ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2003, p. 1968–1971 Vol. 47, No. 6
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.6.1968–1971.2003

In Vitro Activities of Dalbavancin and Nine Comparator Agents against Anaerobic Gram-Positive Species and Corynebacteria

Ellie J. C. Goldstein,[1,2]* Diane M. Citron,[1] C. Vreni Merriam,[1] Yumi Warren,[1] Kerin Tyrrell,[1] and Helen T. Fernandez[1]

R. M. Alden Research Laboratory, Santa Monica, California 90404,[1] and the University of California at Los Angeles School of Medicine, Los Angeles, California 90073[2]

Received 17 October 2002/Returned for modification 21 February 2003/Accepted 10 March 2003

Dalbavancin is a novel semisynthetic glycopeptide with enhanced activity against gram-positive species. Its comparative in vitro activities and those of nine comparator agents, including daptomycin, vancomycin, linezolid, and quinupristin-dalfopristin, against 290 recent gram-positive clinical isolates strains, as determined by the NCCLS agar dilution method, were studied. The MICs of dalbavancin at which 90% of various isolates tested were inhibited were as follows: *Actinomyces* spp., 0.5 μg/ml; *Clostridium clostridioforme*, 8 μg/ml; *C. difficile*, 0.25 μg/ml; *C. innocuum*, 0.25 μg/ml; *C. perfringens*, 0.125 μg/ml; *C. ramosum*, 1 μg/ml; *Eubacterium* spp., 1 μg/ml; *Lactobacillus* spp., >32 μg/ml, *Propionibacterium* spp., 0.5 μg/ml; and *Peptostreptococcus* spp., 0.25 μg/ml. Dalbavancin was 1 to 3 dilutions more active than vancomycin against most strains. Dalbavancin exhibited excellent activity against gram-positive strains tested and warrants clinical evaluation.

The development of resistance in gram-positive organisms, including *Staphylococcus aureus* strains that are resistant to both oxacillin and vancomycin (9), has accentuated the need for new antimicrobial agents. Dalbavancin (BI 397) is a novel semisynthetic amide derivative of the glycopeptide MDL 62,476 that has enhanced activity against aerobic gram-positive species (2, 4, 5). Due to its very long half-life (9 to 12 days), it is under investigation at a dosage interval of 1 week. Little has been published regarding its activity against either fastidious aerobic bacteria or anaerobes. In order to evaluate the potential efficacy of dalbavancin against this broad spectrum of isolates, we determined its comparative in vitro activity against 290 recent aerobic and anaerobic clinical isolates.

Strains were recently isolated from clinical specimens obtained from adult patients between 1996 and 2002 and were identified by standard criteria (6, 10). The strains were consecutive isolates, except when needed to make at least 10 isolates per species. *Staphylococcus aureus* ATCC 29213 and *Eubacterium lentum* ATCC 43055 were tested simultaneously with the appropriate plates and environments. The numbers and species of clinical isolates tested are given in Table 1.

The suppliers of standard laboratory powders were as follows: dalbavancin, Versicor, Inc. (King of Prussia, Pa.); vancomycin, Eli Lilly & Co. (Indianapolis, Ind.); linezolid and clindamycin, Pharmacia (Kalamazoo, Mich.); quinupristin-dalfopristin, Aventis Pharmaceuticals (Somerset, N.J.); imipenem, Merck & Co. (West Point, Pa.); piperacillin-tazobactam, Wyeth-Ayerst (Philadelphia, Pa.); and metronidazole, Searle (Skokie, Ill.).

Susceptibility testing was performed according to National Committee for Clinical Laboratory Standards (NCCLS) standards (7, 8) by using an agar dilution method with (i) Mueller-Hinton agar and an inoculum of 10^4 CFU per spot for corynebacteria or (ii) brucella agar supplemented with hemin, vitamin K_1, and 5% laked sheep blood and an inoculum of 10^5 CFU per spot for anaerobic species. Daptomycin was supplemented with Ca^{2+} (50 mg/liter) as suggested by the manufacturer.

