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A Post Marketing Survey of Intravenous Daptomycin in Japanese Patients

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Abstract

Introduction：Daptomycin is an antibiotic that shows bactericidal activity against a wide variety of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*（MRSA）. It is approved in Japan, for patients with bacteremia, right-sided infective endocarditis, and skin and skin tissue infections caused by MRSA. This post-marketing survey（PMS）was conducted, to investigate the safety and effectiveness of daptomycin in daily clinical practice.

Methods：Patients that newly received daptomycin were included. Safety was assessed by analyzing adverse events that were judged to have an undeniable causal relationship as adverse drug reactions（ADRs）. Overall effectiveness was assessed by clinical judgment and microbiological response findings. The incidence of ADRs and overall effectiveness were summarized by patient characteristics.

Results：Data was collected from 1,013 patients. In the safety analysis（n＝974）, 15.61％ of patients reported ADRs. The ADR reported with highest frequency was hepatic function abnormal（2.67％）. In the effectiveness analysis（n＝470）, overall effectiveness（88.3％）and high microbiological response rates（68.9％）were observed. Additionally, there were no major differences in the frequencies of ADRs and overall effectiveness by patient characteristics.

Conclusions：In this large scale PMS survey the long-term safety and effectiveness

Key words：daptomycin, MRSA, post-marketing, safety, Japan

of daptomycin, from previous clinical trials, were demonstrated under daily clinical practice, in all subgroups.

Introduction

Daptomycin（CUBICIN®）is a cyclic lipopeptide antibiotic that exhibits rapid and concentration-dependent bactericidal activity against a wide variety of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*（MRSA）[1]. It has been approved in Japan since 2011 for adult patients with bacteremia, right-sided infective endocarditis（IE）, and skin and skin tissue infections（SSTIs）, such as necrotizing fasciitis, caused by MRSA[2]. Daptomycin acts at the bacterial membrane and the mechanism of action is to inhibit RNA, DNA and protein synthesis by rapid depolarization and a corresponding loss of membrane potential[3]. This mechanism of action is unique and is believed to make daptomycin a suitable treatment for bacterial infections that are resistant to other antibiotic compounds[4)5]. Daptomycin is recommended as one of the first-line drugs for bacteremia and IE in the Japanese guideline[6].

A phase Ⅲ trial in Japan was conducted for MRSA-associated SSTI, bacteremia, and right-sided IE[7)8]. Daptomycin was found to be effective for treating MRSA-associated infections and was generally well tolerated[7)8]. In US clinical trials, daptomycin was found to be non-inferior to standard therapy for *S. aureus* bacteremia and right-sided IE[9]. Additionally, the safety and effectiveness of daptomycin were found to be comparable with conventional therapies in treating SSTIs[10].

The objective of this post-marketing survey was to investigate the safety and effectiveness of daptomycin in daily clinical practice in Japan, and also to collect rare safety events or other information, which could not be fully captured in clinical trials. We focused on important survey items including the safety and effectiveness in patients with comorbid renal impairment, the frequency of increased blood creatine phosphokinase（CPK）and musculoskeletal disorder adverse reactions, and peripheral neuropathy. Additionally, as adverse events of interest, hypersensitivity, eosinophilic pneumonia, alanine aminotransferase（ALT）increased and aspartate aminotransferase（AST）increased were investigated.

To date there has been a lack of real world data on the long-term safety and effectiveness of daptomycin treatment for MRSA in Japanese daily clinical practice. This survey was, therefore, conducted to address these clinical questions, by collecting data from over 1,000 patients including cases of long-term use with the aim of providing useful information to health care providers.

Ⅰ Patients and Methods

1. Patient population

This post-marketing survey was conducted from June 1, 2012 to May 31, 2018 at 176 medical institutions and 173 sites consented to the publication of data. Patients that received first time administration of daptomycin were included by the prospective central registration method, as shown in **Figure 1**.

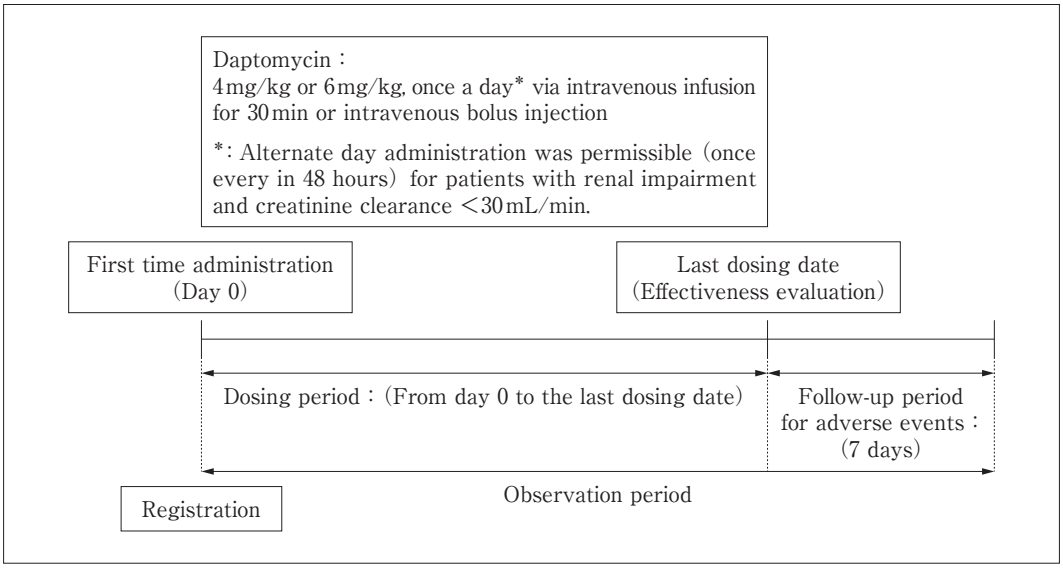

Figure 1 Survey flow

Since this survey was conducted under daily clinical practice, all the background, safety and effectiveness measurements were conducted according to the standard procedure at each medical institution and the data were collected in case report forms.

Patients included in this survey had been prescribed daptomycin for treating the following infections in which MRSA was the indicated strain：bacteremia, right-sided IE, and SSTIs. The dose of daptomycin was specified by indication；6 mg/kg/day for bacteremia and IE and 4 mg/kg/day for deep skin infection, secondary infection（e.g. trauma, burn and surgical wound）, and secondary infection of erosion and ulcer. Daptomycin is recommended to be administered intravenously either by infusion for 30 min or by bolus injection[8]. Patients diagnosed with severe comorbid renal impairment（creatinine clearance by the Cockcroft-Gault equation：＜30 mL/min or on hemodialysis or continuous ambulatory peritoneal dialysis）at baseline were prescribed on alternate days.

