Dalbavancin (formerly BI397) Activity Against Selected Populations of Antimicrobial-Resistant Gram-Positive Pathogens

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AMENDED ABSTRACT

Background

Gram-positive (GP) pathogens have rapidly evolved resistance (R) mechanisms as new antimicrobials have been clinically introduced. Novel candidate agents such as DAL, a long-acting glycopeptide, were challenged in vitro by an international collection of GP organisms with defined R mechanisms.

Methods

Nearly 400 GP-R strains were selected from strains isolated in 2001 - 2002. All tests were performed by reference NCCLS (M7-A6) methods and DAL was compared to > 20 other antimicrobials. Where needed, DAL results were compared to susceptible (S) subsets or wildtypes (WT) to assess potency variations against linezolid (LZD), quinupristin/dalfopristin (Q/D), penicillin (PEN) or vancomycin (VAN)-R strains.

Results

Generally, DAL was more potent than VAN or teicoplanin (TEIC). However, TEIC-non-susceptible (NS) CoNS strains also had slightly elevated DAL MICs compared to WT, but they remained ≤ 1 μg/ml. DAL inhibited *van B* enterococci and was active against other R, non-*vanA* enterococcal species. VAN was also active against Q/D-R CoNS (4) and *S. aureus* (4).

	DAL MIC (μg/ml):			
Organism (no. tested)	50%	90%	Range	% ≤ 1
Staphylococci				
VAN at 4 μg/ml (3)	0.12	-	0.12-0.5	100
VISA (10)	0.06	1	0.06-2	90
TEIC-NS CoNS (15)	0.12	0.25	0.03-0.25	100
Q/D-R (8)	0.06	-	0.03-0.06	100
Enterococci				
VAN-R (74)	8	32	≤0.015->32	27
Q/D-R *E. faecium* (33)	0.06	8	≤0.015->32	88
LIN-R (9)	0.12	-	≤0.015->32	55
Streptococci				
PEN-R pneumococcus (202)	≤0.015	≤0.015	≤0.015-0.03	100
3GC-R pneumococcus (16)[a]	≤0.015	≤0.015	≤0.015-0.03	100
PEN-R viridans group (5)	≤0.015	-	≤0.015-0.03	100

a. 3GC-R = ceftriaxone-R (MIC, ≥ 4 μg/ml).

Other LIN-R isolates (five strains) had the following DAL MIC results: *S. aureus* (0.03 - 0.06 μg/ml), *S. oralis* (≤ 0.015 μg/ml), and CoNS (0.03 μg/ml). R to ß-lactams, macrolides or lincosamides and LZD did not adversely affect DAL activity.

Conclusions

DAL, a new glycopeptide with once weekly dosing, was documented to be active against numerous GP-R species isolates, at rates comparable to TEIC or VAN. Unique features of this agent favors continued clinical development.

INTRODUCTION

Increasing and novel resistance mechanisms are presenting challenges to existing antimicrobials. Oxacillin-resistance in staphylococci and glycopeptide-resistance in enterococci have accentuated the need for the development of new antimicrobial agents. In addition, resistance to newly introduced Gram-positive active compounds such as linezolid, quinupristin/dalfopristin and telithromycin have recently been documented.

Dalbavancin is a novel dimethylaminopropyl amide derivative of the glycopeptide A40926 and is currently in early Phase III clinical trials. Dalbavancin has exhibited a wide spectrum of activity against Gram-positive cocci including multi-drug resistant organisms. In vivo studies have shown that dalbavancin effectively reduced bacterial loads in mouse models of septicaemia, endocarditis and lung infection in immunocompetent as well as neutropenic mice.

In addition, the long half-life of dalbavancin (9 to 12 days) documented in clinical studies, permits once-weekly dosing. We evaluated the spectrum and potency of dalbavancin against a subset of a worldwide collection of Gram-positive organisms, focusing specifically on those species and strains displaying the most problematic resistance phenotypes.