The results of the study are shown in Table 1. Overall, 263 of 290 (91%) of isolates tested were inhibited by ≤1 μg of dalbavancin/ml. Dalbavancin exhibited excellent in vitro activity against the gram-positive strains tested with the exception of several *Lactobacillus* species. Dalbavancin was typically 1 to 3 dilutions more active than vancomycin against most of the strains and fivefold more active against *C. innocuum*. Dalbavancin (MIC_{90} [MIC at which 90% of the isolates tested are inhibited], 8 μg/ml) was less active than vancomycin (MIC_{90}, 1 μg/ml) against *C. clostridioforme*, a gram-negative-appearing species, but had MICs similar to those of daptomycin and linezolid. Against three strains of *C. difficile* for which the MICs of linezolid and quinupristin-dalfopristin were 8 μg/ml, dalbavancin had MICs of 0.125 to 0.25 μg/ml.

Dalbavancin inhibited all *Corynebacterium* species, including *Corynebacterium amycolatum* and *Corynebacterium jeikeium*, at ≤1 μg/ml (MIC_{90}, 0.5 μg/ml). Vancomycin, linezolid, and quinupristin-dalfopristin had similar activities against corynebacteria; daptomycin was more active against *Corynebacterium amycolatum* (MIC_{90}, 0.06 μg/ml) but was markedly less active against other *Corynebacterium* spp. (MIC_{90}, 8 μg/ml). *Actinomyces israelii* strains that were resistant to daptomycin and linezolid were susceptible to dalbavancin, which was two- to sixfold more active than vancomycin. *Lactobacillus acidophilus* and *Lactobacillus casei* strains that were resistant to vancomycin also required >32 μg of dalbavancin/ml for inhibition. One strain of *Lactobacillus oris* required 4 μg of dalbavancin/ml for inhibition. One strain of *Eubacterium saburreum* required 2 μg of dalbavancin/ml for inhibition. Overall, 263 of 290 (91%) of isolates tested were inhibited by doses of ≤1 μg of dalbavancin/ml.

Dalbavancin demonstrated potent activity (<1 μg/ml)

* Corresponding author. Mailing address: 2021 Santa Monica Blvd., Ste. 740 East, Santa Monica, CA 90404. Phone: (310) 315-1511. Fax: (310) 315-3662. E-mail: EJCGMD@aol.com.

TABLE 1. Comparative in vitro activities of dalbavancin against anaerobic gram-positive bacteria and corynebacteria

