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Oritavancin: a novel glycolipopeptide active against Gram-positive pathogens including multiresistant strains

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ABSTRACT

Oritavancin is a glycolipopeptide antibiotic under investigation for the treatment of serious infections caused by Gram-positive bacteria. Oritavancin has demonstrated rapid dose-dependent bactericidal activity towards vancomycin-susceptible and -resistant enterococci, meticillin-susceptible and -resistant *Staphylococcus aureus*, vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA (hVISA), vancomycin-resistant *S. aureus* (VRSA) and small-colony variants of *S. aureus*. It is also active against *Clostridium difficile*. Upon intravenous administration, oritavancin displays a three-compartment pharmacokinetic model, dose proportionality, a distribution volume of ca. 110 L, a terminal elimination half-life in excess of 2 weeks and it is not metabolised. Its pharmacodynamic properties make it an ideal antibiotic for a once-daily or even single-dose regimen. Oritavancin is currently under review by the US Food and Drug Administration. So far, oritavancin has demonstrated efficacy in two pivotal Phase III trials conducted in patients with complicated skin and skin-structure infections in which oritavancin was compared with vancomycin plus cefalexin. In both trials, the primary endpoint (clinical cure in clinically evaluable patients at first follow-up with a 10% non-inferiority margin) was met, with the advantages of shorter duration of therapy and fewer adverse events. Further results indicating its activity against bacteria growing in biofilms as well as stationary-phase bacteria open the way for its use to treat prosthetic device infections, which is to be investigated in upcoming trials.

1. Introduction

The glycopeptide antibiotic oritavancin is currently under investigation for the treatment of serious Gram-positive bacterial infections. The compound was developed by Eli Lilly (Indianapolis, IL) in the 1990s to replace vancomycin, but its introduction into the market has been severely delayed, mainly because of ownership changes.

2. Chemistry and mechanism of action

Oritavancin is a second-generation semisynthetic lipoglycopeptide [1,2] that inhibits the biosynthesis of bacterial cell wall peptidoglycan by binding to either D-Ala-D-Ala- or D-Ala-D-Lac-containing residues in peptidoglycan precursors [3]. The drug also disrupts the membrane of Gram-positive bacteria [1,4]. This dual action mode, which distinguishes the molecule from vancomycin and other single-mechanism therapeutic agents, results in enhanced antimicrobial activity against Gram-positive organisms and also renders the antibiotic active against strains resistant to first-generation glycopeptides, such as vancomycin-resistant enterococci (VRE), vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA) and isolates that are not susceptible to daptomycin and linezolid [1,5,6]. In killing experiments, oritavancin shows very rapid and highly concentration-dependent bactericidal activity (3 log reduction in bacterial counts after 1–8 h) in conditions where vancomycin requires at least 8–24 h to reach the same effect [7–9].

In addition to conferring activity against drug-resistant microorganisms, the multiple mechanisms of action may also reduce the probability that oritavancin resistance will develop during clinical use.

3. Antimicrobial activity

Oritavancin shows potent activity against staphylococci, enterococci and streptococci, regardless of their resistance to antibiotics of the same class, and is even active against strains with a multiresistant phenotype [9–17]. Table 1 shows the interpretive criteria for minimum inhibitory concentration (MIC) susceptibility tests proposed by the US Food and Drug Administration (FDA); the manufacturer's proposed criteria are indicated in bold [18]. The in vitro activity of oritavancin against common Gram-positive pathogens is shown in Table 2.

Oritavancin also acts against intracellular small-colony variants of *S. aureus*, incriminated in some persistent infections (e.g. osteomyelitis) [16]. In addition to effects on Gram-positive aerobes, oritavancin has proved active against *Clostridium perfringens*, *Clostridium difficile*, *Peptostreptococcus* spp. and *Propionibacterium acnes* [17].

Oritavancin has also revealed a concentration-dependent post-antibiotic effect lasting some 2 h for 1× MIC and 4–8 h for 4× MIC against meticillin-resistant *S. aureus* (MRSA) and VRE, respectively [19]. Synergy with other antibiotics has not been extensively studied. In association with gentamicin, linezolid, moxifloxacin and rifampicin, oritavancin acts synergistically against meticillin-susceptible *S. aureus* (MSSA), VISA and VRSA [20]. A synergistic effect against vancomycin-resistant

Enterococcus faecalis is produced when oritavancin is added to gentamicin [21]. Combinations with ampicillin, quinupristin/dalfopristin and gentamicin are synergistic against vancomycin-resistant *Enterococcus faecium* [22].

