ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2009, p. 4762–4771 Vol. 53, No. 11
0066-4804/09/$12.00 doi:10.1128/AAC.00952-09

Comparative In Vitro Activity Profile of Oritavancin against Recent Gram-Positive Clinical Isolates[▽]

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Received 9 July 2009/Returned for modification 20 August 2009/Accepted 26 August 2009

Oritavancin activity was tested against 15,764 gram-positive isolates collected from 246 hospital centers in 25 countries between 2005 and 2008. Organisms were *Staphylococcus aureus* ($n = 9,075$), coagulase-negative staphylococci ($n = 1,664$), *Enterococcus faecalis* ($n = 1,738$), *Enterococcus faecium* ($n = 819$), *Streptococcus pyogenes* ($n = 959$), *Streptococcus agalactiae* ($n = 415$), group C, G, and F streptococci ($n = 84$), and *Streptococcus pneumoniae* ($n = 1,010$). Among the evaluated staphylococci, 56.7% were resistant to oxacillin. The vancomycin resistance rate among enterococci was 21.2%. Penicillin-resistant and -intermediate rates were 14.7% and 21.4%, respectively, among *S. pneumoniae* isolates. Among nonpneumococcal streptococci, 18.5% were nonsusceptible to erythromycin. Oritavancin showed substantial in vitro activity against all organisms tested, regardless of resistance profile. The maximum oritavancin MIC against all staphylococci tested ($n = 10,739$) was 4 μg/ml; the MIC_{90} against *S. aureus* was 0.12 μg/ml. Against *E. faecalis* and *E. faecium*, oritavancin MIC_{90}s were 0.06 and 0.12, respectively. Oritavancin was active against glycopeptide-resistant enterococci, including VanA strains ($n = 486$), with MIC_{90}s of 0.25 and 1 μg/ml against VanA *E. faecium* and *E. faecalis*, respectively. Oritavancin showed potent activity against streptococci ($n = 2,468$); MIC_{90}s for the different streptococcal species were between 0.008 and 1 μg/ml. These data are consistent with previous studies with respect to resistance rates of gram-positive isolates and demonstrate the spectrum and in vitro activity of oritavancin against a wide variety of contemporary gram-positive pathogens, regardless of resistance to currently used drugs. The data provide a foundation for interpreting oritavancin activity and potential changes in susceptibility over time once oritavancin enters into clinical use.

Gram-positive infections remain a clinical challenge due to increasing rates of resistance to currently available antimicrobial agents (37). Among *Staphylococcus aureus* strains, the prevalence of methicillin (meticillin) resistance in both hospital and community settings is increasing (19). Reports of increased numbers of *S. aureus* isolates with decreased susceptibility to glycopeptides have also emerged (2). Similar increases in vancomycin-resistant enterococci, penicillin-nonsusceptible pneumococci, and erythromycin-nonsusceptible streptococci have been reported (13, 27, 28, 31). Against this backdrop, the need to develop new agents is clear, with special attention to agents that can overcome existing mechanisms of resistance.

Oritavancin is a semisynthetic bactericidal lipoglycopeptide under clinical development for the treatment of serious infections caused by a variety of gram-positive species, including drug-resistant enterococci, staphylococci, and streptococci (30). Like the glycopeptides vancomycin and teicoplanin, oritavancin inhibits cell wall synthesis (1, 4, 25). Additionally, oritavancin differs from vancomycin and teicoplanin by partially inhibiting RNA synthesis (4) and collapsing transmembrane electrochemical potential and increasing membrane permeability (6). These additional activities help to explain the rapid concentration-dependent bactericidal activity of oritavancin in vitro, even against isolates with reduced susceptibility to vancomycin and teicoplanin (12, 26, 30). Oritavancin's multiple mechanisms of action are hypothesized to forestall the development of high-level resistance to this agent.

The recent development of methods for oritavancin susceptibility testing indicates that oritavancin MICs reported prior to 2006 underestimate the potency of the drug because of the physicochemical property of the drug to bind to laboratory plasticware (3). A revised broth microdilution method for oritavancin, one that includes polysorbate 80 to minimize binding to labware, has been approved by the Clinical Laboratory Standards Institute (10). This method was used in the present surveillance study, and our study represents the first report of an oritavancin surveillance program using polysorbate 80 methodology.

Current and ongoing surveillance initiatives seek to establish an in vitro activity profile of oritavancin against contemporary gram-positive bacterial populations, including those resistant to currently available agents that may be used to treat gram-positive infections. The goals of the present study were to research the potential utility of oritavancin against clinical pathogens and to establish baseline MIC susceptibility data prior to the availability of oritavancin in clinical settings, against which further susceptibility studies could be compared. To these ends, we collected 15,764 recent gram-positive clinical isolates between 2005 and 2008 from 246 geographically dispersed hospital centers and tested their susceptibility to oritavancin as well as to antimicrobial agents currently used in the clinical setting.

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▽ Published ahead of print on 8 September 2009.

TABLE 1. Geographic distribution of strains characterized in this study

Organism(s)	No. of strains collected from:			Total no. of strains collected
	United States	European Union and Israel	Asia	
Staphylococcus aureus	7,439	766	870	9,075
Staphylococcus epidermidis	1,089	248	58	1,395
Staphylococcus haemolyticus	125	103	41	269
Enterococcus faecalis	1,228	355	155	1,738
Enterococcus faecium	588	150	81	819
Streptococcus pyogenes	642	244	73	959
Streptococcus pneumoniae	903	107	NC[a]	1,010
Streptococcus agalactiae	133	230	52	415
Group C, G, and F streptococci	64	11	9	84
Total	12,211	2,214	1,339	15,764

[a] NC, not collected.

(Parts of this study have been presented previously in abstract form [15, 16, 18, 34].)

