Oritavancina

Un nuovo lipoglicopeptide long-acting

Daniele Roberto Giacobbe, MD, PhD

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Conflicts of interest

- Investigator-initiated grants (Pfizer, Gilead Italia, Shionogi)
- Personal fees for speaker/consultant (Pfizer, Tillotts Pharma)

Characteristics of oritavancin

- Semisynthetic lipoglycopeptide
- Structurally similar to vancomycin
- May retain some activity in presence of VanA and VanB-mediated vancomycin-resistance

Brade KD, et al. Infect Dis Ther 2016; 5:1–15
Biavasco F, et al. Antimicrob Agents Chemother 1997; 41:2165–2172
Cooper RD, et al. J Antibiot (Tokyo) 1996; 49:575–581
Domenech O, et al. Biochim Biophys Acta 2009; 1788:1832–1840

Characteristics of oritavancin

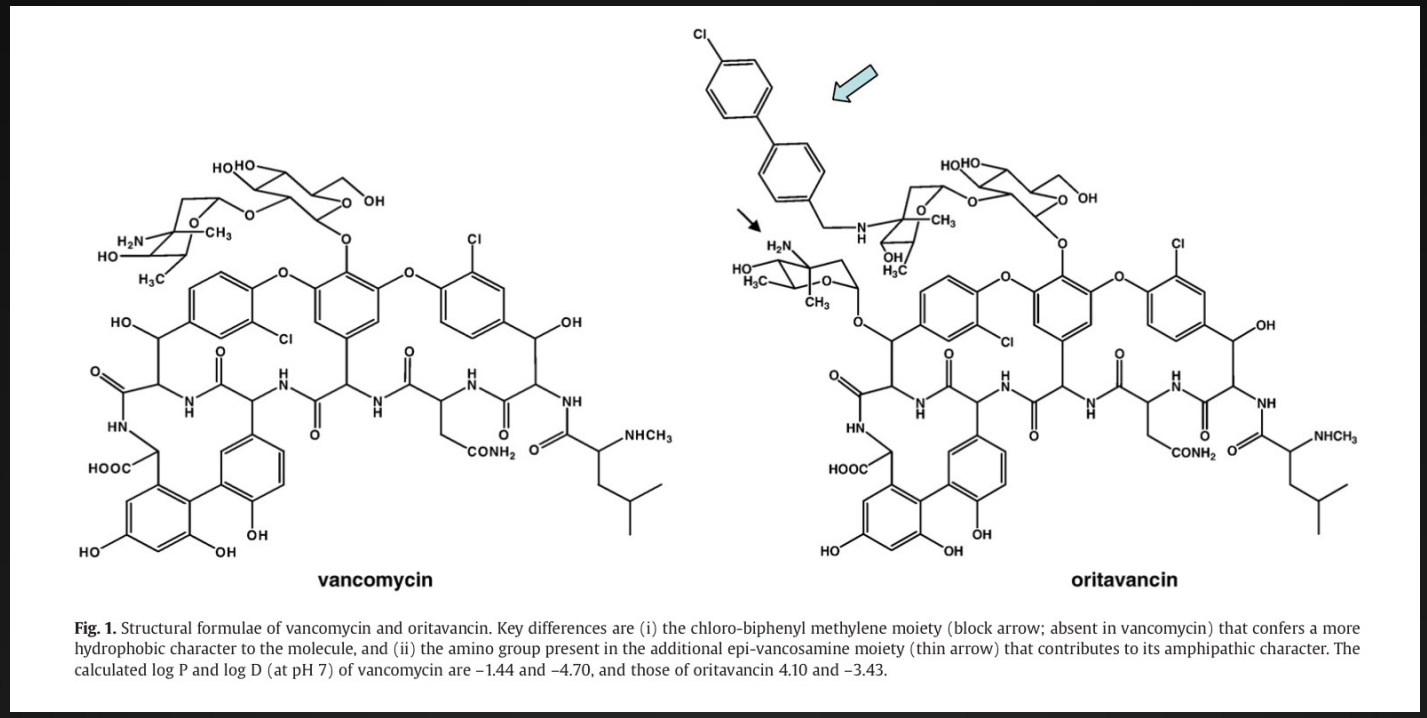

Fig. 1. Structural formulae of vancomycin and oritavancin. Key differences are (i) the chloro-biphenyl methylene moiety (block arrow; absent in vancomycin) that confers a more hydrophobic character to the molecule, and (ii) the amino group present in the additional epi-vancosamine moiety (thin arrow) that contributes to its amphipathic character. The calculated log P and log D (at pH 7) of vancomycin are −1.44 and −4.70, and those of oritavancin 4.10 and −3.43.

