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ORIGINAL RESEARCH

Evaluating oritavancin for Gram-positive infections: a systematic review of on-label and off-label use

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Abstract

Background: Oritavancin is a long-acting lipoglycopeptide antibiotic approved for acute bacterial skin and skin structure infections (ABSSSI) with potential applicability across difficult-to-treat Gram-positive infections such as osteomyelitis, bacteraemia and endocarditis. This systematic review evaluates the efficacy, safety and clinical use of oritavancin across on-label and off-label indications.

Methods: MEDLINE and CENTRAL were searched (2011–2024) for randomized trials, retrospective cohorts, case series and real-world evidence reporting clinical outcomes following oritavancin administration. Risk of bias was assessed using Critical Appraisal Skills Programme (CASP) tools for randomized clinical trials and cohort studies.

Results: Twenty-five studies met inclusion criteria: 11 evaluating ABSSSI (n=2311) and 14 assessing off-label use (n=692), including for osteomyelitis, bacteraemia and endocarditis. Across ABSSSI randomized clinical trials, oritavancin demonstrated clinical cure rates of 79.6–83.3%, comparable to those of vancomycin. In retrospective studies, clinical success rates ranged from 85% to 88% in ABSSSI retrospective studies and from 70% to 100% in off-label studies. Adverse events were primarily mild to moderate.

Conclusions: Oritavancin is effective for ABSSSI and may be a promising treatment alternative for selected Gram-positive off-label indications requiring prolonged therapy. Standardized dosing strategies and prospective trials are needed to define optimal regimens for off-label indications.

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Keywords: acute bacterial skin and skin structure infections, bacteraemia, endocarditis, long-acting lipoglycopeptide, off-label use, oritavancin, osteomyelitis.

Citation

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Introduction

Gram-positive pathogens pose a significant challenge in the field of medicine, often requiring prolonged courses of intravenous (IV) antibiotic therapy.[1,2] However, prolonged IV treatments, hospitalization costs, toxicities and the increase in antibiotic resistance, particularly with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), have underscored the need for more effective treatment options.[3] Standard antibiotic therapy typically involves multiple IV

injections, which can be complicated for outpatient parenteral antimicrobial therapy due to catheter-related infections, travel restrictions and high failure rates amongst people with drug abuse disorders.[3–5] Moreover, the financial burden associated with hospitalization further adds to the challenge.[6]

Oritavancin, a long-acting lipoglycopeptide (laLGP), represents a promising therapeutic option in the treatment of Gram-positive infections.[7] It has a triple mechanism of action that explains its potent in vitro and bactericidal activity. Oritavancin has concentration-dependent bactericidal activity and an extended half-life (245 hours), maintaining serum and tissue therapeutic concentrations for more than 7 days.[6] Due to its long terminal half-life, oritavancin requires only a single or a few injections offering a convenient and patient-friendly administration route.[8] A new formulation of oritavancin was developed to allowed shorter infusion time (1 hour *versus* 3 hours) and lower volume of dilution after reconstitution (250 mL *versus* 1 L) compared to the conventional oritavancin formulation, as reported by Hoover et al.[9] Additionally, oritavancin exhibits a broad-spectrum activity against Gram-positive pathogens, making it an effective alternative to other common treatments.[10] Importantly, oritavancin has demonstrated efficacy against vancomycin-resistant pathogens, further enhancing its therapeutic value.[11] Whilst the FDA has specifically approved oritavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI), emerging literature suggests the potential for extending its use to other complicated infections such as osteomyelitis, septic arthritis and endocarditis.[12,13] This seems reasonable given that has bactericidal activity against non-replicating bacteria, activity against bacteria embedded in biofilms, and good penetration into bone according to animal models.[14]

Considering the evolving evidence surrounding the extended applications of oritavancin, it is crucial to conduct a systematic review to comprehensively assess its effectiveness, particularly in off-label treatment. Our review aims to compare studies examining the efficacy of oritavancin in both on-label and off-label use. By evaluating a range of randomized controlled trials, case studies, and retrospective cohort analyses published between 2011 and 2024, we gather the available evidence to elucidate the clinical cure and clinical success rates associated with oritavancin treatment.

Methods

Search strategy

Published articles (from 2011 to 2024) that reported outcomes of clinical studies using oritavancin for on-label and off-label indications were identified through literature searches in MEDLINE/PubMed and Cochrane Central Register of Controlled trials (CENTRAL). The search terms were as follows: for the on-label indication: ("oritavancin" OR "ORI" OR "LY333328") AND ("ABSSSI" OR "SSSI" OR "SSTI" OR "MSSA" OR "MRSA" OR "VRSA" OR "VRE" OR "VSE"); for the off-label indications: ("oritavancin" OR "ORI" OR "LY333328") AND ("endocarditis" OR "bacterial endocarditis" OR "infective endocarditis" OR "osteomyelitis" OR "bacteraemia" OR "bacteremia" OR "persistent bacteraemia" OR "bone/joint infection").

Selection criteria

Two independent reviewers searched the literature and evaluated the studies for inclusion. Randomized control trials, case control studies, case reports/series, retrospective cohort analyses and real-world studies were considered eligible for inclusion. For on-label oritavancin treatment, inclusion criteria were as follows: adult patients (≥18 years) with a diagnosis of ABSSSI suspected or proven to be caused by a Gram-positive pathogen (the presence of wound infection, cellulitis, erysipelas or a major cutaneous abscess was required, with each lesion surrounded by erythema, oedema or an induration of at least 75 cm^2); oritavancin as a treatment agent; and inclusion of at least one control agent. For off-label studies, inclusion criteria were as follows: adult patients (≥18 years) who received a diagnosis of major cutaneous abscess (with each lesion surrounded by erythema, oedema or an induration of at least 75 cm^2) or endocarditis or microbiologically confirmed osteomyelitis infection or bacteraemia; oritavancin as a treatment agent; and inclusion of at least one control agent. Studies not written in English language, reporting no data on efficacy and safety, secondary analyses of published data, or including paediatric patients were excluded.