MATERIALS AND METHODS

Isolates and sources. Table 1 describes the isolates tested as well as the geographic regions from which they were obtained. All isolates in this study were recent (2005 to 2008) clinical isolates subcultured from adult and pediatric patient specimens. With the exception of *S. aureus*, for which isolates with resistance to oxacillin were preferentially collected to ensure large testing volumes of this phenotype across the evaluated regions, isolates were collected at random. Isolates were from 246 medical centers in 25 countries: 182 centers from the United States (across all nine U.S. Census Bureau regions), 52 centers from the European Union, 1 center from Israel, and 11 centers from Asia. The hospital laboratories from which the isolates were submitted included those categorized as community, teaching, veterans, children's, reference laboratory, and university hospitals. The isolates came from both inpatients (including those in intensive care units) and outpatients. Specimen sources included respiratory tract, skin and skin structure (including wound), blood, and urine (staphylococci and enterococci only). Upon receipt at the central laboratory (Eurofins Medinet, Chantilly, VA), each organism was cultured and the identity of each organism was confirmed using standard routine microbiological methodology (8).

Susceptibility assay. All isolates were tested centrally at Eurofins Medinet by broth microdilution (11). Oritavancin assays included 0.002% polysorbate 80 throughout (3, 10). Commercial frozen panels containing oritavancin and comparators were prepared by TREK Diagnostic Systems, Inc. (Cleveland, OH). Oritavancin was supplied by Targanta Therapeutics (now The Medicines Company, Parsippany, NJ). All MIC data were interpreted according to CLSI M100-S18 criteria (9), where applicable.

QC. The quality control (QC) strains *Enterococcus faecalis* ATCC 29212, *E. faecalis* ATCC 51299, *S. aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619 were tested in accordance with CLSI methodology, and results were controlled with published QC ranges (10, 11). Oritavancin susceptibility tests for *E. faecalis* ATCC 51299, a QC strain for high-level aminoglycoside resistance, were performed for reference purposes, as oritavancin QC ranges for this organism have not been defined.

RESULTS

Overall resistance profile of the isolates. Among the 9,075 strains of *S. aureus* isolated, more than half (4,882; 53.8%) were resistant to oxacillin. As noted above, oxacillin-resistant *S. aureus* isolates were preferentially selected. By geography, methicillin-resistant *S. aureus* (MRSA) isolates comprised 52.9%, 68.5%, and 48.9% of the evaluated *S. aureus* isolates from the United States, the European Union and Israel, and Asia, respectively. A total of 1,905 (21%) of the *S. aureus* isolates were multiple drug resistant (MDR), where MDR is defined as concurrent resistance (or nonsusceptible) to at least three of the following agents: clindamycin, erythromycin, oxacillin, trimethoprim-sulfamethoxazole, vancomycin, daptomycin (nonsusceptible), and linezolid (nonsusceptible). A total of 2,568 (52.6%) of the MRSA isolates had a profile of clindamycin susceptibility and erythromycin resistance; this phenotypic profile is often used as a phenotypic marker for community-associated MRSA (22). All isolates of *S. aureus* were susceptible to vancomycin and teicoplanin.

Of the 1,664 coagulase-negative staphylococcus (CoNS) isolates, 1,211 (72.8%) were oxacillin resistant. Oxacillin-resistant CoNS isolates comprised 72.2%, 73.5%, and 75.0% of the evaluated CoNS isolates from the United States, the European Union and Israel, and Asia, respectively. A total of 664 (39.9%) of the CoNS isolates were MDR, where MDR is defined as for *S. aureus* above.

Among the 1,738 *E. faecalis* isolates, only 87 (5%) were not susceptible to vancomycin. Of these, 74.7% were of the VanA phenotype (resistant to both vancomycin and teicoplanin) and 19.5% were of the VanB phenotype (resistant to vancomycin but susceptible to teicoplanin). The incidence of vancomycin-nonsusceptible *E. faecalis* isolates that could not be classified as VanA or VanB was 5.7%. While the vancomycin-nonsusceptible *E. faecalis* isolates from the United States constituted 72% VanA and 19.6% VanB, all nonsusceptible isolates from the European Union and Israel ($n = 21$) were VanA and all nonsusceptible isolates from Asia ($n = 5$) were VanB.

Among the 819 *Enterococcus faecium* isolates, 469 (57.3%) were not susceptible to vancomycin. Of these, 89.8% were of the VanA phenotype and 6.2% were of the VanB phenotype. The incidence of vancomycin-nonsusceptible *E. faecium* isolates that could not be classified as VanA or VanB was 4.1%. A total of 72.2% of the *E. faecium* isolates from the United States were vancomycin nonsusceptible, comprising 89.9% of the VanA type and 6.6% of the VanB type. Lower numbers of vancomycin-nonsusceptible *E. faecium* isolates were obtained in the European Union and Israel and in Asia (22% and 13.6%, respectively) than in the United States; the majority of these isolates (~90%) were of the VanA type in both regions.

Penicillin-nonsusceptible (resistant and intermediate) pneumococci accounted for 36% of all isolates; 14.7% of the isolates were fully resistant to penicillin. A total of 36.2% of pneumococci from the United States were nonsusceptible to penicillin, with 14.5% of the isolates being fully resistant. A total of 34.6% of pneumococci from the European Union and Israel were nonsusceptible to penicillin, with 15.9% of the isolates being fully resistant.

Overall, nonsusceptibility to erythromycin was found at rates of 13.7%, 29.4%, and 20.2% for isolates of *Streptococcus pyogenes*, *Streptococcus agalactiae*, and group C, F, and G streptococci, respectively. The rates were 10.9%, 14.3%, and 35.6% among *S. pyogenes* isolates from the United States, the European Union and Israel, and Asia, respectively. The rates were 43.6%, 20%, and 34.6% among *S. agalactiae* isolates from the United States, the European Union and Israel, and Asia, respectively. The rates were 17.2%, 36.4%, and 22.2% among the group C, F, and G streptococcus isolates from the United States, the European Union and Israel, and Asia, respectively.

