Clinical experience with daptomycin in Europe: the first 2.5 years

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Objectives: To describe the patient populations and infections being treated with daptomycin, as well as the efficacy and safety outcomes.

Patients and methods: Data from the European Cubicin Outcomes Registry and Experience (EU-CORE[SM]), retrospectively collected at 118 institutions between January 2006 and August 2008, were analysed.

Results: Daptomycin treatment was documented in 1127 patients with diverse infections, including complicated skin and soft tissue infections (33%), bacteraemia (22%), endocarditis (12%) and osteomyelitis (6%). It was used empirically, before microbiological results became available, in 53% of patients. *Staphylococcus aureus* was the most common pathogen (34%), with 52% of isolates resistant to methicillin; coagulase-negative staphylococci and enterococci were also frequent, with 22% of *Enterococcus faecium* isolates resistant to vancomycin. Daptomycin was used as first-line therapy in 302 (27%) patients. When used second line, the most common reasons for discontinuation of previous antibiotic were treatment failure and toxicity or intolerance. The use of concomitant antibiotics was reported in 65% of patients. Most frequent doses were 6 mg/kg (47%) and 4 mg/kg (32%). The median duration of daptomycin therapy was 10 days (range 1–246 days) in the inpatient setting and 13 days (range 2–189 days) in the outpatient setting. The overall clinical success rate was 79%, with a clinical failure rate of <10% for all infection types. Low failure rates were observed in first- and second-line therapy (6% and 8%, respectively). Daptomycin demonstrated a favourable safety and tolerability profile regardless of treatment duration.

Conclusions: Daptomycin has a relevant role in the treatment of Gram-positive infections.

Keywords: cyclic lipopeptide, Gram-positive infections, registry

Introduction

Daptomycin (Cubicin®), the first-in-class cyclic lipopeptide antibiotic, was approved in Europe for the treatment of complicated skin and soft tissue infections (cSSTIs) in 2006 and for the treatment of right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* and *S. aureus* bacteraemia (SAB) when associated with RIE or with cSSTI in 2007.[1] By mid-2010, daptomycin had been used to treat an estimated 1 000 000 patients with serious Gram-positive infections worldwide.[2] The clinical experience with daptomycin in Europe since its approval has been captured by the European Cubicin Outcomes Registry and Experience (EU-CORE[SM])—a multicentre, retrospective, non-interventional registry sponsored by Novartis Pharma AG.

EU-CORE was designed to collect data on the characteristics [patient population, infections, pathogens and adverse events (AEs)] and clinical outcomes of patients receiving daptomycin. It mirrors the Cubicin Outcomes Registry and Experience (CORE®)—an ongoing programme that has been conducted by Cubist Pharmaceuticals to describe the experience with daptomycin in the USA, the methodology for which is described elsewhere.[3–5] The primary objectives of the EU-CORE programme are: to characterize and describe the population of patients receiving daptomycin and the infections and pathogens treated with daptomycin in the clinical setting; to evaluate the clinical outcomes of daptomycin therapy; to characterize, describe and evaluate the safety and tolerability of daptomycin; and to describe daptomycin prescribing patterns. Any institution at

which patients have received at least one dose of commercially available daptomycin since 2006 can participate. Data collection will always reflect up-to-date clinical practice, as the three data collection periods were defined in the study protocol, which was finalized in 2007, as follows: first collection period including patients treated after first regulatory approval in Europe in early 2006 until summer 2008, second period from summer 2008 to summer 2009, and third collection period from summer 2009 to summer 2010. This will allow for comparison of patterns of clinical use of daptomycin over time. Yearly database locks were planned to occur at the end of September 2008, 2009 and 2010. It is expected that each database lock will include data from ~1000–1400 patients. Documented cases of patients who completed daptomycin treatment, including a minimum post-treatment observation period of 30 days until 1 month before the yearly database lock, will be included in each of the respective collection periods as well as in the final study analysis.

The efficacy and safety of daptomycin have been established in clinical trials in cSSTIs[6] and in SAB with or without infective endocarditis (IE).[7] However, because of their rigorous nature (e.g. inclusion and exclusion criteria and the requirement for protocol adherence), clinical trials may not always reflect the true experience with a drug in clinical practice.[8] Patient registries such as EU-CORE provide insight into real-world clinical experience with daptomycin and build on the evidence base from clinical trials. This report describes the data from the first 2.5 years of daptomycin use for the treatment of Gram-positive infections from first European approval on 19 January 2006 until 31 August 2008.

