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Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan

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***Objectives*: To compare the efficacy and safety of linezolid and vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in Japan.**

***Methods*: Patients with nosocomial pneumonia, complicated skin and soft-tissue infections or sepsis caused by MRSA were randomized to receive linezolid (600 mg every 12 h) or vancomycin (1 g every 12 h).**

***Results*: One hundred patients received linezolid and 51 received vancomycin with outcomes evaluated at the end of therapy (EOT) and at the follow-up (FU), 7–14 days later. At EOT, clinical success rates in the MRSA microbiologically evaluable population were 62.9% and 50.0% for the linezolid and vancomycin groups, respectively; and microbiological eradication rates were 79.0% and 30.0% in the two groups, respectively ($P < 0.0001$). At FU, the clinical success rates were 36.7% for both groups and the microbiological eradication rates were 46.8% and 36.7%, respectively. Reversible anaemia (13%) and thrombocytopenia (19%) were reported more frequently in linezolid patients; laboratory analysis showed mild decrease in platelet counts with full recovery by FU. The mean platelet count in linezolid patients with thrombocytopenia was 101 000/mm^3. Significantly low platelet counts (<50 000/mm^3) were observed more frequently in patients receiving vancomycin than in linezolid patients (6% versus 3%). Mean changes in haemoglobin levels between the two groups were not different.**

***Conclusions*: Linezolid is as effective as vancomycin for the treatment of MRSA infections and may be more effective than vancomycin in achieving microbiological eradication. Haematological adverse events were reported more frequently in linezolid-treated patients; analysis of laboratory data showed a mild reversible trend towards lower platelet counts.**

Keywords: MRSA, nosocomial infections, therapy

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen worldwide.[1] In Japan, cases of hospital-acquired severe MRSA infection began to be reported from the mid-1980s. Currently, the number of patients with MRSA infection in Japan is estimated to be ~300 000 with an MRSA incidence in hospital of ~60%.[2] Inpatient surveillance in selected sentinel clinics conducted by the Japanese Nosocomial Infection Surveillance (JANIS) of the Ministry of Health, Labour and Welfare shows that 92.7% of infections with drug-resistant bacteria were MRSA, and there were more than

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46.5 cases per clinic of MRSA infection reported in 2003, up from 24.9 cases per clinic in 1999.[3] Shimada *et al*.[4] reported on bacterial isolates from 16 Japanese hospitals in 2002; of 578 total isolates reported, 77 were *S. aureus*, of which 43 were MRSA (55.8%). The incidence of hospital infection has stabilized over the last 5 years at around 0.8 MRSA infections per 100 hospital admissions.[5]

In Japan, arbekacin, vancomycin and teicoplanin are currently approved for use in the treatment of MRSA infections.[6,7] However, all three drugs have a narrow therapeutic range and require therapeutic drug monitoring, particularly in patients with renal dysfunction. Potential adverse effects of vancomycin include renal toxicity and 'red-man' syndrome.[8,9] Teicoplanin has advantages over vancomycin, such as a longer half-life allowing once-daily dosing and fewer adverse reactions. However, teicoplanin has a protein-binding rate of ~90%, which may compromise therapeutic efficacy in some cases.[10] Bacterial strains resistant to arbekacin have been reported in Japan.[11,12]

Owing to the prevalence of vancomycin-resistant enterococci (VRE) and the presence of a vancomycin resistance gene in plasmids, the emergence of vancomycin-resistant *S. aureus* (VRSA) is unavoidable. Indeed, 199 patients with VRE infection have been reported to Japanese authorities since 2000.[3,13] Furthermore, circulating vancomycin-intermediate–resistant strains of *S. aureus* (VISA) and β-lactam antibiotic induced vancomycin-resistant MRSA have been reported in Japanese hospitals.[7,14,15] No reports of infection with VRSA have appeared in Japan, but several cases have been reported in the United States.[16,17] New antibiotics that are effective against vancomycin-resistant bacteria are needed.