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Mechanism(s) of action

- Inhibition of transglycosylation (similar to vancomycin)
- Inhibition of transpeptidation (contributing to its activity against vancomycin-resistant strains)
- Membrane depolarization and permeabilization

Zhanel GG, et al. Drugs 2010; 70:859–886
Munch D, et al. Antimicrob Agents Chemother 2015; 59:772–781
Zhanel GG, et al. Clin Infect Dis 2012; 54(Suppl 3):S214–S219.

Mechanism(s) of action

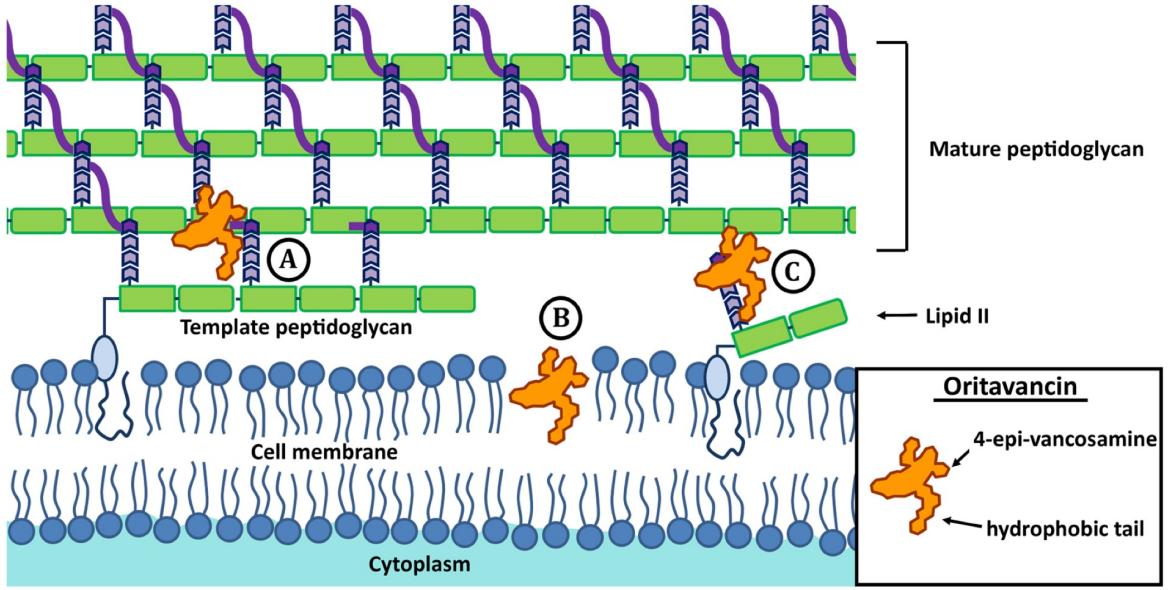

Fig. 3 Oritavancin bacterial binding sites. **a** Oritavancin binding to template peptidoglycan at cleft between hydrophobic tail group and 4-epi-vancosamine. **b** Oritavancin hydrophobic tail group insertion into bacterial cell membrane. **c** Oritavancin binding to D-alanyl-D-alanine stabilized by hydrophobic tail group

Brade KD, et al. Infect Dis Ther 2016; 5:1–15

In vitro activity

- Potent *in vitro* activity against staphylococci (including MRSA), streptococci, and enterococci
- Activity has also been observed against strains of daptomycin-nonsusceptible MRSA, VRE, and *E. faecium* with elevated daptomycin MIC and reduced susceptibility to linezolid

Mendes RE, et al. J Antimicrob Chemother 2015; 70:498–504
Brade KD, et al. Infect Dis Ther 2016; 5:1–15
Vidaillac C, et al. Diagn Microbiol Infect Dis 2011; 71:470–473
Carvalhaes CG, et al. Antimicrob Agents Chemother 2022; 66:e0166721

PK characteristics

- Prolonged terminal half-life of 200–300 hours
- Large Vd and high protein binding (85–90%)
- Elimination mainly through the reticuloendothelial system (no adjustments for kidney or hepatic failure)

Rubino CM, et al. Antimicrob Agents Chemother 2015; 59:3365–3372.
Mitra S, et al. Infect Drug Resist 2015; 8:189–197
Brade KD, et al. Infect Dis Ther 2016; 5:1–15
Bassetti M, et al. Expert Opin Drug Saf 2019; 18:635–650