Organism (*n*)[a] and agent	In vitro activity of dalbavancin (μg/ml)		
	Range	MIC_{50}	MIC_{90}
Actinomyces israelii (11)			
Dalbavancin	0.06–0.5	0.25	0.25
Vancomycin	0.5–1	0.5	1
Daptomycin	0.125–>32	2	8
Linezolid	0.125–16	0.5	16
Quinupristin-dalfopristin	0.06–0.25	0.125	0.25
Imipenem	≤0.015–0.25	≤0.015	0.25
Piperacillin-tazobactam	0.02–4	0.02	4
Penicillin G	0.02–0.5	0.02	0.25
Metronidazole	0.06–>32	16	32
Clindamycin	0.02–0.5	0.125	0.25
Actinomyces spp. (38)[b]			
Dalbavancin	0.03–0.5	0.025	0.5
Vancomycin	0.25–1	0.5	1
Daptomycin	0.02–>32	4	16
Linezolid	0.25–1	0.5	1
Quinupristin-dalfopristin	0.06–0.5	0.125	0.25
Imipenem	≤0.015–0.25	0.06	0.125
Piperacillin-tazobactam	0.02–2	0.5	1
Penicillin G	0.02–0.25	0.06	0.25
Metronidazole	0.06–>32	32	>32
Clindamycin	0.02–>32	0.125	0.5
Clostridium clostridioforme (14)			
Dalbavancin	2–8	4	8
Vancomycin	0.25–1	0.5	1
Daptomycin	0.25–8	2	8
Linezolid	2–8	4	8
Quinupristin-dalfopristin	0.5–32	0.5	8
Imipenem	0.5–4	2	2
Piperacillin-tazobactam	0.125–>64	1	64
Penicillin G	0.25–>32	0.5	>32
Metronidazole	0.02–0.5	0.06	0.125
Clindamycin	0.02–2	0.25	2
Clostridium difficile (26)			
Dalbavancin	0.125–0.5	0.25	0.25
Vancomycin	0.5–2	1	2
Daptomycin	0.25–4	1	2
Linezolid	1–16	2	8
Quinupristin-dalfopristin	0.25–8	0.5	4
Imipenem	2–>16	4	16
Piperacillin-tazobactam	4–16	8	16
Penicillin G	1–4	2	4
Metronidazole	0.125–1	0.25	0.5
Clindamycin	2–>32	8	>32
Clostridium innocuum (15)			
Dalbavancin	0.125–0.5	0.25	0.25
Vancomycin	8–16	16	16
Daptomycin	4–8	4	8
Linezolid	2–4	2	4
Quinupristin-dalfopristin	0.25–2	0.5	1
Imipenem	1–2	2	2
Piperacillin-tazobactam	0.5–4	1	2
Penicillin G	0.25–1	0.5	0.5
Metronidazole	0.25–1	0.5	1
Clindamycin	0.25–32	0.5	>32
Clostridium perfringens (10)			
Dalbavancin	0.03–0.125	0.06	0.125
Vancomycin	0.5	0.5	0.5
Daptomycin	0.5–1	1	1
Linezolid	1–2	2	2
Quinupristin-dalfopristin	0.25–0.5	0.5	0.5
Imipenem	0.06–0.25	0.125	0.25
Piperacillin-tazobactam	0.02–0.5	0.125	0.5
Penicillin G	0.02–0.125	0.06	0.125
Metronidazole	0.5–2	1	2
Clindamycin	0.06–1	1	2
Clostridium ramosum (15)			
Dalbavancin	0.25–1	1	1
Vancomycin	1–4	4	4
Daptomycin	8–>32	32	>32
Linezolid	4–8	8	8
Quinupristin-dalfopristin	0.25–4	0.5	4
Imipenem	0.125–0.5	0.25	0.5
Piperacillin-tazobactam	0.06–1	0.125	0.5
Penicillin G	0.02–1	0.125	1
Metronidazole	0.5–2	1	2
Clindamycin	0.125–>32	2	>32
Clostridium spp.[c] (16)			
Dalbavancin	≤0.015–1	0.125	0.5
Vancomycin	0.25–>32	0.5	2
Daptomycin	0.06–16	1	8
Linezolid	0.5–4	1	4
Quinupristin-dalfopristin	0.125–0.5	0.25	0.5
Imipenem	≤0.015–2	0.125	1
Piperacillin-tazobactam	0.02–2	0.25	2
Penicillin G	0.02–0.5	0.125	0.5
Metronidazole	0.02–2	0.5	2
Clindamycin	0.02–8	0.06	4
Eubacterium spp.[d] (25)			
Dalbavancin	0.06–2	0.25	1
Vancomycin	0.25–2	0.5	2
Daptomycin	0.06–>32	0.5	16
Linezolid	0.25–8	2	4
Quinupristin-dalfopristin	0.02–1	2	4
Imipenem	≤0.015–0.5	0.03	0.5
Piperacillin-tazobactam	0.02–16	0.02	16
Penicillin G	0.02–2	0.125	2
Metronidazole	0.02–1	0.25	1
Clindamycin	0.02–1	0.06	0.5
Lactobacillus spp.[e] (23)			
Dalbavancin	0.06–>32	0.5	>32
Vancomycin	0.25–>32	1	>32
Daptomycin	0.25–>32	2	>32
Linezolid	0.5–8	4	8
Quinupristin-dalfopristin	0.125–2	0.5	2
Imipenem	≤0.015–8	0.125	2
Piperacillin-tazobactam	0.02–8	0.5	2
Penicillin G	0.02–4	0.25	1
Metronidazole	0.5–>32	>32	>32
Clindamycin	0.02–>32	0.125	2
Propionibacterium spp.[f] (15)			
Dalbavancin	0.03–0.5	0.25	0.5
Vancomycin	0.5–1	0.5	1
Daptomycin	0.5–>32	1	16
Linezolid	0.25–1	0.5	1
Quinupristin-dalfopristin	0.06–0.25	0.06	0.2
Imipenem	≤0.015–0.06	0.03	0.06
Piperacillin-tazobactam	0.02–1	0.02	0.5
Penicillin G	0.02–0.125	0.06	0.125
Metronidazole	8–>32	>32	>32
Clindamycin	0.02–0.25	0.02	0.125

