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ORIGINAL ARTICLE

Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections

Naoki Aikawa · Shinya Kusachi · Hiroshige Mikamo · Yoshio Takesue · Shinichi Watanabe · Yoshiyuki Tanaka · Akiko Morita · Keiko Tsumori · Yoshiaki Kato · Tomoko Yoshinari

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Abstract Daptomycin is a lipopeptide antibiotic active against gram-positive organisms and recently approved for marketing in Japan. This study investigates the efficacy and safety of daptomycin in Japanese patients with skin and soft tissue infections (SSTIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) for regulatory filing in Japan. Overall, 111 Japanese patients with SSTI were randomized in this open-label, randomized, active-comparator controlled, parallel-group, multicenter, phase III study. Patients received intravenous daptomycin 4 mg/kg once daily or vancomycin 1 g twice daily for 7–14 days. Efficacy was determined by a blinded Efficacy Adjudication Committee. Among patients with SSTIs caused by MRSA, 81.8 % (95 % CI, 69.1–90.9) of daptomycin recipients and 84.2 % (95 % CI, 60.4–96.6) of vancomycin recipients achieved a successful clinical response at the test-of-cure (TOC) visit. The microbiological success rate against MRSA at the TOC visit was 56.4 % (95 % CI, 42.3–69.7) with daptomycin and 47.4 % (95 % CI, 24.4–71.1) with vancomycin. Daptomycin was generally well tolerated; most adverse events were of mild to moderate severity. The measurement of daptomycin concentration in plasma revealed that patients with mild or moderate impaired renal function showed similar pharmacokinetics profiles to patients with normal renal function. Clinical and microbiological responses, stratified by baseline MRSA susceptibility, suggested that patients infected with MRSA of higher daptomycin MIC showed a trend of lower clinical success with a P value of 0.052 by Cochran–Armitage test. Daptomycin was clinically and microbiologically effective for the treatment of MRSA-associated SSTIs in Japanese patients.

Keywords Daptomycin · MRSA · Vancomycin · Skin infection · Soft tissue infection · SSTI

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N. Aikawa
Emergency and Critical Care Medicine, School of Medicine, Keio University, Tokyo, Japan

S. Kusachi
Department of Surgery, Toho University Medical Center Ohashi Hospital, Tokyo, Japan

H. Mikamo
Department of Infection Control and Prevention, Aichi Medical University, Aichi, Japan

Y. Takesue
Department of Infection Control and Prevention, Hyogo College of Medicine, Hyogo, Japan

S. Watanabe
Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

Y. Tanaka · A. Morita · K. Tsumori · Y. Kato · T. Yoshinari (✉)
Japan Development, MSD K.K., Kitanomaru Square, 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo 102-8667, Japan
e-mail: tomoko.yoshinari@merck.com

Introduction

Daptomycin (CUBICIN) is a novel cyclic lipopeptide that is derived from the fermentation of a strain of *Streptomyces roseosporus*. In contrast to other antibacterial agents, daptomycin targets multiple aspects of bacterial membrane function. Upon oligomerization on a bacterial membrane, daptomycin causes rapid depolarization, leading to a loss of membrane potential that ultimately inhibits RNA, DNA, and protein synthesis [1, 2]. Because of this novel

mechanism of action, daptomycin is an appropriate option for treating bacteria resistant to other antibacterial agents [3, 4]. In vitro, daptomycin has demonstrated rapid, concentration-dependent bactericidal activity against many clinically significant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) [5–7].

In clinical trials, the efficacy of daptomycin in the treatment of complicated skin and soft tissue infections (cSSTIs) caused by gram-positive bacteria was demonstrated in an analysis of two comparative phase III studies in a total of 1,092 patients [8]. In overseas studies, daptomycin 4 mg/kg was not inferior to the active comparator (vancomycin 1 g twice daily or a semisynthetic penicillin). In the daptomycin group, only 28 cases were microbiologically evaluable as MRSA infections. Thus, the efficacy data on MRSA-associated infection were limited.