Drug interactions

- Oritavancin is a weak inhibitor of CYP2C9 and CYP2C19, and an inducer of CYP3A4 and CYP2D6
- Patients treated with warfarin and receiving oritavancin should be monitored for possible bleeding

Bassetti M, et al. Curr Opin Infect Dis 2021; 34:96-108

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Alteration of lab tests

- Possible alterations of some coagulation tests in the first hours/days after oritavancin administration (e.g., prolonged PT and prolonged aPTT) because of interaction of oritavancin with the phospholipid reagent
- i.v. unfractionated heparin sodium is contraindicated for up to 5 days after oritavancin administration, owing to inability to reliably monitor coagulation tests
- The results of the chromogenic factor Xa and the thrombin time assays are not affected by oritavancin administration
- False increase in vancomycin concentrations

Bassetti M, et al. Curr Opin Infect Dis 2021; 34:96-108
Smelter FM, et al. J Clin Pharmacol 2022; 62:472-478
Belley A, et al. Antimicrob Agents Chemother 2017; 61:e01968–16

Indication and dosage (EMA)

- ABSSSI in adults
- 1,200 mg administered as a single dose by intravenous infusion over 3 hours (in glucose 5%)

https://www.ema.europa.eu/

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Efficacy in RCTs

Study [ref] (type of study)	Investigational drugs (dosage)	Comparator/s (dosage)	Primary endpoint	Disease and study population of the primary analysis	Cured/total (rates, %)	Percent difference (95% CI)
SOLO I [45] (noninferiority)	Oritavancin (1200 mg i.v. on day 1)	Vancomycin (15 mg/kg q12h i.v. for 7–10 days)	*Early clinical response* (cessation of spreading or a reduction in the size of the baseline lesion, the absence of fever, and the absence of a need for rescue antibiotic medication; assessed at 48–72-h)	ABSSSI *MITT population* Oritavancin Vancomycin	 391/475 (82.3) 378/479 (78.9)	 3.4 (−1.6 to 8.4) Reference
SOLO II [44] (noninferiority)	Oritavancin (1200 mg i.v. on day 1)	Vancomycin (15 mg/kg q12h i.v. for 7–10 days)	*Early clinical response* (cessation of spreading or reduction in the size of the baseline lesion, absence of fever, and no rescue antibiotic medication; assessed at 48–72-h)	ABSSSI *MITT population* Oritavancin Vancomycin	 403/503 (80.1) 416/502 (82.9)	 −2.7 (−7.5 to 2.0) Reference

Corey GR, et al., N Engl J Med 2014; 370:2180–2190
Corey GR, et al., Clin Infect Dis 2015; 60:254–262
Bassetti M., et al. Curr Opin Infect Dis 2020; 33:110-120

Safety in RCTs

- Safety of oritavancin in the SOLO studies was similar to vancomycin (most common AEs were nausea and headache in both arms)
- SAE were 7.4% for oritavancin vs. 7.3% for vancomycin in SOLO I
- SAE were 4.4% for oritavancin vs. 4.6% for vancomycin in SOLO II

Corey GR, et al., N Engl J Med 2014; 370:2180–2190
Corey GR, et al., Clin Infect Dis 2015; 60:254–262

Observational studies in ABSSSI

- Retrospective single-center
- 118 outpatients with ABSSSI
- 56 received oritavancin(the others received vancomycin, daptomycin, dalbavancin, or other antibiotics)
- Clinical cure 73.2% for oritavancin and 48.3% for other agents (P 0.03)

Anastasio PJ, et al. Infect Dis Ther 2017; 6:115–128

Observational studies in ABSSSI

- Multicenter, retrospective
- 151 inpatients with ABSSSI treated with oritavancin and early discharged
- All-cause readmission 6.6%
- Infection-related readmission of 2.6%