Data extraction and outcomes

Data from the selected papers included the author, year of publication, study design, number of patients, population characteristics (% males and mean age), type of infection, treatment dosage and posology, comparison to other antibiotics, adverse events (AEs), follow-up, and therapy outcome. The primary outcome of the review was clinical cure, intended as the resolution of all signs/symptoms of infection (fever, white blood cell count, C-reactive protein) and no additional antibiotic therapy required. The secondary outcome was clinical success, intended as the composite of clinical cure or clinical improvement (partial resolution of clinical signs and symptoms) or the proportion of patients in clinical failure. The different definitions were revised and assigned for consistency for each retrieved study. The time of assessment was heterogeneous and was not used to define the two outcomes. Readmission rates,

length of stay and adverse events for each study were also reported. The main pathogens of interest (MRSA, methicillin-susceptible *Staphylococcus aureus* (MSSA), *Streptococcus* spp., *Enterococcus* spp., VRE) reported in the studies were also collected.

Critical appraisal tool

To quantify the quality of each study, the critical appraisal tool the Critical Appraisal Skills Programme (CASP) was used to evaluate randomized clinical trials and retrospective studies with the relevant questionnaire. Results of the CASP are reported in Tables S1 and S2 of the Supplementary Material (available at: https://www.drugsincontext.com/wp-content/uploads/2026/02/dic.2025-9-4-Suppl.pdf).

PRISMA compliance and registration statement

This review was performed in accordance with PRISMA 2020 guidelines, including eligibility criteria, structured search methods, risk of bias assessment and transparent reporting. A PRISMA flow diagram is provided in Figure 1. This review was not registered in PROSPERO due to its retrospective nature and time constraints. Future reviews will be prospectively registered.

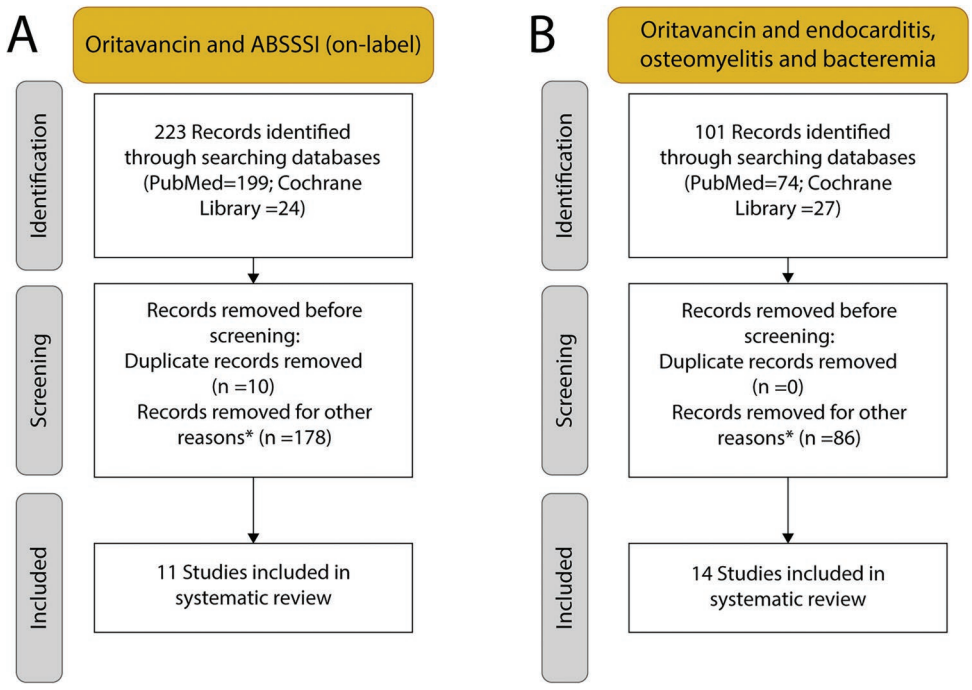
Ethical approval

Ethics approval was not required for this study; the results are based on previously publicly available data and do not involve any new studies of human or animal subjects performed by any of the authors.

Results

A total of 223 studies evaluating the on-label use of oritavancin in patients with ABSSSI were found (199 from PubMed and 24 from CENTRAL; Figure 1A). After duplicate screening (*n*=10), 178 papers were excluded as non-relevant (list of reasons including not being a clinical trial/randomized clinical trial, the full test was not conducted, not in line with inclusion criteria, in vitro study, in vivo animal study, no data on efficacy, no data on efficacy and safety, non-clinical research, or being a secondary analysis of published data, pharmacokinetic analysis, or conference paper). The final selection included 11 papers in the analysis (Figure 1A), of which 6 were retrospective cohort studies[15–20] and 5 were randomized clinical trials.[9,21–24] A total of 101 studies assessing oritavancin use in off-label treatment of other complicated infections were identified (74 from PubMed and 27 from CENTRAL; Figure 1B). No duplicates were identified in this search. After full-text

Figure 1. Flow chart according PRISMA 2020 guidelines depicting the selection process of studies included in the review.



*List of reasons for exclusion: review (not a clinical trial/randomized clinical trial), the full text was not conducted, not in line with inclusion criteria, in vitro study, in vivo animal study, no data on efficacy, no data on efficacy and safety, non-clinical research, secondary analysis of published data, pharmacokinetic analysis, conference paper.

screening, 87 papers did not fulfil the inclusion criteria. At the end of the selection process, 14 studies were included in the analysis (Figure 1B), of which 11 were retrospective cohort studies[16,17,25–33] and 3 were case reports.[34–36] Oritavancin indications included treatment of complicated bacteraemia (*n*=10), osteomyelitis (*n*=9) or endocarditis (*n*=5). Three studies were included for both on-label and off-label analysis.[16,17,31] One study evaluated the clinical success of both oritavancin and dalbavancin treatment without any distinction between the two agents with both laLGPs having a similar activity.[16]