Oritavancin activity is diminished by large inocula [19] but not by an acid pH or the growth phase of the bacteria [23]; it effectively kills bacteria in stationary phase or in biofilms [24].

Oritavancin, like aminoglycosides and to some extent quinolones, is therefore a highly concentration-dependent bactericidal antibiotic with prolonged intense effects [25].

4. Mechanism of resistance

Resistance to oritavancin, although feasible in laboratory conditions, has not yet been described among clinical isolates. At least two potential pathways exist for the development of resistance to oritavancin, namely via current glycopeptide resistance mechanisms (e.g. *van* operons) or the VISA-type cell wall thickening mechanism. Oritavancin MIC_{90} values (MICs for 90% of organisms) and MIC distributions for staphylococcal and enterococcal surveillance isolates suggest a lack of cross-resistance with VanA, VanB or VanC phenotypes or with VISA phenotype staphylococci. Cross-resistance with oritavancin has not been observed for other antimicrobials, including vancomycin.

However, a single-step mechanism of moderate-level resistance to oritavancin (MIC ≤ 16 μg/mL) has been described in enterococcal isolates with the VanA or VanB

phenotype [21,26]. It is not known whether or not stable mutant selection will occur in oritavancin-treated VRE [27].

5. Pharmacokinetics

Oritavancin is administered intravenously to achieve systemic exposure effective for complicated skin and soft-tissue infections (cSSTIs); its oral bioavailability is low. Like other glycopeptides, it is poorly absorbed across an intact gastrointestinal tract owing to its high molecular weight (1989 Da).

Pharmacokinetic parameters of oritavancin in Phase II and Phase III studies are summarised in Table 3. Oritavancin displays a three-compartment linear pharmacokinetic model and dose proportionality [28,29]. No substantial increase in maximum concentration (C_{max}) (ca. 30% increase) has been observed after 10 days of dosing, although some 2.8-fold increase in minimum concentration (C_{min}) occurs, likely reflecting the wide tissue distribution and accumulation of oritavancin [18,30].

Unlike vancomycin, oritavancin is 86–90% bound to human plasma proteins [31].

In animal studies, oritavancin is extensively distributed in the liver, skin, kidneys, spleen and lungs, with ca. 60%, 20%, 3%, 2% and 2–10% of the administered dose detected at each site, respectively [3,28,32,33]. Oritavancin penetrates bone [34] and cardiac vegetations [21,35–37]. Entry into the cerebrospinal fluid amounts to 1–5% of the unbound plasma drug concentration [38].

Two recent studies presented as meeting posters have assessed oritavancin levels attained in the lungs [3, 39]. In the first study, the pharmacokinetics/pharmacodynamics of oritavancin against *Streptococcus pneumoniae* in plasma and epithelial lining fluid (ELF) was addressed in a mouse pneumonia model. Analysis of the correlation between log reduction in bactericidal titre and area under the concentration–time curve (AUC)/MIC ratio indicated a 2 log reduction in bacterial burden when the AUC/MIC ratio in ELF (site of interest) was ≥4790. The possibility of achieving this concentration in humans seems to be feasible with oritavancin at a dose of 800 mg every 24 h for 5 days [3]. In the second study, projected oritavancin efficacy in lung infections due to *S. aureus* was assessed using a population pharmacokinetic model based on plasma and ELF pharmacokinetics determined in 20 human subjects who received oritavancin at the same dose [800 mg intravenous (i.v.) every 24 h for 5 days] [39]. Pharmacokinetic parameter estimates were used to simulate plasma and ELF AUCs after short and standard courses of oritavancin therapy. The simulations indicated a need for front-loaded regimens to achieve adequate ELF AUCs within 3 days. Given oritavancin MIC values for *S. aureus* ($MIC_{50/90}$ = 0.03/0.12 μg/mL) and ELF AUCs (site of interest) for oritavancin at 800 mg i.v. every 24 h × 5 days, levels effective against *S. aureus* were not reliably achievable. According to the study researchers, use of these doses of oritavancin for *S. aureus*, although effective against pneumococci, warrants further analysis. A mild to moderate reduction in the potency of oritavancin by surfactant has been reported although the effect is much lower than that with daptomycin [40].