This survey was conducted in accordance with the requirements of the pharmaceutical affairs law and the ministerial ordinance of "Good Post-Marketing Study Practice".

2. Safety assessments

To investigate safety information, all reported adverse events（AEs）were collected from all patients who received any dose of daptomycin. Adverse drug reactions（ADRs）were defined as AEs for which the causal relationship to daptomycin could not be ruled out by an investigator or company.

These ADRs were classified according to the Medical Dictionary for Regulatory Activities/Japanese version（MedDRA/J Ver. 22.1）. As one of the important survey items and adverse events of special interest, CPK（CPK value shifts and frequency of musculoskeletal disorder ADRs including blood CPK increased）, eosinophilic pneumonia, and frequency of peripheral neuropathy ADRs were collected. Other adverse events

of special interest were hypersensitivity and AST and ALT increased.

We investigated the safety information by patient characteristics, with special interest in ADR frequency in patients with comorbid renal impairment, as well as elderly patients, patients with long-term administration（defined as duration of administration ≥42 days）, intravenous bolus injection and by first daily dose.

3. Effectiveness assessments

To assess effectiveness, overall effectiveness and microbiological test results were collected. Overall effectiveness of daptomycin was judged by an investigator based on symptoms before and after administration, rated as effective（cured or improved）, ineffective, or not evaluable. Overall effectiveness was also investigated by patient characteristics；comorbid renal impairment, infection type, use of concomitant antibacterial drugs, and intravenous bolus injection which were characteristics of special interest.

Microbiological test results were judged by an investigator as positive or negative, respectively.

4. Statistical analysis

Data were summarized descriptively. The safety analysis set was defined as patients registered in the survey who received any dose of daptomycin for any indication and who had recorded AE information available. The effectiveness analysis set excluded patients from the safety analysis set as follows：patients who were prescribed daptomycin outside the indicated infection types and causative bacteria, including infections in which the causative bacteria were unknown；received non-approved regimen doses；and for whom overall effectiveness or microbiological test results were not available.

The frequency of ADRs and overall effectiveness were summarized and compared by patient demographic and clinical characteristics. To explore safety in patients with severe comorbid renal impairment, ADR frequency by patient characteristics was also summarized in a subset of patients with a creatinine clearance of ＜30 mL/min or on dialysis. To evaluate safety with long-term daptomycin administration, ADR frequency was also summarized by the time of onset. CPK values were summarized in patients with musculoskeletal disorder AEs at the time of occurrence of the first AE event and the CPK values before daptomycin administration.

Fisher's test was conducted when the number of categories was 2, excluding categories with 0 patients；when the number of categories, excluding unknown, was ≥3, the Cochran-Armitage test was used for ordinal data and the chi-square test was used for non-ordinal data. All statistical tests were calculated using SAS® Release 9.4（SAS Institute, Inc., Cary, NC）and considered statistically significant at $p<0.05$.

Ⅱ Results

1. Patient disposition

Of 1,050 patients registered at 173 institutions, case report forms were collected from 1,013 patients（**Figure 2**）. A total of 974 patients were included in the safety analysis set（39 patients were excluded；30 for contract violation, 9 for registration violation and 1 for duplication）. From the safety analysis set, 504 patients were excluded for the effectiveness analysis；the reasons were

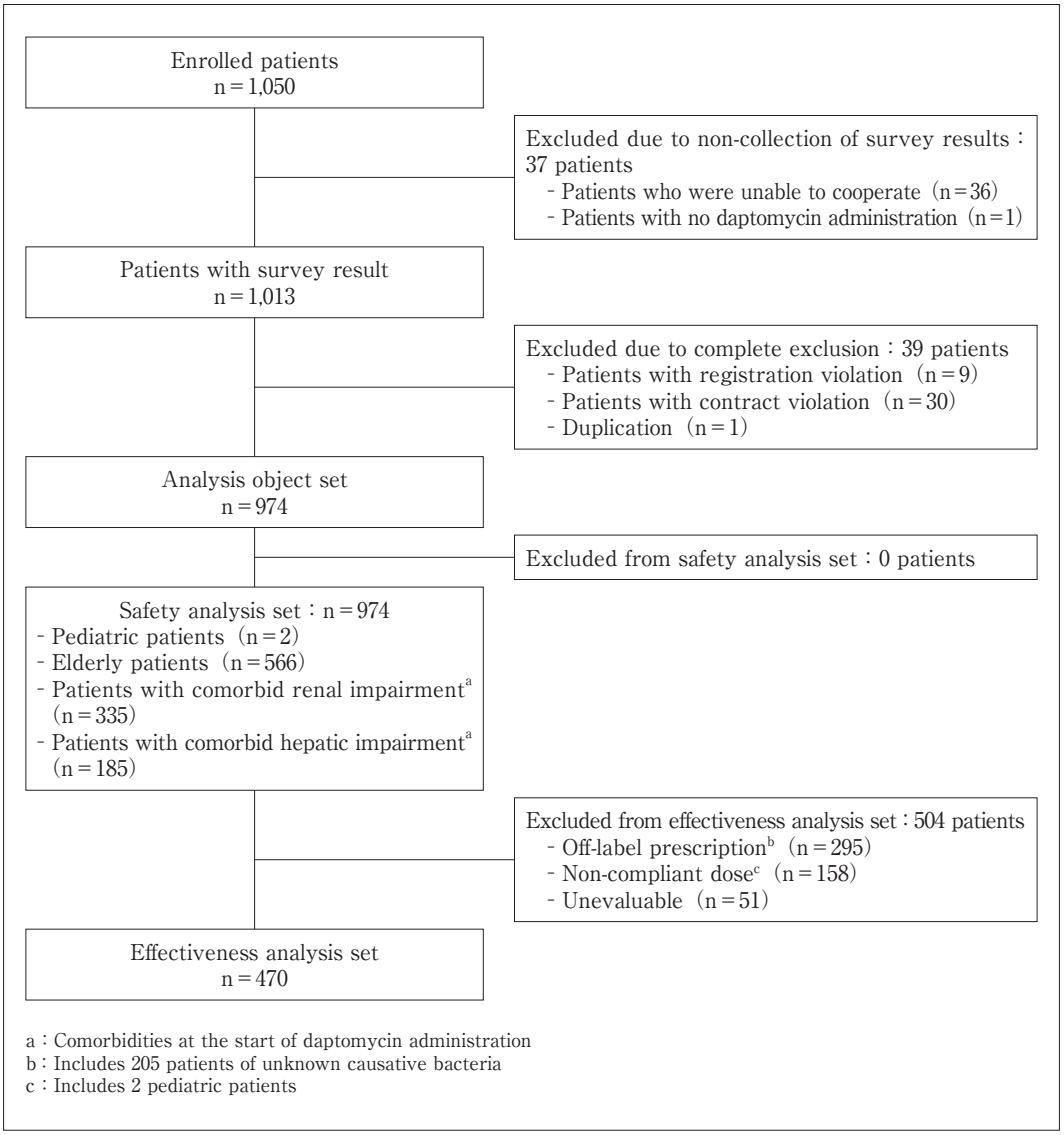

Figure 2 Patient flow

off-label prescription in 295 patients (205 in whom the causative bacterial strain was not identified), non-compliant dose in 158 patients and 51 patients who were unevaluable. The effectiveness analysis set included 470 patients.