Patients and methods

Patients and data collection

The purpose of this study is to collect real-world data about the non-controlled prescribing use and impact of daptomycin. Therefore, a non-interventional, multicentre, retrospective design was chosen. Investigators were asked to voluntarily include as many patients as available. Patients could be retrospectively included if they were treated with at least one dose of daptomycin and if all relevant information was entered in the case report form (CRF). Patients who received daptomycin as part of a controlled clinical trial were not eligible for inclusion. Investigators at >100 institutions across Europe collected anonymous demographic, antibiotic, microbiological and clinical data from medical records using a standardized CRF and protocol. Argentinean sites were also allowed to participate, as overall enrolment predictions were uncertain and daptomycin had just been approved in that country. Written informed consent that complies with the ICH Good Clinical Practice guideline was obtained if required by the institutional review board or ethics committee and/or local data privacy regulations, and the protocol was approved by the health authority and the institutional review board or ethics committee, as required, in each country. Investigators were trained on the CRF and received written instructions to further guide the collection of patient data. Each patient is uniquely identified in the study by a combination of his/her centre number and patient number. All data are entered on standardized CRFs exclusively according to the investigator's judgement. Data from the CRFs are entered into the study database by certified contract research organization staff working on behalf of the sponsor. After database lock, all available data were distributed to all authors of the manuscript, who take part in scheduled publication committee meetings. All information collected reflected standard practice in each site. There was no intervention or restriction in clinical practice. Patient data can be recorded into this

registry after a minimum of 30 days from the end of daptomycin therapy to permit the capture of AEs/serious AEs (SAEs). The CRFs collected the following information: treatment period; demographics; underlying diseases; pregnancy; neutropenia; antimicrobials; use of other antibiotics and statins; renal function; creatine phosphokinase (CPK) concentrations; diagnosis and current infection details; doses of current antibiotic treatment; duration of inpatient and/or outpatient treatment; outcomes; AEs and SAEs occurring between treatment onset and 30 days after last dose of daptomycin; and discharge information. No instructions were provided concerning drug discontinuation, study completion or post-study treatment. However, the reasons for study drug discontinuation, reason for completion of daptomycin treatment and antibiotic use after daptomycin treatment were captured. In cases of multiple infection, investigators entered the type of infection in order of clinical significance (i.e. primary or secondary infection) for which the patient received daptomycin.

In the database, the primary infection was always automatically assigned to the disease of higher hierarchy according to the following predefined severity classification (in order of most to least severe): endocarditis; osteomyelitis; bacteraemia; other [CNS infection, foreign body/prosthetic infection, metastatic abscess, necrotizing fasciitis, necrotizing infection, surgical/non-surgical antibiotic prophylaxis, septic arthritis and urinary tract infection (UTI)/pyelonephritis]; cSSTI; uncomplicated skin and soft tissue infection (uSSTI). This classification was needed to allow for analysis standardization and was based on experts' and sponsor's judgement taking into consideration clinical prognosis, probability of microbiology eradication and consequences of treatment failure. Safety analysis included all reports of AEs, the severity of which was determined by the investigators. AEs were recorded regardless of their relationship to daptomycin therapy. The overall methodology of this registry, including the definitions mentioned in the following section, is aligned with the CORE registry methodology. It is possible to merge the databases to perform combined or comparative analyses between different regions, as recently published by Gonzalez-Ruiz et al.[9]

Definitions

Clinical outcomes at the end of daptomycin therapy were assessed by investigators using the following protocol-defined criteria: cure—clinical signs and symptoms resolved and/or no additional antibiotic therapy necessary, or negative culture reported at the end of therapy; improved—partial resolution of clinical signs and symptoms and/or additional antibiotic therapy warranted at the end of therapy; failure—inadequate response to therapy, worsening or new/recurrent signs and symptoms, need for a change in antibiotic therapy, or positive culture reported at the end of therapy; and non-evaluable, unable to determine response due to insufficient information. The term clinical success was used to describe patients with an outcome of cure or improved. The safety population included all documented patients who received at least one dose of daptomycin and for whom any safety parameters were assessed (the statement that no AEs occurred was considered a valid assessment). The efficacy population included all documented patients who received at least one dose of daptomycin and for whom clinical outcome was assessed.