In vitro studies in macrophages have revealed up to a 300-fold intracellular accumulation of oritavancin [41,42]. It enters cultured macrophages by adsorptive

endocytosis and concentrates in the lysosomes from where its efflux is slow. Thus, oritavancin shows intraphagocytic activity against organisms such as *S. aureus* capable of surviving within lysosomes.

Mean population-predicted half-lives in Phase II and Phase III patients are similar to those in healthy subjects with predicted α, β and γ half-lives of ca. 2, 31 and 393 h, respectively. The property of intracellular accumulation (together with its high protein binding capacity) may contribute to the prolonged half-life of the drug.

There is no evidence that oritavancin is metabolised [32]. At up to 2 weeks after administration, ≤5% of the dose of oritavancin is recovered in urine and ≤1% in faeces.

In general, oritavancin dose adjustments are not needed for patients with mild, moderate or severe kidney disease [43], with mild to moderate liver impairment [44] or for other intrinsic factors (age, gender or race) [45], and dose adjustment should not be required in patients on haemodialysis [46].

6. Pharmacokinetics/pharmacodynamics

6.1. Pharmacokinetic/pharmacodynamic (PK/PD) profile

Through dose-fractionation mouse thigh infection models, it is possible to determine the PK/PD index best correlated with efficacy and the size of this index needed for a given level of effect. Unlike glycopeptides such as vancomycin, whose bactericidal activity in vitro is time-dependent, the in vitro activity of oritavancin is concentration-

dependent [47,48]. This means that in animal models of infection, $AUC_{0–24}$:MIC or C_{max}:MIC ratios should be predictive of the efficacy of oritavancin.

Using a neutropenic mouse thigh model of *S. aureus* infection, Boylan et al. [49] assessed the pharmacokinetics and pharmacodynamics of oritavancin at doses of 0.5–20 mg/kg body weight. The study suggested that a dose of 1.5 mg/kg/day in man would provide plasma concentrations sufficient for effective treatment of SSTI. It also showed that a higher, less frequent dose of oritavancin would be more active than the same total dose when divided, supporting the hypothesis that the C_{max}:MIC ratio would be more predictive of oritavancin efficacy in the clinic. This study has recently been confirmed [48].

In an FDA analysis of non-clinical data, an unbound $AUC_{0–24}$ target of ca. 7 μg h/mL was reported for bacterial stasis [18,50]. The MIC of oritavancin for *S. aureus* in that study was 0.06 μg/mL, giving a target figure of ca. 117. The MIC_{90} of oritavancin against *S. aureus* determined in over 5000 clinical isolates was 0.12 μg/mL. Since the mean unbound $AUC_{0–24}$ determined in Phase II and III trials was 17.4 μg h/mL, this gives a mean $AUC_{0–24}/MIC_{90}$ for oritavancin-treated patients of 145 (17.4/0.12), indicating that the proposed dosing regimen exceeds the non-clinical PK/PD target predicted for efficacy in most patients. However, estimated probabilities were not adjusted for expected or observed treatment duration and may be considered conservative. The difference between this model and the general complicated skin and skin-structure infection (cSSSI) disease process in humans is that the immune response to pyogenic infection is largely blunted or absent in the model.

These data suggest that oritavancin dosing strategies should aim for high C_{max} concentrations rather than long periods of unbound concentrations in plasma exceeding the MIC.

6.2. Pharmacokinetics/pharmacodynamics for dose selection

The main pharmacokinetic model used to assess the efficacy of oritavancin for treating cSSSIs is the skin blister fluid model. Using such a model, two dosing regimens for the treatment of cSSSIs were tested in 16 healthy male subjects [29]. Each subject (eight per dose group) received 200 mg of oritavancin once daily for 3 days or a single 800 mg dose. Mean drug concentrations in blister fluid exceeded the oritavancin MIC_{90} for *S. aureus* strains (2 μg/mL) by ca. 2–5.5-fold and 1.5–3-fold at 12 h and 24 h, respectively, after both dosing regimens [29].