MATERIALS AND METHODS

Bacterial Isolates

A total of 380 Gram-positive strains with resistant phenotypes were selected from a large worldwide collection of isolates from 2001 and 2002. The resistant subset included: *S. aureus* (four strains, quinupristin/dalfopristin [Q/D] resistant; 10 strains, vancomycin-intermediate; five strains, linezolid-resistant), coagulase-negative staphylococci ([CoNS]; three strains, vancomycin MIC=4 μg/ml; four strains, Q/D-resistant; 15 strains teicoplanin non-suceptible), *E. faecium* (54 strains vancomycin-resistant; 33 strains Q/D-resistant; six strains linezolid-reistant), *E. faecalis* (20 strains, vancomycin-resistant; three strains linezolid-resistant), *S. pneumoniae* (202 strains penicillin resistant; 16 strains ceftriaxone-resistant) and viridans group streptococci (five strains penicillin-resistant).

Susceptibility Testing

All tests were performed by reference NCCLS (M7-A6) methods using Mueller-Hinton broth, supplemented with 2 to 5% lysed horse blood for testing streptococci. Validated dry-form panels for susceptibility testing were manufactured by TREK Diagnostics (Cleveland, OH, USA). Dalbavancin laboratory grade powder was provided by Vicuron, Inc. (King of Prussia, PA, USA) and other antimicrobial powders used for comparative testing were obtained from their respective manufacturer or purchased from Sigma Chemical (St. Louis, MO, USA).

Dalbavancin was compared to over 20 other antimicrobial agents including: vancomycin, teicoplanin, linezolid, levofloxacin, amoxicillin/clavulanic, ceftriaxone, clindamycin, erythromycin, quinupristin/dalfopristin, penicillin, chloramphenicol and doxycycline. Where needed, dalbavancin results were compared to susceptible subsets (wild-type) to assess potency variations against linezolid-, quinupristin/dalfopristin-, penicillin- or vancomyin-resistant strains.

COMMENTS

- Generally, dalbavancin was more potent than vancomycin or teicoplanin. However, teicoplanin-non-susceptible coagulase-negative staphylococci had slightly elevated dalbavancin MIC values when compared to those from wild-type strains, but remained ≤ 1 μg/ml.
- Dalbavancin activity was independent of resistances to ß-lactams, macrolides or lincosamides.
- All resistant organisms tested, with the exception of enterococci, were inhibited by ≤ 2 μg/ml of dalbavancin. Vancomycin-resistant enterococci showed dalbavancin MIC values higher (three strains at ≥ 32 μg/ml) than those of wild-type strains.
- Penicillin-resistant and ceftriaxone-resistant *S. pneumoniae* strains were highly susceptible to dalbavancin with MIC_{90}s of ≤ 0.015 μg/ml. All strains were inhibited at ≤ 0.03 μg/ml of dalbavancin.
- Linezolid-resistant staphylococci remained susceptible to dalbavancin (MIC_{50}s, ≤ 0.03 μg/ml).
- Only linezolid (MIC_{90}, 2 μg/ml) was completely active (100.0% susceptibility) against vancomycin- and Q/D-resistant *E. faecium*.
- Dalbavancin (MIC_{90}, 0.25 μg/ml) was the most potent compound tested against teicoplanin-non-susceptible CoNS and remained active against Q/D-resistant and vancomycin-resistant CoNS.

Table 1. Activity of selected antimicrobial agents tested against multi-drug-resistant Gram-positive strains collected worldwide.