On-label studies

A summary of the on-label included studies is provided in Table 1. In most of the on-label studies, oritavancin was administered in a single dose and compared to the standard of care (SoC) or vancomycin treatment.[15,16,18–20,22–24] Two studies evaluated oritavancin activity administered at different dosing regimens: a 200 mg daily dose for 3–7 days, a single 1200 mg dose, an infrequent 80 mg dose with the option for an additional 400 mg dose on day 5,[21] or single *versus* multiple doses.[17] Hoover et al. evaluated the pharmacokinetics, tolerability and safety of a novel formulation of oritavancin with a higher concentration and shorter time of infusion than the conventional treatment.[9] Generally speaking, oritavancin treatment demonstrated a comparable efficacy to conventional treatments in reported outcomes, whilst allowing less frequent injections and reducing both length of hospital stay (LOS) and costs. Three studies evaluated the clinical cure of single-dose oritavancin treatment both at the end of treatment and at follow-up, compared to multiple-doses of vancomycin treatment. In the three randomized, double-blind studies, oritavancin treatment proved to be non-inferior to multiple vancomycin doses and with similar rates of occurrence of AEs, reaching clinical cure in 79.6–83.3% of cases after 14–21 days from treatment completion.[22–24] Oritavancin single-dose treatment proved to be as effective as vancomycin treatment in another retrospective study. At 30 days follow-up, clinical cure was achieved in both groups in 90.2% of patients, with a significant reduction in LOS (19.5 h for oritavancin *versus* 85.98 h for vancomycin).[18] When oritavancin treatment was compared to other SoC treatments (daptomycin, dalbavancin, vancomycin or others), rates of successful outcome were similar (90.2% for oritavancin and 77.4% for SoC), although clinical cure at 30 days was significantly higher in the oritavancin cohort (73.2%) compared to the SoC cohort (48.4%). Notably, average LOS was significantly shorter (1 day *versus* 7.2 days, respectively), and hospitalization costs were lower (US$2319 less/person).[15] In another multicentre, randomized, double-blind study, different oritavancin doses were compared for clinical cure at 21–29 days. Reported clinical success rates were 72.4% (55/76) in the daily-dose group (200 mg), 81.5% (66/81) in the 1200 mg single-dose group, and 77.5% (55/71) in the infrequent-dose group (800 mg dose, with the option for an additional 400 mg on day 5). Within the same dosage groups, the clinical success rates for patients with MRSA at baseline were 78.3% (18/23), 73.0% (27/37) and 87.0% (20/23), respectively.[21]

Oritavancin use was evaluated in another retrospective study that considered both on-label and off-label applications. In the ABSSSI subgroup, clinical success was achieved in 89% of cases, with most patients receiving a single dose (380/401, 94.8%) and a minority receiving more than one dose (21/401, 5.2%). Unfortunately, a comparison of the different dosages for this subgroup was not available but rather a general clinical success rate of 87.7% (356/406) for the single-dose cohort and of 93.8% (30/32) for the multiple-dose cohort, comprising also other off-label applications, was given.[17] Hoover et al. evaluated the safety profile of their novel, more concentrated formulation described above.[9] AEs with the novel formulation proved to be lower (48%) compared to the conventional formulation (59.6%). One study evaluated the clinical efficacy of oritavancin (*n*=14) or dalbavancin (*n*=40) for ABSSSI and treatment of other complicated infections after previous antibiotic administration.[16] Clinical cure with absence of microbiological signs of infection within 60 months was reported in 86% of patients (pool results for oritavancin and dalbavancin), with oritavancin being also effective for VRE infections. Two studies evaluated the clinical success in terms of readmission rates. Whittaker et al. reported a significantly lower readmission rate for oritavancin-treated patients (7.1%) compared to SoC-treated patients (18.0%), with a lower LOS (3.5 days *versus* 5.6 days, respectively).[19] Saddler et al. reported readmission rates of oritavancin *versus* SoC at two timepoints of 30 and 60 days.[20] In both cases, oritavancin treatment proved to more frequently avoid the need for hospitalizing patients than SoC (10.1% *versus* 60.7% at 30 days, 12.7% *versus* 60.7% at 60 days), as well as reducing the costs (5.9% lower).[19,20] In both studies, all patients had prior antibiotic failures (in the second one, all patients had prior vancomycin failure) and similar comorbidity incidence in the two treatment groups.[19,20]

Regarding the pathogen reported in the studies, in randomized clinical trials of single-dose oritavancin for ABSSSI, the prevalence of MRSA ranged from 19.9% to 23%, MSSA from 29.8% to 37.9%, whilst *Streptococcus* spp. (6.5–9.5%) and *Enterococcus faecalis* (1.2–1.4%) were less common.[21–24] Clinical cure and clinical success rates with single-dose oritavancin were similar or higher for MSSA (82.8% clinical cure; 90.9% clinical success) compared with MRSA (83.3% clinical cure; 73.0% clinical success).[21,24]

Table 1. Summary of on-label studies.