Results

Patient demographics and clinical characteristics

A total of 116 institutions in Europe and two institutions in Argentina registered patients in the study during the report period. The largest number of sites was in Spain, 49 in total spread across the country. Countries with 10–20 sites were Germany, Greece and the UK. Fewer than 10 sites were registered

in Austria, France, Italy and Slovenia. A total of 1127 patients were registered in the EU-CORE database during the reporting period, all of whom were included in both the efficacy and safety populations. Only eight patients from Argentina were included; therefore, the reported results largely reflect European use of the drug. Patients had a mean age of 59.2 years (range 1–93 years), with 46% of patients aged ≥65 years; a mean body weight of 75.4 kg (range 6–180 kg); and the majority (64%) of patients were male (Table 1). Hypertension and diabetes mellitus were the most common significant underlying diseases,

Table 1. Baseline patient characteristics (*N*=1127)

Characteristic	Patients, *n* (%)
Gender	
female	404 (36)
male	723 (64)
Age, mean, years (SD)	59.2 (18)
Age groups	
<65 years	610 (54)
≥65 years (including ≥75 years)	514 (46)
≥75 years	237 (21)
Body weight, mean, kg (SD)	75.4 (18)
Race, Caucasian	1087 (97)
Neutropenia at baseline or during daptomycin therapy	75 (7)
Renal function	
CL_{CR}<30 mL/min	152 (14)
receiving dialysis	104 (9)
Frequent significant underlying disease (>7%)[a]	
hypertension	338 (30)
diabetes mellitus	292 (26)
valvular heart disease	162 (14)
cancer	160 (14)
chronic renal failure	145 (13)
cardiac arrhythmias	141 (13)
other cardiovascular disease	133 (12)
peripheral cardiovascular disease	114 (10)
congestive heart failure	108 (10)
acute coronary syndromes	103 (9)
anaemia (all haematological disease)	83 (7)
immunosuppression	80 (7)
chronic obstructive pulmonary disease	79 (7)
Country of treatment	
Spain	345 (31)
Greece	231 (21)
Germany	230 (20)
UK	183 (16)
Austria	62 (6)
Italy	53 (5)
France	8 (1)
Argentina	8 (1)
Slovenia	7 (1)

SD, standard deviation.
[a]Patients may have one or more underlying disease. Severity of underlying co-morbidities was not captured.

occurring in 30% and 26% of patients, respectively. Other frequent underlying co-morbid conditions included cancer (14%) and chronic renal failure (13%), and 14% of patients had a creatinine clearance (CL_{CR}) of <30 mL/min.

Of the wide range of primary infection types treated with daptomycin, cSSTIs were the most frequent, accounting for 33% of the patient population. Patients with bacteraemia (*n*=244; 22%), endocarditis (*n*=136; 12%), uSSTI (*n*=123; 11%), osteomyelitis (*n*=64; 6%) and infections classified as other (*n*=185; 16%) were also enrolled.

Microbiology

Daptomycin was used empirically (i.e. before culture results were known) in 596 (53%) patients. Methicillin-resistant *S. aureus* (MRSA) was the suspected pathogen in 327 (55%) of these patients, with methicillin-susceptible *S. aureus* (MSSA) suspected in 96 (16%) patients.

Culture results were available for 1029 (91%) patients prior to, or shortly after, initiation of daptomycin therapy (Table 2). *S. aureus* was the most commonly cultured pathogen (346 patients; 34%), with 52% of these isolates confirmed as being resistant to methicillin—a trend that was observed for all of the commonly treated infections. Coagulase-negative staphylococci (CoNS), *Enterococcus faecium* and *Enterococcus faecalis* were also among the most frequent pathogens (22%, 5% and 5% of patients for whom culture results were available, respectively), although the isolation frequency of CoNS and enterococci was higher for bacteraemia patients than for other infection types. Vancomycin resistance was more common among *E. faecium* isolates (22%) than *E. faecalis* isolates (6%).

