, similar efficacy was observed among patients with bacteremia (cure rates ranged from 51.5% to 60% in the linezolid group and from 46.9% to 70% in the vancomycin group) (table 6). Among 6 bacteremic patients who had failure of linezolid therapy, 1 died before EOT, secondary to an unrelated aspiration pneumonia; 2 had sepsis (1 due to *Klebsiella* species and 1 due to *Candida* species); and 1 had persistent infection that resulted from an infected dialysis catheter that was not removed. Of the remaining 2 patients, 1 had myeloma and blood cultures that were persistently positive for *S. aureus,* and 1 had persistently negative blood culture results and died of "uncontrolled sepsis." Two of the 3 bacteremic patients who had failure of vancomycin therapy died of sepsis or multiple-system organ failure before EOT; the other died of respiratory failure and severe thrombocytopenia after treatment. Development of drug-resistant strains as the reason for clinical failure was not detected in either group.

Logistic regression analysis revealed that, at baseline, there were no differences between the linezolid and vancomycin groups with respect to the conditions assessed but did reveal that there were differences between patients with and patients without specific baseline comorbidities. ITT patients with cardiac, hepatic, or respiratory conditions were at a significantly increased risk of treatment failure, regardless of treatment group.

Safety data. Adverse events were generally mild to moderate in severity and of limited duration, and they usually did not result in discontinuation of study medication; however, a higher percentage of linezolid-treated patients experienced gastrointestinal effects (table 7). Fewer than 5% of patients in each group discontinued study medication because of an adverse event (4.2% of patients [10 of 240] in the linezolid group vs. 4.5% of patients [10 of 220] in the vancomycin group; P = .842). A higher proportion of patients in the linezolid group than patients in the vancomycin group had ⩾1 drug-related adverse event (as judged by the investigator). This difference was due to a higher frequency of gastrointestinal events (diarrhea and nausea) and special senses events (i.e., changes in taste perception). The incidence of pseudomembranous colitis due to *Clostridium difficile* was 0.4% (1 of 240 patients) in the linezolid group and 1.4% (3 of 220) in the vancomycin group, despite a higher frequency of drug-related diarrhea in the linezolid group. The rate of occurrence of serious adverse events (26.7% of patients [64 of 240] in the linezolid group vs. 25.5% [56 of 220] in the vancomycin group; P = .767) and death was not significantly different between the treatment groups (16.7% [40 of 240] vs. 13.6% [30 of 220]; P = .4). A poststudy effort to collect missing hospital discharge data identified an additional 7 deaths (mortality rates, 18.3% [44 of 240 patients] in the linezolid group vs. 15.0% [33 of 220] in the vancomycin group; P = .4) [20]. None of these deaths were considered to be related to receipt of study medication.

Changes in the results of serum chemical and hematologic assays were similar between the 2 treatment groups. Mean serum chemistry values remained within normal ranges. Mean WBC and neutrophil counts decreased in both groups during the study, a finding consistent with resolution of infection. Mean hemoglobin levels increased: the mean increases from baseline were 0.24 g/dL in the linezolid group and 0.95 g/dL in the vancomycin group (P = .008). For platelet counts, the mean decrease from baseline was greater for the vancomycin group (3.5×10^3 cells/mm^3 decrease in the linezolid group vs. 25.5×10^3 cells/mm^3 in the vancomycin group), but the dif-

Table 6. Clinical cure rates by site of infection in a study of linezolid versus vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Type of infection, study population	Linezolid group, by outcome			Vancomycin group, by outcome		
	Cure	Indeterminate	Missing	Cure	Indeterminate	Missing
Skin and soft-tissue						
ITT[a]	64/99 (64.6)	13	10	54/87 (62.1)	12	9
MRSA-ITT	37/53 (69.8)	6	1	32/43 (74.4)	6	2
Evaluable MRSA	27/34 (79.4)	0	0	22/30 (73.3)	2	2
Pneumonia						
ITT[a]	20/39 (51.3)	7	4	16/32 (50.0)	8	9
MRSA-ITT	12/23 (52.2)	6	2	14/26 (53.8)	6	2
Evaluable MRSA	9/12 (75.0)	0	0	12/16 (75.0)	1	0
Urinary tract						
ITT[a]	6/10 (60.0)	1	1	8/11 (72.7)	2	2
MRSA-ITT	2/5 (40.0)	1	0	2/3 (66.7)	2	1
Evaluable MRSA	0/1 (0.0)	0	0	1/1 (100)	1	1
Other[b]						
ITT[a]	12/24 (50.0)	5	1	8/19 (42.1)	2	2
MRSA-ITT	6/12 (50.0)	2	0	3/7 (42.9)	1	0
Evaluable MRSA	3/6 (50.0)	0	0	2/3 (66.7)	1	0
Bacteremia[c]						
ITT[a]	17/33 (51.5)	6	6	15/32 (46.9)	6	2
MRSA-ITT	13/23 (56.5)	4	2	10/20 (50.0)	4	0
Evaluable MRSA	9/15 (60.0)	0	0	7/10 (70.0)	0	0

