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Drug Evaluation

Monthly Focus: Anti-infectives

Daptomycin: a novel agent for Gram-positive infections

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The alarming increase in the incidence of Gram-positive infections, including those caused by resistant bacteria, has sparked renewed interest in novel antibiotics. One such agent is daptomycin, a novel lipopeptide antibiotic with proven bactericidal activity *in vitro* against all clinically relevant Gram-positive bacteria. These include resistant pathogens, such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide intermediately susceptible *Staphylococcus aureus* (GISA), coagulase-negative staphylococci (CNS) and penicillin-resistant *Streptococcus pneumoniae* (PRSP), for which there are very few therapeutic alternatives. Daptomycin provides rapid, concentration-dependent killing and a relatively prolonged concentration-dependent post-antibiotic effect *in vitro*. Spontaneous acquisition of resistance to daptomycin occurs rarely. Daptomycin exhibits linear pharmacokinetics, minimal accumulation with once-daily dosing, and low plasma clearance and volume of distribution. Phase II clinical trials indicate that daptomycin at doses of 2 mg/kg q24 h and 3 mg/kg q12 h is efficacious against skin and soft tissue infections and bacteremia, respectively. In addition, results in endocarditis suggested potential efficacy with higher doses. On the basis of clinical trials to date, it appears that daptomycin has an excellent safety profile, with the incidence and nature of serious adverse events comparable to those observed with conventional therapy. Adverse events associated with other classes of antimicrobials (nephrotoxicity, local irritation, ototoxicity, hypersensitivity, and gastrointestinal effects) were uncommon with daptomycin. Minimal skeletal muscle toxicity was seen at only the highest dose tested (4 mg/kg q12 h), predicted by elevations in serum creatinine phosphokinase, and readily reversible upon discontinuation of treatment. There were no signs of toxicity in cardiac or smooth muscle. Phase II and III clinical trials are underway to evaluate daptomycin for the treatment of Gram-positive bacteremia and complicated skin and soft tissue infections, respectively. Daptomycin holds promise as a rapidly acting and highly effective antibiotic for Gram-positive infections.

Keywords: *antibiotics, bacteremia, coagulase-negative staphylococci, daptomycin, endocarditis, glycopeptide intermediately susceptible Staphylococcus aureus, Gram-positive bacteria, methicillin-resistant Staphylococcus aureus, penicillin-resistant Streptococcus pneumoniae, resistance, skin infection, soft tissue infection, vancomycin-resistant enterococci*

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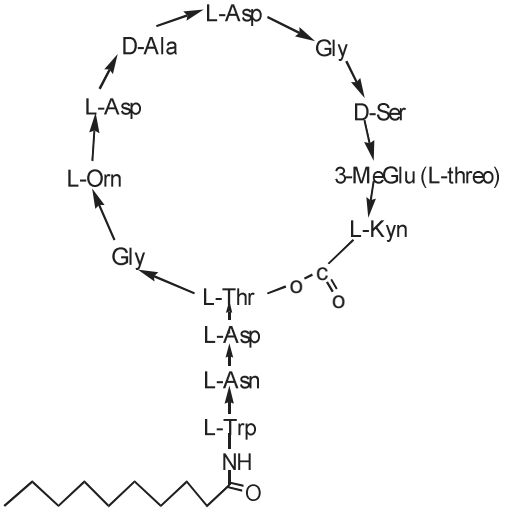
Figure 1: Amino acid structure and location of decanoic acid side-chain of daptomycin.



1. Introduction

Daptomycin is a unique cyclic lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus*. It is comprised of a decanoyl side-chain linked to the N-terminal tryptophan of a cyclic 13–amino acid peptide (**Figure 1**). Daptomycin is an antimicrobial agent with bactericidal activity against all clinically important Gram-positive bacteria, including resistant pathogens for which there are very limited therapeutic alternatives. These resistant pathogens include VRE, MRSA, GISA, CNS, and PRSP [1-6].

Daptomycin was discovered in the early 1980s by scientists at Eli Lilly and Company (Lilly) and was subsequently developed as an iv. drug for the treatment of serious Gram-positive infections. Nineteen Phase I and two Phase II clinical studies involving more than 370 subjects were conducted in the 1980s and early 1990s. The results with skin and soft tissue infections and bacteremia were highly encouraging. Results in the treatment of endocarditis suggest potential efficacy at higher doses. At a dose higher than those tested in Phase II trials, mild, reversible skeletal muscle toxicity was observed, prompting Lilly in 1991 to suspend voluntarily clinical investigation of daptomycin. This decision was made prior to the recent marked increase in the incidence of Gram-positive infections and bacterial antibiotic resistance to current therapies.