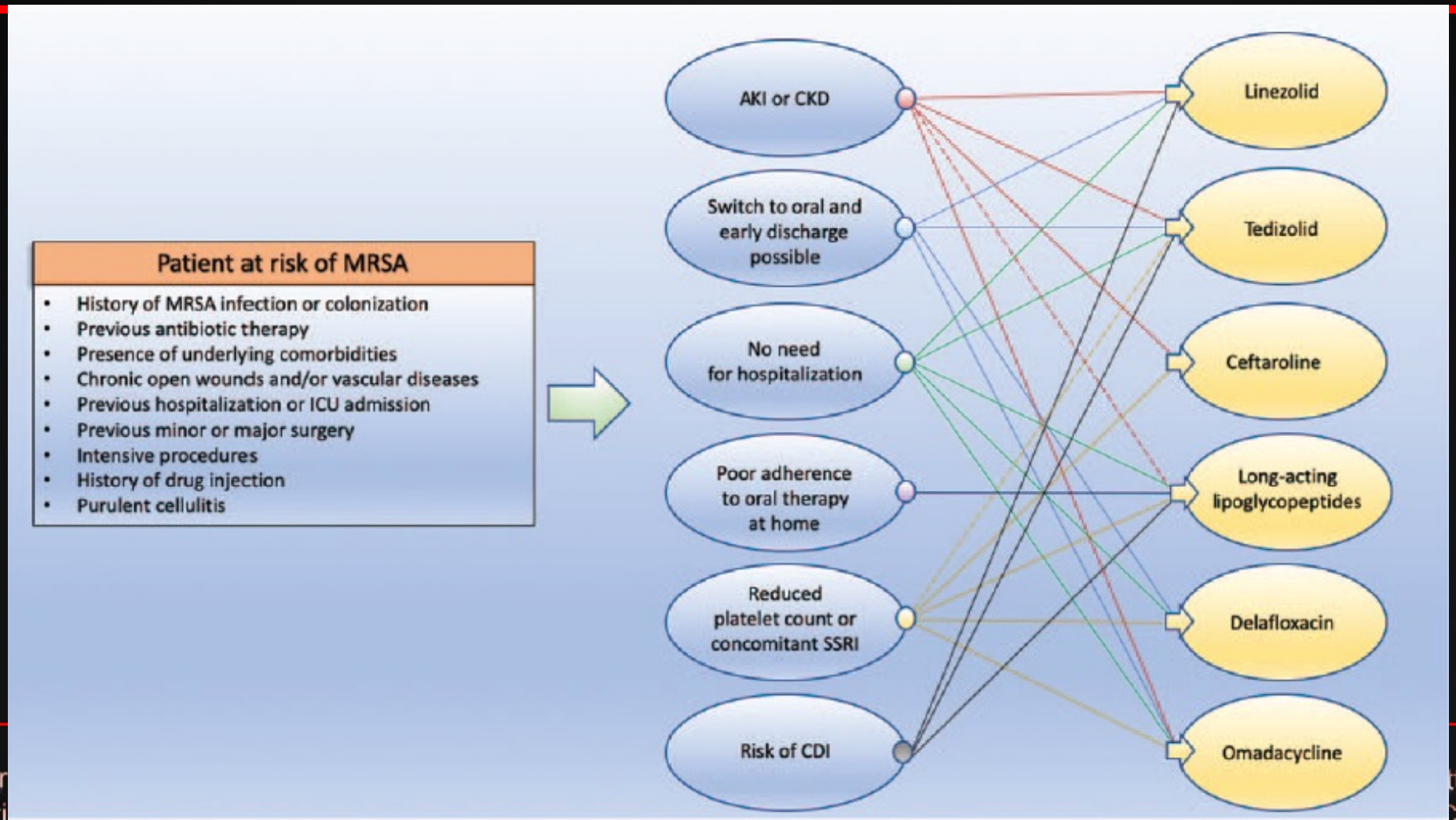
Estrada S, et al. Drugs Real World Outcomes 2020; 7:6–12

Observational studies in ABSSSI

- Multicenter, retrospective
- 120 and 6695 outpatients with ABSSSI receiving oritavancin and vancomycin, respectively
- Lower frequency of 30-day admission in oritavancin-treated patients (6.1% vs. 16.2%, P<0.01)

Lodise TP, et al. Open Forum Infect Dis 2019; 6:ofz475

Positioning of oritavancin for ABSSSI



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Observational studies in other infections