NOTE. Data are no. of patients or no. of patients with cure/ total no. of patients (%), based on the number of patients assessed and excluding those with indeterminate or missing outcomes. ITT, intent-to-treat (i.e., all treated patients); MRSA-ITT, ITT patients with confirmed MRSA infection at baseline; evaluable MRSA, patients infected with MRSA who met clinical and microbiological evaluability criteria.

[a] For the linezolid group, $n = 240$; for the vancomycin group, $n = 220$.

[b] Includes catheter-associated infection, intra-abdominal or pelvic infection, laryngotracheobronchitis, mediastinitis, infected device, bacteremia secondary to parotitis, empyema, peripheral collection from lumbar fistula, peritonitis, sinusitis, and subgaleal empyema. One patient with right-side endocarditis was also included in this category for purposes of analysis.

[c] Includes bacteremia secondary to known infections and bacteremia of unknown source.

ference was not statistically significant ($P = .230$). The 2 treatment groups had similar percentages of patients who had, at any time during the study, ⩾1 substantially abnormal serum chemical or hematolgogic assay result (defined as twice the upper limit of the normal range or, if the baseline value was abnormal, twice the baseline value for serum chemical values and <75% of the lower limit of the normal range or, if the baseline value was abnormal, <75% of the baseline value for hematologic values), except with respect to platelet counts. Substantially low platelet counts were noted in 23 (10.0%) of 230 patients in the linezolid group and in 6 (2.9%) of 210 patients in the vancomycin group ($P = .003$). Most of these linezolid-treated patients had decreased platelet counts at baseline or underlying risk factors associated with thrombocytopenia; none had a drug-related bleeding event. Drug-related thrombocytopenia was reported in only 4 of these patients, each of whom was receiving concomitant heparin, warfarin, or aspirin therapy. The thrombocytopenia resolved in 2 patients, 1 patient was lost to follow-up, and 1 died of underlying comorbidities after life-support measures were withdrawn.

No clinically significant differences were noted between groups with respect to urinalysis results, vital sign measurements, or findings of physical examination. Drug interactions between study medications and other concomitant medications were not evident. The incidence of possibly monoamine oxidase inhibitor–related adverse events was similar between treatment groups, and the occurrence of these events did not require the discontinuation of study medication.

DISCUSSION

This study is the largest reported comparator-controlled study to date of patients with presumed MRSA infections. More than 200 enrolled patients had culture-proven MRSA infections, and >100 patients met clinical and microbiological evaluability criteria. The 2 treatment groups were similar with respect to base-

Table 7. Summary showing the most frequent adverse events, by category, in a study of linezolid versus vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* infections.

Category of adverse event, specific event	No. (%) of patients		*P*
	Linezolid group (n = 240)	Vancomycin group (n = 220)	
All			
Diarrhea	26 (10.8)	9 (4.1)	.006
Nausea	23 (9.6)	10 (4.5)	.037
Vomiting	15 (6.3)	8 (3.6)	.199
Anemia	13 (5.4)	8 (3.6)	.361
Urinary tract infection	13 (5.4)	16 (7.3)	.413
⩾1 event	164 (68.3)	136 (61.8)	.143
Drug related			
Diarrhea	9 (3.8)	0 (0.0)	.004
Nausea	6 (2.5)	1 (0.5)	.073
Dyspepsia	3 (1.3)	0 (0.0)	.096
Non–application site pruritus	1 (0.4)	3 (1.4)	.275
Anaphylaxis	0 (0.0)	2 (0.9)	.139
Abnormal renal function	0 (0.0)	2 (0.9)	.139
⩾1 event	44 (18.3)	18 (8.2)	.001
Serious			
Sepsis	8 (3.3)	8 (3.6)	.859
Respiratory failure	5 (2.1)	4 (1.8)	.838
Multiple-system organ failure	4 (1.7)	5 (2.3)	.639
⩾1 event	64 (26.7)	56 (25.5)	.767

line clinical characteristics across the study populations. However, as expected, cure rates were lower among patients with multiple comorbid conditions, because of underlying illnesses, a finding that is consistent with the results of other studies [46–48]. Most patients received ⩾7 days of treatment, and 60% of patients completed treatment and follow-up visits.

