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Daptomycin for the treatment of infective endocarditis: results from European CUBICIN® Outcomes Registry and Experience

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INTRODUCTION AND PURPOSE

- Infective endocarditis (IE), primarily caused by Gram-positive bacteria, is associated with a high rate of morbidity and mortality, and represents a large burden on the healthcare system[1]
- Successful treatment of IE remains challenging because resistance of pathogens to commonly used antimicrobials is increasing. IE can be fatal if not treated aggressively with antibiotics or a combination of antibiotics and surgery[2-4]
- Daptomycin is a cyclic lipopeptide antibiotic active against Gram-positive bacteria and is indicated for the treatment of *Staphylococcus aureus* bloodstream infections, including right-sided endocarditis[5,6]
- Daptomycin is bactericidal and is associated with concentration-dependent activity; hence, high-doses of daptomycin can penetrate bacterial biofilms and help to prevent the emergence of bacterial resistance[1]
- The European CUBICIN® Outcomes Registry and Experience (EU-CORE℠) was a retrospective, multicentre registry, designed to collect real-world data on the use of daptomycin for Gram-positive infections across 18 countries in Europe (12), Latin America (5) and Asia (1)
- This analysis evaluated the clinical outcomes in patients with IE

METHODS

- Data were collected using standardised case report forms for patients with IE who had received at least one dose of daptomycin between January 2006 and April 2012; follow-up data were collected for 2 years
- Patients who had received daptomycin as part of a controlled clinical trial were excluded
- The clinical outcome was assessed as success (cured or improved), failure or non-evaluable both at the end of daptomycin treatment and at follow-up (**Table 1**)

Table 1. Definitions of clinical outcomes

Response*		
Success (cured or improved)	**Cured**	**Improved**
	• Clinical signs and symptoms resolved (and/or) • No additional antibiotic therapy necessary (or) • Negative culture at the end of therapy	• Partial resolution of clinical signs and symptoms (and/or) • Additional therapy (e.g., oral antibiotics) at the end of therapy
Failure	• Worsening or new/recurrent signs/symptoms (or) • Need for a change in antibiotic therapy (or) • Positive culture reported at the end of therapy	
Non-evaluable	• Unable to determine response due to insufficient information	

*Assessed by the investigator

- Adverse events (AEs) and serious AEs (SAEs) up to 30 days post-treatment, regardless of their relationship to daptomycin, were recorded

RESULTS

Patient demographics and baseline characteristics

- Of 6075 patients included in the EU-CORE registry, 610 were diagnosed with IE as primary infection, of whom 414 (68%) had left-sided IE (LIE), 149 (24%) had right-sided IE (RIE) and 47 (8%) had both left- and right-sided IE (LRIE)
- Demographics and baseline characteristics, including underlying diseases, are summarised in Table 2. The majority of patients had a significant underlying disease, most commonly cardiovascular, gastrointestinal, pulmonary and/or renal disease (**Table 2**)

Table 2. Patient demographics and baseline disease characteristics

Parameters	LIE N=414, n (%)	RIE N=149, n (%)	LRIE N=47, n (%)
Gender, male	260 (63)	104 (70)	30 (64)
Age (years), median (range)	62 (10–91)	58 (1–90)	63 (24–87)
≥65 years	187 (45)	56 (38)	22 (47)
Race, Caucasian	355 (86)	124 (83)	40 (85)
Significant underlying diseases* (>10% of patients in every group)	378 (91)	133 (89)	43 (91)
Cardiovascular	322 (78)	93 (62)	34 (72)
Gastrointestinal	55 (13)	24 (16)	7 (15)
Pulmonary	51 (12)	21 (14)	9 (19)
Renal	83 (20)	25 (17)	12 (26)

LIE, left-sided infective endocarditis; RIE, right-sided infective endocarditis; LRIE, left- and right-sided infective endocarditis; SD, standard deviation
*The listed underlying diseases were known past medical history of diseases

Primary pathogen culture

- Details of the primary infecting pathogens are depicted in **Table 3**. The most common primary pathogen was *S. aureus* (LIE 37%, RIE 48% and LRIE 38%)
- Methicillin-resistant *S. aureus* (MRSA) was identified in 39 (14%) patients with LIE, 11 (10%) patients with RIE and 3 (10%) patients with LRIE

Table 3. Primary pathogens

Pathogen	LIE N=414, n (%)	RIE N=149, n (%)	LRIE N=47, n (%)
Culture positive	274 (66)	110 (74)	29 (62)
Staphylococcus aureus	101 (37)	53 (48)	11 (38)
Methicillin-susceptible	50 (18)	39 (35)	7 (24)
Methicillin-resistant	39 (14)	11 (10)	3 (10)
Methicillin susceptibility unknown	12 (4)	3 (3)	1 (3)
Staphylococcus epidermidis	49 (18)	30 (27)	2 (7)
***Staphylococcus* spp. - coagulase negative**	32 (12)	13 (12)	6 (21)
Enterococcus faecium	7 (3)	–	1 (3)
Non-VRE	3 (1)	–	–
VRE	2 (1)	–	1 (3)
Vancomycin susceptibility unknown	2 (1)	–	–
Enterococcus faecalis	34 (12)	6 (5)	3 (10)
Non-VRE	30 (11)	5 (5)	2 (7)
Vancomycin susceptibility unknown	4 (1)	1 (1)	1 (3)
Other*	51 (19)	8 (7)	6 (21)
Culture negative	101 (24)	23 (15)	6 (13)