Linezolid has reliable *in vitro* activity against methicillin-susceptible and methicillin-resistant staphylococci and streptococci. It can be given intravenously (iv) or as a 100% bioavailable oral dose,[18] allowing for a switch from iv to oral therapy after initial clinical improvement. As the mechanism of action is different for oxazolidinones and glycopeptides, isolates resistant to vancomycin have been uniformly susceptible to linezolid,[19] and linezolid also shows efficacy against these resistant isolates in a murine model.[20] There have been reports of the successful use of linezolid for MRSA infection following treatment complications with arbekacin, vancomycin or teicoplanin in Japan.[21]

This study was designed to evaluate the efficacy and safety of linezolid for the treatment of Japanese patients with nosocomial MRSA infections. Vancomycin was chosen as the comparator as it is the global standard therapeutic drug for MRSA infections.

Materials and methods

Study design

This randomized, open-label, comparator-controlled, multicentre study was conducted from October 2001 until January 2004 at 84 sites in Japan. The goal of the study was to compare linezolid with vancomycin for the treatment of patients with confirmed or suspected MRSA-related pneumonia, complicated skin and soft-tissue infection (cSSTI) or sepsis. However, the study was not designed to demonstrate statistical equivalence or superiority. The Institutional Review Board or Independent Ethics Committee at each study site approved the study protocol. Prior to enrolment, written informed consent was obtained from all patients or from a guardian if the patient was unable to sign the informed consent.

Study population

Patients with pneumonia, cSSTI or sepsis were enrolled in the study and randomized in a 2:1 ratio to receive linezolid or vancomycin for 7–28 days. General and infection-specific inclusion and exclusion criteria are listed in Table 1. All prior therapies within 14 days of the start of administration and any additional antimicrobial therapy were recorded.

Treatment

Patients were randomized to receive either linezolid 600 mg iv or orally or vancomycin 1 g iv, each given every 12 h. The investigator judged when it was appropriate to switch to oral linezolid after a minimum of 3 days of iv treatment. Vancomycin dose levels and intervals were adjusted by monitoring blood drug concentrations in patients with renal disorders and in elderly patients. The duration of treatment was 7–21 days for pneumonia and cSSTI and 7–28 days for sepsis.

Patients could receive aztreonam or gentamicin (or other aminoglycosides with no activity against the isolated MRSA) for Gram-negative coverage. If the pathogen was resistant to aztreonam and/or gentamicin, patients could receive another antibiotic at the discretion of the investigator, but this drug could not be effective against the patient's isolated MRSA.

Efficacy variables

Patients were evaluated at the end of therapy (EOT) and at the follow-up (FU) evaluation, 5–16 days post-treatment. The primary efficacy variables were clinical outcome and microbiological outcome. Secondary efficacy variables included clinical findings and symptoms, body temperature and white blood cell count, lesion size for patients with cSSTI, and summaries of chest radiographs or chest computed tomography (CT) findings for patients with pneumonia.

Four populations were defined for the analysis in this study and were: (i) the intent-to-treat (ITT) population, all patients who received one or more doses of the study medication; (ii) the clinically evaluable (CE) population, patients in the ITT population who met enrolment criteria, did not receive antibiotic therapy before the start of study medication that continued during the study (prior antibiotic use that stopped at study start was acceptable), received study medication for a minimum of 2 days and 4 doses if a clinical failure or 5 days and 10 doses if a clinical cure, were at least 80% compliant with study medication, did not receive potentially effective concomitant antibiotic(s) against MRSA for an adverse event (AE) or intercurrent illness during the study period, and had required FU assessment; (iii) the modified intent-to-treat (MITT) population, all patients in the ITT population with culture-confirmed (*S. aureus*) pathogen at baseline; and (iv) the microbiologically evaluable (ME) population, all patients in the CE population with culture-confirmed *S. aureus* at baseline and baseline pathogen was not resistant to study medications. Analyses for MITT and ME populations were conducted in patients in whom MRSA was detected (MITT-MRSA and ME-MRSA, respectively). The ME-MRSA population was the primary population for analysis of efficacy.