2. Patient characteristics

In the safety analysis set (974 patients), the median age was 68.0 years, and 566 patients (58.1%) were aged ≥65 years, a majority (326 patients) of whom were aged ≥75 years (**Table 1**). The most common infection type was SSTIs (56.1%), followed by bacteremia (41.7%) and IE (1.4%). Regarding the causative bacterial strain, MRSA was detected in 527 patients (54.1%). A total of 335 patients (34.4%) had comorbid renal impairment at baseline. Demographic char-

Table 1 Patient demographics

	Safety analysis (n＝974)	Effectiveness analysis (n＝470)
	n（%）	n（%）
Sex		
Male	632（64.9）	303（64.5）
Female	342（35.1）	167（35.5）
Age（years）		
＜15	2（ 0.2）	0（ 0.0）
≥15-＜25	21（ 2.2）	7（ 1.5）
≥25-＜35	29（ 3.0）	13（ 2.8）
≥35-＜45	81（ 8.3）	32（ 6.8）
≥45-＜55	90（ 9.2）	48（10.2）
≥55-＜65	185（19.0）	85（18.1）
≥65-＜75	240（24.6）	117（24.9）
≥75	326（33.5）	168（35.7）
Infection type		
Bacteremia	406（41.7）	216（46.0）
IE	14（ 1.4）	1（ 0.2）
Right-sided IE	3（ 0.3）	1（ 0.2）
Left-sided IE	11（ 1.1）	0（ 0.0）
SSTIs	546（56.1）	253（53.8）
Deep skin infection	141（14.5）	68（14.5）
Secondary infections（e.g. trauma, burn and surgical wound）	353（36.2）	151（32.1）
Secondary infection of erosion and ulcer	52（ 5.3）	34（ 7.2）
Others	8（ 0.8）	0（ 0.0）
Causative bacteria[a, b]		
MRSA	527（54.1）	376（80.0）
Suspected MRSA	5（ 0.5）	2（ 0.4）
Staphylococcus	155（15.9）	92（19.6）
Other gram-positive organisms	69（ 7.1）	5（ 1.1）
Gram-negative organism	21（ 2.2）	3（ 0.6）
Unknown	205（21.0）	0（ 0.0）

（continued）

(continued)

	Safety analysis (n＝974)	Effectiveness analysis (n＝470)
	n (%)	n (%)
Severity before administration		
Mild	109 (11.2)	51 (10.9)
Moderate	478 (49.1)	228 (48.5)
Severe	344 (35.3)	164 (34.9)
Unknown	43 (4.4)	27 (5.7)
Pretreatment drug (antibacterial drug only)		
No	289 (29.7)	141 (30.0)
Yes	668 (68.6)	325 (69.1)
Unknown	17 (1.7)	4 (0.9)
Switching from other MRSA treatments		
No	771 (79.2)	372 (79.1)
Yes	185 (19.0)	93 (19.8)
Unknown	18 (1.8)	5 (1.1)
Use of concomitant drug		
No	126 (12.9)	66 (14.0)
Yes	835 (85.7)	401 (85.3)
Unknown	13 (1.3)	3 (0.6)
Complications (overall)		
No	128 (13.1)	53 (11.3)
Yes	831 (85.3)	409 (87.0)
Unknown	15 (1.5)	8 (1.7)
Hepatic impairment (comorbid)		
No	770 (79.1)	372 (79.1)
Yes	185 (19.0)	88 (18.7)
Unknown	19 (2.0)	10 (2.1)

(continued)

（Table 1　continued）

	Safety analysis (n＝974)	Effectiveness analysis (n＝470)
	n（%）	n（%）
Renal impairment（comorbid）		
No	624（64.1）	265（56.4）
Yes	335（34.4）	197（41.9）
Unknown	15（ 1.5）	8（ 1.7）
Degree of comorbid renal impairment		
Creatinine clearance[c]：≥30-＜50 mL/min	49（14.6）	30（15.2）
Creatinine clearance[c]：＜30 mL/min or on dialysis	224（66.9）	132（67.0）
Dialysis		
No	811（83.3）	373（79.4）
Yes	156（16.0）	92（19.6）
Unknown	7（ 0.7）	5（ 1.1）

IE；infective endocarditis, MRSA；methicillin-resistant *Staphylococcus aureus*, SSTIs；skin and soft tissue infections

a：Total exceeds 100% as includes duplications
b：8 patients had 2 causative bacteria
c：Estimated by Cockcroft-Gault equation

acteristics did not differ between the safety and effectiveness analysis sets.

3. Safety

Of 974 patients, 152 patients（15.61%）reported at least one ADR（**Table 2** summarizes the ADRs reported by ≥0.5%）. The ADRs reported with highest frequencies were hepatic function abnormal（2.67%, 26 patients）, blood CPK increased（2.46%, 24 patients）, renal impairment（1.54%, 15 patients）, and blood alkaline phosphatase increased（1.13%, 11 patients）. Regarding other adverse events of special interest, peripheral neuropathy and eosinophilic pneumonia were not reported. Hypersensitivity was also not reported and ALT and AST increased were reported by 9 patients each（0.92%）.

CPK values were not available for many patients, and therefore, analysis included 41 patients in total. The mean value〔mean（standard deviation, S.D.）〕increased to 703.13 IU/L（757.860）at the time of musculoskeletal disorder AE onset or blood CPK increased from before daptomycin administration〔126.32 IU/L（151.059）〕.