According to the results of a 25-year longitudinal study in 10,000 Japanese hospitalized patients with infectious respiratory diseases, the proportion of *Staphylococcus aureus*-related infections caused by MRSA strains increased rapidly in 1986 and, between 1990 and 2005, MRSA accounted for approximately 60 % of all *S. aureus* infections in this study [9]. In a separate study conducted between 2004 and 2008, 45.5 % of all *S. aureus* isolates detected in inpatients were MRSA strains [10].

In Japan, daptomycin has been developed and approved within the category of anti-MRSA drugs, although intravenous daptomycin is approved in more than 70 countries for use against gram-positive bacteria susceptible to daptomycin, including methicillin-susceptible *S. aureus* (MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysagalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). A single phase I study examining single and multiple doses of daptomycin in Japanese subjects was previously conducted in Japan [11]. No serious adverse events occurred in this study.

We conducted a phase III study in SSTI and bacteremia patients for the purpose of regulatory filing in Japan. In this report, as a part of the registry study, the safety and efficacy of daptomycin in Japanese patients with MRSA-associated SSTIs are reported by comparing them to those of vancomycin. The pharmacokinetics of daptomycin in Japanese patients and susceptibilities of the isolated pathogens are also reported.

Patients and methods

Study design, patients, and treatment

This is a randomized, open-label, active-comparator controlled, parallel-group, multicenter, phase III study conducted across 61 Japanese medical institutions between 2008 and 2010. Male and female patients aged ≥20 years who required hospitalization and treatment with systemic antibacterial agents and gave consent to participate in the study were included. Inclusion criteria were (1) isolation of MRSA from specimens obtained within 3 days before starting treatment or the detection of gram-positive cocci and a strong suspicion of MRSA infection; and (2) presence of at least three of the following: drainage/exudate, erythema, fluctuance, localized warmth, pain/tenderness, swelling/induration, temperature >37.5 °C (oral) or 37 °C (armpit), out-of-normal-range WBC count, stab-cell >15 %, pulse rate >90/min, respiratory rate >20/min, positive CRP (C-reactive protein). Patients were excluded from the study for any of the following reasons: previous systemic antimicrobial therapy for >24 h during the previous 3 days (unless unresponsive to ≥72 h antibiotic therapy or detection of a resistant pathogen); presence of osteomyelitis, infectious arthritis, pneumonia (known or suspected), or human immunodeficiency virus (HIV) infection; presence or potential for developing severe neutropenia (neutrophils <500/μl); shock, uncontrollable hypotension; oliguria, undergoing hemodialysis or peritoneal dialysis; blood creatine phosphokinase (CPK) level ≥2 × the upper limit of normal (ULN); creatinine clearance <30 ml/min; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥5 × the ULN; total bilirubin ≥3.0 mg/dl. Patients with perirectal abscess, myositis, concomitant gangrene requiring debridement, multiple infected ulcers, or third-degree burns covering >10 % of the body surface area; septicemia; only surgery and/or drainage required to cure infection; or allergy or contraindications to vancomycin were also excluded.

Patients were randomized 4:1 to receive intravenous daptomycin (4 mg/kg over 30 min) once daily or vancomycin (1 g over at least 60 min) twice daily for 7–14 days. During therapeutic drug monitoring, the doses of vancomycin were adjusted based on age, renal function, and drug concentrations during therapeutic drug monitoring based on the discretion of investigators, and the trough concentrations were not recorded.

Assessments

Clinical and microbiological response at test-of-cure (TOC) was used as the primary endpoint for efficacy evaluation in this study.

Clinical responses at TOC were evaluated by study investigators within 7–14 days of the last dose of study medication and confirmed by the Efficacy Adjudication Committee (EAC), which was composed of five medical experts blinded to study therapy. By definition, a successful clinical response had to meet all the following criteria: an

EAC-confirmed clinical response of "cured" (resolution of clinically significant signs and symptoms) or "improved" (partial resolution of clinically significant signs and symptoms) at both end-of-treatment (EOT) and TOC; the patient did not receive a non-study antibacterial agent that could potentially have been effective against the causative pathogen; 4 days or more of study drug administration to the patient.

