REVIEW

Treatment of staphylococcal infections with cyclic lipopeptides

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ABSTRACT

Daptomycin is the first of a new class of antibiotics, the cyclic lipopeptides, for which a novel mechanism of action is hypothesised. Owing to its mode of action, daptomycin is rapidly bactericidal without being bacteriolytic, is active against static- and growing-phase bacteria, and has a low resistance rate *in vitro*. Phase III clinical trials have demonstrated that daptomycin is as effective as standard therapy for the treatment of complicated skin and soft-tissue infections associated with Gram-positive infections, and daptomycin-treated patients benefited from a reduced time to clinical resolution. Daptomycin has also been shown to be as effective as standard therapy in the treatment of bacteraemia associated with *Staphylococcus aureus*, with or without endocarditis. These results indicate that daptomycin is a useful therapeutic option for treating Gram-positive infections, particularly those caused by *S. aureus*.

Keywords Bacteraemia, daptomycin, infective endocarditis, MRSA, review, *S. aureus*

Clin Microbiol Infect 2008; **14** (Suppl. 2): 10–16

INTRODUCTION

The cyclic lipopeptides are one of the most recent antibiotic classes with a novel mode of action to gain marketing approval. Their introduction comes at a time of growing concern over the dearth of new antibiotics under development [1]. Daptomycin is the first antibiotic in this new class to acquire marketing approval. It is currently licensed in the USA for the treatment of complicated skin and skin-structure infections caused by Gram-positive organisms and bacteraemia, with or without right-sided endocarditis caused by *Staphylococcus aureus* [2]. More recently, it has also been approved by the European Medicines Agency for the treatment of complicated skin and soft-tissue infections (cSSTIs), right-sided infective endocarditis due to *S. aureus* bacteraemia (SAB), and SAB when associated with right-sided endocarditis or cSSTIs [3].

The magnitude of the healthcare burden associated with invasive methicillin-resistant *S. aureus* (MRSA) has been quantified for the US population in 2005 as a standardised incidence rate of 31.8 per 100 000 persons, as compared with the incidence of other important invasive pathogens, such as *Streptococcus pneumoniae* or *Haemophilus influenzae*, which ranged from 14.0 per 100 000 to <1 per 100 000 [4,5]. Moreover, the study showed that MRSA infections are no longer confined to healthcare institutions; MRSA strains isolated from community-acquired infections are becoming increasingly common. In this context, the activity of daptomycin against both MRSA and methicillin-susceptible *S. aureus* (MSSA) makes it an attractive alternative to standard therapies, particularly as the incidence of MRSA with reduced susceptibility to vancomycin—the current reference standard for the treatment of MRSA—is increasing [6,7,8].

The antibacterial activity of daptomycin is believed to be mediated through depolarisation of the bacterial cell membrane. Daptomycin inserts into and irreversibly binds within the bacterial cell membrane in a calcium-dependent process [9,10] (Fig. 1). Subsequent oligomerisation of daptomycin molecules within the membrane leads to the formation of pores or ion channels, which allow potassium efflux from the bacterial cytoplasm, thus destroying the ion concentration gradient [11]. This depolarises the cell membrane and causes rapid cell death through the inhibition

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B. Eisenstein is a full-time employee of Cubist Pharmaceuticals, Inc., a company that sells and markets CUBICIN (daptomycin for injection), which is discussed in this review.

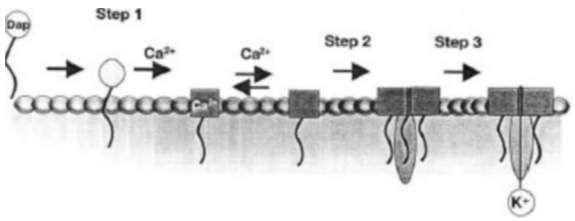

Fig. 1. Mode of action of daptomycin. Daptomycin inserts into the bacterial membrane in a calcium-dependent fashion. Oligomerisation and disruption of the bacterial membrane follows, and leads to depolarisation of the bacterial membrane through release of ions, which in turn leads to the disruption of intracellular processes. From Silverman *et al.* [10]

of DNA, RNA and protein synthesis [12]. This mode of action endows daptomycin with a broad spectrum of activity against Gram-positive bacteria. It is bactericidal without being bacteriolytic, a feature that contributes to reducing overstimulation of the immune response by bacteria and prolongation of inflammation [13], which can result in severe inflammatory response syndrome [14,15]. Furthermore, daptomycin is active in both the static and growth phases of bacteria [16], a property that is highly unusual [15]. In-vitro experiments have demonstrated the difficulty with which bacterial resistance to daptomycin develops [9,10,17], and the novel mechanism of action of daptomycin means that cross-resistance is unlikely to develop [18].