Table 3 summarizes the frequency of ADRs by patient characteristics. By infection type, frequency was higher for IE（21.43%, 3/14 patients）, followed by bacteremia（19.46%, 79/406 patients）and SSTIs（12.82%, 70/546 patients）. By causative bacteria, the incidence was higher for suspected MRSA（40.00%, 2/5 patients）and *Staphylococcus*（18.06%, 28/155 patients）, than for MRSA（14.61%,

Table 2 Adverse drug reactions observed in five or more patients (n = 974)

	Number of patients (%)
Number of patients, n (%) with ADR	152 (15.61)
Hepatobiliary disorders	38 (3.90)
Hepatic function abnormal	26 (2.67)
Liver disorder	7 (0.72)
Skin and subcutaneous tissue disorders	10 (1.03)
Rash	5 (0.51)
Renal and urinary disorders	17 (1.75)
Renal impairment	15 (1.54)
General disorders and administration site conditions	11 (1.13)
Pyrexia	6 (0.62)
Investigations	76 (7.80)
Alanine aminotransferase increased	9 (0.92)
Aspartate aminotransferase increased	9 (0.92)
Blood creatine phosphokinase increased	24 (2.46)
Blood creatinine increased	7 (0.72)
Blood lactate dehydrogenase increased	8 (0.82)
Blood urea increased	5 (0.51)
Gamma-glutamyltransferase increased	6 (0.62)
White blood cell count decreased	5 (0.51)
White blood cell count increased	6 (0.62)
Blood alkaline phosphatase increased	11 (1.13)
Hepatic enzyme increased	6 (0.62)

ADR ; adverse drug reaction
MedDRA/J version (22.1)

77/527 patients).

The ADR frequency was similar between patients aged ≥15 to <65 years (15.52%, 63/406 patients) and those aged ≥65 years (15.55%, 88/566 patients). The frequency did not substantially increase in those aged ≥75 years (16.87%, 55/326 patients).

Regarding renal impairment, the frequency of ADRs was higher in patients with comorbid renal impairment (20.90%, 70/335 patients) than in those without comorbid renal impairment (13.14%, 82/624 patients). Among patients with severe comorbid renal impairment at baseline, more patients receiving concomitant drugs reported ADRs than those without (20.00%, 40/200 patients vs. 0%, 0/19 patients) (**Table 4**).

The ADR frequency was higher in patients

Table 3 Adverse drug reactions by patient characteristics

	n	ADR			p-value
		n	Number of adverse events	Proportions of patients with ADR (%)	
Total	974	152	228	(15.61)	
Sex					
Male	632	111	166	(17.56)	Fisher p = 0.026
Female	342	41	62	(11.99)	
Age (years)					
＜15	2	1	2	(50.00)	CA p = 0.442
≥15-＜25	21	5	9	(23.81)	
≥25-＜35	29	6	8	(20.69)	
≥35-＜45	81	14	19	(17.28)	
≥45-＜55	90	14	21	(15.56)	
≥55-＜65	185	24	41	(12.97)	
≥65-＜75	240	33	50	(13.75)	
≥75	326	55	78	(16.87)	
Infection type					
Bacteremia	406	79	125	(19.46)	χ^2 p = 0.088
IE	14	3	4	(21.43)	
Right-sided IE	3	2	3	(66.67)	
Left-sided IE	11	1	1	(9.09)	
SSTIs	546	70	99	(12.82)	
Deep skin infection	141	18	22	(12.77)	
Secondary infections (e.g. trauma, burn and surgical wound)	353	45	68	(12.75)	
Secondary infection of erosion and ulcer	52	7	9	(13.46)	
Others	8	0	0	(0.00)	
Causative bacteria[a]					
MRSA	527	77	108	(14.61)	
Suspected MRSA	5	2	3	(40.00)	
Staphylococcus	155	28	51	(18.06)	
Other gram-positive organisms	69	14	20	(20.29)	
Gram-negative organism	21	2	2	(9.52)	
Unknown	205	30	45	(14.63)	

(continued)

(continued)

	n	ADR			p-value	
		n	Number of adverse events	Proportions of patients with ADR (%)		
Severity before administration						
Mild	109	11	14	(10.09)	CA	p = 0.292
Moderate	478	81	117	(16.95)		
Severe	344	56	87	(16.28)		
Unknown	43	4	10	(9.30)		
First daily dose (per body weight) (mg/kg/day)						
＜4	20	3	3	(15.00)	CA	p = 0.003
4	240	23	24	(9.58)		
＞4-＜6	177	29	43	(16.38)		
6	409	69	105	(16.87)		
＞6	128	28	53	(21.88)		
Administration method						
Intravenous infusion	943	148	218	(15.69)	χ^2	p = 0.857
Intravenous bolus injection	30	4	10	(13.33)		
Switch between intravenous infusion and intravenous bolus injection	1	0	0	(0.00)		
Total administration period (days)						
Daily administration						
＜7	217	33	54	(15.21)	CA	p = 0.649
≥7-＜14	264	35	48	(13.26)		
≥14-＜28	199	38	48	(19.10)		
≥28-＜42	42	4	10	(9.52)		
≥42-＜84	26	5	9	(19.23)		
≥84	2	0	0	(0.00)		
Alternate day administration						
＜7	120	17	24	(14.17)	CA	p = 0.356
≥7-＜14	73	14	27	(19.18)		
≥14-＜28	23	4	4	(17.39)		
≥28-＜42	7	2	4	(28.57)		
≥42-＜84	1	0	0	(0.00)		
≥84	0	0	0	−		

(continued)

（Table 3　continued）

	n	ADR			p-value
		n	Number of adverse events	Proportions of patients with ADR (%)	
Dosing interval					
Daily administration	750	115	169	(15.33)	Fisher　p＝0.675
Alternate day administration	224	37	59	(16.52)	
Pretreatment drug（antibacterial drug only）					
No	289	33	50	(11.42)	Fisher　p＝0.016
Yes	668	118	177	(17.66)	
Unknown	17	1	1	(5.88)	
Switching from other MRSA treatments					
No	771	116	170	(15.05)	Fisher　p＝0.217
Yes	185	35	57	(18.92)	
Unknown	18	1	1	(5.56)	
Other MRSA treatments[b]					
VCM	104	18	27	(17.31)	
TEIC	33	9	16	(27.27)	
ABK	6	1	1	(16.67)	
LZD	40	7	13	(17.50)	
Others	3	0	0	(0.00)	
Use of concomitant drug					
No	126	9	13	(7.14)	Fisher　p＝0.004
Yes	835	142	214	(17.01)	
Unknown	13	1	1	(7.69)	
Use of concomitant drugs other than antibacterial agents					
No	272	26	39	(9.56)	Fisher　p＜0.001
Yes	687	125	188	(18.20)	
Unknown	15	1	1	(6.67)	
Use of concomitant antibacterial drug					
No	341	36	53	(10.56)	Fisher　p＝0.001
Yes	620	115	174	(18.55)	
Unknown	13	1	1	(7.69)	

