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Development of daptomycin for Gram-positive infections

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Gram-positive bacteria are an important cause of serious infections, particularly those originating in hospitals, and are becoming increasingly resistant to many antibiotics hitherto regarded as standard therapy for these infections.¹ Daptomycin is an investigational antibiotic that kills most clinically significant Gram-positive bacteria.^{2–4} These include resistant pathogens for which there are very few therapeutic alternatives, such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide intermediately susceptible *S. aureus* (GISA), coagulase-negative staphylococci (CNS) and penicillin-resistant *Streptococcus pneumoniae* (PRSP).

The cyclic lipopeptide daptomycin (Figure 1) is a fermentation product of *Streptomyces roseosporus*. It was discovered in the early 1980s, at Eli Lilly and Company (Lilly), and was developed as LY 146032 for intravenous treatment of serious Gram-positive infections. Nineteen Phase 1 and two Phase 2 clinical studies involving more than 370 subjects were conducted in the 1980s and early 1990s. The results in skin and soft tissue infections and bacteraemia were encouraging, and clinical results with endocarditis suggested the potential for efficacy at higher doses.^{3,4} However, Lilly was not satisfied with the overall clinical results observed with the twice-daily dosing regimen utilized in these studies. In 1997, Cubist Pharmaceuticals Inc. (Cubist) licensed worldwide rights from Lilly with the intention of developing daptomycin for the treatment of serious Gram-positive infections in hospitalized patients. Clinical trials conducted by Cubist commenced in the USA and Europe in 1999.

Daptomycin has a unique mechanism of action, killing Gram-positive bacteria by disrupting multiple aspects of bacterial plasma membrane function without penetrating into the cytoplasm.^{5–7} The drug exhibits rapid, concentration-dependent bactericidal activity *in vitro* against Gram-positive organisms, including enterococci (Figure 2).^{8–13} It acts against most clinically significant Gram-positive bacteria but not against Gram-negative bacteria. Daptomycin's

antibacterial activity against antibiotic-resistant strains such as MRSA, VRE and PRSP is comparable to that against antibiotic-susceptible strains of these species. The MIC of daptomycin for antibiotic-susceptible strains is typically four-fold lower than that of vancomycin.

Daptomycin produces a post-antibiotic effect (PAE) and regrowth times *in vitro* that are prolonged and concentration dependent.^{8,14} PAEs lasting from 1 to 6 h were observed against *Enterococcus faecalis* and *S. aureus* after exposure to daptomycin concentrations ranging from 0.25 to 16 mg/L (from one- to eight-fold the MIC).

Spontaneous acquisition of resistance to daptomycin is rare.^{15,16} Resistant organisms have been isolated by serial passage in liquid media containing incremental sub-inhibitory concentrations of daptomycin. Resistant isolates of *S. aureus* have also been isolated following chemical mutagenesis with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.¹⁶

The results of *in vitro* interaction studies suggest that daptomycin will not adversely affect the activity of other antimicrobials. Against 70 clinical isolates, interactions with 25 antimicrobials were additive or indifferent; antagonism was not observed.⁴ Synergic interactions occurred between daptomycin and gentamicin against staphylococci and enterococci.

Daptomycin has been shown to be effective in a number of *in vivo* animal models of bacterial infection of the soft tissues, bloodstream, kidneys, heart, lungs and bone, including those caused by Gram-positive strains resistant to standard therapies (e.g. MRSA and VRE).^{4,15,17–27} Pharmacodynamic studies in mice have suggested that daptomycin's bactericidal activity is concentration dependent.^{28–30}

In laboratory animals, daptomycin has been associated with adverse effects that involve skeletal muscle, kidneys, the gastrointestinal tract and the nervous system.⁴ Skeletal muscle is the tissue most sensitive to the adverse effects of daptomycin. Mild myopathy was easily predicted and monitored by measuring serum creatine phosphokinase

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(CPK) concentrations and was reversible upon cessation of therapy. Axonal degeneration of peripheral nerves occurred at dose levels approximately four-fold higher than for myopathy. Renal and gastrointestinal toxicities were noted only in rats. Skeletal muscle adverse effects were depend-

ent on dosing frequency as well as dose level. Dog studies showed that skeletal muscle adverse effects were greater with fractionated compared with once-daily administration of the same total daily dose.³¹ Thus, once-daily dosing may increase the therapeutic-toxicity ratio by increasing efficacy and decreasing skeletal muscle adverse effects, as demonstrated in pharmacokinetic/pharmacodynamic models.