	MIC μg/ml			Category:	
Organism/antimicrobial agent (no. tested)	50%	90%	Range	% susceptible	% resistant
Penicillin-resistant *S. pneumoniae* (202)					
Dalbavancin[a]	≤0.015	≤0.015	≤0.015-0.03	-[a]	-[a]
Amoxicillin/Clavulanate	2	8	≤2-16	79.2	11.9
Ceftriaxone	1	1	≤0.25-8	91.6	4.0
Vancomycin	0.25	0.5	0.12-0.5	100.0	0.0
Clindamycin	≤0.06	>8	≤0.06->8	64.0	34.0
Eythromycin	4	>32	≤0.25->32	25.6	72.9
Quinupristin/Dalfopristin	0.25	0.5	0.12-1	100.0	0.0
Levofloxacin	1	1	0.5->4	98.5	1.5
Linezolid	1	1	≤0.25-2	100.0	0.0
Quinupristin/Dalfopristin-resistant *E. faecium* (33)					
Dalbavancin[a]	0.06	8	≤0.015->32	-[a]	-[a]
Penicillin	16	>32	1->32	43.9	56.1
Vancomycin	1	>16	0.25->16	87.9	12.1
Chloramphenicol	8	16	≤2->16	84.8	3.0
Doxycycline	≤0.5	>4	≤0.5->4	63.6	36.4
Teicoplanin	0.25	>16	≤0.12->16	87.9	12.1
Linezolid	2	2	1-2	100.0	0.0
Levofloxacin	2	>4	0.25->4	60.6	27.3
Vancomycin-resistant *E. faecium* (54)					
Dalbavancin[a]	8	32	0.03->32	-[a]	-[a]
Penicillin	>32	>32	1->32	3.6	96.7
Chloramphenicol	8	8	≤2->16	92.7	3.6
teicoplanin	>16	>16	≤2->16	14.5	69.1
Quinupristin/Dalfopristin	1	1	0.25-8	98.2	1.8
Linezolid	2	2	0.5->16	98.2	1.8
Levofloxacin	>4	>4	1->4	3.6	96.4
Vancomycin-resistant *E. faecalis* (20)					
Dalbavancin[a]	4	32	≤0.015->32	-[a]	-[a]
Penicillin	4	16	2-32	80.0	20.0
Chloramphenicol	8	>16	4-.16	55.0	35.0
Teicoplanin	>16	>16	≤0.12->16	30.0	70.0
Quinupristin/Dalfopristin	>8	>8	4-.8	5.0	95.0
Linezolid	1	2	0.5-2	100.0	0.0
Levofloxacin	>4	>4	1->4	5.0	95.0
Teicoplanin-non-susceptible coagulase-negative staphylococci (15)					
Dalbavancin[a]	0.12	0.25	0.03-0.25	-[a]	-[a]
Penicillin	>32	>32	1->32	0.0	100.0
Oxacillin	>8	>8	0.12->8	13.3	80.0
Vancomycin	2	2	1-4	100.0	0.0
Chloramphenicol	4	>16	≤2->16	66.7	33.3
Tetracycline	≤4	>8	≤4->8	86.7	13.3
Quinupristin/Dalfopristin	0.25	1	0.12-1	100.0	0.0
Linezolid	1	1	0.5-1	100.0	0.0
Levofloxacin	4	>4	0.25->4	33.3	46.7

a. No breakpoint has been established by NCCLS.

Table 2. Dalbavancin activity with specific resistant subsets of Gram-positive cocci.

	Dalbavancin MIC μg/ml:		
Organism (no. tested)	50%	90%	Range
Vancomycin-intermediate staphylococci (10)	0.06	1	0.06-2
CoNS with vancomycin MIC = 4 μg/ml (3)	0.12	-	0.12-0.5
Quinupristin/Dalfopristin-resistant staphylococci[a] (8)	0.06	-	0.03-0.06
Linezolid-resistant Gram-positives[b] (14)	0.06	32	≤0.015->32
Penicillin-resistant viridans group streptococci[c] (5)	≤0.015	-	≤0.015-0.03
3GC-R pneumococcus (16)[d]	≤0.015	≤0.015	≤0.015-0.03

a. Includes: *S. aureus* (four strains), *S. xylosis* (one strain), *S. epidermidis* (one strain), *S. sciuri* (one strain) and CoNS (one strain not identified to species level).
b. Includes: *S. aureus* (three strains) and *E. faecalis* (three strains), *S. epidermidis* (one strain), *S. oralis* (one strain) and *E. faecium* (six strains). The range of dalbavancin MICs for non-enterococcal species was ≤ 0.015 - 0.03 μg/ml.
c. Includes: *S. mitis* (one strain), *S. oralis* (one strain) and *S. viridans* (three strains not identified to species).
d. 3GC-R = ceftriaxone-R (MIC, ≥ 4 μg/ml).

CONCLUSIONS

- Dalbavancin, a novel glycopeptide, exhibited activity against a wide spectrum of resistant Gram-positive isolates at rates comparable to teicoplanin and vancomycin.
- Dalbavancin was active against most of the resistant organisms including *Van B* enterococci, non-Van A enterococcal species, all resistant staphylococcal species and all penicillin-resistant *S. pneumoniae*.
- The enhanced spectrum of dalbavancin against resistant Gram-positive organisms and favorable pharmacokinetics, such as long half-life permitting once-weekly dosing, favor continued clinical development of this compound.

SELECTED REFERENCES

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A6.* Wayne, PA:NCCLS.