Continued on following page

TABLE 1—*Continued*

Organism (*n*)[a] and agent	In vitro activity of dalbavancin (μg/ml)		
	Range	MIC_{50}	MIC_{90}
Peptostreptococcus spp.[g] (30)			
Dalbavancin	≤0.015–0.5	0.125	0.25
Vancomycin	0.125–1	0.25	0.5
Daptomycin	0.02–32	0.25	1
Linezolid	0.5–2	0.5	2
Quinupristin-dalfopristin	0.125–0.5	0.25	0.5
Imipenem	≤0.015–0.25	0.03	0.125
Piperacillin-tazobactam	0.05–8	0.05	1
Penicillin G	0.02–4	0.125	0.25
Metronidazole	0.125–1	0.5	1
Clindamycin	0.02–1	0.125	0.5
Corynebacterium amycolatum (14)			
Dalbavancin	0.25–0.5	0.25	0.5
Vancomycin	0.25–0.5	0.5	0.5
Daptomycin	0.02–0.125	0.06	0.06
Linezolid	0.25–0.5	0.25	0.5
Quinupristin-dalfopristin	0.125–0.25	0.25	0.25
Imipenem	0.03–>16	0.125	>16
Piperacillin-tazobactam	0.02–32	8	16
Penicillin G	0.125–>32	1	4
Clindamycin	0.125–>32	2	>32
Corynebacterium jeikeium (12)			
Dalbavancin	0.5	0.5	0.5
Vancomycin	0.5	0.5	0.5
Daptomycin	0.125–0.5	0.125	0.25
Linezolid	0.25–0.5	0.5	0.5
Quinupristin-dalfopristin	0.125–1	0.25	0.5
Imipenem	0.06–>16	>16	>16
Piperacillin-tazobactam	8–>64	>64	>64
Penicillin G	0.5–>32	>32	>32
Clindamycin	1–>32	>32	>32
Corynebacterium spp.[h] (26)			
Dalbavancin	≤0.015–1	0.25	0.5
Vancomycin	0.25–4	0.5	1
Daptomycin	0.02–8	0.125	8
Linezolid	0.125–1	0.5	1
Quinupristin-dalfopristin	0.06–2	0.25	1
Imipenem	≤0.015–4	0.03	0.25
Piperacillin-tazobactam	0.02–16	0.25	16
Penicillin G	0.02–4	0.125	1
Clindamycin	0.02–>32	>32	>32