Oritavancin activity against staphylococci. Oritavancin showed substantial in vitro activity against all *S. aureus* isolates in this study (Table 2) (MIC range of ≤0.004 to 4 μg/ml; MIC_{90} of 0.12 μg/ml). The oritavancin MIC was not impacted by the oxacillin phenotype of the strains; identical MIC modes and MIC_{90}s were found for oxacillin-susceptible and oxacillin-resistant isolates (Table 2). Oritavancin was more potent than the comparator agents tested in this study against *S. aureus*, with an MIC_{90} that was 16-, 8-, 8-, and 4-fold lower than those of linezolid, vancomycin, teicoplanin, and daptomycin, respectively. By geographic regions, the oritavancin MIC_{90}s were 0.12 μg/ml, 0.25 μg/ml, and 0.06 μg/ml for *S. aureus* isolates from the United States, the European Union and Israel, and Asia, respectively. Against CoNS, oritavancin also showed potent activity, with an MIC range of ≤0.004 to 1 μg/ml and an MIC_{90} of 0.25 μg/ml against all *Staphylococcus epidermidis* isolates and with an MIC range of 0.008 to 1 μg/ml and an MIC_{90} of 0.12 μg/ml against all *Staphylococcus haemolyticus* isolates. Oxacillin susceptibility had little impact on oritavancin activity against CoNS isolates. The oritavancin MIC_{90} against *S. epidermidis* was at least twofold lower than those of the comparators. The oritavancin MIC_{90} against *S. haemolyticus* was at least fourfold lower than those of the comparators. Across the geographic regions, the oritavancin MIC_{90}s were nearly identical (0.25 μg/ml for the United States and for the European Union and Israel and 0.12 μg/ml for Asia) for *S. epidermidis* isolates and identical (0.12 μg/ml) for *S. haemolyticus* isolates.

There were eight *S. aureus* and two CoNS isolates that were nonsusceptible to daptomycin (daptomycin MIC of >1 μg/ml). The oritavancin MICs for these isolates ranged from 0.015 to 2 μg/ml. There were 11 CoNS isolates that were nonsusceptible to linezolid (linezolid MIC of >4 μg/ml). The oritavancin MICs for these isolates ranged from 0.03 to 0.25 μg/ml.

Oritavancin activity against enterococci. Oritavancin showed robust activity in vitro against all *E. faecalis* isolates, with an MIC range of ≤0.0005 to 1 μg/ml and an MIC_{90} of 0.06 μg/ml (Table 2). According to the MIC_{90}s, oritavancin was more potent against *E. faecalis* than any of the comparators studied. The oritavancin MIC_{90}s against *E. faecalis* were impacted by vancomycin susceptibility, increasing from 0.06 μg/ml for vancomycin-susceptible isolates to 1 μg/ml for vancomycin-nonsusceptible isolates (Table 2). Among the vancomycin-nonsusceptible *E. faecalis* isolates, the oritavancin MIC_{90}s were 1 μg/ml and 0.06 μg/ml against VanA and VanB isolates, respectively. Regardless of the vancomycin susceptibility profile, no *E. faecalis* isolate with an oritavancin MIC that exceeded 1 μg/ml was encountered in this study. Identical MIC_{90}s (0.06 μg/ml) were found for all *E. faecalis* isolates from the United States and from the European Union and Israel; the MIC_{90} for the Asian isolates was 0.12 μg/ml. Also, the MIC_{90}s for the VanA isolates from the United States and from the European Union and Israel were the same (1 μg/ml). Oritavancin showed significant activity in vitro against all *E. faecium* isolates, with an MIC range of ≤0.0005 to 1 μg/ml and an MIC_{90} of 0.12 μg/ml (Table 2). According to the MIC_{90}s, oritavancin was more potent against *E. faecium* than any of the comparators studied. The oritavancin MIC_{90}s for *E. faecium* isolates were also impacted by vancomycin susceptibility; the MIC_{90} against vancomycin-susceptible isolates was 0.03 μg/ml, while that for vancomycin-nonsusceptible isolates was 0.25 μg/ml (Table 2). Among the vancomycin-nonsusceptible *E. faecium* isolates, the oritavancin MIC_{90}s were 0.25 μg/ml and 0.06 μg/ml against VanA and VanB isolates, respectively. No *E. faecium* isolate in this surveillance had an oritavancin MIC that exceeded 1 μg/ml. For the geographic regions, the MIC_{90}s were 0.25 μg/ml, 0.12 μg/ml, and 0.03 μg/ml for all *E. faecium* isolates from the United States, the European Union and Israel, and Asia, respectively. The MIC_{90}s were 0.25 μg/ml, 0.5 μg/ml, and 0.25 μg/ml for the vancomycin-nonsusceptible isolates from the United States, the European Union and Israel, and Asia, respectively. The MIC_{90}s were 0.25 μg/ml, 0.5 μg/ml, and 0.25 μg/ml among the VanA isolates from the United States, the European Union and Israel, and Asia, respectively.

Oritavancin activity against streptococci. Oritavancin showed potent in vitro activity against *S. pneumoniae*, with an MIC range of ≤0.0005 to 0.5 μg/ml and an MIC_{90} of 0.008 μg/ml. Penicillin susceptibility did not impact oritavancin activity against pneumococci. Similar MIC_{90}s (0.004 μg/ml and 0.008 μg/ml) were found between isolates from the United States and isolates from the European Union and Israel, regardless of penicillin susceptibility profile. According to the MIC_{90}s, oritavancin was the most active of the tested drugs against pneumococci.