With once-daily administration, daptomycin exhibits linear pharmacokinetics and minimal accumulation with doses up to 6 mg/kg in healthy volunteers.⁴ Plasma clearance is low, resulting in part from high protein binding (87–94%).³² Excretion of the drug occurs primarily via the kidney, with approximately 80% of the total dose, of which two-thirds is intact drug, recovered in the urine. There is low potential for interference with hepatically metabolized drugs,⁴ although daptomycin may displace other protein-bound drugs.

The efficacy of daptomycin in a range of animal models suggests that it may be clinically useful in treating a wide variety of Gram-positive bacterial infections. Two multi-centre, randomized Phase 2 trials evaluated the clinical efficacy of daptomycin compared with conventional therapy (β -lactam agents or vancomycin) in a total of 285 patients.^{3,4} Daptomycin demonstrated activity against a variety of causative organisms, including *S. aureus*. Efficacy against skin and soft tissue infections was comparable to that of conventional therapy. Clinical cure or improvement occurred in 29 of 30 (96.6%) evaluable patients treated with daptomycin, 2 mg/kg once daily, compared with 37 of 39 (94.9%) treated with conventional therapy. The number of evaluable patients was low for several reasons, including the fact that many of those enrolled did not have a bacteriologically confirmed infection and there was a high number of heroin addicts, who did not complete follow up,

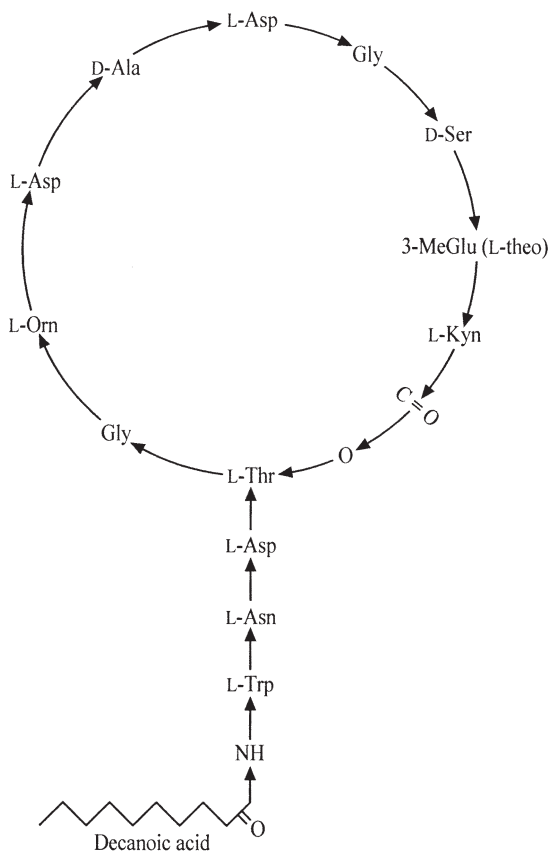


Figure 1. Amino acid structure and location of decanoic acid side chain of daptomycin.

