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In vitro activity of oritavancin (LY333328), vancomycin, clindamycin, and metronidazole against *Clostridium perfringens*, *Propionibacterium acnes*, and anaerobic Gram-positive cocci

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Abstract

Using an agar dilution method, we determined the in vitro activity of oritavancin, vancomycin, clindamycin and metronidazole against 114 unique clinical isolates of Gram-positive anaerobes. MIC_{90}s (μg/mL) for oritavancin were as follows: *Clostridium perfringens* 1.0, *Propionibacterium acnes* 0.25, *Peptostreptococcus anaerobius* 0.25, *Peptoniphilus asaccharolyticus* 0.5, *Finegoldia magna* 0.25, *Micromonas. micros* 0.25, and *Anaerococcus prevotii* 0.25. On a weight basis, oritavancin is slightly more active than vancomycin against the strains tested. The oritavancin MICs are comparable to those previously reported against staphylococci and enterococci. Oritavancin shows excellent potential for treatment of infections containing Gram-positive anaerobes such as these.

Keywords: Oritavancin; Vancomycin; Anaerobes; Susceptibility

1. Introduction

Oritavancin is the *N*-alkyl-*p*-chlorophenylbenzyl derivative of chloroeremomycin currently in Phase III clinical trials for infections caused by vancomycin-susceptible and -resistant organisms. Similar to other glycopeptide antibiotics, oritavancin inhibits bacterial cell wall formation by blocking the transglycosylation step in peptidoglycan synthesis. Unlike vancomycin, oritavancin is strongly dimerized and can anchor to the cytoplasmic membrane, which enhances its activity against vancomycin-susceptible and -resistant organisms.

Gram-positive anaerobic bacteria are often isolated from cultures that harbor aerobic and facultative pathogens. Frequently, the accompanying aerobic and facultative strains are multi-drug-resistant, and the choice of appropriate therapy has become increasingly limited. Oritavancin is an attractive alternative to conventional antimicrobials and is currently being developed for infections caused by Gram-positive organisms. Its activity against enterococci is not affected by *vanA* or *vanB* mediated vancomycin-resistance. Oritavancin efficacy against streptococci is not affected by penicillin-intermediate or high level resistance, and its efficacy against staphylococci is not affected by methicillin or vancomycin-resistance [1–5].

To confirm that oritavancin is active against anaerobic Gram-positive pathogens, which are often present in polymicrobial infections, we tested the drug's activity against 114 unique clinical isolates of *Clostridium perfringens, Propionibacterium acnes,* and anaerobic Gram-positive cocci. Metronidazole, clindamycin and vancomycin were included for comparison.

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2. Materials and methods

MICs were determined using the agar dilution method as described in NCCLS M11-A6 [6]. Brucella agar supplemented with vitamin K_1, hemin, and laked sheep blood was the test medium. The antimicrobial agents were obtained as follows: Oritavancin, Focus Technologies, Herndon, VA; clindamycin, Pharmacia, Kalamazoo, MI; metronidazole, Searle, Skokie, IL; vancomycin, Eli Lilly, Indianapolis, IN. They were reconstituted according to the manufacturer's instructions, serially diluted and added to molten agar for preparation of plates. Antimicrobial-free plates were included for growth controls. Aerotolerance testing was repeated at the time of the MIC determinations.

The test strains were isolated from clinical specimens within the past five years and were identified by standard criteria [7] and stored at −70 °C in 20% skim milk. Prior to testing, they were transferred at least twice on Brucella agar supplemented with vitamin K_1, hemin and sheep blood (Hardy Diagnostics). On the day of the test, cell paste was suspended into Brucella broth to the turbidity of the 0.5 McFarland standard. The suspensions were pipetted into the wells of the Steers replicator head. The inocula were applied to the plates with the replicator device that delivered approximately 10^5 CFU per spot. After absorbing the inoculum, the plates were inverted and placed into anaerobe jars with anaerobe generators (Oxoid) and incubated at 36 °C for 2 days. The MICs were read as the lowest concentration of drug that completely inhibited growth or resulted in a drastic change in appearance compared to the growth control. Quality control strains included *Staphylococcus aureus* ATCC 29213, *Bacteroides fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741, and *Eubacterium lentum* ATCC43055.

3. Results and discussion

The results are presented in Table 1.

Overall, oritavancin MICs were similar to those of vancomycin. Oritavancin was twofold more active than vancomycin against *P. acnes*, *P. anaerobius*, *F. magna*, *M. micros*, and *A. prevotii*, but twofold less active against *C. perfringens* and *P. asaccharolyticus*. All strains tested were susceptible to ⩽1 μg/mL of oritavancin. Clindamycin-resistance was present in two strains of *P. asaccharolyticus*, two strains of *F. magna*, and one strain of *A. prevotii*. All strains of *P. acnes* were resistant to metronidazole as were two strains each of *M. micros* and *P. anaerobius*. Our results are similar to the oritavancin MICs reported by Sillerstrom et al. [8].

Table 1
In vitro activity (μg/mL) of oritavancin against Gram-positive anaerobic bacteria

Antimicrobial agent	Minimum inhibitory concentration (μg/mL)		
Organism (no.)	Range	50%[a]	90%[a]
Clostridium perfringens (28)			
Oritavancin	0.25–1	0.5	1
Vancomycin	0.25–0.5	0.25	0.5
Clindamycin	⩽0.03–4	0.5	2
Metronidazole	0.5–8	2	4
Propionibacterium acnes (11)			
Oritavancin	0.125–0.25	0.125	0.25
Vancomycin	0.25–0.5	0.25	0.5
Clindamycin	⩽0.03–0.06	0.06	0.06
Metronidazole	>64	>64	>64
Peptostreptococcus anaerobius (15)			
Oritavancin	0.06–0.5	0.125	0.25
Vancomycin	0.06–0.5	0.25	0.5
Clindamycin	⩽0.03–0.5	0.06	0.5
Metronidazole	0.125–>64	1	64
Peptoniphilus asaccharolyticus (17)			
Oritavancin	⩽0.03–0.5	0.25	0.5
Vancomycin	0.06–0.5	0.06	0.25
Clindamycin	⩽0.03–>64	0.125	>64
Metronidazole	0.25–4	1	2
Finegoldia magna (12)			
Oritavancin	⩽0.03–0.25	0.06	0.25
Vancomycin	0.05–0.25	0.25	0.25
Clindamycin	⩽0.03–>64	0.125	8
Metronidazole	0.06–2	0.5	0.5
Micromonas micros (15)			
Oritavancin	⩽0.03–0.5	0.125	0.25
Vancomycin	0.5–1	0.5	0.5
Clindamycin	⩽0.03–4	0.25	1
Metronidazole	0.25–>64	0.5	64
Anaerococcus prevotii (16)			
Oritavancin	⩽0.03–1	⩽0.03	0.25
Vancomycin	0.06–1	0.25	1
Clindamycin	⩽0.03–>64	0.06	0.5
Metronidazole	0.125–>64	1	4

[a]Concentrations at which 50% and 90% of strains tested were inhibited.

4. Conclusion

Oritavancin has excellent activity against the Gram-positive anaerobes tested and shows potential for treatment of infections containing anaerobes such as these. Clinical trials to expand these observations are indicated.

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