（continued）

(continued)

	n	ADR			p-value
		n	Number of adverse events	Proportions of patients with ADR (%)	
Complications (overall)					
No	128	11	16	(8.59)	Fisher p = 0.013
Yes	831	141	212	(16.97)	
Unknown	15	0	0	(0.00)	
Hepatic impairment (comorbid)					
No	770	111	159	(14.42)	Fisher p = 0.019
Yes	185	40	68	(21.62)	
Unknown	19	1	1	(5.26)	
Renal impairment (comorbid)					
No	624	82	121	(13.14)	Fisher p = 0.002
Yes	335	70	107	(20.90)	
Unknown	15	0	0	(0.00)	
Degree of comorbid renal impairment					
Creatinine clearance[c] : ≥30-<50 mL/min	49	15	19	(30.61)	Fisher p = 0.077
Creatinine clearance[c] : <30 mL/min or on dialysis	224	41	63	(18.30)	
Dialysis					
No	811	122	183	(15.04)	Fisher p = 0.188
Yes	156	30	45	(19.23)	
Unknown	7	0	0	(0.00)	

ADR : adverse drug reaction, IE : infective endocarditis, MRSA : methicillin-resistant *Staphylococcus aureus*, VCM : vancomycin, TEIC : teicoplanin, ABK : arbekacin, LZD : linezolid, SSTIs : skin and soft tissue infections, CA : Cochran-Armitage

a : Total exceeds 100% as includes duplications
b : Includes duplications
c : Estimated by Cockcroft-Gault equation

who received 6 mg/kg/day (16.87%, 69/409 patients) than those who received 4 mg/kg/day (9.58%, 23/240 patients). Additionally, in patients who received >6 mg/kg/day, the ADR frequency (21.88%, 28/128 patients) was higher than other dose levels (**Table 3**).

By total administration period (days) the ADR frequency was higher for the treatment period of ≥42 to <84 days in patients who received daily administration (19.23%, 5/26 patients) and for the treatment days of ≥28 to <42 days in patients who received alternate day administration (28.57%, 2/7 patients). There was no significant difference in the frequency of ADRs among categories of total administration periods (days) (**Table 3**).

Table 4 Adverse drug reaction among patients with severe comorbid renal impairment at baseline (creatinine clearance：＜30 mL/min or on dialysis)

	n	ADR			p-value
		n	Number of events	Proportion of patients with ADR (%)	
Total	224	41	63	(18.30)	
Sex					
Male	143	28	42	(19.58)	Fisher p＝0.591
Female	81	13	21	(16.05)	
Age (years)					
＜15	0	0	0	−	CA p＝0.607
≥15-＜25	2	0	0	(0.00)	
≥25-＜35	1	0	0	(0.00)	
≥35-＜45	8	2	2	(25.00)	
≥45-＜55	18	3	3	(16.67)	
≥55-＜65	46	9	17	(19.57)	
≥65-＜75	60	8	12	(13.33)	
≥75	89	19	29	(21.35)	
Infection type					
Bacteremia	104	22	35	(21.15)	χ^2 p＝0.544
IE	4	0	0	(0.00)	
Right-sided IE	1	0	0	(0.00)	
Left-sided IE	3	0	0	(0.00)	
SSTIs	115	19	28	(16.52)	
Deep skin infection	37	4	7	(10.81)	
Secondary infections (e.g. trauma, burn and surgical wound)	59	12	17	(20.34)	
Secondary infection of erosion and ulcer	19	3	4	(15.79)	
Others	1	0	0	(0.00)	
Causative bacteria[a]					
MRSA	122	23	38	(18.85)	
Suspected MRSA	2	0	0	(0.00)	
Staphylococcus	26	5	7	(19.23)	
Other gram-positive organisms	20	3	4	(15.00)	
Gram-negative organism	5	1	1	(20.00)	
Unknown	50	10	14	(20.00)	

(continued)

(continued)

	n	ADR			p-value	
		n	Number of events	Proportion of patients with ADR (%)		
Severity before administration						
Mild	12	1	1	(8.33)	CA	p=0.294
Moderate	88	14	18	(15.91)		
Severe	118	23	35	(19.49)		
Unknown	6	3	9	(50.00)		
First daily dose (per body weight) (mg/kg/day)						
＜4	6	0	0	(0.00)	CA	p=0.075
4	56	8	9	(14.29)		
＞4-＜6	38	7	9	(18.42)		
6	102	19	29	(18.63)		
＞6	22	7	16	(31.82)		
Administration method						
Intravenous infusion	216	39	58	(18.06)	Fisher	p=0.641
Intravenous bolus injection	8	2	5	(25.00)		
Switch between intravenous infusion and intravenous bolus injection	0	0	0	−		
Total administration period (days)						
Daily administration						
＜7	15	2	5	(13.33)	CA	p=0.919
≥7-＜14	14	4	4	(28.57)		
≥14-＜28	7	4	5	(57.14)		
≥28-＜42	3	0	0	(0.00)		
≥42-＜84	3	0	0	(0.00)		
≥84	0	0	0	−		
Alternate day administration						
＜7	95	15	22	(15.79)	CA	p=0.644
≥7-＜14	63	11	20	(17.46)		
≥14-＜28	18	4	4	(22.22)		
≥28-＜42	5	1	3	(20.00)		
≥42-＜84	1	0	0	(0.00)		
≥84	0	0	0	−		

(continued)

(Table 4　continued)

	n	ADR			p-value
		n	Number of events	Proportion of patients with ADR (%)	
Dosing interval					
Daily administration	42	10	14	(23.81)	Fisher　p＝0.375
Alternate day administration	182	31	49	(17.03)	
Use of concomitant drug					
No	19	0	0	(0.00)	Fisher　p＝0.028
Yes	200	40	62	(20.00)	
Unknown	5	1	1	(20.00)	
Complications (overall)					
No	0	0	0	−	Fisher　−
Yes	224	41	63	(18.30)	
Hepatic impairment (comorbid)					
No	153	24	36	(15.69)	Fisher　p＝0.125
Yes	64	16	26	(25.00)	
Unknown	7	1	1	(14.29)	
Dialysis					
No	67	11	18	(16.42)	Fisher　p＝0.708
Yes	156	30	45	(19.23)	
Unknown	1	0	0	(0.00)	

ADR；adverse drug reaction, IE；infective endocarditis, MRSA；methicillin-resistant *Staphylococcus aureus*, SSTIs；skin and soft tissue infections, CA；Cochran-Armitage

a：Total exceeds 100% as includes duplications

Regarding long-term safety, most patients received daptomycin for ＜28 days, with only 44 patients receiving daptomycin for ≥42 days (4 for ≥84) (**Table 5**). The proportion of patients that reported any ADRs in the period ≥42 to ＜84 days (10.00%, 4/40 patients) and ≥84 days (25.00%, 1/4 patients) of treatment was greater than those whose treatment was ＜7 days (7.80%, 76/974 patients)；while almost half of the ADR events were reported ＜7 days, and the ADRs reported ≥42 days was observed only once by one patient each. No ADRs were observed for which incidence tended to increase with administration period.