In 1997, Cubist Pharmaceuticals, Inc. (Cubist) licensed worldwide rights for daptomycin from Lilly. In today's environment of increasingly prevalent antimicrobial resistance, daptomycin may provide greater utility than existing therapies. Cubist is conducting Phase II and III trials evaluating daptomycin in bacteremia and complicated skin and soft tissue infections, respectively. Doses used in these trials are lower than those previously associated with transient skeletal muscle toxicity. In addition a Phase II study in hospitalised patients with Gram-positive urinary tract infections is planned. The results of these trials should be available at the end of the year 2000, and daptomycin may be approved for clinical use as early as 2001.

2. Microbiology

2.1 Mechanism of action

Although the precise mechanism of action of daptomycin is not completely understood, it is clearly distinct from that of other antibiotics, including β-lactams, aminoglycosides, glycopeptides and macrolides. Daptomycin kills Gram-positive bacteria by disrupting multiple aspects of bacterial plasma membrane function, while not penetrating into the cytoplasm. Potential antibacterial mechanisms include inhibition of peptidoglycan synthesis, inhibition of lipoteichoic acid synthesis [7-9] and dissipation of bacterial membrane potential [10-11].

2.2 *In vitro* antibacterial spectrum

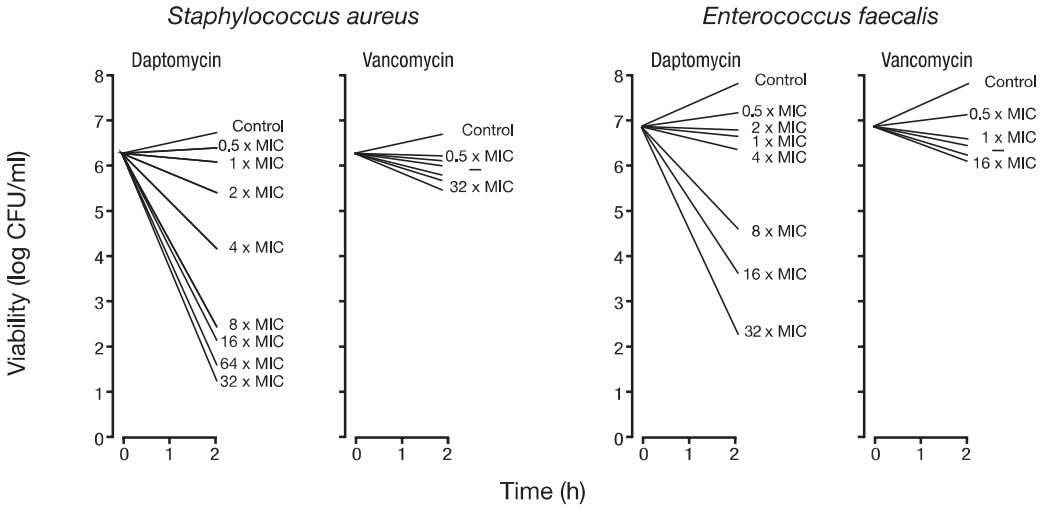
The spectrum of activity for daptomycin includes most clinically significant Gram-positive bacteria; it does not act against Gram-negative bacteria. **Table 1** summarises the activity of daptomycin *vs.* vancomycin against recent (1996 - 1998) Gram-positive isolates chosen for their diverse susceptibilities to other antibiotics [6,12-15]. The clinical isolates were obtained from diverse locations, representing all geographic areas in the USA. Minimum inhibitory concentration $(MIC)_{90}$ values for daptomycin are below the proposed break point of 2 μg/ml for staphylococci (including methicillin-susceptible *S. aureus,* MRSA, *Staphylococcus epidermidis* and CNS), streptococci (including penicillin-susceptible and penicillin-resistant *S. pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae,* and viridans streptococci), enterococci (including vancomycin-susceptible and vancomycin-resistant

Table 1: *In vitro* activity against Gram-positive bacteria: daptomycin *vs.* vancomycin.