Microbiological responses at TOC were confirmed by the EAC and were based on culture results for causative gram-positive cocci isolated at baseline. A successful microbiological response was defined as "eradication of pathogen" (admission pathogen absent in culture) or "presumed eradication of the pathogen" (no material available for culture but patient was deemed as cured or improved by the study investigator).

The primary efficacy analysis was conducted in the modified intent-to-treat (MITT)-MRSA population, which included all patients who received at least one dose of study drug and in whom MRSA infection was confirmed on screening cultures. The microbiological efficacy in patients with gram-positive infections other than MRSA was also assessed in an exploratory manner. The clinical and microbiological success rates were calculated by treatment group for the primary efficacy endpoints, and 95 % confidence intervals were calculated using the Clopper–Pearson method. Safety analyses were conducted in the all-patients-as-treated population, which consisted of all randomized patients who received at least one dose of the study treatment. Safety parameters included adverse experiences as assessed by investigators, laboratory tests, and vital signs. CPK was set as one of the important safety parameters because CPK elevation was observed in dog toxicology studies and in the early period of clinical development when daptomycin was frequently administered. CPK >500 U/l was defined as predefined limits of change.

Minimum inhibitory concentration (MICs) of baseline MRSA isolates were measured manually by the broth microdilution method according to the CLSI testing guidelines (M7-A7, 2006) at Mitsubishi Chemical Medience Corporation, Tokyo, Japan. Daptomycin was provided from Cubist Pharmaceuticals, and the frozen panel including daptomycin, vancomycin, linezolid, teicoplanin, arbekacin, and oxacillin was prepared by Eiken Chemical Co. The relationship between clinical response and in vitro susceptibility was investigated by Cochran–Armitage test in an exploratory manner.

Pharmacokinetics analysis

Blood samples for determining daptomycin plasma concentration were obtained at screening, day 4 pre-infusion, the end-of-infusion, 30 min to 2 h post-dose, 4–10 h post-dose, and day 5 pre-infusion. The plasma concentration of daptomycin was measured by reverse-phase high performance liquid chromatography (HPLC) (Waters WISP 717 plus), and pharmacokinetics were calculated using a population pharmacokinetic method based on 18 non-Japanese studies (10 phase I studies and 8 phase II/III studies) and 2 Japanese studies (1 phase I study and the present study). The population PK profiles in patients with gram-positive infections (cSSSI) were determined using a two-compartment model with linear elimination characteristics. $T_{1/2}$, CL/wt, $AUC_{0-24\ h}$, and C_{max} were calculated and are shown after stratification for renal function (CL_{cr}) at baseline.

Results

Patient disposition

Of the 111 patients who were randomized, 88 received daptomycin and 22 received vancomycin. The baseline characteristics of the population as treated are presented in Table 1. Age, gender, body weight, creatinine clearance, and prior use of antibiotics were similar between the treatment groups. The doses of vancomycin were maintained in 17 patients, but increased in 3 patients and decreased in 2 patients based on the therapeutic drug monitoring results of the treatment period. A total of 110 patients with SSTIs received at least one dose of the study drug and were included in the safety population. Thirty-six (36) patients with no MRSA identified as causative pathogen (33 patients receiving daptomycin 4 mg/kg and 3 patients receiving vancomycin) were excluded from the efficacy analysis of MITT-MRSA population.

Efficacy evaluation

The rates of clinical and microbiological success for MITT-MRSA population are shown in Table 2. Because the patients were randomized regardless of the causative pathogen, the number of patients in MITT-MRSA resulted in a ratio of approximately 3:1 for daptomycin and vancomycin. Clinical success was achieved by 81.8 % (45/55 patients; 95 % CI, 69.1–90.9) of daptomycin recipients and 84.2 % (16/19; 95 % CI, 60.4–96.6) of vancomycin recipients. In patients with wound or burn, which were the most common causes, 81.6 % (31/38 patients) of daptomycin recipients and 84.6 % (11/13) of vancomycin recipients achieved clinical success. The rate of microbiological success against MRSA was 56.4 % (31/55 patients; 95 % CI, 42.3–69.7) in daptomycin recipients and 47.4 % (9/19; 95 % CI, 24.4–71.1) in vancomycin recipients. Daptomycin was also effective against a number of