Similarly, oritavancin showed good in vitro activity against *S. pyogenes* isolates, with an MIC range of ≤0.0005 to 0.5 μg/ml and an MIC_{90} of 0.25 μg/ml. Erythromycin susceptibility did not impact oritavancin activity against *S. pyogenes*. Similar MICs (0.12 μg/ml or 0.25 μg/ml) were found for isolates from the United States, the European Union and Israel, and Asia, regardless of erythromycin susceptibility phenotype. According to the MIC_{90}s, levofloxacin, linezolid, and tetracycline were less active than oritavancin against *S. pyogenes* isolates; the other comparators were more active than oritavancin.

Oritavancin showed substantial in vitro activity against *S. agalactiae*, with an MIC range of 0.001 to 1 μg/ml and an MIC_{90} of 0.25 μg/ml. The erythromycin susceptibility profile did not impact oritavancin activity against *S. agalactiae* isolates. Similar MICs (0.12 μg/ml and 0.25 μg/ml) were found for isolates from the United States, the European Union and Israel, and Asia, regardless of whether they were susceptible or nonsusceptible to erythromycin.

Oritavancin showed good in vitro activity against group C, F, and G streptococci, with an MIC range of 0.0005 to 1 μg/ml and an MIC_{90} of 0.5 μg/ml. Erythromycin susceptibility did not impact oritavancin activity against *S. agalactiae*. MIC_{90}s were similar (0.25 to 0.5 μg/ml) for isolates that were susceptible or nonsusceptible to erythromycin.

DISCUSSION

Prior to 2006, susceptibility testing of oritavancin did not include 0.002% polysorbate 80 in the assay, a recommendation that is made in the current CLSI guidelines (10). The inclusion of polysorbate 80 in the broth microdilution assay minimizes oritavancin losses to test vessel surfaces (3). To our knowledge, this study represents the first report of an oritavancin surveillance study using the updated methodology for testing. Reflective of the loss of oritavancin due to binding to labware in the absence of polysorbate 80, the oritavancin MIC_{90}s reported here for enterococci and staphylococci are considerably lower

TABLE 2. Activities of oritavancin and selected comparators against gram-positive isolates

Organism(s) and phenotype(s) (no. of isolates tested)[e]	Agent	MIC (μg/ml)		% of isolates		
		Range	90%	Susceptible	Intermediate	Resistant
S. aureus						
All (9,075)	Oritavancin	≤0.004–4	0.12	—[b]	—	—
	Vancomycin	≤0.25–2	1	100.0	0.0	0.0
	Teicoplanin	≤0.06–16	1	100.0	0.0	0.0
	Clindamycin	≤0.03–>4	>4	75.7	0.2	24.1
	Daptomycin[a]	0.06–4	0.5	99.9	—	—
	Erythromycin	≤0.06–>8	>8	32.6	2.1	65.3
	Linezolid	≤0.25–4	2	100.0	—	—
	Oxacillin	≤0.06–>8	>8	46.2	—	53.8
	Trimethoprim-sulfamethoxazole	≤0.25–>4	≤0.5	97.3	—	2.7
Ox S (4,193)	Oritavancin	≤0.004–0.5	0.12	—	—	—
	Vancomycin	≤0.25–2	1	100.0	0.0	0.0
	Teicoplanin	≤0.06–4	1	100.0	0.0	0.0
	Clindamycin	≤0.03–>4	0.25	91.8	0.2	8.0
	Daptomycin[a]	0.06–2	0.5	99.9	—	—
	Erythromycin	≤0.06–>8	>8	60.7	3.4	35.9
	Linezolid	≤0.25–4	2	100.0	—	—
	Oxacillin	≤0.06–2	0.5	100.0	—	0.0
	Trimethoprim-sulfamethoxazole	≤0.25–>4	≤0.5	98.5	—	1.5
Ox R (4,882)	Oritavancin	≤0.004–4	0.12	—	—	—
	Vancomycin	≤0.25–2	1	100.0	0.0	0.0
	Teicoplanin	≤0.06–16	1	100.0	0.0	0.0
	Clindamycin	≤0.03–>4	>4	61.9	0.2	37.9
	Daptomycin[a]	0.06–4	0.5	99.9	—	—
	Erythromycin	≤0.06–>8	>8	8.4	1.0	90.5
	Linezolid	≤0.25–4	2	100.0	—	—
	Oxacillin	4–>8	>8	0.0	—	100.0
	Trimethoprim-sulfamethoxazole	≤0.25–>4	≤0.5	96.3	—	3.7
S. epidermidis						
All (1,395)	Oritavancin	≤0.004–1	0.25	—	—	—
	Vancomycin	≤0.25–4	2	100.0	0.0	0.0
	Clindamycin	≤0.03–>4	>4	65.0	0.5	34.5
	Daptomycin[a]	≤0.12–2	0.5	99.9	—	—
	Erythromycin	≤0.06–>8	>8	32.2	0.6	67.2
	Linezolid[a]	≤0.25–>16	1	99.4	—	—
	Oxacillin	≤0.06–>8	>8	27.3	—	72.7
	Teicoplanin	0.12–32	4	99.2	0.6	0.1
	Trimethoprim-sulfamethoxazole	≤0.25–>4	>4	63.4	—	36.6
Ox S (381)	Oritavancin	≤0.004–1	0.25	—	—	—
	Vancomycin	≤0.25–2	2	100.0	0.0	0.0
	Teicoplanin	0.12–32	4	99.7	0.0	0.3
	Clindamycin	≤0.03–>4	>2	88.2	0.8	11.0
	Daptomycin	≤0.12–1	0.5	100.0	—	—
	Erythromycin	≤0.06–>8	>8	53.8	0.8	45.4
	Linezolid[a]	≤0.25–8	1	99.7	—	—
	Oxacillin	≤0.06–0.25	0.12	100.0	—	0.0
	Trimethoprim-sulfamethoxazole	≤0.25–>4	>4	76.9	—	23.1
S. epidermidis						
Ox R (1,014)	Oritavancin	≤0.004–1	0.25	—	—	—
	Vancomycin	0.25–4	2	100.0	0.0	0.0
	Teicoplanin	0.25–32	4	99.0	0.9	0.1
	Clindamycin	≤0.03–>4	>4	56.3	0.4	43.3
	Daptomycin[a]	≤0.12–2	0.5	99.8	—	—
	Erythromycin	≤0.12–>8	>8	24.1	0.6	75.3
	Linezolid[a]	≤0.25–>16	1	99.2	—	—
	Oxacillin	0.5–>8	>8	0.0	—	100.0
	Trimethoprim-sulfamethoxazole	≤0.25–>4	>4	58.3	—	41.7
S. haemolyticus						
All (269)	Oritavancin	0.008–1	0.12	—	—	—
	Vancomycin	≤0.25–2	2	100.0	0.0	0.0
	Teicoplanin	0.25–>32	8	95.5	2.6	1.9
	Clindamycin	0.06–>4	>2	70.3	1.9	27.9