In-vitro and in-vivo studies have demonstrated that daptomycin is more rapidly bactericidal than vancomycin [19,20]. Clinical trials support these findings and demonstrate that daptomycin is a viable alternative to vancomycin for treating cSSTIs and SAB; certain study outcomes, e.g., duration of effective therapy and time to clinical resolution, also indicate that daptomycin may provide advantages over the current standard-of-care regimens [21,22].

SKIN AND SOFT-TISSUE INFECTIONS

The term SSTI describes a wide variety of infections affecting the epidermis, dermis and subcutaneous tissues, and these can be classified according to four levels of severity and the presence of co-morbidities [23]. In general, class 1 represents uncomplicated SSTIs (e.g., boils and simple abscesses), whereas classes 2–4 encompass

Table 1. Predisposing factors for developing skin and soft-tissue infections [14]

Advanced age
Reduced arterial perfusion
Neuropathy
Diabetes mellitus
Chronic venous insufficiency
Obesity
Malnutrition
Compromised immune function
Disruption of the skin

cSSTIs, i.e., SSTIs complicated by co-morbidities and/or systemic involvement on a scale of increasing severity [24] (e.g., infected ulcers and necrotising fasciitis). Patients with cSSTIs present with a spectrum of clinical manifestation, depending on the depth of soft-tissue involvement, the pathogen(s) present and the degree of systemic compromise. Diagnosing cSSTIs is not straightforward, because there are no specific symptoms that define cSSTIs. Infections can be asymptomatic during the initial stages and it can be difficult to differentiate between uncomplicated and complicated infections [23]. Nonetheless, several predisposing factors for the development of cSSTIs have been identified [14] (Table 1).

Clinical studies of daptomycin in skin and soft-tissue infections

Daptomycin received marketing authorisation in the USA and the EU for the treatment of cSSTIs on the basis of the findings of two phase III international, multicentre, randomised, investigator-blinded trials (DAP-SST-98-01 and DAP-SST-99-01) conducted between 1999 and 2001 [21]. The trials compared daptomycin (4 mg/kg intravenously once daily for 7–14 days) with either vancomycin (1 g intravenously every 12 h) or penicillinase-resistant semi-synthetic penicillins (nafcillin, cloxacillin, flucloxacillin or oxacillin; 4–12 g intravenously once daily) in the treatment of 1092 patients (total sum of both trials) with cSSTIs due to Gram-positive bacteria, and who required hospitalisation. Investigators assigned the comparator regimen depending on baseline diagnosis. Patients were then randomised 1:1 to receive daptomycin (n = 534) or the pre-assigned comparator regimen (n = 558) (Fig. 2). The primary outcomes were based on clinical and microbiological assessments performed at baseline and

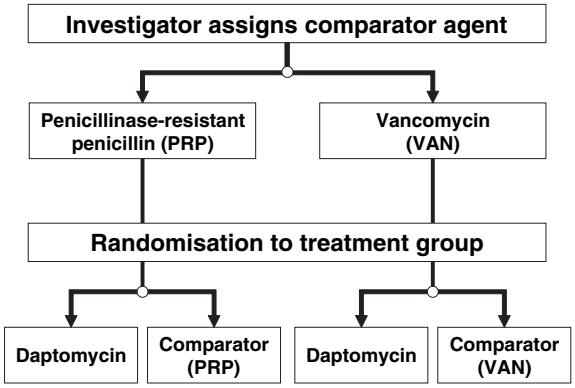

Fig. 2. Study design of DAP-SST-98-01 and DAP-SST-99-01 [21].