Micro-organism	N Total = 973	MIC range (μg/ml) Daptomycin	Vancomycin
Classically 'susceptible' strains			
S. aureus (MSSA) [6,12,14]	134	0.03 - 2	0.25 - 2
S. epidermidis (MSSE) [12,14]	54	0.06 - 0.5	0.25 - 2
Staphylococcus spp. (Coag. Neg.) [6,14]	37	0.25 - 2	2 - 4
S. pneumoniae [6]	15	0.0075 - 0.06	0.015 - 5
Staphylococcus haemolyticus [14]	20	0.03 - 1	0.5 - 4
S. pyogenes [6,14]	61	0.015 - 0.5	0.25 - 1
E. faecalis [6,14]	56	0.03 - 2	0.5 - 4
E. faecium [14]	28	0.5 - 2	0.5 - 4
S. agalactiae [14]	31	0.12 - 0.25	0.25 - 0.5
Streptococci Group C [14]	9	0.03 - 0.25	0.25 - 0.5
Streptococci Group G [14]	10	0.015 - 0.06	0.25 - 0.5
Streptococci viridans [14]	37	0.12 - 2	0.5 - 1
L. monocytogenes [14]	25	2 - 8	1 - 1
Corynebacterium jeikeium [14]	21	0.12 - 0.5	0.12 - 1
Clostridium clostridiiforme [15][§]	11	1 - 8	0.5 - 1
C. difficile [15]	10	2 - 2	0.5 - 2
Clostridium innocuum [15]	11	8 - > 16	8 - 16
Clostridium perfringens [15]	10	0.5 - 2	1 - 1
Clostridium ramosum [15]	10	> 16	4 - 4
Peptostreptococcus spp. [15]	10	0.5 - 2	0.25 - 0.5
'Intermediately susceptible' strains			
S. aureus (GISA) [13]	8	0.25 - 2	2 - 8
S. epidermidis (GISE) [13]	3	0.5 - 1	8
S. haemolyticus [13]	1	1	8
Classically 'resistant' strains			
S. aureus (MRSA) [6,12,14]	155	0.06 - 2	0.25 - 2
S. epidermidis (MRSE) [12]	29	0.06 - 1	0.5 - 2
Staphylococcus spp. (MRS) [14]	56	0.004 - 1	0.25 - 4
S. pneumoniae (PRSP) [6]	40	< 0.03 - 1	0.06 - 2
E. faecalis (VRE) [14]	14	0.5 - 1	8 - > 64
E. faecium (VRE) [6,14]	67	0.5 - 2	> 64 - 1024

[§] Agar dilution method, 25 mg/l Ca^{2+}.

Figure 2: *In vitro* kill rates: daptomycin *vs.* vancomycin [16].
In vitro kill rates for *S. aureus* and *E. faecalis*. Daptomycin minimum inhibitory concentration (MIC) = 1 μg/ml; vancomycin MIC = 4 μg/ml. (Adapted from HANBERGER H, NILSSON LE, MALLER R, ISAKSSON B. *Antimicrob. Agents Chemother*. (1991) **35**:1710-1716. Reprinted with permission. © American Society for Microbiology.)



strains), *Clostridium difficile,* and *Propionibacterium acnes.* Antibacterial activity against classically 'resistant' strains is comparable to that against classically 'susceptible' strains. In addition, the MIC value for daptomycin against susceptible strains is typically 4-fold lower than that of vancomycin. These results are in agreement with previous studies, with the exception of the findings for *Listeria monocytogenes*, which in earlier studies appeared to be more susceptible [1,3].

2.3 Bactericidal activity

Unlike glycopeptide antibiotics, daptomycin exhibits rapid, concentration-dependent bactericidal activity *in vitro* against Gram-positive organisms, including enterococci. This has been demonstrated with both time-kill curves and broth dilution methodology. Using the standard definition of a 3-log reduction in viable organisms, daptomycin, but not vancomycin, is bactericidal against both *S. aureus* and *Enterococcus faecalis* (**Figure 2**) [16]. The *S. aureus* initial kill rate of daptomycin is exceptionally rapid: a greater than 3-$\log_{10}$ reduction in viable organisms is typically achieved in less than 1 h at daptomycin concentrations 4 - 8 times the MIC value [6,16-17]. In contrast, vancomycin typically takes 6 - 24 h to achieve a 3-$\log_{10}$ kill at equivalent concentrations. Faster bactericidal activity has been demonstrated with daptomycin *vs.* vancomycin in logarithmic as well as stationary phases of bacterial growth [18]. Daptomycin also is rapidly bactericidal *in vitro* against enterococci (2 h for a 3-$\log_{10}$ kill) whereas vancomycin generally does not exhibit bactericidal activity against enterococci [19-26].

2.4 Post-antibiotic and sub-MIC effects

Daptomycin produces a post-antibiotic effect (PAE), regrowth times and sub-MIC effects *in vitro* that are prolonged and concentration-dependent. PAEs lasting from 1 - 6 h were observed against *E. faecalis* and *S. aureus* following exposure to daptomycin concentrations ranging from 0.25 - 16 μg/ml (from 1- to 8-fold the MIC value). Using viable-cell counts, exposure to 15 μg/ml daptomycin for 2 h produced PAEs of 2.4 - 5.3 h and 3.5 - 3.9 h in four clinical *S. aureus* isolates and two clinical *E. faecalis* isolates, respectively [27]. A PAE of 6.3 - 6.7 h was observed for strains of both *S. aureus* and *E. faecalis* following use of bioluminescent techniques [16]. Effective regrowth time following the PAE appears to be concentration-dependent [28]. Daptomycin also exerts antimicrobial effects at sub-MIC concentrations. In one study, *S. aureus* exposed to daptomycin at concentrations one-quarter the MIC level were phagocytosed and killed in significantly greater numbers than were non-exposed bacteria [29].

2.5 Resistance

Spontaneous acquisition of resistance to daptomycin is rare. No spontaneously resistant mutants were obtained for any Gram-positive organism tested when challenged at eight times the MIC value (resistance

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