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TABLE 2—*Continued*

Organism(s) and phenotype(s) (no. of isolates tested)[e]	Agent	MIC (μg/ml)		% of isolates		
		Range	90%	Susceptible	Intermediate	Resistant
	Daptomycin	≤0.03–1	0.5	100.0	—	—
	Erythromycin	≤0.12–>8	>8	21.6	0.0	78.4
	Linezolid[a]	≤0.25–>16	1	99.3	—	—
	Oxacillin	≤0.06–>8	>8	26.8	—	73.2
	Trimethoprim-sulfamethoxazole	≤0.25–>4	>4	67.7	—	32.3
Ox S (72)	Oritavancin	0.008–0.25	0.06	—	—	—
	Vancomycin	≤0.25–2	1	100.0	0.0	0.0
	Teicoplanin	0.25–8	4	100.0	0.0	0.0
	Ciprofloxacin	≤0.06–>4	>4	84.0	4.0	12.0
	Clindamycin	0.06–>2	0.12	95.8	1.4	2.8
	Daptomycin	≤0.12–0.5	0.5	100.0	—	—
	Erythromycin	≤0.12–>8	>8	48.6	0.0	51.4
	Linezolid	0.5–2	1	100.0	—	—
	Oxacillin	≤0.06–0.25	0.25	100.0	—	0.0
	Trimethoprim-sulfamethoxazole	≤0.25–>4	0.5	97.2	—	2.8
Ox R (197)	Oritavancin	0.015–1	0.12	—	—	—
	Vancomycin	≤0.25–2	2	100.0	0.0	0.0
	Teicoplanin	0.25–>32	8	93.9	3.6	2.5
	Clindamycin	0.06–>4	>4	60.9	2.0	37.1
	Daptomycin	≤0.03–1	0.5	100.0	—	—
	Erythromycin	≤0.12–>8	>8	11.7	0.0	88.3
	Linezolid[a]	≤0.25–>16	1	99.0	—	—
	Oxacillin	0.5–>8	>8	0.0	—	100.0
	Trimethoprim-sulfamethoxazole	≤0.25–>4	>4	56.9	—	43.1
E. faecalis						
All (1,738)	Oritavancin	≤0.0005–1	0.06	—	—	—
	Vancomycin	≤0.12–>256	2	95.0	0.3	4.7
	Teicoplanin	≤0.03–256	0.25	96.3	0.0	3.7
	Ampicillin	≤0.25–32	1	99.9	—	0.1
	Daptomycin[a]	0.06–>4	2	99.9	—	—
	Gentamicin (high-level testing)[f]	≤500–>500	>500	65.4	—	34.6
	Levofloxacin	≤0.03–>16	>16	61.2	0.3	38.4
	Linezolid	0.25–32	2	99.8	0.0	0.2
	Streptomycin (high-level testing)[g]	≤1,000–>1,000	>1,000	70.1	—	29.9
Vanc S (1,651)	Oritavancin	≤0.0005–1	0.06	—	—	—
	Vancomycin	≤0.12–4	2	100.0	0.0	0.0
	Teicoplanin	≤0.03–4	0.25	100.0	0.0	0.0
	Ampicillin	≤0.25–32	1	99.9	—	0.1
	Daptomycin[a]	0.06–>4	2	99.9	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	67.8	—	32.2
	Levofloxacin	≤0.03–>16	>16	64.4	0.4	35.2
	Linezolid	0.25–32	2	99.9	0.0	0.1
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	71.3	—	28.7
Vanc NS (87)	Oritavancin	0.015–1	1	—	—	—
	Vancomycin	8–>256	>256	0.0	5.7	94.3
	Teicoplanin	0.12–256	256	25.3	0.0	74.7
	Ampicillin	≤0.25–4	2	100.0	—	0.0
	Daptomycin[a]	0.5–>4	2	98.9	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	19.5	—	80.5
	Levofloxacin	>4–>16	>16	0.0	0.0	100.0
	Linezolid	0.5–16	2	98.9	0.0	1.1
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	48.3	—	51.7
VanA (65)[c]	Oritavancin	0.03–1	1	—	—	—
	Vancomycin	>128–>256	>256	0.0	0.0	100.0
	Teicoplanin	32–256	256	0.0	0.0	100.0
	Ampicillin	≤0.25–2	2	100.0	—	0.0
	Daptomycin[a]	0.5–>4	2	98.5	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	16.9	0.0	83.1
	Levofloxacin	>4–>16	>16	0.0	0.0	100.0
	Linezolid	0.5–16	2	98.5	0.0	1.5
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	49.2	—	50.8
VanB (17)[d]	Oritavancin	0.015–0.06	0.06	—	—	—
	Vancomycin	32–>256	>256	0.0	0.0	100.0
	Teicoplanin	0.12–8	8	100.0	0.0	0.0
	Ampicillin	≤0.25–4	2	100.0	—	0.0