A Phase II clinical trial of the safety and efficacy of oritavancin at single or infrequent doses for the treatment of cSSSIs (SIMPLIFI study) has recently been completed [51]. In this randomised, double-blind, active comparator study, clinical efficacy as test of cure was measured at first follow-up on Day 21. Also examined as one of the secondary endpoints was the safety of oritavancin in each patient. In the study, 302 patients were randomised to one of three treatment arms in which they received either 200 mg of oritavancin i.v. daily for a minimum of 3 days up to a maximum of 7 days (‘daily dose’), or a single dose of 1200 mg of oritavancin i.v. (‘single dose’), or a single dose of 800 mg of oritavancin i.v. with an optional second dose of 400 mg i.v. given on Day 5 at the investigator’s discretion (‘infrequent dose’). The primary efficacy endpoint was clinically and statistically comparable across all three treatment groups, including patients with infections due to MRSA: clinically evaluable, daily

dose 72%, single dose 81.5% [absolute difference 9.5%, 90% confidence interval (CI) –2.5 to 18.2] and infrequent dose 77.5% (absolute difference 5.5%, 90% CI –6.8 to 15.4); for MRSA these values were daily dose 78.3%, single dose 73.0% (absolute difference -5.3%, 90% CI –25.1 to 12.9) and infrequent dose 87.0% (absolute difference 8.7%, 90% CI –6.9 to 15.4). Secondary efficacy endpoints were also comparable across the three treatment arms. No differences were detected in the incidence or severity of adverse events in the treatment population. Rates of infusion-related adverse events were low in all groups and were comparable with those seen in the two Phase III clinical trials of oritavancin in cSSSIs. However, these data, compiled from a meeting presentation and information on the manufacturer's website (http://media.integratir.com/targ/PressReleases/SIMPLIFI_final102208.pdf), have not been published and have therefore not been subjected to peer-review.

As already mentioned, in a recent pharmacokinetic study based on data from human volunteers given oritavancin 800 mg daily for 5 days, levels associated with efficacy against *S. aureus* were not reliably achieved in ELF [39]. Hence, oritavancin may not be sufficiently effective for the treatment of *S. aureus* pneumonia.

7. In vivo animal studies

The use of oritavancin in several disease states has been evaluated in numerous animal models, including a rat model of catheter-related infection [52], two different rabbit models of meningitis [38,53], a rat model of MSSA and three rabbit models of MRSA and VRE endocarditis [21,35–37]. In all these models, oritavancin eradicated infection when used alone or in combination with other agents. In the rabbit model of endocarditis induced by a glycopeptide-susceptible strain of *E. faecalis* and two

glycopeptide-resistant transconjugants, oritavancin plus gentamicin was the only bactericidal regimen that was efficient against all three strains [21].

In the mouse *S. aureus* bacteraemia model, oritavancin showed a dose–response relationship with efficacy at all human equivalent (HEQ) dose regimens (100, 400 or 800 mg daily for 72 h or a single 1200 mg dose). The daily HEQ dose of 100 mg was sufficient to protect 100% of mice at 72 h post infection. The single HEQ dose of 1200 mg oritavancin was able to reduce *S. aureus* to undetectable levels in the blood and to reduce significantly the bacterial burden in the spleen. This efficacy correlates well with data from studies conducted in other bloodstream infection models [35,36,52] and supports further development of oritavancin's use to treat bacteraemia.

In a hamster model of *C. difficile* infection, oritavancin was better than vancomycin at prolonging survival and preventing disease relapse [54]. When formulated in polyethylene glycol 400, oritavancin kept vegetative and spore cell numbers under the detection limit for ≥20 days and no animal died after a 5-day treatment course. In a previous in vitro model of the human gut, oritavancin instillation markedly and rapidly reduced vegetative numbers and spores of *C. difficile* as well as its cytotoxin titres [55]. Toxin recrudescence was not observed following cessation of oritavancin, in contrast to observations when vancomycin was used in this model. The conclusion to be drawn is that oritavancin therapy may be more effective in treating *C. difficile*-associated diarrhoea than vancomycin as it may prevent recrudescence of *C. difficile* spores. These results warrant further development of the drug for use as a therapeutic agent for *C. difficile* infection in humans.

8. Clinical trials in humans

Oritavancin has been tested in 19 clinical trials and has demonstrated clinical effectiveness in two pivotal Phase III trials conducted in patients with cSSSIs due to Gram-positive pathogens. However, neither of these trials has been published. The first trial (ARRD) was a 517-patient, randomised, double-blind, parallel-group trial in which 3 days of i.v. oritavancin (1.5 mg/kg/day and 3.0 mg/kg/day) was compared with i.v. vancomycin 10–15 mg/kg twice daily for 3–7 days followed by oral cefalexin 500–1000 mg twice daily to complete up to 14 days of therapy [56]. In the first follow-up visit (Day 28 $\pm$ 7), respective success rates were 76%, 76% and 80% in 384 clinically and 256 bacteriologically evaluable patients. For patients with MRSA infections these figures were 61.5% (8/13), 76.9% (10/13) and 72.7% (8/11), respectively.