Author, year (ref.)	Patients	M/F	Age (years)	Trial	Study design	Intervention	Comparison	Follow up	Adverse events	Outcomes[a]	Pathogen[b]	CASP score
Clinical trials												
Corey, 2014 [22]	954 patients (475 oritavancin *versus* 479 vancomycin)	63.4% *versus* 62.8%	46.2±14.2, 44.3±14.5	SOLO I	Randomized, double-blind trial	Single-dose oritavancin (1200 mg)	Twice-daily vancomycin for 7–10 days	Primary endpoint[a]: 48–72 hours Secondary endpoint (clinical cure): 7–14 days	Mostly mild, including nausea (11% *versus* 8.9%), headache (7.2% *versus* 7.9%), vomiting (4.9% *versus* 3.7%), diarrhoea (4.9% *versus* 3.5%)	Primary endpoint: 82.3% *versus* 78.9% Secondary endpoint (clinical cure): 79.6% *versus* 80.0%	MRSA: 21.9% MSSA: 23% *Streptococcus* spp.: 6.5% *versus* 7.9% *Enterococcus faecalis*: 1.4% *versus* 1.0% Primary endpoint:MRSA: 80.8% *versus* 80.9% MSSA: 82.8% *versus* 83.6% *Streptococcus* spp.: 92.3 *versus* 87.5% *Enterococcus faecalis*: 85.7% *versus* 80.0%	9
Corey, 2015 [23]	1005 patients (503 *versus* 502)	67.2% *versus* 68.3%	45.0±13.4, 44.4±14.3	SOLO II	Randomized, double-blind trial	Single-dose oritavancin (1200 mg)	Twice-daily vancomycin for 7–10 days	Primary outcome:[a] 48–72 hours Secondary outcome (clinical cure): 7–14 days	Mostly mild, including nausea (8.9% *versus* 12%), headache (7% *versus* 5.6%), vomiting (4.4% *versus* 5.6%), cellulitis (3.4% *versus* 3%)	Primary endpoint:[a] 80.1% *versus* 82.9% Secondary endpoint (clinical cure): 82.7% *versus* 80.5%	MRSA: 19.9% *versus* 20.1% MSSA: 29.8% *versus* 31.2% *Streptococcus*: 9.5% *versus* 11.3 *Enterococcus faecalis*: 1.2% *versus* 1.4% Primary endpoint: MRSA: 83.2% *versus* 84.9% MSSA: 84.0% *versus* 87.3% *Streptococcus*: 75.0% *versus* 87.7% *Enterococcus faecalis*: 83.3% *versus* 85.7%	9

(*Continued*)

Table 1. (Continued)

Author, year (ref.)	Patients	M/F	Age (years)	Trial	Study design	Intervention	Comparison	Follow up	Adverse events	Outcomes[a]	Pathogen[b]	CASP score
Clinical trials												
Corey, 2016 ([24])	405 (204 *versus* 201)	61.8% *versus* 63.7%	42.5±12.2, 41.2±13.5	SOLO I and II	Randomized, multicentre, double-blind non-inferiority trial	Single-dose oritavancin (1200 mg)	Twice-daily vancomycin for 7–10 days	Primary outcome: 48–72 hours, Secondary outcome: 14–24 days	–	–	Primary endpoint MSSA: 82.8% *versus* 85.7% MRSA: 81.4% *versus* 80.6% *Enterococcus faecalis*: 84.6% *versus* 83.3% Secondary endpoint (clinical cure) MSSA: 82.4% *versus* 83.3% MRSA: 83.3% *versus* 84.1% *Enterococcus faecalis*: 61.5% *versus* 75.0%	9
Dunbar, 2011 ([21])	302 (100 in the daily-dose group, 99 in the 1200 mg-single-dose group, and 103 in the infrequent-dose group)	–	>18	SIMPLIFI	Randomized, multicentre, double-blind trial	A daily oritavancin dose (200 mg) 3–7 days, a single dose (1200 mg), or an infrequent dose (800 mg dose, with an additional 400 mg on day 5)	Different oritavancin dosages	TOC (21–29 days)	Mostly mild, including nausea, phlebitis, diarrhoea, headache, infusion site extravasation, vomiting, and constipation, mostly mild (56% daily dose, 55.6% single-dose and 61.2% infrequent-dose group)	Clinical success:[c] 72.4% daily dose 81.5% single dose 77.5% infrequent dose	MRSA: 23% daily dose *versus* 27.3% single dose *versus* 22.3% infrequent dose MSSA: 23% daily dose *versus* 37.4% single dose *versus* 15.5% infrequent dose Clinical success in MRSA: 78.3% daily dose 73.0% single dose 87.0% infrequent dose Clinical success in MSSA: 56.5% daily dose 90.9% single dose 68.8% multiple dose	8

(*Continued*)

Table 1. (Continued)

Author, year (ref.)	Patients	M/F	Age (years)	Trial	Study design	Intervention	Comparison	Follow up	Adverse events	Outcomes[a]	Pathogen[b]	CASP score
Clinical trials												
Hoover, 2022 ([9])	102 (50 NF; 52 CF)	65.7% *versus* 34.3%	44.3±12.6		Randomized, multicentre, open-label study	Single-dose oritavancin NF (infused over 1 hour)	Single-dose oritavancin CF (infused over 3 hours)	Primary outcome: AUC after single-dose infusion Secondary outcome: safety and tolerability	Mostly mild; 22–22.0% *versus* 38.5% reported TEAE related to study drug; 1 had cellulitis in NF group, 3 had severe or higher TEAE in CF group: hypersensitivity, cellulitis and overdose	Similar AUC for both formulations	NA	7
Retrospective studies												
Anastasio, 2017 ([15])	118 patients (59 oritavancin and 59 SoC)	49.2% *versus* 35.6%	65.3±16.7, 63.8±16.5	–	Single-centre, retrospective, observational study	Single-dose oritavancin (1200 mg)	SoC (daptomycin, dalbavancin, vancomycin, other)	5–30 days (mean 16.7)	–	Clinical cure: 73.2% *versus* 48.4%	MRSA: 15% MSSA: 4% *Enterococcus* spp.: 4%	6
Helton, 2020 ([18])	122 (61 oritavancin, 61 vancomycin)	59% *versus* 67.2%	41.8±14.9, 47.2±14.3	–	Retrospective cohort analysis of patients who presented to the ED or OBS with a skin and soft tissue infection	Single-dose oritavancin (1200 mg)	Twice-daily vancomycin for 7–10 days	30 days	–	LOS: 19.5 h *versus* 85.98 h 30-day readmission 9.8 *versus* 9.8	NA	7
Morrisette, 2019 ([37])	56 patients (14 oritavancin, 40 dalbavancin, 2 treated with both)	59% males (no distinction)	46.7±15.4, no distinction	–	System-wide, retrospective cohort of adult patients	Single-dose oritavancin or dalbavancin	Previous SoC treatment	6 months	Mild AEs in 11% of patients, including itching, nausea, chest tightness, oedema, headache and one case of acute kidney injury (possibly by other drugs)	Clinical success:[c,d] 85% of patients with ABSSSI Reduction in LOS: 9.18 days/person	MRSA: 7.14% MSSA: 12.5% *Enterococcus faecalis*: 19.7% VRE: 7.1% Clinical success in 100% MRSA 85% MSSA 100% *Enterococcus faecalis* 0% VRE	4