Table 1 Baseline demographic of all patients

Baseline characteristic[a]	Daptomycin 4 mg/kg qd ($n = 88$)	Vancomycin 1 g bid ($n = 22$)
Age (years), median (range)	69.0 (22–92)	70.0 (29–82)
Gender (male)	47 (53.4)	15 (68.2)
Bodyweight (kg), median (range)	54.00 (28.3–117.8)	52.25 (36.5–78.3)
CL_{cr} (ml/min), median (range)	78.14 (23.1–260.8)	78.17 (37.7–153.7)
<30	1 (1.1)	0 (0.0)
≥30 to <50	17 (19.3)	5 (22.7)
≥50 to <80	28 (31.8)	7 (31.8)
≥80	41 (46.6)	10 (45.5)
Prior anti-MRSA antibiotics[b]	10 (11.4)	2 (9.1)

qd once daily, *bid* twice daily, CL_{cr} creatinine clearance, *MRSA* methicillin-resistant *Staphylococcus aureus*

[a] Unless otherwise specified, values are expressed as *n* (%)

[b] Anti-MRSA agent used within 28 days before the start of study drug administration

Table 2 EAC-assessed clinical and microbiological success rate for MITT-MRSA at TOC

Analysis group and disease type	Daptomycin 4 mg/kg qd		Vancomycin 1 g bid		
	n/*N*[a]	Success % (95 % CI[b])	*n*/*N*[a]	Success % (95 % CI[b])	*P* value[g]
Clinical success					
MITT-MRSA	45/55	81.8 (69.1–90.9)	16/19	84.2 (60.4–96.6)	0.593
Deep skin infection[c]	4/6	66.7	0/0	0.0	–
Wound or burn[d]	31/38	81.6	11/13	84.6	0.597
Erosion or ulcer[e]	9/9	100.0	4/5	80.0	0.090
Other infection[f]	1/2	50.0	1/1	100.0	0.760
Microbiological success					
MITT-MRSA	31/55	56.4 (42.3–69.7)	9/19	47.4 (24.4–71.1)	0.250
Deep skin infection[c]	4/6	66.7	0/0	0.0	–
Wound or burn[d]	23/38	60.5	7/13	53.8	0.338
Erosion or ulcer[e]	4/9	44.4	2/5	40.0	0.438
Other infection[f]	0/2	0.0	0/1	0.0	0.500

qd once daily, *bid* twice daily, *EAC* Efficacy Adjudication Committee, *MITT* modified intent-to-treat, *MRSA* methicillin-resistant *Staphylococcus aureus*, *TOC* test-of-cure

[a] *n*/*N* number of patients with an EAC-assessed clinical or microbiological success/number of patients in the analysis population

[b] Calculated using the Clopper–Pearson method

[c] Including cellulitis and abscess-related disease

[d] Including secondary infections of wounds, surgical wounds, burns, and gastric fistulas

[e] Including secondary infections of diabetic and nondiabetic ulcers and decubitus

[f] Including impetigo contagiosa, pyoderma, and genital psoriasis

[g] *P* value is based on Miettinen and Nurminen methods

other gram-positive cocci including MSSA and *E. faecalis* that were shown to be the cause of infection at baseline (Table 3).

Safety evaluation

Adverse events occurred in 70.5 and 86.4 % of patients treated with daptomycin and vancomycin, respectively (Table 4). Events considered to be related to the study drug occurred in 21.6 % (daptomycin) and 27.3 % (vancomycin) of patients, and six and four serious adverse events occurred in daptomycin recipients and vancomycin recipients, respectively. A drug-related serious adverse event (anaphylactic shock) occurred in one patient treated with daptomycin; this event occurred just after the initial dosing and resolved 4 days after drug treatment discontinuation.