Table 1. Summary of inclusion and exclusion criteria

Category	Criteria
Inclusion	>20 years old, with body temperature >38°C (oral) or <36°C (axillary). Known or suspected MRSA infection, with signs and symptoms of active pneumonia, cSSTI or sepsis. Expected to survive study.
Pneumonia	MRSA proven or suspected from a specimen of sputum, bronchoalveolar lavage or transthoracic aspiration, taken before initiation of treatment. Chest X-ray consistent with the diagnosis of pneumonia. CT scans could be used as supportive evidence. Signs and symptoms included two or more of the following: cough, purulent sputum, abnormal auscultatory findings, signs of respiratory failure, signs of dyspnoea, worsening of tracheal aspirate fluid in mechanically ventilated patients. One of the following was required: leukocytosis or leukopenia (defined as WBC count >10 000/mm^3 or <4500/mm^3, respectively), band neutrophils >15%, pulse rate >120 beats/min or systolic hypotension.
cSSTI	Signs and symptoms included erythema, swelling, fluctuation, drainage, tachycardia, hypotension or leucocytosis. Infections could include adnexal infection, diffuse infection, secondary infection of a burn, ulcer, abscess, external injury or postoperative wound. Carrier of MRSA, repetitive infection of MRSA, received an ineffective prior antibacterial agent, infection developed at least 48 h after hospitalization.
Sepsis	Known or suspected MRSA infection causing sepsis. Suspected MRSA infection defined as having two or more of the following: MRSA carrier or repetitive infection of MRSA, ineffective prior antibacterial agent, MRSA from indwelling catheter, Gram-positive pathogen identified, infection developed at least 48 h after hospitalization. Heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ >32 torr, WBC count >12 000 cells/mm^3 or <4000/mm^3, or >10% immature neutrophils.
Exclusion	Endocarditis, osteomyelitis or a central nervous system infection or neutropenia (absolute neutrophil count <500/mm^3). Received >24 h of treatment with a potentially effective antimicrobial such as teicoplanin or arbekacin, or received other investigational drugs, within 3 and 30 days of study entry, respectively. Hypersensitive or intolerant to linezolid or vancomycin. Systemic corticosteroid therapy (prednisolone equivalent >10 mg/day) >14 days was prohibited for concomitant use.
Exclusion, pneumonia	Condition that made assessment of therapeutic response on X-ray or CT scan difficult, such as lung cancer, active tuberculosis or pyothorax. Mixed fungal or viral infection requiring systemic therapy.
Exclusion, cSSTI	Uncomplicated skin and soft-tissue infections; medical conditions in which inflammation could be prominent after bacterial eradication, such as secondary infection in eczema or dermatitis; decubitus, ischaemic ulcers, necrotizing fasciitis, gas gangrene, diabetic foot ulcer or burns >20% of total body surface; abscesses that required only surgical drainage for cure; bacteraemia or sepsis associated with meningitis.

MRSA, methicillin-resistant *Staphylococcus aureus*; cSSTI, complicated skin and soft-tissue infection; CT, computed tomography; WBC, white blood cell.

Clinical outcome was determined at the EOT visit as cured, improved or failed. The success rate at EOT was defined as the number of cures and improvements divided by the number of cures, improvements and failures. Cured was defined as resolution of the clinical signs and symptoms of infection when compared with baseline; improved was defined as improvement in two or more, but not all, clinical signs and symptoms of infection when compared with baseline; failed was defined as persistence or progression of baseline clinical signs and symptoms of infection; and indeterminate was defined as unable to assess. At FU, outcome was defined in three categories: cured, failed or indeterminate. The cure rate at FU was defined as the number of cures divided by the number of cures and failures. The clinical success rates in both groups reflected an automatic outcome of failure for patients receiving prohibited antimicrobials prior to FU.

Because of the differences in standards in Japan for hospitalization, information on duration of hospital stay was not collected.

Laboratory analyses

Specimens for Gram stain and culture were obtained from all patients, excluding patients with sepsis, at study admission. If the microbiological test results were negative, study medication could still be continued as long as clinical improvement was shown. Laboratory tests were performed by Mitsubishi-Kagaku Bio Chemical Laboratories, Inc. Standard testing performed included haematology, chemistry and microbiology.