(*Continued*)

Table 1. (Continued)

Author, year (ref.)	Patients	M/F	Age (years)	Trial	Study design	Intervention	Comparison	Follow up	Adverse events	Outcomes[a]	Pathogen[b]	CASP score
Retrospective studies												
Redell, 2019 ([38])	440 patients (skin and soft tissue 401, bacteraemia 7, other complicated infections 32)	53.2% males (no distinction)	57.8±16.4	CHROME	Multicentre, retrospective, observational study	Single (92.7%) or multiple (7.3%) oritavancin doses	Single *versus* multiple doses	30 days	AEs in 6.6% of patients, including pruritic, nausea, vomiting and asthenia	Clinical success:[c] 88.1% (87.7% *versus* 9.38%) Clinical cure (64.5% *versus* 82.5%)	MRSA: 14.5% MSSA: 10% *Streptococcus* spp.: 3.4%	7
Saddler, 2021 ([20])	107 patients (79 oritavancin, 28 SoC)	62% *versus* 61%	51.3±17.2, 57.6±21.3	–	Retrospective cohort study	Single oritavancin dose (1200 mg) after previously failed SoC	SoC after antibiotic therapy failure	Readmission at 30 and 90 days	–	aLOS: 2.12–2.59 days Readmissions rates: 30-day 10.1% *versus* 60.7% 90-day: 12.7% *versus* 60.7%	MRSA: 12.7% *versus* 17.9% MSSA: 13.9% *versus* 14.3%	6
Whittaker, 2020 ([19])	199 patients (99 oritavancin, 100 step-down antibiotics)	63.6% *versus* 58%	47±16, 48±13	–	Retrospective, descriptive cohort study	Single-dose oritavancin (1200 mg)	Conventional oral step-down antibiotic therapy	Average LOS and readmission at 30 days	–	LOS 3.5 *versus* 5.6 days 30-day readmission 7.1% *versus* 18.% 30-day readmission with infection progression 1% *versus* 7%	MRSA: 6.7% *versus* 11.6% MSSA: 26.7% *versus* 30.2%	4

When two values are reported, the first value refers to intervention, and the second value refers to control. [a]The primary outcome of SOLO studies was defined as cessation of spreading or reduction in lesion size, absence of fever, and no need for administration of a rescue antibiotic 48 to 72 hours after administration of oritavancin. [b]In clinical trial pathogens are calculated from the total population enrolled in the oritavancin arm. [c]Clinical success was the defined as the patients not classified as 'clinical failure'. [d]Pooled for both oritavancin and dalbavancin.

ABSSSI, acute bacterial skin and skin structure infections; AEs, adverse events; aLOS, average length of stay; AUC, area under the curve concentration/time; CASP, Critical Appraisal Skill Program; CF, conventional formulation; ED, emergency department; F, female; LOS, length of stay; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-resistant *Staphylococcus aureus*; NA, not available; NF, new formulation; OBS, observation unit; SoC, standard of care; TOC, test of cure; TEAE, treatment-emergent adverse event; VRE, vancomycin-resistant enterococci.

In retrospective studies, MRSA accounted for 6.7–15% of cases and MSSA for 4–26.7%. *Enterococcus* spp. were less frequently reported with a prevalence ranging from 4% to 19.5%.[15–17,19,20]

Off-label studies

Table 2 summarizes the off-label studies included in this review. One of the most common off-label indication for oritavancin was bacteraemia, evaluated in ten studies.[17,25,26,28,30,31,33,34,36] In four studies, bacteraemia was cured in the totality of the cases after oritavancin treatment.[16,17,28,36] Bacteraemia resolution was observed after one dose in two of these studies.[16,17] In a case report, oritavancin treatment was effective in treating VRE bacteraemia in an immunocompromised patient with chronic lymphoblastic leukaemia, with one dose every 48 hours, followed by a weekly treatment.[36] In a series of case studies, oritavancin treatment was effective in the treatment of MRSA, MSSA and enterococcal bacteraemia with 7/10 cases achieving clinical cure after a single dose.[25] MRSA and MSSA were also successfully treated, reaching no recurrence in 1-year follow-up in 74% of patients in another retrospective study.[31] One case study described a recurrent VRE bacteraemia occurring after treatment with daptomycin, tigecycline and linezolid in a patient having a prosthetic cardiac valve. The patient had an initial clearance of bacteraemia after receiving oritavancin but a recurrence was documented 7 weeks after finishing treatment. The valve was excised, and the culture was positive, so the patient completed a second course of oritavancin with a final resolution. Of note, the minimum inhibitory concentration of oritavancin was 0.5 mg/L, namely several fold higher than that for *E. faecium* (0.008 mg/L).[34] Oritavancin was more effective than SoC in treating bacteraemia according to a retrospective study, in which 92.6% reach clinical success (as the remaining 7.4% were classified as clinical failure) compared to 82.6% of patients in SoC group at 30 days.[30] Bacteraemia was successfully treated in 86% of patients in another study, where 10% of patients also had infective endocarditis.[33] The treatment resulted in an earlier discharge for 94% of patients with a mean US$44,938 saved per patient. In another study, one patient was treated with oritavancin for recurrent VRE bacteraemia. Although the treatment resulted in VRE clearance, and thus in a clinical improvement, the patient developed an unrelated pneumonia and subsequently multi-system organ failure, finally dying because of these complications.[26]