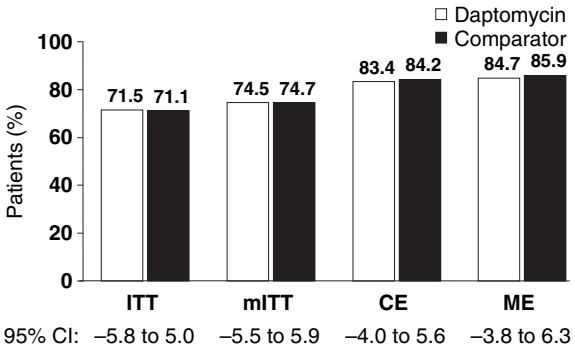

Fig. 3. Clinical success rates (defined as cure or improvement sufficient to warrant discontinuing antibiotic treatment) of daptomycin and comparators in studies DAP-SST-98-01 and DAP-SST-99-01 [21]. Ninety-five percent confidence intervals are given for the rate in the comparator group minus that for the daptomycin group. ITT, intention to treat; mITT, modified intention to treat; CE, clinically evaluable; ME, microbiologically evaluable.

6–20 days after administration of the last treatment dose (for the regulatory dossier prepared for the European Medicines Agency, analyses were based on a test of cure assessed at 7–13 days after the final treatment [25]). Clinical success was defined as 'resolution of signs and symptoms such that no further antibiotic therapy was required' at the test of cure, and further evaluation was carried out at a post-study visit 20–28 days after the final dose, to determine whether there was a clinical relapse or new infection. Patients were considered to be treatment failures if an inadequate response to therapy was observed at any stage of the investigation.

Diagnoses in the intention-to-treat (ITT) population across both arms of the study included major abscesses (26% in the daptomycin treatment arm and 22% in the comparator arm), wound infections (42% and 46%, respectively), diabetic ulcer infections (11% and 13%, respectively), and non-diabetic ulcer infections (13% and 13%, respectively). *S. aureus* was the Gram-positive pathogen most frequently cultured from the primary infection site (71% in the daptomycin arm and 69% in the comparator arm); the majority of these were methicillin-susceptible (54% and 51% of all isolates in each arm, respectively). Several patients were infected with multiple organisms; the most frequently occurring combination was *S. aureus* and *Streptococcus pyogenes*. No vancomycin-resistant enterococcal infections were detected in the studies.

Daptomycin was deemed to be non-inferior to the comparator regimens, as measured by the clinical success rate in all analysed patient populations (ITT; modified ITT; clinically evaluable; microbiologically evaluable) (Fig. 3). Although differences were observed in clinical success rates stratified by organism, these rates were similar for daptomycin and the comparator regimens. Subanalyses indicated no significant differences between the two arms in the treatment of MSSA and MRSA in the microbiologically evaluable population. The success rate was lower in both the daptomycin and comparator regimen arms for MRSA (75.0% and 69.4%, respectively) than for MSSA (85.9% and 87.0%, respectively). A possible explanation for the reduced success of all treatments against MRSA is a higher incidence of co-morbidities in the MRSA population (author's unpublished observations).

A significant difference in favour of daptomycin was observed for the duration of therapy among patients who were successfully treated with intravenous therapy alone. A total of 63% of patients receiving daptomycin required only 4–7 days of therapy, as compared with 33% in the comparator arm ($p < 0.0001$). This could be attributable to the increased in-vivo bactericidal activity of daptomycin as compared with vancomycin, which has been demonstrated in mice but has yet to be shown against other comparator agents *in vivo* [19]. An alternative, and perhaps more likely, explanation for this difference is that reduced lysis of the invading bacteria, as they are killed, results in reduced immunopathology [13].

The safety profile for daptomycin was similar to that of the comparator agents, with no significant

differences being observed in the frequency, distribution and severity of adverse events. Daptomycin has been reported to have the potential for causing muscle toxicity [26]; however, close monitoring of creatine phosphokinase (CPK) levels did not reveal a significant difference between daptomycin-treated (2.8%) and comparator-treated (1.8%) patients in terms of CPK elevations, and there was no significant difference in the rate of musculoskeletal adverse events [2]. Furthermore, among patients with elevated CPK levels prior to commencing therapy, the frequency with which CPK levels returned to normal was greater in the daptomycin arm [2].

Overall, these clinical trials demonstrated that daptomycin, given at 4 mg/kg once daily, is as safe and effective as standard therapy for the treatment of cSSTIs caused by Gram-positive pathogens.