[a] *n* = number of isolates tested.
[b] Includes *A. gerensceriae* (*n* = 1), *A. graevenitzii* (*n* = 1), *A. meyeri* (*n* = 3), *A. naeslundii* (*n* = 5), *A. neuii* (*n* = 1), *A. odontolyticus* (*n* = 8), *A. radingae* (*n* = 1), *A. schalii* (*n* = 1), *A. turicensis* (*n* = 7), and *A. viscosus* (*n* = 9), as well as *Arcanobacterium pyogenes* (*n* = 1).
[c] Includes *C. bifermentans* (*n* = 2), *C. butyricum* (*n* = 2), *C. cadaveris* (*n* = 2), *C. cochlearium* (*n* = 2), *C. fallax* (*n* = 2), *C. glycolicum* (*n* = 2). *C. novyi A* (*n* = 1), *C. oroticum* (*n* = 1), and *C. paraputrificum* (*n* = 2).
[d] Includes *E. brachy* (*n* = 1), *E. combesii* (*n* = 1), *E. contortum* (*n* = 2), *E. lentum* (*n* = 5), *E. limosum* (*n* = 4), *E. saburreum* (*n* = 4), *E. tenue* (*n* = 1), *E. timidum* (*n* = 4), and *E. yurii* (*n* = 3).
[e] Includes *L. acidophilus* (*n* = 2), *L. brevis* (*n* = 1), *L. casei* (*n* = 5), *L. catenaforme* (*n* = 3), *L. fermentans* (*n* = 2), *L. jensenii* (*n* = 1), *L. minutus* (*n* = 2), *L. oris* (*n* = 1), *L. plantarum* (*n* = 5), and *L. rhamnosus* (*n* = 1).
[f] Includes *P. acnes* (*n* = 5), *P. avidum* (*n* = 4), *P. granulosum* (*n* = 5), and *P. propionicus.*
[g] Includes *P. anaerobius* (*n* = 7) and *P. asaccharolyticus* (*n* = 6), as well as *Finegoldia magna* (formerly *P. magnus*) (*n* = 6), *Micromonas micros* (formerly *P. micros*) (*n* = 6), and *P. prevotii* (*n* = 5).
[h] Includes *C. accolans* (*n* = 1), "*C. aquaticum*" (*n* = 2), *C. falsenii* (*n* = 1), *C. minutissimum* (*n* = 4), *C. pseudodiphtheriticum* (*n* = 4), *C. striatum* (*n* = 4), *C. urealyticum* (*n* = 1), *Corynebacterium* CDC group G (*n* = 1), and *Corynebacterium* sp. and (no good fit [*n* = 3]), as well as *Dermabacter hominis* (*n* = 4) and *Rothia* sp. (*n* = 1).

against a broad spectrum of gram-positive anaerobes and fastidious aerobes including *Actinomyces* species, *Propionibacterium* spp., *Peptostreptococcus* spp., and *Clostridium* species, including *Clostridium perfringens* and *Clostridium difficile* but excluding *Clostridium clostridioforme*. Dalbavancin was typically 1 to 3 dilutions more active than vancomycin against most of the strains, and fivefold more active against *Clostridium innocuum*. Dalbavancin was less active than vancomycin against *Clostridium clostridioforme*, a gram-negative-appearing species, but had MICs similar to those of daptomycin and linezolid. Dalbavancin had MICs of 0.125 to 0.25 μg/ml against three strains of *Clostridium difficile* with linezolid and quinupristin-dalfopristin MICs of 8 μg/ml. Its overall activity compared favorably with that of the other agents tested.

Lactobacilli have been associated with vaginal health, whereas depletion has been associated with an increased risk of urinary tract infections and bacterial vaginosis (1, 11). Many patients self-medicate and take probiotic products containing *Lactobacillus acidophilus* whenever placed on antimicrobial agents. Glycopeptides have variable activity against *Lactobacillus* species; this appears to be due to the pentapeptide structure in nascent cell wall peptidoglycan (3). Goldstein et al. (4) reported on the activity of MDL 63,246, a precursor to dalbavancin, against a very limited number of *Lactobacillus* strains and found it to be active against *Lactobacillus acidophilus*, whereas *Lactobacillus casei*, *Lactobacillus fermentans*, and *Lactobacillus plantarum* required higher concentrations for inhibition. In the present study, dalbavancin had limited activity (MICs ≥ 32 μg/ml) against *Lactobacillus acidophilus* and *Lactobacillus casei* but was active against *Lactobacillus fermentans* (MICs ≤ 0.25 μg/ml); this finding could be viewed as a positive health factor allowing maintenance of the normal vaginal flora. Its activity against other *Lactobacillus* spp., such as *Lactobacillus catenaforme*, *Lactobacillus fermentans*, and *Lactobacillus plantarum*, showed inhibition at ≤1 μg/ml and, given appropriate pharmacokinetics, might allow its use in the therapy of infections caused by those species.