Table 2. Confirmed primary infecting pathogens in patients for whom culture results were obtained (*N*=1029)

Organism isolated	Patients, *n* (%)[a]
S. aureus[b]	346 (34)
MRSA	181 (18)
MSSA	47 (5)
Staphylococcus epidermidis	114 (11)
Other CoNS	112 (11)
E. faecium[b]	50 (5)
VRE	11 (1)
non-VRE	26 (3)
E. faecalis[b]	48 (5)
VRE	3 (0.3)
non-VRE	36 (4)
Other[c]	131 (13)
Culture negative	212 (21)
Missing results	16 (2)

VRE, vancomycin-resistant enterococci.
[a]Percentage of total number of patients with culture results.
[b]A proportion of isolates had unknown susceptibility.
[c]Other pathogens include streptococci, *Staphylococcus* spp., *Enterococcus* spp., *Corynebacterium* spp. and Gram-negative pathogens.

Table 3. Most frequently (>10%) used antibiotics prior to daptomycin therapy ($N=1127$)

Antibiotic	Patients, n (%)[a]	Duration, median days (range)	Reason for discontinuation, n (%)[b]			
			failure	antibiotic spectrum narrowed	non-susceptible Gram-positive organism	toxicity/ intolerance
Glycopeptide	318 (28)	7 (1–60)	114 (36)	30 (9)	16 (5)	57 (18)
Penicillin	297 (26)	5 (1–70)	91 (31)	31 (10)	35 (12)	10 (3)
Fluoroquinolone	174 (15)	7 (1–242)	68 (39)	18 (10)	22 (13)	2 (1)
Carbapenem	169 (15)	10 (1–180)	44 (26)	18 (11)	14 (8)	2 (1)
Aminoglycoside	164 (15)	6 (1–62)	32 (20)	15 (9)	13 (8)	19 (12)
Cephalosporin	137 (12)	4 (1–56)	42 (31)	19 (14)	15 (11)	3 (2)
Oxazolidinone	129 (11)	9 (1–64)	50 (39)	9 (7)	6 (5)	21 (16)

[a]Percentage of the safety population.
[b]Percentage of the population of patients that received the specific drug.

Previous and concomitant antibiotic therapy

The majority of patients ($n=791$; 70%) had received previous antibiotic therapy for their designated primary infection, but information regarding prior antibiotic therapy was not available for 34 (3%) patients. Glycopeptides were the most frequently used class of antibiotic prior to daptomycin (318 patients; 28%), vancomycin being the most common (243 patients; 22%). An oxazolidinone was also used in a high proportion of patients (129 patients; 11%) prior to daptomycin (Table 3).

Treatment failure was the most common reason for discontinuation of previous antibiotic therapy, accounting for treatment discontinuation in 551 (49%) patients. Other common reasons for switching therapy to daptomycin were narrowing of the antibiotic spectrum (17%), non-susceptible Gram-positive organisms (13%) and toxicity/intolerance (11%). Discontinuation of prior antibiotic therapy due to toxicity or intolerance was observed most frequently with glycopeptides (57 of 318 patients; 18%) and oxazolidinones (21 of 129 patients; 16%), with discontinuation due to treatment failure reported for 114 (36%) patients receiving glycopeptides and 50 (39%) patients receiving oxazolidinones. The use of antibiotics concomitantly with daptomycin was common (737 patients; 65%), and the three most frequently used antibiotic classes were carbapenems (265 patients; 24%), aminoglycosides (167 patients; 15%) and fluoroquinolones (155 patients; 14%).

Daptomycin prescribing patterns

Daptomycin was the first-line therapy for treatment of the primary infection in 302 (27%) patients. Daptomycin was used as monotherapy in 117 (39%) patients receiving the drug first line compared with 227 (30%) patients receiving daptomycin as second-line therapy. The most frequently prescribed dose of daptomycin was 6 mg/kg ($n=530$; 47%) followed by 4 mg/kg ($n=365$; 32%), with only a small proportion of patients receiving alternative doses (<4 mg/kg: $n=20$, 2%; >6 mg/kg: $n=84$, 8%; >4 mg/kg; and <6 mg/kg: $n=123$; 11%). Doses of 4 mg/kg every 48 h (as indicated for cSSTI patients with $CL_{CR}<30$ mL/min)[1] were recorded as 4 mg/kg. For uSSTIs, cSSTIs, UTIs, necrotizing infections and metastatic abscess, the most frequently used dose was 4 mg/kg (46%, 47%, 56%, 60% and 100%, respectively). A dose of 6 mg/kg was the most frequently used for bacteraemia

(61%), IE (65%), foreign body/prosthetic infection (52%), osteomyelitis (69%), septic arthritis (57%), necrotizing fasciitis (60%) and surgical prophylaxis (50%).