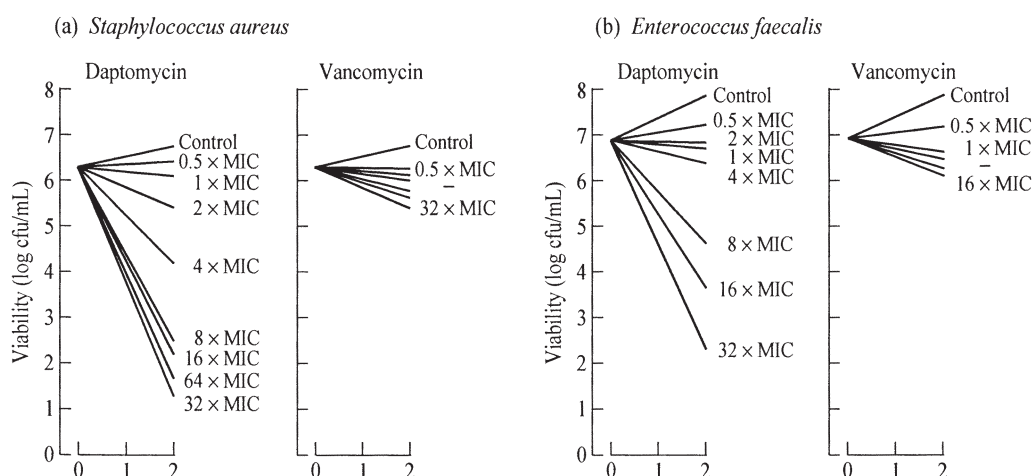


Figure 2. *In vitro* kill rates with daptomycin and vancomycin for (a) *Staphylococcus aureus* and (b) *Enterococcus faecalis*. Daptomycin MIC = 1 mg/L; vancomycin MIC = 4 mg/L. (Adapted with permission from Hanberger, H., Nilsson, L. E., Maller, R. & Isaksson, B. (1991). *Antimicrobial Agents and Chemotherapy* 35, 1710–6. Reprinted with permission. © American Society for Microbiology.)

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among those recruited. A favourable bacteriological outcome (i.e. pathogen eliminated) occurred with daptomycin and conventional therapy in 96.1% and 93.9% of evaluable patients, respectively.

When daptomycin was administered to patients with bacteraemia as a 6 mg/kg loading dose followed by 3 mg/kg every 12 h for up to 34 days, it produced a favourable clinical outcome and bacteriological cure in 17 of 19 (89.5%) evaluable patients. The number of conventionally treated patients was too small for meaningful comparison.

Intravenous daptomycin given to healthy male subjects in Phase 1 studies was well tolerated at single doses of up to 6 mg/kg and multiple doses of up to 3 mg/kg every 12 h.⁴ In the Phase 2 trials, adverse events and rates of discontinuation due to such events were comparable between patients receiving daptomycin or conventional treatments. No serious adverse effects were considered to be related to daptomycin or conventional therapy. Daptomycin was not associated with neurotoxicity at any dose level tested.

Only at the highest multiple-dose level evaluated was daptomycin found to be associated with mild, reversible skeletal muscle adverse events. Transient muscle weakness and myalgia were noted in two of five Phase 1 study subjects receiving daptomycin at 4 mg/kg 12 hourly after 6 and 11 days of administration, respectively. Elevations in CPK concentrations (shown to be 100% comprised of the MM isoenzyme) preceded these events by 2–3 days. CPK levels rose rapidly, and weakness with moderate to severe myalgia of the hands, wrists and/or forearms, was reported. Mobility was not affected, and no changes occurred in vibratory sensation or electromyography. CPK levels peaked at 10 000–20 000 U/L 1 day after daptomycin was discontinued and approached baseline about 1 week later. All signs of muscle toxicity subsided as CPK concentrations returned to normal. No effects on cardiac or smooth muscle were detected, consistent with the results in volunteers.

On the basis of pre-clinical and Phase 1 and 2 clinical studies, daptomycin shows promise for the treatment of a wide variety of Gram-positive infections, including those resistant to standard therapy. The drug is being compared currently with standard therapy for the treatment of complicated skin and soft tissue infections in randomized, prospective, investigator-blinded Phase 3 clinical trials. Daptomycin is being administered at 4 mg/kg once daily, as pre-clinical data indicate that this dosage optimizes both efficacy and safety.

A Phase 2 bacteraemia study that commenced in March 1999 is designed to validate pre-clinical data regarding the efficacy and safety of once-daily dosing. Two once-daily regimens (6 mg/kg od and 4 mg/kg od) are being compared with the twice-daily daptomycin regimen (3 mg/kg bd) that has been evaluated previously in bacteraemia. Vancomycin or oxacillin (on the basis of pathogen susceptibilities) is the comparator treatment. The results of this study will be used to guide dosage selection for further studies of bloodstream infections. Complicated Gram-positive urinary tract infec-

tion will be studied in Phase 3 comparative, randomized trials. Further studies may include the evaluation of daptomycin for the treatment of endocarditis.

A broad spectrum of antibacterial activity, rapid, concentration-dependent bactericidal activity, low frequency of resistance, linear pharmacokinetics and a once-daily dosing regimen are factors that suggest that daptomycin may be a useful antibiotic for the treatment of Gram-positive infections. The drug's potential efficacy against resistant pathogens adds to its appeal and the results of clinical trials will provide more data on its safety and efficacy against infections caused by such strains.

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