The second trial (ARRI) of similar design enrolled 1267 patients with cSSSIs who were randomised to either i.v. oritavancin 200 mg/day for 3–7 days followed by oral placebo or to i.v. vancomycin 15 mg/kg twice daily for 3–7 days followed by oral cefalexin 1000 mg twice daily [57]. Clinical cure rates were 79% and 76% for the oritavancin and vancomycin/cefalexin groups, respectively, and in bacteriologically evaluable patients (n = 686) bacteriological eradication rates were 75% and 73% for oritavancin and vancomycin/cefalexin, respectively. For the microbiologically evaluable population, MRSA eradication rates in the oritavancin group compared to the vancomycin/cephalexin group were as follows: 61.4% (54/88) vs. 65.8% (25/38), respectively.

In both trials, the primary endpoint (clinical cure in clinically evaluable patients at first follow-up with a 10% non-inferiority margin) was reached, with the advantage of a shorter duration of therapy in both the low and higher dose oritavancin treatment arms (first trial 5.3 days and 5.7 days, respectively, versus 11.9 days for vancomycin/cefalexin, $P < 0.0001$; second trial 5.3 days vs. 10.9 days, $P < 0.0001$).

When the results of the two Phase III trials were combined, oritavancin demonstrated efficacy and a good safety profile in all types of patients and especially in immunocompromised patients, including patients with diabetes [58,59].

At the time of writing, the use of oritavancin to treat Gram-positive bacteraemia has been assessed in two studies. The first study, which was an open-labelled, non-controlled, Phase II trial (H4Q-MCARRC), examined the safety and efficacy of 7–10 days of oritavancin given as one of three possible dosing regimens (loading dose/daily maintenance dose): 3/2 mg/kg (n = 5); 4/3 mg/kg (n = 5); or 5/4 mg/kg (n = 17) [60]. Given the limited data obtained in the 3/2 mg/kg and 4/3 mg/kg dose groups, 10 qualified patients in the 5/4 mg/kg dose group were selected for further analysis. Oritavancin was generally well tolerated. In nine of these ten patients, the primary endpoint (bacteriologic eradication) was achieved 5 days after the end of therapy.

The second study (H4Q-MCARRM) was a Phase II, open-labelled, randomised, non-inferiority trial comparing 10–14 days of oritavancin given as doses of 5, 6.5, 8 or 10 mg/kg i.v. daily with the use of a comparator for the treatment of *S. aureus* bacteraemia [61]. The comparator was vancomycin 15 mg/kg i.v. every 12 h for

MRSA or a β-lactam agent for MSSA. The working hypothesis was that the safety of different dose levels of oritavancin is at least equivalent to that of vancomycin. The primary endpoint was bacteriological cure and clinical improvement at 5–12 days post therapy. In 84 evaluable patients, oritavancin was non-inferior to the comparator at all the doses tested. Success rates for patients given oritavancin at 5, 6.5, 8 and 10 mg/kg were 83%, 71%, 67% and 80%, respectively, whilst the comparator success rate was 70%. Bacterial eradication was recorded in 83%, 86%, 79% and 85% of the oritavancin-treated patients versus 78% in the comparator arm. Lastly, clinical cure was achieved in 83%, 71%, 71% and 80% of patients in the oritavancin groups versus 74% in the comparator group. Safety results were comparable across all treatment groups. Adverse effects were not increased by raising dose levels of oritavancin.

9. Drug administration

Oritavancin is administered intravenously. In clinical trials, oritavancin has been used at doses of 1.5–3 mg/kg. Phase III trials have examined the use of a daily dose of 3 mg/kg or 200 mg for a treatment duration of 3–7 days [56,57].

The recommended dose of oritavancin for the treatment of cSSSIs is a once-daily 200 mg dose for patients with a body weight less than or equal to 110 kg, and a dose of 300 mg for patients over 110 kg [62].

Dosing regimens for short-course therapy established in a population pharmacokinetic model [63] were used to support dose selection for the Phase II SIMPLIFI study. In this study, clinical efficacy was similar for the standard 200 mg i.v.

daily dose for 3–7 days (the Phase III regimen) compared with the single 800 mg dose and with an infrequent dose (800 mg on Day 1/optional 400 mg on Day 5) [51].