Table 3 Microbiological success by causative pathogens other than MRSA

Causative pathogen	*n*/*N* (%)	
	Daptomycin 4 mg/kg qd	Vancomycin 1 g bid
Methicillin-susceptible *Staphylococcus aureus*	10/16 (62.5)	1/2 (50.0)
Enterococcus faecalis	7/10 (70.0)	0/0 (0.0)
Streptococcus equisimilis	0/3 (0.0)	0/0 (0.0)
Streptococcus agalactiae	0/1 (0.0)	1/1 (100.0)
Streptococcus pyogenes	1/1 (100.0)	1/1 (100.0)
Enterococcus faecium	0/1 (0.0)	1/1 (100.0)
Coagulase-negative *Staphylococcus*	1/1 (100.0)	0/0 (0.0)
Staphylococcus haemolyticus	1/1 (100.0)	0/0 (0.0)
Staphylococcus schleiferi	0/1 (0.0)	0/0 (0.0)
α-Hemolytic *Streptococcus*	0/1 (0.0)	0/0 (0.0)
γ-Hemolytic *Streptococcus*	1/1 (100.0)	0/0 (0.0)
Enterococcus gallinarum	0/1 (0.0)	0/0 (0.0)
Peptostreptococcus anaerobius	1/1 (100.0)	0/0 (0.0)
Peptostreptococcus magnus	0/1 (0.0)	0/0 (0.0)

n/*N* number of microbiological successes/number of patients with causative pathogen

Table 4 Summary of all adverse events and specific adverse events occurring with a frequency >5 % among patients treated with daptomycin or vancomycin

	Daptomycin 4 mg/kg qd ($N = 88$) *n* (%)	Vancomycin 1 g bid ($N = 22$) *n* (%)	*P* value[a]
Summary			
Any adverse event	62 (70.5)	19 (86.4)	0.934
Clinical event	51 (58.0)	17 (77.3)	0.952
Laboratory event	26 (29.5)	7 (31.8)	0.582
Drug-related adverse event	19 (21.6)	6 (27.3)	0.714
Clinical event	9 (10.2)	4 (18.2)	0.848
Laboratory event	13 (14.8)	4 (18.2)	0.653
Serious adverse event	6 (6.8)	4 (18.2)	0.951
Drug-related serious adverse event	1 (1.1)	0 (0.0)	0.309
Clinical adverse events (>5 % in either daptomycin- or vancomycin-treated patients)			
Pruritus	2 (2.3)	2 (9.1)	0.936
Erythema	0 (0.0)	2 (9.1)	0.998
Pyrexia	6 (6.8)	2 (9.1)	0.643
Diarrhea	2 (2.3)	2 (9.1)	0.936
Laboratory adverse events (>5 % in either daptomycin- or vancomycin-treated patients)			
AST increased	9 (10.2)	3 (13.6)	0.676
ALT increased	9 (10.2)	3 (13.6)	0.676
C-reactive protein increased	4 (4.5)	2 (9.1)	0.798

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *n* number of patients experiencing an event

[a] *P* value is based on Miettinen and Nurminen methods

Elevation of ALT and AST was the most common adverse event in both daptomycin and vancomycin groups. CPK >500 U/l was found in one daptomycin recipient (maximum level, 2,545 U/l) and in one vancomycin recipient (maximum level, 592 U/l). These CPK elevations were not associated with clinical symptoms, and they resolved within 6 days after the last dose in the daptomycin recipient. In addition, 9.1 % of daptomycin recipients and 9.1 % of vancomycin recipients had CPK levels >200 U/l. Furthermore, none of the CPK elevations in this study led to study discontinuation or was serious. Overall, three patients with SSTIs died (one in daptomycin group; two in

vancomycin group), but none of the deaths was considered drug related.

Pharmacokinetic evaluation with various renal functions

Pharmacokinetic parameters according to renal function are shown in Table 5. Following the administration of daptomycin 4 mg/kg once daily, the mean CL/wt values in patients with mild (CL_{cr}, 50–80 ml/min), moderate (CL_{cr}, 30 to <50 ml/min), and severe (CL_{cr}, <30 ml/min) renal impairment were approximately 15, 15, and 38 % lower, respectively, than those in patients with normal renal function (CL_{cr}, >80 ml/min). The mean steady-state systemic exposure (AUC), and $t_{1/2}$, for daptomycin increased with decreasing renal function, although the mean AUC was not markedly different for patients with CL_{cr} 30–80 ml/min compared with those with normal renal function. The AUC for one patient with CL_{cr} <30 ml/min was approximately 1.4 times higher than that in patients with normal renal function.