Oritavancin was used in the treatment of endocarditis in five studies.[16,25,31,33,34] In one study, endocarditis was successfully treated in all three included cases with multiple doses of laLGPs, resulting in a 100% clinical success rate.[16] One case report described a 38-year-old woman who actively injected drugs and received a single dose of oritavancin for native tricuspid valve infective endocarditis caused by *Streptococcus agalactiae*, following 3 days of vancomycin and 4 days of ceftriaxone; the episode was ultimately considered a clinical failure, as she required valve replacement surgery 3 months later.[25] Another case study reported oritavancin use on a 73-year-old patient with VRE bacteraemia and prosthetic valve endocarditis.[34] Although blood cultures were negative after oritavancin treatment, the case was difficult to assess due to the need of surgery and of other antibiotics over the course of treatment. Endocarditis was reported in 7 (10%) patients within a bacteraemia cohort, and in this cohort, 86% of the patients achieved clinical success.[33] However, the study did not specify the proportion of patients with endocarditis that contributed to this outcome. In another study, which included 7 (7.3%) patients with endocarditis in the population analyzed, showed that 74% of the global population remained free of recurrence at 1-year follow-up, though the outcomes specific to the endocarditis subgroup were not reported.[31]

Osteomyelitis was treated with oritavancin in nine studies.[16,17,26–29,31,32,35] The largest of these (262 patients) focused on the retrospective analysis of acute osteomyelitis treatment with multiple oritavancin doses, comparing treatment with dalbavancin administration.[32] The treatments showed comparable efficacy, reaching clinical cure in 76% of patients with oritavancin and 79% with dalbavancin (p=0.556). AEs were low in both arms but with a higher percentage in the oritavancin group (7% *versus* 2%), though it should be mentioned that AEs recorded in retrospective studies should be interpreted cautiously. The second largest comparative study (150 patients), compared oritavancin (two doses 1 week apart in the majority of cases) to daptomycin (at an average of 6.2 mg/kg and a mean duration of 27.5 days), showing higher rates of clinical cure with oritavancin (73.3% *versus* 33.3%), and AEs were uncommon (2.7% *versus* 5.4%).[29] In another large retrospective study, 118/134 patients achieved clinical cure (88.1%) at the end of treatment timepoint. Post-therapy assessment at 3–6 months after treatment revealed a relapse or persistent infection in 13/134 (9.7%) patients. Overall, clinical success of patients evaluable at both end of treatment and at post-therapy assessment was 80% (104/130).[28] A single dose of laLGPs proved to be effective in reaching clinical success in 11/12 cases of osteomyelitis (93%).[16] Similar results are observed in another study where a single dose of oritavancin led to clinical success in 9/10 patients with osteomyelitis (8 cures, 1 improvement, 90% success).[17] In the same study, oritavancin was also used for joint infection treatment including septic arthritis, synovitis and prosthetic joint infections. Clinical success was observed in 5/7 patients (71.4%).[17] Osteomyelitis was

Table 2. Summary of the off-label included studies.

Author, year (ref.)	Patients	M/F	Age (years)	Study design	Infection	Intervention	Comparison	Follow up	Adverse events	Outcome[a]	Pathogen[b]	CASP score
Bandaranayake, 2024[39]	95 patients	62.1% males	55 male, 57.5 female	Retrospective study	Osteomyelitis, ABSSSI, vertebral infection, bacteraemia, infective endocarditis, other infections	At least one oritavancin dose	–	1 year	13.7% of patients, mostly (85%) during the infusion	74% of patients with no recurrence in 1 year	MRSA: 12.6% MSSA: 27.4% *Streptococcus*: 8.4% *Enterococcus*: 3.1% (1 VRE)	3
Brownell, 2020 [27]	75 patients	57.3% males	50	Single-centre, retrospective case study	ABSSSI, wound infections, osteomyelitis and septic arthritis	1–72 oritavancin doses	–	28 days	12% of patients reported AEs, including back pain, rash, flushing, pruritus, headache, shortness of breath and pancytopenia in one patient that resolved after 1 week	Clinical success: 93.2% Clinical cure: 46.6%	MRSA: 17.8% MSSA: 31.5% *Streptococcus* spp.: 18.1% *Enterococcus* spp.: 12.7% VRE: 5.8%	6
Dahesh, 2019 [35]	1 patient	1 male	59	Case report	Multidrug-resistant *Enterococcus faecium* vertebral osteomyelitis	Oritavancin 1.2 g i.v. weekly for 2 weeks then decreased to 800 mg i.v. weekly for 8 weeks with concomitant ampicillin 12 g/day	–	–	–	Oritavancin and ampicillin were effective in treating deep spine vancomycin-resistant *E. faecium* infection associated with hardware	*E. faecium*	/
Jalali, 2024 [36]	1 patient	1 male	48	Case report	Vancomycin-resistant *E. faecium* (VRE) bacteraemia	Intravenous oritavancin 1200 mg every 48 hours, then once weekly	–	128 days	–	Clearance of blood cultures after oritavancin treatment	VRE	/

(*Continued*)

Table 2. (Continued)

Author, year (ref.)	Patients	M/F	Age (years)	Study design	Infection	Intervention	Comparison	Follow up	Adverse events	Outcome[a]	Pathogen[b]	CASP score
Johnson, 2015 ([34])	1 patient	1 male	73	Case report	VRE bacteraemia and prosthetic valve endocarditis	Oritavancin 1200 mg twice weekly	–	10 weeks	Anorexia and nausea (100% – 1 patient)	Bacteraemia clearance after oritavancin treatment, recurrence after 7 weeks, and final resolution after a second oritavancin treatment	VRE	/
Moenster, 2023 ([30])	96 patients	96.3% males	62 in oritavancin group, 69 in SoC	Retrospective study	Bacteraemia	At least one oritavancin or SoC dose	SoC	30 days	–	Clinical success:[c] 92.6% *versus* 81.2%	MRSA: 22.2% *versus* 24.6% MSSA: 33.3% *versus* 46.4% *Streptococcus* 29.6% *versus* 29.2% *Enterococcus* 3.7% *versus* 8.7%	6
Morrisette, 2019 ([37])	56 patients (14 oritavancin, 40 dalbavancin, 2 treated with both)	59% males, no distinction	46.7±15.4, no distinction	System-wide, retrospective cohort of adult patients	ABSSSI, osteomyelitis, endocarditis, bacteraemia, pneumonia	Single dose of oritavancin or dalbavancin	Previous SoC treatment	6 months	Mild AEs in 11% of patients, including itching, nausea, chest tightness, oedema, headache and one case of acute kidney injury (possibly by other drugs)	Clinical success:[c,d] 92% osteomyelitis 50% endocarditis 100% catheter-related bacteraemia	NA	4