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TABLE 2—*Continued*

Organism(s) and phenotype(s) (no. of isolates tested)[e]	Agent	MIC (μg/ml)		% of isolates		
		Range	90%	Susceptible	Intermediate	Resistant
	Daptomycin	0.5–2	2	100.0	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	29.4	0.0	70.6
	Levofloxacin	>4–>16	>16	0.0	0.0	100.0
	Linezolid	1–2	2	100.0	0.0	0.0
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	41.2	—	58.8
E. faecium						
All (819)	Oritavancin	≤0.0005–1	0.12	—	—	—
	Vancomycin	0.03–>256	>256	42.7	1.0	56.3
	Teicoplanin	≤0.015–>256	64	47.1	1.5	51.4
	Ampicillin	≤0.25–>256	>256	12.7	—	87.3
	Daptomycin[a]	≤0.12–>4	4	98.4	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	68.3	—	31.7
	Levofloxacin	≤0.03–>16	>16	12.2	2.4	85.3
	Linezolid	≤0.12–16	2	99.3	0.4	0.4
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	44.8	—	55.2
Vanc S (350)	Oritavancin	≤0.0005–0.25	0.03	—	—	—
	Vancomycin	0.03–4	1	100.0	0.0	0.0
	Teicoplanin	≤0.015–8	1	100.0	0.0	0.0
	Ampicillin	≤0.25–>256	256	27.7	—	72.3
	Daptomycin[a]	≤0.12–>4	4	98.3	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	74.9	—	25.1
	Levofloxacin	≤0.03–>16	>16	28.3	5.7	66.0
	Linezolid	≤0.12–4	2	99.4	0.6	0.0
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	56.0	—	44.0
Vanc NS (469)	Oritavancin	≤0.0005–1	0.25	—	—	—
	Vancomycin	8–>256	>256	0.0	1.7	98.3
	Teicoplanin	0.12–>256	128	7.7	2.6	89.8
	Ampicillin	1–>256	>256	1.5	—	98.5
	Daptomycin[a]	≤0.12–>4	4	98.5	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	63.3	—	36.7
	Levofloxacin	≤0.03–>16	>16	0.2	0.0	99.8
	Linezolid	0.5–16	2	99.1	0.2	0.6
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	36.5	—	63.5
VanA (421)[c]	Oritavancin	0.004–1	0.25	—	—	—
	Vancomycin	32–>256	>256	0.0	0.0	100.0
	Teicoplanin	32–>256	128	0.0	0.0	100.0
	Ampicillin	1–>256	>256	1.0	—	99.0
	Daptomycin[a]	0.12–>4	4	98.8	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	62.9	—	37.1
	Levofloxacin	≤0.03–>16	>16	0.2	0.0	99.8
	Linezolid	0.5–8	2	99.5	0.0	0.5
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	36.1	—	63.9
VanB (29)[d]	Oritavancin	0.004–0.06	0.06	—	—	—
	Vancomycin	32–>256	256	0.0	0.0	100.0
	Ampicillin	8–>256	>256	3.4	—	96.6
	Daptomycin[a]	0.25–>4	4	93.1	—	—
	Gentamicin (high-level testing)	≤500–>500	>500	75.9	—	24.1
	Levofloxacin	>4–>16	>16	0.0	0.0	100.0
	Linezolid	0.5–16	2	93.1	3.4	3.4
	Streptomycin (high-level testing)	≤1,000–>1,000	>1,000	34.5	—	65.5
	Teicoplanin	0.12–8	8	100.0	0.0	0.0
S. agalactiae						
All (415)	Oritavancin	0.001–1	0.25	—	—	—
	Vancomycin	0.25–0.5	0.5	100.0	0.0	0.0
	Clindamycin	≤0.015–>1	>1	81.9	0.5	17.6
	Erythromycin	≤0.015–>2	>2	70.6	0.7	28.7
	Levofloxacin	0.25–>8	1	97.8	0.0	2.2
	Penicillin	≤0.015–0.12	0.06	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–1	0.12	—	—	—
Eryth S (293)	Oritavancin	0.001–1	0.25	—	—	—
	Vancomycin	0.25–0.5	0.5	100.0	0.0	0.0