Susceptibility of MRSA isolates

Susceptibility of all the MRSA isolates at screening was measured. The daptomycin minimum inhibitory concentration (MIC) value of all 74 baseline MRSA isolates was below the CLSI and US FDA breakpoint of susceptibility of ≤1 μg/ml. The MIC_{90} (MIC range) for daptomycin, vancomycin, linezolid, teicoplanin, arbecacin, and oxacillin were 0.5 (0.25–1), 1 (0.5–2), 2 (1–4), 4 (0.25–8), 2 (0.25–4), and >128 (16 to >128) μg/ml, respectively.

Clinical and microbiological responses at TOC stratified by baseline MRSA susceptibility are shown in Table 6. Patients infected with MRSA of higher-MIC daptomycin showed a trend of lower clinical success with a P value of 0.052 by Cochran–Armitage test. The trend analysis per each type of infection was also tested. The response rate in wound or burn showed numerically similar trends (MIC 0.25, 0.5, and 1 showed clinical response of 87.5, 82.4, and 50.0 %, respectively). However, that was not statistically significant ($P = 0.343$), probably because of the limited number of samples ($n = 38$). The trend of microbiological success over each MIC was not clear ($P = 0.846$).

Discussion

This study was conducted to investigate the efficacy, tolerability, and pharmacokinetics of daptomycin in Japanese patients with SSTIs and bacteremia caused by MRSA. Because the bacteremia arm was designed as a noncomparative study and the number of patients was very limited (four patients as MITT-MRSA), only the results in SSTI patients are shown in this report. In addition to daptomycin, four anti-MRSA drugs (vancomycin, linezolid, teicoplanin, and arbekacin) are available in Japan. Glycopeptides (vancomycin and teicoplanin) and aminoglycosides (arbekacin) are known to cause renal toxicity, and these drugs are administered with the provision that their plasma concentrations are monitored [12]. Linezolid, an oxazolidinone, is known to cause myelosuppression, and its usage is essentially limited to 28 days in Japan [13]. Daptomycin is expected to add another choice to the treatment of MRSA infections in Japanese patients without the safety limitations of these other drugs. Thus, it is important to confirm the safety profile of daptomycin, including CPK elevations, exposure levels with regard to renal function, and its efficacy against MRSA infections in Japanese patients.

Because this study was conducted in support of the new drug application of daptomycin in Japan, it was important to collect as many patients who had received daptomycin as possible. Thus, patients were randomized to daptomycin in much higher proportion than to vancomycin. As this was

Table 5 Population pharmacokinetic parameters for daptomycin 4 mg/kg at steady state according to baseline renal function

Renal function status	$t_{1/2}$ (h)	CL/wt (ml/h/kg)	$AUC_{0-24\ h}$ (μg h/ml)	C_{max} (μg/ml)
Normal (CL_{cr} >80 ml/min) $N = 38$	9.31 ± 1.77	13.6 ± 6.7	337 ± 115	45.5 ± 12.1
Mild impairment (CL_{cr} 50 to 80 ml/min) $N = 28$	11.80 ± 2.79	11.5 ± 4.3	400 ± 136	46.0 ± 12.5
Moderate impairment (CL_{cr} 30 to <50 ml/min) $N = 15$	14.58 ± 3.52	11.6 ± 6.5	414 ± 163	39.5 ± 14.2
Severe impairment (CL_{cr} <30 ml/min) $N = 1$	16.20	8.5	470	52.3

Values are mean ± SD

CL_{cr} creatinine clearance estimated using the Cockcroft–Gault equation with actual body weight, *CL/wt* total clearance from plasma adjusted for body weight, *$AUC_{0-24\ h}$* area under the plasma concentration–time curve from time 0 to 24 h, *C_{max}* maximum plasma concentration

Table 6 Clinical and microbiological responses stratified by the susceptibility of baseline MRSA to daptomycin