SAB AND INFECTIVE ENDOCARDITIS

Bacteraemia is defined as the presence of cultivatable bacterial organisms in the bloodstream, which may be transient and inconsequential, intermittent or persistent [27]. Intermittent bacteraemia suggests that the bacteria originate from an extravascular site, entering the bloodstream via the lymphatic system, whereas persistent bacteraemia suggests an intravascular source (e.g., endocarditis) [28]. Bacteraemia can be clinically significant because of the risk of complications and the potential to progress to sepsis, defined as the presence of clinical signs and symptoms of infection, i.e. a generalised inflammatory reaction, in addition to the presence of bacteraemia [28]. This reaction is characterised by numerous symptoms, e.g., fever and increased heart rate, respiratory rate and white blood cell counts. Patients are defined as having severe sepsis if there are concomitant signs of hypotension, hypoperfusion or dysfunction of organs distant from the site of infection [27].

S. aureus is a significant cause of bacteraemia in both nosocomial and community settings [29], and is associated with complications that include deep tissue abscesses, osteomyelitis and infective endocarditis, particularly in bacteraemic episodes of more than 48 h [30,31]. The rise of antibiotic-resistant strains of *S. aureus* impacts on both the prognosis and treatment of SAB; meta-analyses have shown that MRSA bacteraemia is associated with increased mortality rates, as compared with MSSA bacteraemia [32,33]. The explanation for this difference goes beyond the presence of excess co-morbidities in the MRSA patients, because meta-analyses that have controlled for underlying co-morbidities still indicate an increased mortality rate [32–34]. With respect to hospital-acquired MRSA, this higher mortality rate is not due to any known difference in virulence between MRSA (as reported during the time of the studies included in the meta-analyses) and MSSA [32]. Findings from a retrospective cohort analysis suggest that delayed treatment significantly increases the rate of mortality and duration of stay [35], while another study has shown that slight decreases in vancomycin susceptibility to MRSA (MIC ≥1.0 mg/L) *in vitro* can affect the clinical susceptibility of MRSA to vancomycin [36]. Therefore, the differences observed in mortality rates between MRSA and MSSA bacteraemia are more likely to be due to delayed treatment, ineffective empirical therapy, and the decreased efficacy of vancomycin as a targeted therapy [31,35].

Treatment options for MSSA and MRSA bacteraemia and infective endocarditis are dependent on the susceptibility of the isolate to antibiotics [31]. At present, MRSA infection is generally treated with vancomycin, whereas, depending on the results of in-vitro susceptibility tests, penicillinase-resistant penicillins and cephalosporin are the traditional options for MSSA infections. However, analyses of the susceptibility of strains of *S. aureus* to vancomycin indicate that susceptibility is decreasing in some geographical areas [8], which has resulted in decreased rates of treatment success [36]. New antibiotics, such as daptomycin, represent a potential solution to this problem. For a more detailed discussion of vancomycin resistance and its implications, the reader is referred to the accompanying article by Jones in this supplement.

An in-vitro pharmacodynamic model with simulated endocardial vegetations demonstrated the potent bactericidal activity of daptomycin against high-inoculum MRSA [16]. Daptomycin 6 mg/kg once-daily (simulating a human therapeutic dose regimen) achieved 99.9% kill (defined as a ≥3 $\log_{10}$ CFU/g reduction in colony count from the initial inoculum) of high-inoculum MRSA within 36 h, and maintained this bactericidal

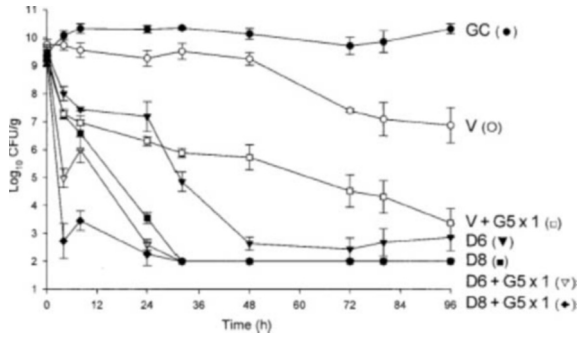

Fig. 4. Comparison of activities of daptomycin (at 6 and 8 mg/kg), and vancomycin alone and in combination with a single dose of gentamicin, against methicillin-resistant *Staphylococcus aureus*. D6, daptomycin 6 mg/kg once daily; D8, daptomycin 8 mg/kg once daily; V, vancomycin given every 12 h; G5 × 1, gentamicin in one 5 mg/kg dose; GC, growth control. From Tsuji [16].