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TABLE 2—*Continued*

Organism(s) and phenotype(s) (no. of isolates tested)[e]	Agent	MIC (μg/ml)		% of isolates		
		Range	90%	Susceptible	Intermediate	Resistant
	Clindamycin	≤0.015–>1	0.06	99.0	0.0	1.0
	Erythromycin	≤0.015–0.25	0.06	100.0	0.0	0.0
	Levofloxacin	0.25–>4	1	98.6	0.0	1.4
	Penicillin	≤0.015–0.12	0.06	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–0.25	0.12	—	—	—
Eryth NS (122)	Oritavancin	0.03–0.5	0.25	—	—	—
	Vancomycin	0.25–0.5	0.5	100.0	0.0	0.0
	Clindamycin	0.03–>1	>1	41.0	1.6	57.4
	Erythromycin	0.5–>2	>2	0.0	2.5	97.5
	Levofloxacin	0.5–>8	1	95.9	0.0	4.1
	Penicillin	≤0.015–0.12	0.06	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–1	0.12	—	—	—
S. pyogenes						
All (959)	Oritavancin	≤0.0005–0.5	0.25	—	—	—
	Vancomycin	≤0.06–1	0.25	100.0	—	—
	Clindamycin	≤0.015–>1	0.06	96.0	0.1	3.9
	Erythromycin	≤0.015–>2	>2	86.3	0.1	13.6
	Levofloxacin	0.06–>4	0.5	99.9	0.0	0.1
	Penicillin	≤0.015–0.12	≤0.03	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–>4	0.12	—	—	—
Eryth S (828)	Oritavancin	≤0.0005–0.5	0.25	—	—	—
	Vancomycin	≤0.06–0.5	0.25	100.0	—	—
	Clindamycin	≤0.015–0.06	0.06	100.0	0.0	0.0
	Erythromycin	≤0.015–0.25	0.06	100.0	0.0	0.0
	Levofloxacin	0.06–2	0.5	100.0	0.0	0.0
	Penicillin	≤0.015–0.12	≤0.03	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–>4	0.12	—	—	—
Eryth NS (131)	Oritavancin	0.004–0.5	0.25	—	—	—
	Vancomycin	0.12–1	0.25	100.0	—	—
	Clindamycin	0.03–>1	>1	71.0	0.8	28.2
	Erythromycin	0.5–>2	>2	0.0	0.8	99.2
	Levofloxacin	0.12–>4	1	99.2	0.0	0.8
	Penicillin	≤0.015–0.12	0.03	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–>4	0.12	—	—	—
S. pneumoniae						
All (1,010)	Oritavancin	≤0.0005–0.5	0.008	—	—	—
	Vancomycin	≤0.06–0.5	0.25	100.0	—	—
	Amoxicillin (amoxicilline)-clavulanate	≤0.015–>8	2	93.1	5.4	1.5
	Ceftriaxone	≤0.015–>4	1	97.0	1.8	1.2
	Cefuroxime-axetil	≤0.12–>4	4	75.9	5.1	18.9
	Clindamycin	≤0.015–>1	>1	86.9	0.2	12.9
	Erythromycin	≤0.015–>2	>2	67.3	0.3	32.4
	Levofloxacin	≤0.12–>8	1	99.1	0.0	0.9
	Penicillin	≤0.03–8	2	64.0	21.4	14.7
	Telithromycin	≤0.002–1	0.25	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–>4	>4	67.3	7.9	24.8
Pen S (646)	Oritavancin	≤0.0005–0.25	0.004	—	—	—
	Vancomycin	≤0.06–0.5	0.25	100.0	—	—
	Amoxicillin-clavulanate	≤0.015–0.25	0.03	100.0	0.0	0.0
	Ceftriaxone	≤0.015–0.25	0.03	100.0	0.0	0.0
	Cefuroxime-axetil	≤0.12–1	≤0.12	100.0	0.0	0.0
	Clindamycin	≤0.015–>1	0.06	97.2	0.2	2.6
	Erythromycin	≤0.015–>2	>2	88.1	0.3	11.6
	Levofloxacin	≤0.12–>8	1	99.5	0.0	0.5
	Penicillin	≤0.03–0.06	≤0.03	100.0	0.0	0.0
	Telithromycin	≤0.002–0.5	0.015	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–>4	1	87.2	6.8	6.0
Pen I (216)	Oritavancin	≤0.0005–0.5	0.008	—	—	—
	Vancomycin	0.12–0.5	0.25	100.0	—	—
	Amoxicillin-clavulanate	≤0.015–4	1	99.5	0.5	0.0
	Ceftriaxone	0.03–4	0.5	99.5	0.0	0.5
	Cefuroxime-axetil	≤0.12–>4	4	56.0	23.6	20.4

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TABLE 2—*Continued*

Organism(s) and phenotype(s) (no. of isolates tested)[e]	Agent	MIC (μg/ml)		% of isolates		
		Range	90%	Susceptible	Intermediate	Resistant
	Clindamycin	≤0.015–>1	>1	84.7	0.0	15.3
	Erythromycin	≤0.015–>2	>2	41.2	0.0	58.8
	Levofloxacin	0.25–>8	1	97.7	0.0	2.3
	Penicillin	0.12–1	1	0.0	100.0	0.0
	Telithromycin	≤0.002–1	0.25	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–>4	>4	50.0	13.4	36.6
Pen R (148)	Oritavancin	0.002–0.015	0.008	—	—	—
	Vancomycin	0.25–0.5	0.5	100.0	—	—
	Amoxicillin-clavulanate	0.5–>8	8	53.4	36.5	10.1
	Ceftriaxone	0.5–>4	2	80.4	12.2	7.4
	Cefuroxime-axetil	2–>4	>4	0.0	0.7	99.3
	Clindamycin	0.03–>1	>1	45.3	0.7	54.1
	Erythromycin	0.03–>2	>2	14.9	0.7	84.5
	Levofloxacin	0.25–>8	1	99.3	0.0	0.7
	Penicillin	2–8	4	0.0	0.0	100.0
	Telithromycin	≤0.002–1	0.5	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	0.25–>4	>4	6.1	4.7	89.2
Group C, G, and F streptococci						
All (84)	Oritavancin	≤0.0005–1	0.5	—	—	—
	Vancomycin	0.12–1	0.5	100.0	—	—
	Clindamycin	≤0.015–>1	0.06	96.4	0.0	3.6
	Erythromycin	≤0.015–>2	2	79.8	3.6	16.7
	Levofloxacin	≤0.03–4	0.5	98.8	1.2	0.0
	Penicillin	≤0.015–0.06	0.06	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–1	0.12	—	—	—
Eryth S (67)	Oritavancin	≤0.0005–1	0.5	—	—	—
	Vancomycin	0.12–1	0.5	100.0	—	—
	Clindamycin	≤0.015–0.12	0.06	100.0	0.0	0.0
	Erythromycin	≤0.015–0.06	0.06	100.0	0.0	0.0
	Levofloxacin	≤0.03–1	0.5	100.0	0.0	0.0
	Penicillin	≤0.015–0.06	0.06	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–1	0.12	—	—	—
Eryth NS (17)	Oritavancin	0.008–0.5	0.25	—	—	—
	Vancomycin	0.12–0.5	0.5	100.0	—	—
	Clindamycin	0.03–>1	>1	82.4	0.0	17.6
	Erythromycin	0.5–>2	>2	0.0	17.6	82.4
	Levofloxacin	0.25–4	0.5	94.1	5.9	0.0
	Penicillin	≤0.015–0.06	0.03	100.0	0.0	0.0
	Trimethoprim-sulfamethoxazole	≤0.06–0.12	0.12	—	—	—