MRSA methicillin-resistant *Staphylococcus aureus*; *TOC* test-of-cure

Treatment group	MIC of daptomycin at baseline (μg/ml)	Clinical response at TOC	Microbiological response at TOC
Daptomycin	0.25	12/13 (92.3 %)	6/13 (46.2 %)
4 mg/kg qd	0.5	32/39 (82.1 %)	25/39 (64.1 %)
$n = 55$	1.0	1/3 (33.3 %)	0/3 (0.0 %)

further compounded by the limited sample size, there was no statistical power to compare the efficacy of the two groups. It should also be noted that the proportion of infection types in each treatment group was not the same in "Deep skin infection" (no patient in vancomycin group) and "Erosion or ulcer" (higher proportion in vancomycin group than in daptomycin group). However, as the majority had "Wound or burn," which was found in similar proportions in the two treatment groups (69.1 % for the daptomycin group and 68.4 % for the vancomycin group), the imbalance in "Deep skin infection" and "Erosion or ulcer" was considered to have a limited impact on the total efficacy results.

In patients with SSTIs, the primary efficacy endpoint, namely, the clinical and microbiological response at TOC in the MITT-MRSA population, was similar between the daptomycin and vancomycin groups, and was also similar to those observed in previously published phase III trials conducted in other countries [8], indicating that daptomycin is effective for the treatment of SSTIs in Japanese patients. In the present study, daptomycin was also found to be effective in treating SSTIs caused by MSSA and *E. faecalis*, which is consistent with reports from previous studies [8].

Daptomycin at a dose of 4 mg/kg once daily was generally well tolerated. There were no drug-related deaths. A drug-related serious adverse event (anaphylactic shock) was reported in one patient treated with daptomycin 4 mg/kg, and this event resolved after discontinuing therapy. Similar to other antibiotics, daptomycin should be used with care in patients with hypersensitivities. Elevated CPK levels have been reported in some daptomycin studies [8, 14–16]. In the present study, the daptomycin and vancomycin groups had each one patient whose CPK increased to >500 U/l, but the levels for both patients subsequently returned to the normal range, and no associated muscular symptoms were observed. These safety data show that the overall safety profile of daptomycin in Japanese patients was similar to the known profiles reported in prior studies.

Daptomycin is eliminated primarily by the kidneys, and the baseline CL_{cr} value in patients is known to be related to the plasma level of daptomycin. The mean AUC was not markedly different in patients with mild or moderate renal impairment compared with patients with normal renal function. However, the AUC for one patient with CL_{cr} <30 ml/min was approximately 1.4 times higher than that for patients with normal renal function. This finding supports the current label, recommending dose modifications in such patients, including its administration every 48 h.

Of all the antibacterial agents tested for susceptibility against the MRSA isolates detected at screening, daptomycin showed potent antibacterial activity, with a MIC_{90} of 0.5 μg/ml. The susceptibility of MRSA isolates in Japan seems similar to that reported elsewhere [6, 7, 17]. Patients with baseline pathogens with a higher MIC tended to show less favorable clinical responses to daptomycin. These data suggest that assessment of pathogen susceptibility can help clinicians select the most appropriate treatment.

In addition to 4 mg/kg daptomycin for the treatment of SSTI, 6 mg/kg daptomycin is indicated for the treatment of bacteremia and infectious endocarditis in Japan and other countries. Furthermore, the safety and efficacy of higher doses of daptomycin (8–12 mg/kg) were clinically investigated in Europe and the United States [16, 18]. Some guidelines on the treatment of MRSA infection also indicate the use of 8–10 mg/kg for the treatment of bacteremia and endocarditis, as recommended by some experts [19, 20]. Because the safety profile in Japanese healthy subjects who received single doses of 2–12 mg/kg and multiple doses of 4–10 mg/kg daptomycin was reported as generally safe [11], it may be interesting to investigate the efficacy of higher doses of daptomycin in Japanese patients having complicated diseases or less susceptible strains against vancomycin (e.g., MIC >2 μg/ml).

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Conflict of interest N.A., S.K., H.M., Y.T., and S.W. served on the Efficacy Adjudication Committee for this study and received per diem stipends from MSD KK for attending the committee. Y.T., A.M., K.T., Y.K., and T.Y. are employees of MSD KK, a group of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA.