(*Continued*)

Table 2. (Continued)

Author, year (ref.)	Patients	M/F	Age (years)	Study design	Infection	Intervention	Comparison	Follow up	Adverse events	Outcome[a]	Pathogen[b]	CASP score
Redell, 2019 ([38])	440 patients (skin and soft tissue 401, bacteraemia 7, other complicated infections 32)	53.2% males, no distinction	57.8±16.4, no distinction	Multicentre, retrospective, observational study	ABSSSI, bacteraemia, osteomyelitis, septic arthritis, prosthetic joint infection, infected bursa	Single (92.7%) or multiple (7.3%) oritavancin doses	–	30 days	Mild AEs 6.6% *versus* 6.3%, serious AEs 0.2% *versus* 0%, discontinuations 1.2% *versus* 3.1%	Clinical success: Osteomyelitis 88.8% Joint infection 71.4% Bacteraemia 100%	MRSA: 14.5% MSSA: 10% *Streptococci*: 3.4%	7
Schulz, 2019 ([26])	17 patients	23.5% males	21–79	Retrospective cohort evaluation study	Complicated infections (osteomyelitis, surgical site infection, intravascular infections, bacteraemia and pneumonia)	2–18 oritavancin 1200 mg doses	–		24% of patients had AEs that required discontinuation but reversed rapidly	Clinical cure: 100%	MRSA: 11.7% MSSA: 17.6% *Enterococcus*: 11.7% (VRE 5.9%)	2
Steuber, 2024 ([32])	262 patients	–	–	Single-centre, retrospective cohort study	Osteomyelitis (66 *versus* 66) Septic joint/PJI (24 *versus* 19) Diabetic foot infections (2 *versus* 2) Other ABSSSI (31 *versus* 26) Endocarditis (2 *versus* 2) Bloodstream infections (13 *versus* 17)	At least one oritavancin dose	Dalbavancin	90 days	7% with oritavancin *versus* 2% with dalbavancin	Clinical cure: 76% *versus* 79% Clinical cure in osteomyelitis: 81% *versus* 74%	NA	6

(*Continued*)

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Table 2. (Continued)

Author, year (ref.)	Patients	M/F	Age (years)	Study design	Infection	Intervention	Comparison	Follow up	Adverse events	Outcome[a]	Pathogen[b]	CASP score
Stewart, 2017 ([25])	10 patients	50% males	46 (26–66)	Retrospective, observational chart review of adult patients	MSSA and enterococcal bacteraemia, bursitis, endocarditis	Single-dose oritavancin (1200 mg), one patient received 3 doses	Different oritavancin doses	5–20 days	30% of patients (nausea in one patient (10%), hearing loss in one patient (10%) that mildly improved)	Clinical cure: 70%	MRSA: 10% MSSA: 60% *Enterococcus* spp.: 10%	1
Texidor, 2024 ([33])	72 patients	61% male	54±16	Retrospective cohort study	Bacteraemia, 10% with infective endocarditis	At least one oritavancin dose	–	90 days	4% of patients had acute kidney failure and 3% infusion-related reactions	Clinical success:[c] 86% Earlier discharge in 94% of patients	MRSA: 17% *Streptococcus* spp.: 26% *Enterococcus* spp.: 10% VRE: 6%	7
van Hise, 2020 ([28])	134 patients with osteomyelitis, 6.7% with identified bacteraemia	49.3% males	60 (19–97), no distinction	Multicentre, retrospective, descriptive study	Acute osteomyelitis, bacteraemia	Single 1200 mg oritavancin dose and then 800 mg weekly thereafter for 4–5 doses	–	7–10 days after last oritavancin dose (ETE), 3–6 months (PTE)	3.7% of patients, including hypoglycaemia-related symptoms and tachycardia	Clinical cure at ETE: 88% Clinical cure at PTE: 80%	MRSA: 68.6% MSSA: 18.6%, *Enterococcus* spp.: 8.2% VRE: 5.2%	7
Van Hise, 2024 ([29])	150 patients	51% male	64.6±13.4	Retrospective, observational study	Osteomyelitis, 28% of which with chronic kidney disease	At least one oritavancin dose	Daptomycin	90 days	2.7% with oritavancin *versus* 5.4% with daptomycin	Clinical cure 73.3% *versus* 33.3%	MRSA: 32.0% *versus* 28.0% MSSA: 42.6% *versus* 37.3% VRE: 2.6% *versus* 12%	6

When two values are reported, the first value refers to intervention, and the second value refers to control. [a]Clinical cure was generally defined as resolution of signs and symptoms and no further treatment, whilst clinical success was defined as the sum of patients assessed as 'cure' and 'improvement'. [b]Pathogen reported refers to baseline pathogen in the overall population. [c]Clinical success was the defined as the patients not classified as 'clinical failure'. [d]Pooled for both oritavancin and dalbavancin.