The activity of dalbavancin against our corynebacteria isolates was generally equivalent to that of vancomycin. Dalbavancin inhibited all *Corynebacterium* spp., including *Corynebacterium amycolatum* and *Corynebacterium jeikeium*, at ≤1 μg/ml (MIC_{90} = 0.5 μg/ml). Linezolid and quinupristin-dalfopristin also had similar activities. In a previous study (3), the dalbavancin MIC range for a smaller number of *Corynebacterium* isolates was found to be <0.03 to 0.13 μg/ml. These differences may be due to actual differences in activity against

various strains or species or to the different methodologies used (agar dilution in the present study versus broth microdilution in the earlier study).

In conclusion, dalbavancin exhibited excellent in vitro activity against most of the gram-positive strains tested, with 263 of 290 (91%) of isolates inhibited by ≤1 μg/ml. Dalbavancin warrants clinical evaluation against infections caused by anaerobic gram-positive bacteria and corynebacteria.

REFERENCES

1. **Cadieux, P., J. Burton, A. W. Bruce, C. Y. Kang, and G. Reid.** 2002. *Lactobacillus* strains and vaginal ecology. JAMA **287:**1940–1941.
2. **Candiani, G., M. Abbondi, M. Borgonovi, G. Rpmano, and F. Parenti.** 1999. In vitro and in vivo antibacterial activity of BI 397, a new semisynthetic glycopeptide antibiotic. J. Antimicrob. Chemother. **44:**179–192.
3. **Ferain, T., J. N. Hobbs, Jr., J. Richardson, N. Bernard, D. Garymn, P. Hols, N. E. Allen, and J. Delcour.** 1996. Knockout of the two *ldh* genes has major impact on peptidoglycan precursor synthesis in *Lactobacillus plantarum*. J. Bacteriol. **178:**5431–5437.
4. **Goldstein, B. P., G. Candiani, T. M. Arain, G. Romano, I. Ciciliato, M. Bereti, M. Abbondi, R. Scotti, M. Mainini, F. Ripamonti, A. Resconi, and M. Debnaro.** 1995. Antimicrobial activity of MDL 63,246, a new semisynthetic glycopeptide antibiotic. Antimicrob. Agents Chemother. **39:**1580–1588.
5. **Jones, R. N., D. J. Biedenbach, D. M. Johnson, and M. A. Pfaller.** 2001. In vitro evaluation of BI 397, a novel glycopeptide antimicrobial agent. J. Chemother. **13**:244–254.
6. **Murray, P. R., E. J. Baron, M. A. Pfaller, F. C. Tenover, and R. H. Yolken.** 1999. Manual of clinical microbiology, 7th ed. American Society for Microbiology, Washington, D.C.
7. **National Committee for Clinical Laboratory Standards.** 2001. Methods for antimicrobial susceptibility testing of anaerobic bacteria, 5th ed. Approved standard M11-A5. National Committee for Clinical Laboratory Standards, Wayne, Pa.
8. **National Committee for Clinical Laboratory Standards.** 2000. Method for dilution antimicrobial susceptibility testing for bacteria that grow aerobically, 5th ed. Approved standard M7-A5. National Committee for Clinical Laboratory Standards, Wayne, Pa.
9. **Sievert, D. M., M. L. Boulton, G. Stoltman, D. Johnson, M. G. Stobierski, F. P. Downes, P. A. Somsel, J. Y. Rudnick, W. Brown, W. Hafeez, T. Lundstrom, E. Flanagan, J. Mitchell, and S. Chang.** 2002. *Staphylococcus aureus* resistant to vancomycin–United States, 2002. Morb. Mortal. Wkly. Rep. **51:**565–567.
10. **Summanen, P., E. J. Baron, D. M. Citron, C. A. Strong, H. M. Wexler, and S. M. Finegold.** 1993. Wadsworth anaerobic bacteriology manual, 5th ed. Star Publishing Co., Belmont, Calif.
11. **Weeks, J. C., H. Nelson, S. Gelber, D. Sargent, and G. Schroeder.** 2002. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy versus open colectomy for colon cancer: a randomized trial. JAMA **287:**321–328.