By administration method, the ADR frequencies were similar in patients who received intravenous infusion (15.69%) and in patients who received intravenous bolus injection (13.33%) (**Table 3**).

4. Effectiveness

Of 470 patients in the effectiveness analysis set, 18 patients were excluded from analysis because overall effectiveness data was not evaluable. Among the 452 patients included in this analysis, the overall effectiveness was 88.3% (399 patients). By causative bacteria, the overall effectiveness was 88.4% (321/363 patients) for MRSA.

Patient characteristics showing considerable differences among categories were age, infection type, first daily dose, pretreatment drug (antibacterial drug only) and use of concomitant drugs other than antibacterial agents (**Table 6**). The overall effectiveness was 92.7% (166/179 patients) in patients aged ≥15 to <65 years and 85.3% (233/273 patients) in patients aged ≥65 years. The overall effectiveness was higher in patients who received 4 mg/kg/day (92.5%, 149/161 patients) than those who received 6 mg/kg/day (87.2%, 143/164 patients). The overall effectiveness for bacteremia, IE and secondary infection of erosion and ulcer was lower than for deep skin infection and secondary infections (e.g. trauma, burn and surgical wound). The overall effectiveness was 87.5% (223/255 patients) in patients who used concomitant antibacterial drugs and 89.7% (174/194 patients) in patients who did not use concomitant antibacterial drugs.

Amongst patients with comorbid renal impairment, the overall effectiveness was 80.8% (21/26 patients) in patients with creatinine clearance of ≥30 to <50 mL/min, and 86.4% (108/125 patients) in patients with creatinine clearance of <30 mL/min or on dialysis.

Whilst the overall effectiveness was 88.3% and the effectiveness was high (≥80%) in almost all subgroups, an overall effectiveness <80% was observed in patients with suspected MRSA as the causative bacteria; patients that received a first daily dose of >6 mg/kg/day; and patients that switched from other MRSA treatment (arbekacin).

Regarding administration method, the overall effectiveness was 88.5% (391/442 patients) in patients who received intravenous infusion and 80.0% (8/10 patients) in patients who received intravenous bolus injection.

Regarding microbiological response, the number of patients for whom results of microbiological testing for MRSA were obtained was only 61 patients. In this population the microbiological response rate was 68.9% (42/61 patients).

Ⅲ Discussion

In the safety analysis set, the overall frequency of ADRs was 15.61%. The ADRs reported with highest frequencies were hepatic function abnormal, followed by blood CPK increased. Effectiveness was demonstrated for overall effectiveness and also microbiological response rates in most patients (88.3% and 68.9%, respectively). Overall, the safety and effectiveness profiles reported in previous clinical trials were demonstrated in this post-marketing survey, conducted under daily clinical practice.

The ADR frequency reported in this survey was lower than in the Japanese phase Ⅲ study (21.6%)[7]. The common ADRs were related to hepatic dysfunction (e.g. ALT and AST increased), as was demonstrated in the phase Ⅲ trial[7]. Furthermore, peripheral neuropathy and eosinophilic pneumonia,

Table 5 Adverse drug reactions by System Organ Class reported by 5 or more patients

	<7 days (n=974)	≥7-<14 days (n=697)	≥14-<28 days (n=370)
	n (%)	n (%)	n (%)
Number of patients, n (%) with ADR	76 (7.80)	52 (7.46)	25 (6.76)
Number of adverse events	111	66	29
Hepatobiliary disorders	23 (2.36)	10 (1.43)	4 (1.08)
Hepatic function abnormal	15 (1.54)	7 (1.00)	3 (0.81)
Liver disorder	5 (0.51)	2 (0.29)	−
Skin and subcutaneous tissue disorders	4 (0.41)	6 (0.86)	−
Rash	2 (0.21)	3 (0.43)	−
Renal and urinary disorders	8 (0.82)	5 (0.72)	3 (0.81)
Renal impairment	7 (0.72)	4 (0.57)	3 (0.81)
General disorders and administration site conditions	7 (0.72)	1 (0.14)	−
Pyrexia	6 (0.62)	−	−
Investigations	37 (3.80)	25 (3.59)	11 (2.97)
Alanine aminotransferase increased	4 (0.41)	3 (0.43)	1 (0.27)
Aspartate aminotransferase increased	5 (0.51)	2 (0.29)	1 (0.27)
Blood creatine phosphokinase increased	9 (0.92)	8 (1.15)	4 (1.08)
Blood creatinine increased	2 (0.21)	4 (0.57)	1 (0.27)
Blood lactate dehydrogenase increased	6 (0.62)	2 (0.29)	−
Blood urea increased	2 (0.21)	−	2 (0.54)
Gamma-glutamyltransferase increased	3 (0.31)	3 (0.43)	−
White blood cell count decreased	1 (0.10)	1 (0.14)	2 (0.54)
White blood cell count increased	4 (0.41)	2 (0.29)	−
Blood alkaline phosphatase increased	5 (0.51)	4 (0.57)	−
Hepatic enzyme increased	5 (0.51)	1 (0.14)	−

ADR；adverse drug reactions

a：The total no. of ADRs observed in the survey is shown；but ADRs by System Organ Class (SOC) are

previously reported overseas[8] were not reported in this Japanese clinical setting. As another item of importance, blood CPK increased ADRs were reported by a smaller proportion (2.46%) of safety analysis set patients, than in clinical trials conducted in foreign countries for bacteremia/IE (6.7%)[9]; and in the Japanese phase Ⅲ study for complex SSTI (9.1%)[7]. Taken together, safety profiles in the present survey were largely consistent with those reported previously.