Linezolid therapy was clinically and microbiologically as effective as standard vancomycin therapy for patients hospitalized with methicillin-resistant staphylococcal infections, including SSTI and nosocomial pneumonia due to MRSA. This effect was consistent across all efficacy assessments. Approximately one-half of the MRSA-ITT patients had a clinical diagnosis of SSTI at baseline, with similar clinical cure and microbiological success rates for linezolid and vancomycin treatments. The consistent outcome results and the use of objective end points (e.g., pathogen eradication) provided a solid basis for comparing efficacy, despite the open-label design of the trial. Regarding aminoglycoside use, in vitro and in vivo models suggest no evidence of synergy between linezolid and aminoglycosides. Although vancomycin and aminoglycosides potentially have synergistic activity against MRSA, few patients received concurrent aminoglycosides for more than 3–4 days in either treatment group, and outcomes were similar for such patients in both groups. Linezolid-resistant MRSA were not detected in this trial, nor have they been detected in any other clinical trial, but infection with these organisms has been reported in a patient receiving oral therapy for peritonitis who had an infected catheter that was not removed [49]. This avascular nidus of infection likely contributed to the development of resistance.

Safety assessment results were similar in the linezolid and vancomycin groups. Most adverse events were mild to moderate and of limited duration. The most common adverse events among linezolid-treated patients were gastrointestinal. The use of oral therapy may account for these differences, because these adverse events are known to be associated with oral antibiotic therapy; alternatively, because of the open-label design, investigators may have been more likely to report adverse events in linezolid-treated patients than in vancomycin-treated patients. No significant differences were noted between treatment groups with respect to serious adverse events, discontinuations due to adverse events, or increased numbers of adverse events because of thrombocytopenia. More than 50% of enrolled patients received a concomitant monoamine oxidase inhibitor–interacting drug, but no clinically relevant or significant monoamine oxidase inhibitor–related events were noted, nor were differences in the results of clinical laboratory assessments noted between treatment groups.

From both the clinical and economic perspectives, gram-

positive bacteria have become increasingly important nosocomial pathogens worldwide [17–19, 50–55]. Widespread use of broad-spectrum antimicrobial agents and the limited potency of some agents has exerted heavy selective pressure in hospital environments; thus, reemergence of resistant gram-positive pathogens, particularly MRSA, is of increasing concern.

Until recently, there were few therapeutic options for the treatment of MRSA infections [13]. Intravenous vancomycin remains the standard therapy, but concerns about *S. aureus* strains with reduced sensitivity to vancomycin and about emerging prevalence of these organisms in the community [6–11] may limit the usefulness of vancomycin in the future. Agents such as teicoplanin and quinupristin-dalfopristin are available in some countries but only in parenteral formulations, which may necessitate prolonged hospitalizations or costly and inconvenient home health care arrangements. Linezolid, in contrast to other anti-MRSA agents, is 100% bioavailable after oral administration [40, 41]. In this study, ~61% of patients received oral linezolid, and most switched to oral therapy within 5 days after the initiation of therapy. The availability of an effective, convenient oral formulation shortens the length of hospital stay [20]. As reported elsewhere [20], in the evaluable population, the median length of stay for the linezolid group was 2 days shorter than it was for the vancomycin group (14 vs. 16 days; $P = .08$), and, among patients with SSTI (ITT population), it was 5 days shorter for the linezolid group (9 vs. 14 days, respectively; $P = .052$). Also, more linezolid-treated than vancomycin-treated patients were discharged during the first 7 days of hospitalization (ITT population: 30% vs. 19%, respectively; $P = .005$) . These results suggest that use of oral linezolid for treatment of presumed MRSA infection may yield potentially significant economic benefits.

In conclusion, empirical intravenous-to-oral linezolid therapy was safe, well tolerated, and as effective as vancomycin in the treatment of nosocomial infections due to MRSA. Linezolid is a suitable alternative to vancomycin for the treatment of MRSA infections and may relieve pressure on vancomycin use.

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