Safety analysis

Safety analyses were performed on the ITT population. Vital signs, AEs and clinical laboratory values were evaluated. AEs were classified as mild, moderate or severe and considered related or unrelated to the study medication by the judgment of the investigator.

Statistical analyses

Comparisons between treatment groups at EOT and FU were carried out using a χ^2 test. Additionally, 95% confidence intervals (CIs) were calculated for the difference in success/cure rate and pathogen eradication rate. The incidences of AEs were compared between treatment groups using a χ^2 test. For clinical laboratory values and vital signs, a paired *t* test was used to evaluate changes within treatment group over time. Mean changes from baseline were compared between treatment groups using a one-way analysis of variance (ANOVA).

Results

Demographics and baseline characteristics

Of 154 patients enrolled in the study, 151 patients received study drug and comprised the ITT population (linezolid, $n = 100$; vancomycin, $n = 51$). The demographics of the two treatment arms were similar (Table 2). The CE population included 93 patients in the linezolid group and 47 patients in the vancomycin group. The MITT-MRSA population consisted of 71 and 34 patients in each treatment group, respectively. In the ME-MRSA group (the primary efficacy population), 62 patients received linezolid and 30 patients received vancomycin (Table 2). Seventy-one (71%) and 32 (62.7%) patients in the linezolid and vancomycin arms, respectively, completed the study.

The typical length of treatment for specific infections was 10–21 days for pneumonia and cSSTI, and 10–28 days for sepsis. The mean durations of treatment were 10.9 ± 5.0 days (range, 1–28 days) and 10.6 ± 5.1 days (range, 1–22 days) in the linezolid and vancomycin arms, respectively. Seventeen patients switched from linezolid iv to oral therapy; in these patients, total mean duration of treatment was 13.4 ± 4.3 days (range, 7–22 days).

Table 2. Demographics and patient disposition

	Linezolid, $n = 100$	Vancomycin, $n = 51$
Age		
mean, years (SD)	68.4 (16.4)	67.5 (16.3)
range, years	22–95	24–96
Sex, *n* (%)		
male	70 (70.0)	36 (70.6)
female	30 (30.0)	15 (29.4)
Weight		
mean, kg (SD)[a]	50.7 (12.8)	53.0 (15.3)
range (min–max), kg	30.0–110.0	29.8–107.0
Completed, *n* (%)	71 (71.0)	32 (62.7)
Discontinued, *n* (%)	29 (29.0)	19 (37.3)
Adverse event, *n* (%)	27 (27.0)	11 (21.6)
Consent withdrawn, *n* (%)	0 (0.0)	1 (2.0)
Lack of efficacy, *n* (%)	2 (2.0)	7 (13.7)
Study population, *n* (%)		
ITT	100 (100)	51 (100)
pneumonia	51 (51.0)	26 (51.0)
cSSTI	31 (31.0)	17 (33.3)
sepsis	18 (18.0)	8 (15.7)
CE	93 (93.0)	47 (92.2)
MITT-MRSA	71 (71.0)	34 (66.7)
ME-MRSA	62 (62.0)	30 (58.8)
pneumonia	35 (56.5)	19 (63.3)
cSSTI	18 (29.0)	10 (33.3)
sepsis	9 (14.5)	1 (3.3)

ITT, intent-to-treat; cSSTI, complicated skin and soft-tissue infection; CE, clinically evaluable; MITT-MRSA, modified intent-to-treat, methicillin-resistant *S. aureus*; ME-MRSA, microbiologically evaluable methicillin-resistant *S. aureus*.
[a]Three patients in the linezolid arm were not weighed.