LIE, left-sided infective endocarditis; RIE, right-sided infective endocarditis; LRIE, left- and right-sided infective endocarditis; vancomycin-resistant enterococci (VRE)
*Other includes *Corynebacterium* spp., *Staphylococcus* spp. (coagulase not specified), *Streptococcus agalactiae* or group B streptococci, *Streptococcus dysgalactiae, Streptococcus pyogenes* or group A streptococci, *Streptococcus* spp., *Enterococcus* spp., viridans streptococci, Gram-negative bacilli, Gram-positive bacilli, and Gram-positive cocci

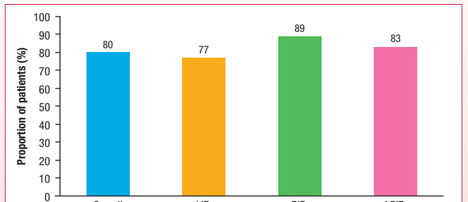
Dosage and duration of daptomycin therapy

- The most commonly prescribed initial dose was 6 mg/kg/day given to 231 (56%), 84 (56%), and 27 (57%) patients with LIE, RIE and LRIE, respectively
- The median duration of outpatient therapy was 21 days (range, 5–85), 21 days (range, 7–50) and 30 days (range, 22–75) for patients with LIE, RIE and LRIE, respectively.
- The median duration for inpatient therapy was 18 days (range, 1–112), 19 days (range, 1–81) and 14 days (range, 5–72) for patients with LIE, RIE and LRIE, respectively
- Heart valves were surgically replaced in 166 LIE, 21 RIE and 11 LRIE patients; while in 14 LIE and 37 RIE patients foreign devices were surgically removed

Treatment outcomes

- Overall clinical success was achieved in 80% of patients (LIE 77%, RIE 89% and LRIE 83%; **Figure 1**)

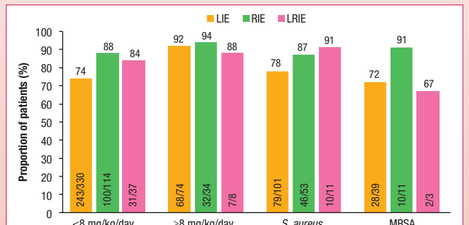
Figure 1. Clinical success by type of endocarditis (efficacy population, N=610)



LIE, left-sided infective endocarditis; RIE, right-sided infective endocarditis; LRIE, left- and right-sided infective endocarditis

- Clinical success rates were numerically higher with daptomycin doses ≥8 mg/kg/day (**Figure 2**)

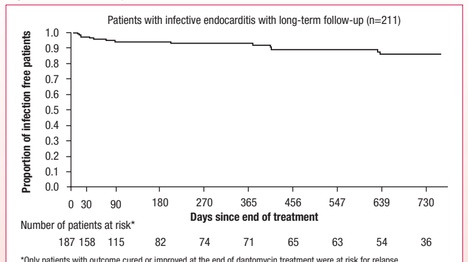
Figure 2. Clinical success by daptomycin dose and infection by *S. aureus*



MRSA, methicillin-resistant *Staphylococcus aureus*; IE, infective endocarditis; LIE, left-sided infective endocarditis; LRIE, left- and right-sided infective endocarditis; RIE, right-sided infective endocarditis

- Success rates against MRSA infections were 72%, 91% and 67% in patients with LIE, RIE and LRIE, respectively
- The overall sustained clinical success rate in patients who were followed for up to 2 years was 87% (LIE, 88%; RIE, 94% and LRIE, 78%)

Figure 3. Time to relapse



*Only patients with outcome cured or improved at the end of daptomycin treatment were at risk for relapse

Safety

- AEs possibly related to daptomycin per the investigator were reported in 18 (4.3%) LIE, 2 (1.3%) RIE and 1 (2.1%) LRIE patients (**Table 4**)
- There were 11 (1.8%) patients (8 with LIE, 2 with RIE and 1 with LRIE) with creatine phosphokinase (CPK) elevation reported as possibly related to daptomycin

Table 4. Summary of AEs and SAEs

	LIE N=414, n (%)	RIE N=149, n (%)	LRIE N=47, n (%)
AEs	98 (23.7)	16 (10.7)	10 (21.3)
SAEs	70 (16.9)	9 (6.0)	10 (21.3)
Discontinuations due to AEs	30 (7.2)	5 (3.4)	2 (4.3)
AEs possibly related to daptomycin*, n (%)	18 (4.3)	2 (1.3)	1 (2.1)
Blood CPK increased	8 (1.9)	2 (1.3)	1 (2.1)
Eosinophilic pneumonia	2 (0.5)	–	–
SAEs possibly related to daptomycin*, n (%)	6 (1.4)	–	–
Blood CPK increased	2 (0.5)	–	–
Eosinophilic pneumonia	2 (0.5)	–	–

AE, adverse event; SAE, serious adverse event; CPK, creatine phosphokinase; LIE, left-sided infective endocarditis; RIE, right-sided infective endocarditis; LRIE, left- and right-sided infective endocarditis
*According to the investigator. AEs and SAEs >1 in any group are presented

CONCLUSIONS

- Daptomycin was well tolerated and effective for the treatment of LIE and LRIE in addition to RIE caused by Gram-positive bacteria, including MRSA
- Numerically higher success rates were observed with daptomycin doses ≥8 mg/kg/day
- Two-year follow-up data showed that a high proportion of patients had a sustained response

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