The median duration of daptomycin therapy was 10 days (range 1–246 days) in the inpatient setting ($n=1097$), with 326 of these patients receiving daptomycin in an intensive care unit for a median duration of 8 days (range 1–90 days). Patients with IE received daptomycin for the longest median duration (16 days; range 1–112 days) whereas the shortest median duration of treatment was for uSSTIs (7 days; range 1–28 days) and UTIs (7 days; range 3–18 days). For patients treated in the outpatient setting ($n=153$), either exclusively or in combination with the inpatient setting, the median duration of outpatient therapy was 13 days (range 2–189 days).

The most common reason for discontinuation of daptomycin therapy was that therapy was completed as needed (639 patients; 57%), and 251 (22%) patients de-escalated therapy to an oral or alternative parenteral agent after clinical improvement. Discontinuation due to treatment failure was reported for 3% of patients ($n=31$) whereas in 4% of patients ($n=48$) the primary reason for discontinuation was due to AEs (see Safety and tolerability section below). The primary reason for discontinuation could not be determined for 5% of patients ($n=60$) and was recorded as 'other' for 9% of patients ($n=98$).

Clinical outcome

Overall, daptomycin treatment was associated with a clinical success rate of 79% (894/1127), and the overall rate of treatment failure was 7.5% (Figure 1). Clinical success rates were highest (>80%) for uSSTIs, endocarditis and cSSTIs, and lowest for infections categorized as other (foreign body/prosthetic infection and UTI, among others). Similarly low failure rates were observed regardless of whether daptomycin was administered as first- or second-line therapy [6% (19/302) versus 8% (60/791), respectively]. The clinical success rate with second-line daptomycin [77% (611/791)] was lower than that when daptomycin was used as first-line therapy [85% (257/302)], although there were more non-evaluable patients in the group receiving daptomycin second line compared with first line [15% (120/791) versus 9% (26/302), respectively].
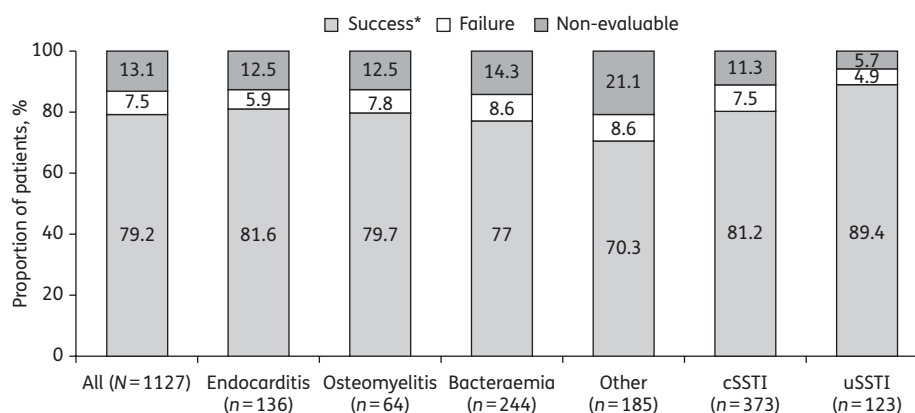
Figure 1. Treatment outcomes by primary infection type (*N*=1127). Data were missing for two patients. *Clinical success: cure or improved outcomes.
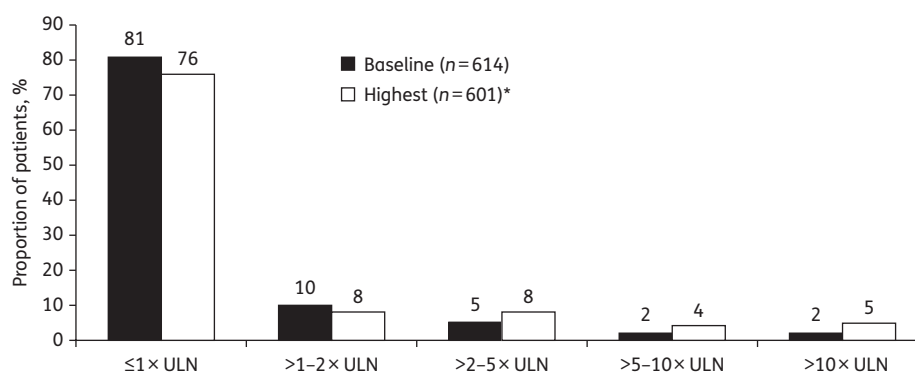