Regarding safety in patients with comor-

by treatment duration time period[a]

≥28-<42 days (n=101)	≥42-<84 days (n=40)	≥84 days (n=4)	Unknown –	Total (n=974)
n（%）	n（%）	n（%）	n（%）	n（%）
4（3.96）	4（10.00）	1（25.00）	11	152（15.61）
6	4	1	12	228
–	–	–	1	38（ 3.90）
–	–	–	1	26（ 2.67）
–	–	–	–	7（ 0.72）
–	–	–	–	10（ 1.03）
–	–	–	–	5（ 0.51）
–	–	–	1	17（ 1.75）
–	–	–	1	15（ 1.54）
–	–	–	3	11（ 1.13）
–	–	–	–	6（ 0.62）
4（3.96）	2（ 5.00）	1（25.00）	1	76（ 7.80）
1（0.99）	–	–	–	9（ 0.92）
1（0.99）	–	–	–	9（ 0.92）
3（2.97）	–	–	–	24（ 2.46）
–	–	–	–	7（ 0.72）
–	–	–	–	8（ 0.82）
–	1（ 2.50）	–	–	5（ 0.51）
–	–	–	–	6（ 0.62）
–	1（ 2.50）	–	–	5（ 0.51）
–	–	–	–	6（ 0.62）
–	–	1（25.00）	1	11（ 1.13）
–	–	–	–	6（ 0.62）

shown only for those categories in which the incidence is ≥5 cases.

bid renal impairment（**Table 3**）, the ADR frequency was higher（20.90%）in patients with comorbid renal impairment than those without（13.14%）. Among patients with severe comorbid renal impairment, more patients with concomitant drugs reported ADRs.

The ADR frequency in patients with comorbid renal impairment in this post-marketing survey was similar to that observed in the Japanese phase Ⅲ study（21.6%）, which excluded patients on hemodialysis or continuous ambulatory peritoneal dialysis[7]. Ad-

Table 6 Overall effectiveness by patient characteristics

	n	Number of effective patients	Effective rate (%)	p-value
Total	452	399	(88.3)	
Sex				
Male	292	254	(87.0)	Fisher p=0.286
Female	160	145	(90.6)	
Age (years)				
<15	0	0	−	CA p=0.003
≥15-<25	7	7	(100.0)	
≥25-<35	12	12	(100.0)	
≥35-<45	32	30	(93.8)	
≥45-<55	47	42	(89.4)	
≥55-<65	81	75	(92.6)	
≥65-<75	111	101	(91.0)	
≥75	162	132	(81.5)	
Infection type				
Bacteremia	202	169	(83.7)	χ^2 p<0.001
IE	1	0	(0.0)	
SSTIs	249	230	(92.4)	
Deep skin infection	68	66	(97.1)	
Secondary infections (e.g. trauma, burn and surgical wound)	147	136	(92.5)	
Secondary infection of erosion and ulcer	34	28	(82.4)	
Others	0	0	−	
Causative bacteria				
MRSA	363	321	(88.4)	
Suspected MRSA	2	1	(50.0)	
Staphylococcus	87	77	(88.5)	
Severity before administration				
Mild	51	45	(88.2)	CA p=0.063
Moderate	222	204	(91.9)	
Severe	153	127	(83.0)	
Unknown	26	23	(88.5)	

(continued)

(continued)

	n	Number of effective patients	Effective rate (%)	p-value	
First daily dose (per body weight) (mg/kg/day)					
＜4	9	9	(100.0)	CA	p＜0.001
4	161	149	(92.5)		
＞4-＜6	80	71	(88.8)		
6	164	143	(87.2)		
＞6	38	27	(71.1)		
Administration method					
Intravenous infusion	442	391	(88.5)	χ^2	p＝0.411
Intravenous bolus injection	10	8	(80.0)		
Switch between intravenous infusion and intravenous bolus injection	0	0	−		
Total administration period (days)					
Daily administration					
＜7	72	60	(83.3)	CA	p＝0.205
≥7-＜14	125	118	(94.4)		
≥14-＜28	98	82	(83.7)		
≥28-＜42	21	21	(100.0)		
≥42-＜84	12	12	(100.0)		
≥84	0	0	−		
Alternate day administration					
＜7	49	42	(85.7)	CA	p＝0.637
≥7-＜14	56	47	(83.9)		
≥14-＜28	14	12	(85.7)		
≥28-＜42	4	4	(100.0)		
≥42-＜84	1	1	(100.0)		
≥84	0	0	−		
Dosing interval					
Daily administration	328	293	(89.3)	Fisher	p＝0.256
Alternate day administration	124	106	(85.5)		

(continued)

(Table 6 continued)

	n	Number of effective patients	Effective rate (%)	p-value
Pretreatment drug (antibacterial drug only)				
No	139	131	(94.2)	Fisher p=0.007
Yes	309	264	(85.4)	
Unknown	4	4	(100.0)	
Switching from other MRSA treatments				
No	360	320	(88.9)	Fisher p=0.355
Yes	87	74	(85.1)	
Unknown	5	5	(100.0)	
Other MRSA treatments[a]				
VCM	52	43	(82.7)	
TEIC	13	12	(92.3)	
ABK	4	3	(75.0)	
LZD	17	15	(88.2)	
Others	1	1	(100.0)	
Use of concomitant drug				
No	65	60	(92.3)	Fisher p=0.401
Yes	384	337	(87.8)	
Unknown	3	2	(66.7)	
Use of concomitant drugs other than antibacterial agents				
No	113	107	(94.7)	Fisher p=0.017
Yes	335	289	(86.3)	
Unknown	4	3	(75.0)	
Use of concomitant antibacterial drug				
No	194	174	(89.7)	Fisher p=0.552
Yes	255	223	(87.5)	
Unknown	3	2	(66.7)	
Complications (overall)				
No	51	48	(94.1)	Fisher p=0.245
Yes	393	344	(87.5)	
Unknown	8	7	(87.5)	

(continued)

(continued)

	n	Number of effective patients	Effective rate (%)	p-value
Hepatic impairment (comorbid)				
No	362	326	(90.1)	Fisher p = 0.077
Yes	80	66	(82.5)	
Unknown	10	7	(70.0)	
Renal impairment (comorbid)				
No	259	233	(90.0)	Fisher p = 0.231
Yes	185	159	(85.9)	
Unknown	8	7	(87.5)	
Degree of comorbid renal impairment				
Creatinine clearance[b] : ≥30-<50 mL/min	26	21	(80.8)	Fisher p = 0.540
Creatinine clearance[b] : <30 mL/min or on dialysis	125	108	(86.4)	
Dialysis				
No	358	321	(89.7)	Fisher p = 0.190
Yes	89	75	(84.3)	
Unknown	5	3	(60.0)	

IE : infective endocarditis, MRSA : methicillin-resistant *Staphylococcus aureus*, VCM : vancomycin, TEIC : teicoplanin, ABK : arbekacin, LZD : linezolid, SSTIs : skin and soft tissue infections, CA : Cochran-Armitage
Of the effectiveness analysis set, patients with the data of overall effectiveness were evaluable were included in this analysis.

a : Include duplications
b : Estimated by Cockcroft-Gault equation

ditionally, there was no specific tendency in the frequency of ADRs by severity of comorbid renal impairment. It was suggested that the frequency of ADRs reported was suppressed by alternate day administration in patients with "severely decreased" comorbid renal function (**Table 4**). Based on these results, it was considered that there are no unknown or heightened safety issues in administration of daptomycin to patients with comorbid renal impairment.