[a] Some isolates were nonsusceptible.
[b] —, CLSI breakpoints do not currently exist.
[c] For *E. faecalis* and *E. faecium*, the VanA phenotype characterizes isolates concurrently resistant to vancomycin and teicoplanin.
[d] For *E. faecalis* and *E. faecium*, the VanB phenotype characterizes isolates resistant to vancomycin and susceptible to teicoplanin.
[e] S, susceptible; I, intermediate; R, resistant; NS, nonsusceptible; Ox, oxacillin; Vanc, vancomycin; Eryth, erythromycin; Pen, penicillin.
[f] High-level testing for gentamicin was at 500 μg/ml per CLSI guidelines (10).
[g] High-level testing for streptomycin was at 1,000 μg/ml per CLSI guidelines (10).

than those reported in previous studies, such as that of Zeckel et al. (39). In that report, the MIC_{90}s for staphylococci and enterococci were 2 μg/ml and 1 μg/ml, respectively, compared to values of 0.12 μg/ml and 0.006/0.12 μg/ml reported in this study. Oritavancin MIC_{90}s for pneumococci were within a doubling dilution between the current study and older studies (0.008 μg/ml in this study, compared to 0.015 μg/ml reported by Zeckel et al. [39]), in line with the previously reported observation that lysed horse blood in streptococcal susceptibility testing medium may substitute for 0.002% polysorbate 80 in minimizing binding of oritavancin to labware vessel surfaces (3). Compared to older studies, this study represents the largest surveillance study of oritavancin, involving nearly 16,000 contemporary gram-positive clinical isolates from diverse geographic regions and patient populations. The results presented here could serve as a benchmark against which other surveillance studies can be compared, especially after oritavancin is introduced into the clinic.

The inclusion of comparator drugs confirmed the high rates of resistance in some organism groups to certain antimicrobial agents, as well as in organisms with the MDR profile. The resistance rates reported here are similar to those reported in other global and local surveillance studies (14, 17, 23, 24, 28, 32, 33, 35, 38). Though the selection of *S. aureus* isolates was biased toward MRSA to provide a comprehensive activity profile for oritavancin against this particular resistance phenotype across diverse geographies, the overall percentage of MRSA isolates in the United States and Asia reflected current MRSA rates in these regions (14, 17). In contrast, the incidence of oxacillin-resistant *S. aureus* isolates from the European Union

and Israel evaluated in the current study exceeded that expected to be observed in this region (current MRSA rates of 0% to 50% have been reported across the European Union, though rates vary by country [20, 33]).

Oritavancin showed promising activity against the gram-positive isolates collected in this study, including strains with defined resistance profiles to other antimicrobial agents. Oritavancin was the most active drug against MRSA, including MDR MRSA. While we did not encounter vancomycin-nonsusceptible staphylococci in this surveillance study, oritavancin has been reported to retain activity against vancomycin-intermediate *S. aureus* (VISA) (MIC_{90} of 1 μg/ml), heterogeneous VISA (hVISA) (MIC_{90} of 1 μg/ml), and vancomycin-resistant *S. aureus* (MIC_{90} of 0.5 μg/ml) (5, 21, 29, 36). It is worth noting that while VISA and hVISA isolates tend to have higher oritavancin MICs than vancomycin-susceptible *S. aureus* isolates (MIC_{90} of 0.12 μg/ml for vancomycin-susceptible *S. aureus* isolates [Table 2]), the oritavancin MIC_{90} against currently available vancomycin-resistant *S. aureus* is a full dilution lower than those for VISA and hVISA.

Three of the 9,075 strains of *S. aureus* that were assessed in this study had oritavancin MICs that were either 1 ($n = 2$) or 2 ($n = 1$) doubling dilutions higher than those for vancomycin (1 μg/ml; $n = 3$) (data not shown); these strains are being characterized further. Oritavancin and vancomycin were equipotent against seven strains of *S. aureus* and against two strains of CoNS; all other staphylococcal isolates in this study were between 1 and 8 doubling dilutions more susceptible to oritavancin than to vancomycin.

Oritavancin demonstrated activity against enterococci, including vancomycin-resistant enterococci of both the VanA and the VanB type. Oritavancin MIC_{90}s of 1 μg/ml and 0.25 μg/ml against VanA *E. faecalis* and *E. faecium*, respectively, compare favorably to those of other investigational lipoglycopeptides, namely, telavancin (16 μg/ml and 8 μg/ml, respectively [14]), and dalbavancin (>4 μg/ml and >4 μg/ml, respectively [7]). Oritavancin is evidently not an inducer of the VanB phenotype, since the MIC_{90}s for VanB strains of enterococci (both *E. faecalis* and *E. faecium*) were identical to the MIC_{90}s against vancomycin-susceptible enterococci.

In conclusion, this study demonstrated oritavancin in vitro activity against recent gram-positive pathogens isolated from three continents. Oritavancin in vitro activity was largely unaffected by the drug resistance profiles of the organisms tested, whether they were staphylococci, enterococci, or streptococci.

ACKNOWLEDGMENTS

We thank the scientific staff at Targanta Therapeutics, The Medicines Company, and Eurofins Medinet, Anti-infective Services, for their contributions to this research.

This work was initiated while The Medicines Company authors were employees of Targanta Therapeutics. Targanta Therapeutics is now a wholly owned subsidiary of The Medicines Company.

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