Figure 2. Baseline and peak serum CPK concentrations. *Values for 16 patients are unknown.

For those patients where MRSA was identified as the primary pathogen, rates of clinical success were similar regardless of whether daptomycin was used as first- (*N*=53) or second- (*N*=134) line therapy: 83% and 80%, respectively. Failure rates were 11% in both groups (6/53 and 15/134 for first- and second-line therapy, respectively). The mean time to clinical improvement was determined for 632 patients deemed to have improved clinically and was 6.3 (standard deviation=8.3) days.

Safety and tolerability

The safety profile of daptomycin was favourable. AEs were reported for 193 (17%) patients, and 109 (10%) patients experienced an SAE. Infections and infestations were the most frequently reported system organ class among all AEs (5%) and SAEs (4%). Septic shock was the most commonly reported AE (2%), which reflects the severity of infections treated in the registry. AEs resulting in discontinuation (regardless of the relationship to daptomycin) occurred in 51 (5%) patients. The most frequent AEs leading to discontinuation were septic shock (six patients) and increases in blood CPK (six patients). In total, 89 (8%) patients experienced AEs requiring significant additional therapy, most frequently due to infection or infestation (*n*=28; 3%); these included septic shock (0.6%), pneumonia (0.4%) and urinary tract infections (0.4%), as well as various Gram-

negative and fungal infections. Eighty-five (8%) patients died while receiving daptomycin therapy—the principal cause of death was infection and infestation (4%, *n*=41), of which septic shock (2%, *n*=19) was the most frequent.

There was no increase in the proportion of patients with $CL_{CR} < 30$ mL/min from initiation [152 patients (14%)] to the end of therapy [151 patients (13%)]. Serum CPK was measured at baseline for 614 (55%) patients and during the course of daptomycin therapy for 617 (55%) patients (Figure 2). At baseline among patients with CPK measured, serum CPK concentrations below or equal to the upper limit of normal (ULN) were reported for 498 (81%) patients, >5–10× ULN in nine (1%) patients and >10× ULN in 14 (1%) patients. During therapy, 459 (74%) patients had a peak serum CPK concentration below or equal to the ULN. CPK elevations >5–10× ULN and >10× ULN were observed in 21 (3%) and 27 (4%) patients, respectively. The mean and median time to highest CPK concentrations was 11 days after initiation of treatment with daptomycin. Elevated CPK concentration was reported as an SAE in only one patient. Although the patient had severe renal impairment at baseline ($CL_{CR} < 30$ mL/min), the daptomycin dosing interval was not adjusted at the start of therapy. Daptomycin treatment at 6 mg/kg once daily was initiated for catheter-related MRSA bacteraemia and left-sided IE in this critically ill patient complicated with haemorrhagic shock. Later the daptomycin dosing interval was

corrected to dosing every 48 h, as recommended in the current label. This patient had a CPK concentration of $>5-10\times$ ULN on day 10 of daptomycin therapy, possibly related to daptomycin, but no AEs indicative of musculoskeletal and connective tissue disorders were reported. Daptomycin therapy was not discontinued and the outcome of the patient's infection was cured. It is relevant to note in this case that the European label, in contrast to the USA, did not have a dose recommendation for the 6 mg/kg dose at the time this patient was treated. The European approval for the 6 mg/kg dose in patients with $CL_{CR} < 30$ mL/min (dose interval 48 h) was obtained in 2010.