Clinical outcomes

At EOT, overall clinical success rates in the ME-MRSA population were 62.9% and 50.0% for the linezolid and vancomycin groups, respectively ($P = 0.24$; Table 3). In patients with pneumonia, success rates were 60.0% (21/35) in the linezolid group and 47.4% (9/19) in the vancomycin group ($P = 0.37$). In patients with cSSTI, success rates were 77.8% (14/18) and 60.0% (6/10; $P = 0.32$) in the linezolid and vancomycin arms, respectively. In patients with sepsis, the success rate was 44.4% (4/9) in the linezolid arm. Only one patient in the vancomycin group had sepsis, and the outcome was assessed as failed at both (EOT and FU) evaluation points.

At FU, the overall clinical cure rates in the ME-MRSA population were 36.7% for both groups (Table 3). In patients with pneumonia, cure rates at FU in the two groups were 32.4% (11/34) and 31.6% (6/19), respectively. In patients with cSSTI, cure rates were 52.9% (9/17) and 50.0% (5/10) for linezolid and vancomycin, respectively. In patients with sepsis, the cure rate at FU was 22.2% (2/9) in the linezolid arm.

Overall in the ME-MRSA population, linezolid was more successful in treating pneumonia and cSSTI than was vancomycin (Figure 1). In the ITT population, the cure rate was 48.4%

Table 3. Clinical outcomes for microbiologically evaluable methicillin-resistant *S. aureus* patients (ME population) at the EOT and FU evaluations

Visit/response	Linezolid	Vancomycin	*P* value
EOT			
n	62	30	
success, *n* (%)[a]	39 (62.9)	15 (50.0)	0.2387
cured, *n* (%)	15 (24.2)	6 (20.0)	
improved, *n* (%)	24 (38.7)	9 (30.0)	
failed, *n* (%)	23 (37.1)	15 (50.0)	
FU			
n	60[b]	30	
cured, *n* (%)	22 (36.7)	11 (36.7)	1.0000
failed, *n* (%)	38 (63.3)	19 (63.3)	

EOT, end of treatment; FU, follow-up.
[a]Success = cured + improved.
[b]Excludes two patients with an outcome of indeterminate.

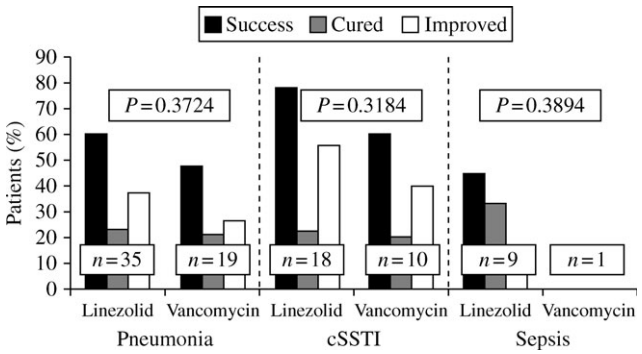

Figure 1. Clinical outcomes for the pneumonia, cSSTI and sepsis subgroups in the microbiologically evaluable methicillin-resistant *S. aureus* group at the EOT visit. Success = cured + improved.

Table 4. Summary of MIC distributions and clinical success rates by vancomycin MIC (MITT population, all patients with MRSA at study admission)

	Linezolid		Vancomycin	
Vancomycin MIC	*n*	clinical success rate (%)	*n*	clinical success rate (%)
0.5	17	35.3	7	42.9
1.0	57	33.3	30	33.3
2.0	1	0	0	—

(45/93) in the linezolid arm compared with 30.6% (15/49) in the vancomycin arm ($P = 0.04$) at the FU evaluation point.

Microbiological outcomes

All isolates of MRSA were susceptible to both linezolid and vancomycin, with no MICs ≥4 mg/L reported. The summary of MIC distributions at baseline is shown in Table 4. There was no relationship between efficacy or failure and MIC. There was only one baseline isolate with an MIC of 2 mg/L, in the linezolid group, and this patient had an unsuccessful outcome. No emergence of resistance to either linezolid or vancomycin occurred during the study.