Although there were statistically significant differences in the frequency of ADRs for some characteristics, there were no major differences in the frequency of these ADRs by patient, clinical, and treatment characteristics. One of the characteristics of the present survey population was the large proportion of daptomycin use in the elderly (≥65 years) and advanced elderly population (≥75 years), accounting for more than half and one third of the patients included in the survey sample, respectively. The ADR frequencies reported in the elderly and ad-

vanced elderly population sample（15.55% and 16.87%, respectively）were similar to those reported in patients aged ≥15 to <65 years（15.52%）.

By treatment patterns, the ADR frequency was higher in patients who received 6 mg/kg/day（16.87%）than in patients who received 4 mg/kg/day（9.58%）（**Table 3**）. This higher frequency with higher dose was considered to be the influence of the infection type for which daptomycin was prescribed, or comorbid diseases. There were no characteristic ADRs observed with long-term administration. The number of patients that received treatment for long-term administration was small and, therefore, higher proportions of ADRs were observed；however, ADRs tended to be reported relatively early <7 days from the first daptomycin dosing date（7.80%）（**Table 5**）. By administration method, the ADR frequency was similar in patients who received intravenous infusion（15.69%）and in patients who received intravenous bolus injection（13.33%）（**Table 3**）. Taken together, favorable safety profiles were seen in all subgroups, regardless of age, dose（4 mg/kg/day or 6 mg/kg/day）, administration period, and administration method（intravenous infusion or intravenous bolus injection）.

The overall effectiveness was 88.3%；and the microbiological response rate was 68.9%, based on a small number of patients whose corresponding data was evaluable（n=61 patients）. Based on the overall effectiveness of 81.8% and microbiological response rate of 56.4%（31/55 patients）in patients with SSTI[7] and 50.0%（2/4 patients）in patients with bacteremia[8] in the Japanese phase Ⅲ study, the effectiveness profile of daptomycin under daily clinical practice was similar to that reported under a clinical trial setting.

Although considerable differences were observed in overall effectiveness for some factors, high overall effectiveness was observed in ≥80% patients across the various subgroups stratified by clinical and treatment characteristics, except for a few small subgroups. Of particular note, treatment with daptomycin was shown to be effective even in ≥80% of the patients with comorbid renal impairment（the effective rate：85.9%）（**Table 6**）, regardless of severity. By infection type, the overall effectiveness observed for bacteremia, IE and secondary infection of erosion and ulcer was lower than for deep skin infection and secondary infections（e.g. trauma, burn and surgical wound）, but higher than the overall effectiveness observed in the Japanese phase Ⅲ study which was 50%（2/4 patients）for bacteremia[8] and 81.8%（45/55 patients）for SSTI[7]. Even though the difference of overall effectiveness was statistically significant between the age groups, overall effectiveness was ≥85% in those aged ≥65 years and ≥80% even in the most advanced age group of ≥75 years old. These results, in total, suggest that no new effectiveness problems were identified from the present survey.

There are some limitations to be considered. First, as this was a post-marketing survey, it was conducted under a daily clinical setting and therefore, whilst it was not possible to compare ADRs and effectiveness, in a similar way to that in clinical trials, the patient population comprised patients of varying demographic backgrounds with different comorbidities. Second, this survey, however, enrolled only patients who visited

designated institutions, during the pre-defined observation period, and adhered to the defined usage conditions. This may have caused a selection bias. Third, in this survey the availability of data was limited ; particularly microbiological test results were available for only 61 patients. Fourth, this survey has no control group and, therefore, the results cannot compare the safety（especially unexpected ADRs）or effectiveness outcomes with those who did not receive any treatment. Fifth, the effectiveness results reported may not be solely attributed to daptomycin, as concomitant drugs or therapies were allowed without restriction. Overall effectiveness results should be interpreted with caution as many patients received concomitant antibacterial drugs. Nevertheless, this is the largest survey conducted in Japan to date, to investigate the long-term safety and effectiveness of daptomycin to treat MRSA infections, in a daily clinical setting. The present results may provide useful information for treatment using daptomycin for MRSA infection.

Conclusion

Daptomycin was well tolerated, in Japanese daily clinical practice and its safety profile was similar to that observed in clinical trials. Moreover, no serious safety problems presented in any subgroups and it was suggested that there were no new safety concerns under various treatment patterns and for various patients, including those with comorbid renal impairment, and in elderly/advanced elderly patients. Daptomycin was shown to be effective for treating Japanese patients with bacteremia, IE, and SSTIs, caused by confirmed MRSA, across various subgroups in daily clinical practice.

This large scale post marketing survey is the first study to include a large patient population, and obtain real world data to confirm the long-term safety and effectiveness of daptomycin in Japanese daily clinical practice.

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Conflicts of Interest

Takayuki Kondo, Masahiro Kimata, Asuka Watanabe and Shinichiroh Maekawa, are all employees of MSD K.K.

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原著

ダプトマイシン（キュビシン®静注用）の使用成績調査

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要　旨

背景：ダプトマイシン（キュビシン®；以下，本剤）はメチシリン耐性黄色ブドウ球菌（MRSA）等グラム陽性菌に対し殺菌作用を有し，MRSAによる敗血症，右心系感染性心内膜炎，深在性皮膚感染症，外傷・手術創および潰瘍等の二次感染を適応として承認されている。本剤の実臨床下での安全性と有効性を確認するため使用成績調査を実施した。

方法：本剤を新たに投与された患者に対し，安全性は本剤との因果関係が否定できない有害事象を副作用として評価し，有効性は調査担当医師の判定に基づく全般改善度と

微生物学的検査による細菌学的効果で評価した。副作用発現割合と全般改善度は患者背景別でも検討した。

結果：1013例から調査票を収集し，安全性解析対象974例のうち15.61％で副作用が報告され，肝機能異常が2.67％と最も発現割合が高かった。有効性解析対象470例にて，全般改善度は88.3％が有効で，細菌学的効果は68.9％であった。副作用発現割合と全般改善度は背景別で特徴的な違いは認められなかった。

結論：今回の大規模調査の結果，臨床試験結果と同様に，本剤は実臨床下でも患者特性にかかわらず長期投与を含む安全性および有効性が示された。

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