Reference	Type of study	Type of infections other than ABSSSI treated with oritavancin (no. patients)	Outcome/s data	Safety data AE (no. patients)
Stewart *et al.* [50]	Retrospective Single center	MSSA BSI (5) MRSA bursitis (1) Group B streptococcal BSI with infective endocarditis (1) CoNS bacteremia (1) MSSA deep tissue infection (1) *Enterococcus* spp. BSI (1)	7/10 Patients (70%) were successfully treated	Nausea (2) Hearing loss (1)
Co *et al.* [43]	Retrospective Single center	Cardiac device infection (7) Diabetic foot infection (3) Osteomyelitis (8) Bacteremia (3)	No readmission within 14 days	NA
Schulz *et al.* [51]	Retrospective Single center	MRSA pneumonia (2) Osteomyelitis (4) VRE hepatic abscess (1) *Staphylococcus lugdunensis* endovascular graft infection (1) VRE bacteremia (1)	Success or improvement in 9/9 cases (100%)	*Assessed in the entire cohort, n = 17, including also patients with ABSSSI* Infusion-related infections (2) Anemia and leukopenia (1)
Chastain and Davis [16]	Retrospective Single center	Osteomyelitis (9)	Clinical cure in 9/9 cases (100%) at 6-month follow-up	No treatment-emergent AE reported

Bassetti M, et al. Curr Opin Infect Dis 2021; 34:96-108

Reference	Type of study	Type of infections other than ABSSSI treated with oritavancin (no. patients)	Outcome/s data	Safety data AE (no. patients)
Morrisette *et al.* [52,53]	Retrospective Multicenter	*Numbers include both dalbavancin-treated and oritavancin-treated patients:* Osteomyelitis (15) Endocarditis (5) CRBSI (2) Pneumonia (2) Various other infections (14)	*Numbers include both dalbavancin-treated and oritavancin-treated patients for whom outcome data was available:* 92% clinical success (11/12) for osteomyelitis, 100% (3/3) for endocarditis, and 100% (2/2) for catheter-related bacteraemia	*The following mild AE include both dalbavancin-treated and oritavancin-treated patients:* Infusion reaction (1) Nausea (1) Chest tightness (1) Line infiltration with edema (1) Acute kidney injury (1) Headache (1)
Redell *et al.* [48]	Retrospective Multicenter	Primary bacteremia (5) Osteomyelitis (18) Septic Arthritis/synovitis (4) Prosthetic joint infection (3) Infected bursa (3) Catheter exit site (1) Maxillary sinus infection (1) Hardware, posterior lumbar tissue (1) Lymphadenitis (1)	In patients with osteomyelitis receiving single-dose oritavancin for completion of treatment, clinical success or improvement was observed in 9/10 cases (90%) Clinical success in patients receiving oritavancin for joint infections was 71.4% (5/7)	*Assessed in the entire cohort, n = 440, including also patients with ABSSSI* Any AE (29) Pruritus (14) *Six AE leading to discontinuation* Infusion site reaction (2) Pruritus, urticaria, and headache (1) Urticaria and pruritus (1) Headache and throat tightness (1) Back pain and flushing (1)
Ahiskali and Rhodes [54]	Retrospective Single center	Bone or joint infections (14) Endocarditis (2) Isolated BSI (3)	*Outcome includes also patients with ABSSSI* Clinical cure was observed in 19/24 patients (79%)	*Assessed in the entire cohort, n = 24, including also patients with ABSSSI* Infusion-related reaction (1) Abdominal pain (1)

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Reference	Type of study	Type of infections other than ABSSSI treated with oritavancin (no. patients)	Outcome/s data	Safety data AE (no. patients)
Brownell *et al.* [42]	Retrospective Single center	Osteomyelitis/septic arthritis (10) Diabetic foot infection (3) Endocarditis (4) Line infection (2) Pneumonia (5) Prosthetic device infection (4) Sepsis (5) Surgical wound infection (12) Other (5)	*Clinical cure or improvement* Osteomyelitis/septic arthritis (100%, 10/10) Diabetic foot infection (100%, 3/3) Endocarditis (100%, 4/4) Line infection (100%, 2/2) Pneumonia (100%, 5/5) Prosthetic device infection (3/3, 100%, 1 missing) Sepsis (3/5, 60%) Surgical wound infection (11/12, 91.7%) Other (4/5, 80%)	Any AE (5) The most frequent AE was back pain (3/75, including also patients with ABSSSI at the denominator)
Van Hise *et al.* [55]	Retrospective Multicenter	Osteomyelitis (134)	Clinical success at the end of treatment (118/134, 88.1%) Relapse or persistent infection (13/134, 9.7%)	Hypoglycemia (3) Tachycardia (1) Tachycardia with chest pain (1)

Conclusions

- Treatment of ABSSSI towards precision medicine
- Role of oritavancin in ABSSSI especially in outpatient with low adherence
- Different, concomitant mechanisms of action possibly impacting positioning in treatment algorithms
- Increasing interest in other indications

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