At EOT, microbiological eradication rates in the ME-MRSA population were 79.0% and 30.0% in the linezolid and vancomycin groups, respectively ($P < 0.0001$). In patients with pneumonia, pathogen eradication rates were 71.4% (25/35) and 26.3% (5/19; $P = 0.0014$), and in patients with cSSTI, the eradication rates were 94.4% (17/18) and 40.0% (4/10; $P = 0.0014$) in the linezolid and vancomycin arms, respectively. Pathogen eradication was 77.8% (7/9) in patients with sepsis in the linezolid arm. There was only one patient with sepsis in the vancomycin arm, and pathogen eradication was not noted at either evaluation point.

At FU, the overall microbiological eradication rates in the ME-MRSA population were 46.8% and 36.7% ($P = 0.36$) for the linezolid and vancomycin groups, respectively (Figure 2). At FU, in patients with pneumonia, pathogen eradication rates were 37.1% (13/35) and 36.8% (7/19), and in patients with cSSTI, they were 72.2% (13/18) and 40.0% (4/10; $P = 0.09$) for the linezolid and vancomycin groups, respectively. Pathogen eradication was 33.3% (3/9) in patients with sepsis in the linezolid arm.

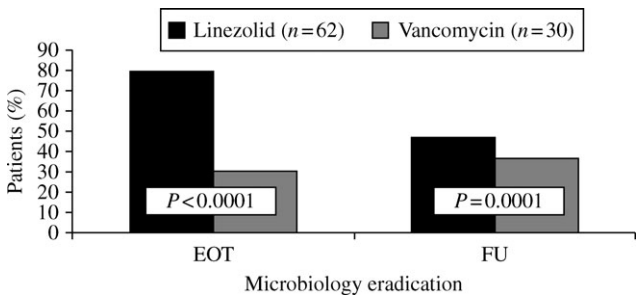

Figure 2. Microbiological outcome for the microbiologically evaluable methicillin-resistant *S. aureus* group at the EOT and FU visits.

Table 5. Treatment-related AEs

AE	Linezolid, $n = 100$	Vancomycin, $n = 51$
Total no. of patients reported (%)	55 (55.0)	22 (43.1)
Total (%)		
laboratory test abnormal	6 (6.0)	0 (0.0)
diarrhoea	10 (10.0)	1 (2.0)
liver function abnormal	6 (6.0)	4 (7.8)
renal function abnormal*	1 (1.0)	5 (9.8)
nausea	6 (6.0)	0 (0.0)
vomiting	5 (5.0)	0 (0.0)
anaemia*	13 (13.0)	1 (2.0)
leucopenia	7 (7.0)	0 (0.0)
thrombocytopenia*	19 (19.0)	1 (2.0)
hyponatraemia	7 (7.0)	0 (0.0)
rash	2 (2.0)	3 (5.9)

*$P < 0.05$ (χ^2 test).

Safety

A total of 156 treatment-related adverse events (AEs) were observed in 55% (55/100) of linezolid patients and 40 AEs were observed in 43.1% (22/51) of vancomycin patients.

Anaemia (13%) and thrombocytopenia (19%) were reported as AEs more frequently in linezolid-treated patients than in vancomycin-treated patients (2%) ($P < 0.05$; Table 5). All of these cases were mild and reversible. In the linezolid arm, recovery of platelet counts had occurred by FU, and no statistically significant difference was noted between treatment groups. Platelet counts often increased through the treatment period in the vancomycin arm but returned to baseline levels by FU (Figure 3). The mean platelet count in linezolid patients with an AE of thrombocytopenia was 101 000/mm^3. Significantly low platelet counts (<50 000/mm^3) after study admission were observed in 6% (3/51) of vancomycin patients and 3% (3/100)

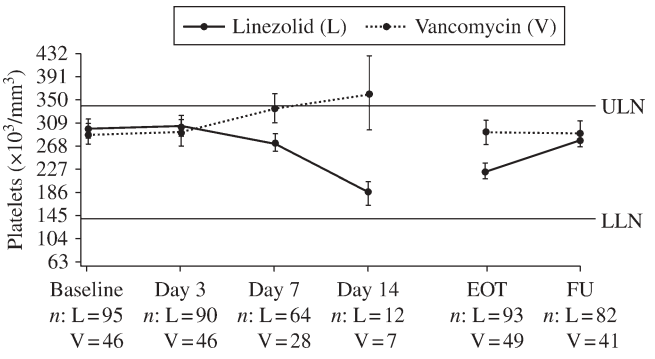

Figure 3. Platelet count at baseline and during and after treatment. ULN, upper limit of normal; LLN, lower limit of normal; EOT, end-of-treatment visit; FU, follow-up visit.