In a recent neutropenic murine thigh infection model, a single 1200 mg dose was much more effective than all other dosing regimens at reducing colony counts at 72 h [64]. These data support further evaluation of the single 1200 mg dose.

10. Adverse events

Published Phase II and III trials have reported similar [56] or lower [57,65] adverse event rates for oritavancin compared with vancomycin/cefalexin. In the two trials, the most common adverse events both for oritavancin and vancomycin/cefalexin were injection-site reactions, nausea and vomiting, and pruritus. However, patients treated with oritavancin showed significantly lower rates of adverse events leading to treatment discontinuation and fewer events potentially related to histamine-like infusion reactions [66]. Other adverse events related to glycopeptides (infusion-site pain, infusion-site phlebitis, phlebitis, infusion-site thrombosis, infusion-site erythema) were similar for the two treatments. In a more recent study in healthy individuals receiving oritavancin, adverse events were mild to moderate, although transient discrete elevations in aspartate aminotransferase and alanine aminotransferase concentrations were noted [32]. Injury to the liver is always a concern with any hepatically cleared drug [67]. However, the results of this study indicate oritavancin is unlikely to cause permanent hepatic damage.

The long half-life of oritavancin could be a problem when dealing with serious effects of allergic reactions since these could be prolonged until levels of oritavancin decrease sufficiently.

Oritavancin shows no nephrotoxicity, ototoxicity or QTc alterations [68]. The intracellular accumulation of oritavancin has raised concerns regarding its possible toxicity. In several tissues, including liver and alveolar macrophages, cell lipid lysosome structures of unclear significance have been described [69]. As more patients are exposed to oritavancin, further monitoring will be necessary to determine the full range of possible adverse effects.

11. Regulatory status

Under the ownership of InterMune, Inc. (Brisbane, CA), two Phase III clinical trials were successfully completed, but in 2005 the rights of the compound were acquired by Targanta Therapeutics, Inc. (St Laurent, QC, Canada). A novel application of the drug to treat cSSSIs was rejected by the FDA in November 2008. Other potential indications for this new antibiotic include bacteraemia and osteomyelitis. In its reply to Targanta's application, the FDA stated that oritavancin had not proved its safety and effectiveness for the treatment of cSSSIs at the dose proposed, particularly in patients with MRSA. Specifically, the FDA requested that a sufficient number of patients with MRSA as the cause of cSSSIs be enrolled in a new well-controlled clinical trial to demonstrate the effectiveness of oritavancin in this subset of patients.

In January 2009, Targanta was acquired by The Medicines Company (Parsippany, NJ), which plans to conduct further trials on patients with MRSA. These new trials are expected to take at least 2 years.

12. Summary

Management of severe Gram-positive infections, especially those caused by *S. aureus*, still poses several clinical challenges [70]. Infections caused by multidrug-resistant organisms are growing at an alarming rate [71,72]. In this context, oritavancin shows promise as a new addition to the current armamentarium of drugs against Gram-positive bacteria: its rapid bactericidal action could prove extremely valuable for the treatment of critically ill and neutropenic patients; its pharmacodynamic properties make it an ideal antibiotic for a once-daily or even a single-dose regimen; and clinical trials conducted so far have confirmed its safety. Moreover, oritavancin offers certain advantages over other drugs: it is effective against *S. aureus*, *E. faecalis* and *E. faecium*, irrespective of their resistance patterns, and unlike dalbavancin it covers VRE; and it can be used in haematologic–oncologic patients with thrombocytopenia.

Other interesting features of oritavancin include its activity against *C. difficile* and against biofilms and stationary-phase cells, along with its proven efficiency in animal models of endocarditis, bacteraemia, catheter-related infection, meningitis and pneumonia.

The hurdles that oritavancin faces relate to the paucity of clinical data available. Clinical efficacy data for the use of oritavancin in infections against which

vancomycin or standard-of-care antibiotics show reduced or null efficacy are also lacking. Finally, the extraordinary long half-life and prolonged tissue retention of the drug are likely to delay further the widespread introduction of oritavancin until longer-term safety and resistance surveillance data become available.

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Competing interests

EB was a member of the advisory board of Targanta Therapeutics, Inc.

Ethical approval

Not required.

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