Ethical approval The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki. It was performed in accordance with the protocol agreed to by the study investigators and the study sponsor, and according to the standards provided by Article 14 Paragraph 3 and Article 80-2 of the Pharmaceutical Affairs Law and the Good Clinical Practice Ordinance.

The study was approved by institutional review boards at each study site. Voluntary, written informed consent was obtained from each patient before study commencement.

Appendix: Study investigators

The following investigators participated in this study: T. Mori (Sapporo Tokushukai Hospital); Y. Shimizu (Sapporo Higashi Tokushukai Hospital); K. Kaneko (National Hospital Organization, Kasumigaura Medical Center); S. Kaneda (National Hospital Organization, Chiba Medical Center); T. Tamaki; S. Hosaka; H. Kuroki (National Center for Global Health and Medicine); T. Ohnishi (Teikyo University Hospital); Y. Saida (Toho University Ohashi Medical Center); M. Adachi (Japan Labour Health and Welfare Organization, Kanto Rosai Hospital); H. Ogino (Shonankamakura General Hospital); Y. Yamagishi (Aichi Medical University Hospital); H. Oshima (National Hospital Organization, Kumamoto Medical Center); Y. Narita (Teine Keijinkai Hospital); K. Fukuyama (Toride Kyodo General Hospital); K. Tsukamoto (Yamanashi Prefectural Central Hospital); A. Ozawa (National Hospital Organization, Shizuoka Medical Center); S. Asai (Chukyo Hospital); H. Konishi (Kishiwada Tokushukai Hospital); T. Morita (Matsubara Tokushukai Hospital); M. Nakano (Sasebo City General Hospital); A. Nagase (National Hospital Organization, Asahikawa Medical Center); F. Otsuka (Tsukuba University Hospital); Y. Moriyama (Tsuchiura Kyodo General Hospital); Y. Morisawa (Jichi Medical University); M. Sugaya (The University of Tokyo Hospital); A. Igarashi (Kanto Medical Center NTT EC); Y. Horiuchi (National Disaster Medical Center); Y. Tanabe (Niigata University Medical and Dental Hospital); H. Tsukada (Niigata City General Hospital); T. Hachiya (Japanese Red Cross Society Suwa Hospital); M. Shirai (National Hospital Organization, Tenryu Hospital); S. Urano (JA Shizuoka Kohseiren Enshu Hospital); K. Yano (Hamamatsu Medical Center); S. Tomoyama (Yaizu City Hospital); H. Kageyama (Iwata City Hospital); T. Kamiya (Rakuwakai Otowa Hospital); M. Mitsunobu (Meiwa Hospital); K. Shinohara (National Hospital Organization, Kochi National Hospital); T. Maekawa (Fukuoka University Chikushi Hospital); M. Nakano (Maebashi Red Cross Hospital); Y. Sato (Fuji Heavy Industries Ltd., Health Insurance Society, General Ota Hospital); Y. Otomo; Y. Inoue (Tokyo Medical and Dental University Hospital Faculty of Medicine); H. Takasu (National Hospital Organization, Yokohama Medical Center); M. Iwasawa (Nagano Red Cross Hospital); D. Manaka (Kyoto-Katsura Hospital); K. Haku (National Hospital Organization, Osaka Medical Center); H. Tsubakihara (National Hospital Organization, Osaka Minami Medical Center); N. Uyama; K. Tsukamoto (Hyogo College of Medicine); H. Hamada (Nikko Memorial Hospital); Y. Mizushima (Kyoaikai Hospital); F. Yoshimi (Ibaraki Prefectural Central Hospital); K. Ishizaka (Kanto Central Hospital of the Mutual Aid Association of Public School Teachers); H. Harada (Yao Tokushukai General Hospital); Y. Sato (National Hospital Organization, Kanmon Medical Center); D. Yoshimura (Fukuoka Saiseikai General Hospital); T. Kusumoto (National Hospital Organization, Beppu Medical Center); A. Imamura (Moriya Keiyu Hospital); all investigators are in Japan.

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