Table 6. Laboratory assays for haemoglobin, haematocrit, red blood cells and platelets

Laboratory assay	Treatment	EOT			FU		
		mean change	SD	*P* value	mean change	SD	*P* value
Hb (g/dL)	linezolid	−0.81	1.49	0.62	−0.71	1.71	0.60
	vancomycin	−0.66	1.74		−0.51	2.40	
Hct (%)	linezolid	−2.92	4.93	0.24	−2.34	5.25	0.64
	vancomycin	−1.85	5.27		−1.84	6.28	
RBCs ($\times 10^6$/mm^3)	linezolid	−0.27	0.51	0.30	−0.26	0.55	0.47
	vancomycin	−0.18	0.53		−0.18	0.65	
Platelets ($\times 10^3$/mm^3)	linezolid	−80.2	140.9	0.0001	−27.2	139.6	0.27
	vancomycin	20.1	126.3		2.0	119.6	

Hb, haemoglobin; Hct, haematocrit; RBCs, red blood cells.

of linezolid patients. Statistically significant decreases from baseline in haemoglobin, haematocrit and red blood cell count were noted at EOT and FU in both treatment groups, with the levels of decrease comparable between the treatment groups (Table 6). No differences in bleeding-related AEs were observed between the linezolid and vancomycin treatment groups. Renal function abnormalities were reported more frequently in vancomycin patients (9.8%) than in linezolid patients (1%; $P < 0.05$).

Serious adverse events (SAEs) without regard to causality were recorded in 19% of linezolid patients and 13.7% of vancomycin patients. There were 10 treatment-related SAEs observed in 9 patients in the linezolid arm. These were pancytopenia, thrombocytopenia and renal failure (two events each); and generalized oedema, hypokalaemia, hyponatraemia and interstitial pneumonia (one event each). In the vancomycin arm, three treatment-related SAEs were observed in two patients: increased serum creatinine, acute renal failure and interstitial pneumonia. In the linezolid and vancomycin groups, respectively, 14% and 13.7% of patients died by FU. Most of the SAEs and AEs that resulted in death were respiratory events including pneumonia. Treatment-related death was reported in one subject in each treatment group, with both patients dying of interstitial pneumonia.

AEs resulted in discontinuation of treatment in 25.0% (25/100) of linezolid patients and 19.6% (10/51) of vancomycin patients. Of these, AEs considered related to study treatment were observed in 16 (16.0%) linezolid patients and 7 (13.7%) vancomycin patients.

Discussion

This study, conducted in Japan, compared linezolid with vancomycin for the treatment of MRSA infections. This study utilized an open-label design because of inherent difficulties in blinding; vancomycin could not be given orally and requires monitoring of levels and dosing adjustment. The mean age of the patients was over 67 years and mean weight was below 53 kg in both treatment arms, indicating a relatively old and small study population. Linezolid was as effective as vancomycin for the treatment of MRSA infections. Clinical outcomes were similar at EOT and FU in both treatment groups. Furthermore, linezolid was significantly more effective at microbiological eradication than was vancomycin at EOT, although efficacy was comparable by the FU visit. The results were similar between treatment groups in patients with pneumonia and cSSTI, but no comparison could be made for patients with sepsis because of the small number of patients in the vancomycin arm.

Worldwide clinical trials with linezolid have demonstrated activity against MRSA infections. Linezolid has significantly better survival and clinical cure rates than vancomycin in patients with nosocomial pneumonia due to MRSA.[22,23] Linezolid was equivalent to vancomycin in the treatment of cSSTIs and demonstrated superior microbiological success rates in the treatment of the subset of patients with cSSTIs caused by MRSA.[24] The current study showed that in patients with cSSTI, the eradication rates at EOT were significantly higher in the linezolid group than in the vancomycin group (94.4% versus 40.0%; $P = 0.0014$). Furthermore, linezolid was shown to be superior to vancomycin in the treatment of patients with MRSA-infected surgical-site infections.[25] The current Japanese trial was not designed to show superiority in the treatment of MRSA infections compared with vancomycin, but these data from worldwide trials suggest that this may be the case.