ABSSSI, acute bacterial skin and skin structure infections; AE, adverse events; CASP, Critical Appraisal Skill Program; ETE, end of treatment; F, female; M, male; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available; PJI, periprosthetic joint infection; PTE, post therapy assessment; SoC, standard of care; VRE, vancomycin-resistant enterococci.

successfully treated with multiple doses of oritavancin in another study, reaching clinical improvement (1/4) or success (3/4).[26] Oritavancin was successful in treating osteomyelitis in 74% of patients also in another retrospective study.[31] In one study the clinical success was considered in light of readmission rates. Oritavancin osteomyelitis treatment resulted in only 10% readmission at 28 days follow-up with a mean 1 day LOS reduction and a US$4707.6 average reduction of hospitalization costs per patient.[27] In a case study, oritavancin was used to treat VRE hardware-associated vertebral osteomyelitis in a 59-year-old man with a previous history of diabetes mellitus and vancomycin-treated bacteraemia.[35] Oritavancin was used in combination with ampicillin and was effective in decreasing the size of the lumbosacral fluid collection and clearance of VRE. After 60 days of treatment, the aspiration showed a methicillin-resistant *Staphylococcus epidermidis* infection, and the treatment was then switched to daptomycin and ceftaroline. During treatment, the patient developed complications related to his comorbidities, such as bradycardia, heart failure and acute kidney injury, and opted to stop all antibiotic treatments, resulting in his death 1 day later, unrelated to oritavancin treatment.

Regarding pathogen analysis, in off-label retrospective studies, MRSA prevalence was generally higher. One study of acute osteomyelitis and bacteraemia reported MRSA in 68.6% of cases,[28] whilst others reported ranges from 10% to 32%.[17,25–27,29–31,33] MSSA prevalence ranged from 10% to 42.6%. Notably, cases of VRE were also observed, reaching up to 5% of reported infections.[26–29,33] Unfortunately, not all studies associated the pathogen with a specific off-label indication, so an analysis of pathogen per indication was not possible.

Discussion

In this systematic review, we evaluated the clinical effectiveness and safety of oritavancin, both for the on-label indication of treating ABSSSI and for the off-label indications in the management of various complicated infections, including bacteraemia, osteomyelitis and endocarditis.

The on-label use of oritavancin for ABSSSI treatment demonstrated consistent clinical effectiveness across multiple studies. Most of these studies compared oritavancin to SoC treatments or vancomycin with a particular focus on single-dose regimens. In three randomized clinical trials, single-dose oritavancin treatment was demonstrated to be non-inferior to multiple doses of vancomycin in terms of clinical cure and safety.[22–24] These comparisons revealed that oritavancin was as effective as conventional treatments whilst offering the advantage of both requiring fewer injections and reducing the LOS.[15,16,18–20] Additionally, oritavancin treatment was associated with lower hospitalization costs, further highlighting its cost-effectiveness.[15,16,20] The use of oritavancin in ABSSSI treatment also resulted in reduced readmission rates with two studies reporting significantly lower readmission rates for oritavancin-treated patients compared to those receiving SoC treatments.[19,20] One study investigated the safety profile of a novel, more concentrated oritavancin formulation with reduced infusion time compared to the conventional one, reporting a lower rate of infusion-related AEs than the conventional formulation.[9] Taken together, these findings indicate that oritavancin is an effective and efficient treatment option for patients with ABSSSI as per on-label indications.

Off-label use of oritavancin primarily focused on bacteraemia, endocarditis and osteomyelitis treatment. Most off-label studies focused on a retrospective analysis of oritavancin treatment without a comparison with other SoC treatments, apart from four studies.[16,29,30,32] In the case of bacteraemia, several studies reported favourable outcomes following oritavancin treatment, achieving improvement just after a single dose.[16,17] However, it should not be overlooked that, in one case of complicated prosthetic valve endocarditis, a 7-week rescue course of oritavancin following prolonged daptomycin and tigecycline treatment failed in eradicating VRE bacteraemia.[34] However, oritavancin appeared to be effective in most cases of bacteremia.[16,17,25,28,30,31,33,36]

Osteomyelitis treatment with oritavancin showed promising results, with various studies reporting high clinical cure and clinical success rates.[16,17,26,28,29,31,32] Both single-dose and multiple-dose regimens were reported to be effective in treating osteomyelitis, and oritavancin also showed promising results in joint infections such as septic arthritis and prosthetic joint infections.[17]

Endocarditis treatment with oritavancin was effective in some cases, leading to clinical success or clinical cure.[31,33,34] However, the outcomes in endocarditis treatment were more variable, with some cases requiring additional interventions or surgeries.[25,34] Unfortunately, one of the major key limitations in most of these studies with off-label prolonged oritavancin therapy is that both the number of redosing and the time for redosing were chosen arbitrarily. Studies included in this review employed heterogeneous regimens, including single 1200 mg doses as well as repeated doses of 800 mg or 1200 mg administered every 7, 10 or 14 days. This is due to no pharmacokinetics/pharmacodynamics target for 1–2 $\log_{10}$ bacterial burden decrease being currently established in preclinical animal models of MRSA and/or VRE infections. Consequently, there is currently no possibility

of identifying a specific threshold of minimum plasma oritavancin concentration to appropriately guide redosing strategies of off-label indications such as osteomyelitis, endocarditis or bacteraemia.

Overall, the off-label use of oritavancin demonstrated potential in the management of complicated infections. These findings suggest that oritavancin may have a broader range of applications beyond its on-label use, providing clinicians with a valuable alternative for certain difficult-to-treat infections. Moreover, the new, more concentrated formulation simplifies the administration and has been related to a lower incidence of AEs, representing a potential valuable candidate for off-label indications.[9] Notably, this review seeks to inform healthcare professionals and researchers about the current state of knowledge surrounding oritavancin, paving the way for informed decision-making and the pursuit of further research.

Conclusions

This systematic review highlights the clinical effectiveness of oritavancin in both on-label and off-label indications with favourable outcomes observed across a range of complicated infections. Overall, the included studies showed that oritavancin-treated patients (2311 in on-label and 692 in off-label studies) showed good clinical results and limited AEs. Oritavancin demonstrates consistent effectiveness in ABSSSI and may be an alternative for selected deep-seated Gram-positive infections in off-label indications requiring prolonged therapy. Clinical evidence outside ABSSSI, even if promising, remains limited, and standardized dosing strategies are needed to guide treatment for osteomyelitis, bacteraemia and endocarditis. The prolonged half-life and single-dose schedule of oritavancin may reduce healthcare utilization where clinically appropriate.

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