SAEs concerning musculoskeletal and connective tissue disorders related to daptomycin were reported in only one patient. Again, although severe renal impairment ($CL_{CR} < 30$ mL/min) was a baseline condition, the daptomycin dosing interval was not adjusted. The patient was treated with daptomycin at 6 mg/kg once daily for 10 days in the outpatient setting to treat an MRSA infection following hip surgery. After 10 days of therapy, CPK elevation ($>10\times$ ULN) accompanied by muscle pain were reported with a clinical diagnosis of rhabdomyolysis, possibly related to daptomycin. Daptomycin treatment was discontinued and the patient recovered.

Discussion

These data show that, during the study period (2006–08), daptomycin was used in Europe and Argentina to treat a variety of Gram-positive infections in a severely ill patient population with multiple co-morbidities, who were commonly infected with drug-resistant pathogens (MRSA, CoNS and vancomycin-resistant enterococci), and almost half of whom were aged ≥65 years. Daptomycin demonstrated a favourable safety and tolerability profile and low overall rates of clinical failure similar to the early results from the CORE database in the USA,[10–13] despite its use in this severely ill population, frequently as second-line or salvage therapy. Although just over half of the patients received daptomycin empirically, $>90\%$ of infections overall were microbiologically documented: staphylococcal species were identified in more than half of patients in whom an infecting pathogen was isolated. MRSA and CoNS were predominant, accounting for $\sim40\%$ of all isolates. The most frequently treated infections were those for which daptomycin is indicated (cSSTIs and bacteraemia); however, additional non-registered Gram-positive infections were treated (including osteomyelitis), probably reflecting an unmet need for licensed treatment options for these diseases. Only eight patients from Argentina were included; therefore, the reported results largely reflect European use of the drug.

The initial dosing in Europe appears to have been higher than was being used initially in the USA. During the first 2 years of the CORE database (2004–06), the median initial dose of daptomycin administered was 4 mg/kg (range 2–12 mg/kg).[14] In EU-CORE, the majority of patients received doses of >4 mg/kg, appearing to correspond to the severity of the type of infections being treated. This could reflect increased confidence with the use of daptomycin following the publication of the initial results from CORE in 2007,[10–13] in addition to the Phase III clinical trial results in SAB with or without IE in 2006,[7] demonstrating the safety and efficacy of the 6 mg/kg dose in these

infections. Furthermore, inclusion of higher than approved doses of daptomycin in treatment guidelines may, in part, account for the use of doses of >6 mg/kg in a small proportion of patients.[15,16]

Daptomycin was typically used as second-line therapy. Notably, a high proportion ($\sim40\%$) had received either a glycopeptide (most commonly vancomycin) or oxazolidinone agent (linezolid) prior to receiving daptomycin, and more than half of these had switched to daptomycin as a consequence of treatment failure, toxicity or intolerance. Daptomycin has an important role as first-line therapy for Gram-positive infections, in terms of both efficacy and cost considerations, the benefit of which is supported by the results observed here.[17] Although patients receiving daptomycin first line had numerically higher clinical success rates than patients receiving daptomycin second line, the uneven numbers of non-evaluable patients between these groups confounds this comparison. Comparison of the failure rates indicates only a 2% difference in treatment failure between the two patient groups. Unlike glycopeptides, daptomycin has proven similar efficacy against both MRSA and MSSA,[6,7] making it an attractive option for empirical therapy of suspected *S. aureus* infections regardless of methicillin resistance risk. Unlike linezolid, daptomycin is bactericidal, which is expected to confer advantages in terms of efficacy, especially in serious infections.[18–20] Experience in EU-CORE appears to support this concept, with 53% of patients receiving daptomycin as empirical therapy.

There is emerging evidence that daptomycin is being used to treat infections caused by other Gram-positive species that are of increasing importance in hospital and outpatient practice,[21–23] particularly in orthopaedic-related and endovascular infections where other long-term treatment options may be limited.[24,25] In addition, alternative therapies are increasingly required to face current trends of rising vancomycin resistance, as demonstrated by the high rate of vancomycin resistance among enterococci in this study (22% in *E. faecium*). This is also reflected in published treatment guidelines where daptomycin is recommended as first alternative to vancomycin when the vancomycin MIC is no longer associated with a significant chance of clinical success.[15,16]