The distribution of vancomycin MICs was relatively tight, with all isolates at study admission having MICs of 0.5–2.0 mg/L; only one isolate in a linezolid-treated patient had an MIC of 2.0 mg/L. Although the clinical success rate was lower in vancomycin-treated patients with a higher vancomycin MIC (1.0 mg/L), the numbers of patients were not sufficient to make any conclusions regarding MIC and outcome.

Overall rates of AEs were similar in linezolid and vancomycin treatment groups. Thrombocytopenia was reported more frequently in linezolid-treated patients, and analysis of quantitative laboratory data confirmed a trend towards lower platelet counts that was reversible after completion of treatment and caused no serious clinical consequences. Furthermore, analysis of laboratory data showed no differences in haemoglobin changes in the two treatment groups. Recently, reports of myelosuppression associated with linezolid use in non-comparative controlled studies[26–28] prompted several investigators to analyse large data sets for haematological effects of linezolid or vancomycin. One study assessed 686 patients with nosocomial pneumonia who

received linezolid or vancomycin, and neither drug was found to increase the risk of thrombocytopenia. Clinically significant thrombocytopenia was uncommon in the analysis, and linezolid was not associated with a greater risk of thrombocytopenia or bleeding in seriously ill patients compared with vancomycin.[29] In a meta-analysis, data from over 2000 linezolid- and comparator-treated patients from seven Phase 3 registration studies were analysed for evidence of myelosuppression. Lower platelet counts were observed in 2.2% of linezolid patients and 1.2% of comparator patients. These changes were consistent with mild, reversible, duration-dependent myelosuppression, normally observed with treatment durations of more than 2 weeks.[30] Lower haemoglobin counts were observed in 4.8% of linezolid patients and 4.5% of comparator patients. In the first 6 months of post-marketing surveillance, haematological abnormalities were reported in 0.1% of linezolid-treated patients, but no irreversible blood dyscrasias were documented.[31] In the light of our data and these documented studies, we recommend the use of haematological tests on a routine basis in patients receiving linezolid to minimize the complications of thrombocytopenia.

The incidence of MRSA infection in Japan is high, with infection rates in hospitals as high as 60%;[2] the problem is seen worldwide including the United Kingdom and Greece (over 40%),[32] although other European countries have much lower infection rates (<1% in the Netherlands, Denmark and Sweden). In the United States, nosocomial infection rates with methicillin-resistant bacteria are approaching 40%.[33] Furthermore, community-acquired MRSA is becoming an increasing problem with associated high morbidity and mortality.[34] The emergence of vancomycin-intermediate–resistant strains of bacteria has been reported across Asia, including in India, South Korea, Japan, the Philippines, Singapore, Thailand and Vietnam.[35] In particular, VISA and heterogeneous vancomycin-intermediate *S. aureus* infections (hVISA) have been reported in Thailand and Korea[36,37] and Japan,[6,14,15] although more recent research has shown that hVISA may be less problematic in Japan than previously thought.[38] VISA strains are quite rare, but hVISA infections, in which a subpopulation of bacteria are resistant to vancomycin, are more common, with up to 5% to 20% of MRSA thought to be hVISA.[39,40] At present, the only documented cases of VRSA have been in the United States,[16,17,19] but reports from around the world are inevitable. The emergence of resistant bacteria underlines the urgent need to develop new antibiotics for their treatment.

In conclusion, this study found that linezolid was as effective as vancomycin for the treatment of patients with pneumonia, cSSTI and sepsis caused by MRSA and may be more effective than vancomycin in achieving microbiological eradication. Thrombocytopenia was associated with linezolid use, but it was mild and reversible on treatment completion and had no serious clinical implications.

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