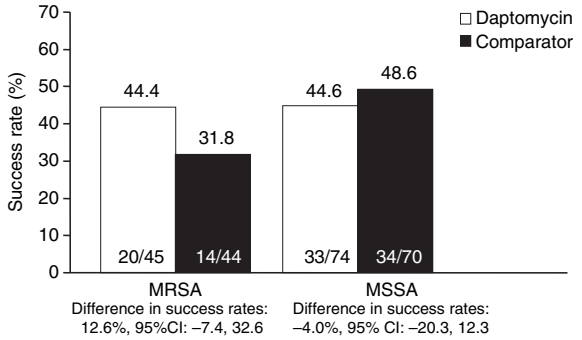

Fig. 5. Clinical success rates of daptomycin and comparators against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteraemia and endocarditis [22]. Ninety-five per cent confidence intervals are given for the difference in success rates between the two treatment arms (daptomycin minus comparator).

activity for 96 h (Fig. 4). In contrast, vancomycin 1 g every 12 h failed to achieve bactericidal activity against MRSA at any time-point. The addition of a single 5 mg/kg dose of gentamicin to vancomycin 5 mg/kg resulted in 99.9% kill at 32 h for MRSA.

The efficacy of daptomycin in the treatment of SAB, with or without endocarditis, has been investigated in an open-label trial of 246 patients randomised to receive either daptomycin 6 mg/kg once-daily or an initial low dose of gentamicin plus an anti-staphylococcal penicillin or vancomycin [22]. The primary outcome was assessed in the modified ITT population (all randomised patients who received at least one dose of study medication, except for those enrolled with suspected left-sided endocarditis before a protocol amendment allowed the inclusion) 42 days after the end of treatment. At this time, clinical failure included microbiological failure, death, failure to obtain blood culture at the 6-week post-therapy test of cure visit, receipt of potentially effective non-study antibiotics before the test of cure, and premature discontinuation. Daptomycin treatment was found to be non-inferior to standard therapy. The clinical success rate in patients with SAB (with or without infective endocarditis) was 44.2% for daptomycin therapy as compared with 41.7% for standard therapy (absolute difference 2.4%; 95% CI – 10.2 to 15.1).

Daptomycin had a success rate in the treatment of MSSA bacteraemia equivalent to comparator treatments (vancomycin plus gentamicin, or semi-synthetic penicillin plus gentamicin) [22] (Fig. 5). However, in a pre-specified analysis of patients infected with MRSA, daptomycin had a higher success rate (44.4%) than vancomycin plus gentamicin (32.6%) in the treatment of MRSA bacteraemia (Rehm *et al.*, Abstract book of the 44th Annual Meeting of the IDSA, 12–15 October 2006, p. 56). Although these data were not statistically significant, the trend in favour of daptomycin was observed across all patient subgroups. These results demonstrate that daptomycin is as effective as comparator agents in treating MSSA bacteraemia and, compared with vancomycin, might have increased efficacy for treating MRSA bacteraemia.

CONCLUSION

Daptomycin represents the first of a new class of antibiotics, the cyclic lipopeptides, and has a novel mechanism of action. Daptomycin has broad bactericidal activity against Gram-positive pathogens, including MSSA and MRSA. Phase III clinical trial data show that the efficacy and safety of daptomycin are similar to those of vancomycin and other standard therapies for the treatment of cSSTIs; however, results from these trials indicate that daptomycin therapy, as compared with standard therapies, might result in more rapid clinical resolution of infections [21].

S. aureus is a significant cause of bacteraemia and infective endocarditis. Success with vancomycin, the reference-standard treatment, is declining in some areas because of the decreasing susceptibility of *S. aureus* strains. Daptomycin has

been shown to be similar to standard therapies for the treatment of infective endocarditis caused by MSSA, whereas sub-analyses indicate that daptomycin may be more effective than standard therapies for treating bacteraemia caused by MRSA.

ACKNOWLEDGEMENTS

The author would like to thank P. A. McCormick of Chameleon Communications International for editorial assistance in the preparation of the manuscript, with funding from Novartis Pharmaceuticals.

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