Prior to optimization of the dosing interval to a once-daily regimen, daptomycin had been associated with reversible CPK elevation and skeletal muscle toxicity.[26] However, in clinical trials with once-daily dosing, daptomycin-associated CPK elevations were demonstrated in 7% of patients receiving the 6 mg/kg dose, only leading to discontinuation of daptomycin in 2.5% of patients, and did not occur in patients receiving the 4 mg/kg dose.[6,7] In agreement with these clinical trial findings, analysis of the EU-CORE database has shown that daptomycin therapy minimally impacts upon serum CPK concentrations as reflected in the low rates of related AEs and discontinuations. It is, however, important to keep in mind that the dosing interval in patients with severe renal impairment ($CL_{CR} < 30$ mL/min) with or without dialysis should be adjusted to 48 h for both approved doses.

Concomitant administration of other antibiotic agents with daptomycin was common, and aminoglycosides were among the most frequent with concomitant use in 15% of patients. Although aminoglycosides are typically associated with nephrotoxicity,[27] the rate of renal and urinary SAEs was very low (1%) overall. This rate was similar to that observed for daptomycin

monotherapy (0.8%) in the pivotal Phase III study in SAB/IE; however, it must be noted that in the pivotal trial, comparator therapy (vancomycin or anti-staphylococcal penicillin, in combination with short-course gentamicin) was associated with significantly higher rates of these SAEs (8%; $P=0.009$).[7] In animal models, daptomycin has been shown to attenuate the nephrotoxicity induced by the administration of gentamicin, leading to postulation that daptomycin may in fact have nephron-protective properties.[28]

Even though the median treatment duration of inpatient therapy was 10 days, 30 (3%) patients were treated with daptomycin in the inpatient setting for >42 days, and the maximum treatment duration documented for an individual patient was 246 days. Most of the patients receiving prolonged therapy had various significant underlying diseases, but in this patient group only two patients had AEs reported as possibly related to daptomycin with no SAEs reported. There are relatively few treatment options available for resistant Gram-positive infections that can be used for long treatment durations without an increased risk of AEs; e.g. myelosuppression and peripheral neuropathy have been related to treatment duration with linezolid, and the maximum recommended treatment duration with this agent is 28 days.[29] Daptomycin might, therefore, represent a useful option for the treatment of chronic complicated infections where extended duration of therapy is required, such as osteoarticular or endovascular infections.

The EU-CORE registry, by its nature, has inherent limitations in that data collection is retrospective, non-comparative, non-blinded and non-randomized, and clinical outcomes are judged by the attending clinician. Although a potential selection bias cannot be excluded, the fact that the study does not include any clinical criterion for patient inclusion (except participation in interventional studies with daptomycin) and is performed in a very large number of participating institutions without restrictions does give credibility to its results. A central laboratory was not used in this registry and therefore site-to-site differences in the quality of microbiological results and other laboratory results cannot be excluded. This registry allows the inclusion of diverse infections and the use of concomitant antibiotics, including broad-spectrum antibiotics. Therefore, the efficacy results are to be interpreted in this context. Despite these limitations, the data collected in EU-CORE provide a useful insight into real-world clinical practice and expand on the evidence base derived from clinical trials. In this kind of registry, clinical information can be obtained from patient populations that urgently need treatment but would otherwise have been excluded from controlled clinical trials due to their baseline conditions,[8] as was the case for patients with severe renal insufficiency in the pivotal trials for cSSTI and SAB/IE.[6,7] The current results are of interest for physicians in different parts of the world, and it is planned to further expand this registry to other continents.

The current results suggest that daptomycin has a relevant role in the therapeutic armamentarium of European physicians for the treatment of Gram-positive infections.

Transparency declarations

A. G.-R. has received fees from Pfizer and Gilead for staff training and being an Advisory Board Member and from Novartis for being an Advisory Board Member and a member of a speakers' panel. A. B.-F. has received fees from Merck and Novartis for being an Advisory Board Member and has spoken at Novartis-sponsored symposia. H. L. has received research grants from Novartis for various transplant and infection projects/studies. R. A. S. is a member of the Novartis Advisory Board, UK and has spoken at Novartis-sponsored symposia. J. L. and R. L. C. are employees of Novartis Pharma AG and own stocks with the company.

Authors were involved in all diverse phases of the study (including enrolment of patients), data analysis and writing of the manuscript. Authors did not receive honoraria for the preparation of this manuscript.

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