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REVIEW ARTICLE

Lipoglycopeptide Antibacterial Agents in Gram-Positive Infections: A Comparative Review

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Abstract Oritavancin, telavancin, and dalbavancin are recently marketed lipoglycopeptides that exhibit remarkable differences to conventional molecules. While dalbavancin inhibits the late stages of peptidoglycan synthesis by mainly impairing transglycosylase activity, oritavancin and telavancin anchor in the bacterial membrane by the lipophilic side chain linked to their disaccharidic moiety, disrupting membrane integrity and causing bacteriolysis. Oritavancin keeps activity against vancomycin-resistant enterococcocci, being a stronger inhibitor of transpeptidase than of transglycosylase activity. These molecules have potent activity against Gram-positive organisms, most notably staphylococci (including methicillin-resistant *Staphylococcus aureus* and to some extent vancomycin-intermediate *S. aureus*), streptococci (including multidrug-resistant pneumococci), and *Clostridia*. All agents are indicated for the treatment of acute bacterial skin and skin structure infections, and telavancin, for hospital-acquired and ventilator-associated bacterial pneumonia. While telavancin is administered daily at 10 mg/kg, the remarkably long half-lives of oritavancin and dalbavancin allow for infrequent dosing (single dose of 1200 mg for oritavancin and 1000 mg at day 1 followed by 500 mg at day 8 for dalbavancin), which could be exploited in the future for outpatient therapy. Among possible safety issues evidenced during clinical development were an increased risk of developing osteomyelitis with oritavancin; taste disturbance, nephrotoxicity, and risk of corrected QT interval prolongation (especially in the presence of at-risk co-medications) with telavancin; and elevation of hepatic enzymes with dalbavancin. Interference with coagulation tests has been reported with oritavancin and telavancin. These drugs proved non-inferior to conventional treatments in clinical trials but their advantages may be better evidenced upon future evaluation in more severe infections.

Key Points

New lipoglycopeptides (telavancin, oritavancin, dalbavancin) differ from vancomycin by the presence of a lipophilic side chain, which profoundly modifies their pharmacokinetic and/or pharmacodynamic profile.

Among these agents, telavancin and oritavancin have multiple modes of action and are highly bactericidal.

Oritavancin and dalbavancin have prolonged half-lives, allowing for their use a single-dose or two-dose (once-a-week) regimen, respectively.

These three drugs are indicated for the treatment of acute bacterial skin and skin structure infections, and telavancin is indicated for hospital-acquired and ventilator-associated bacterial pneumonia.

1 Introduction

Glycopeptide antibacterials (vancomycin, teicoplanin) were introduced on the market as early as the 1950s and 1980s, respectively. Over the last 6 years, three new drugs have been registered and commercialized (see

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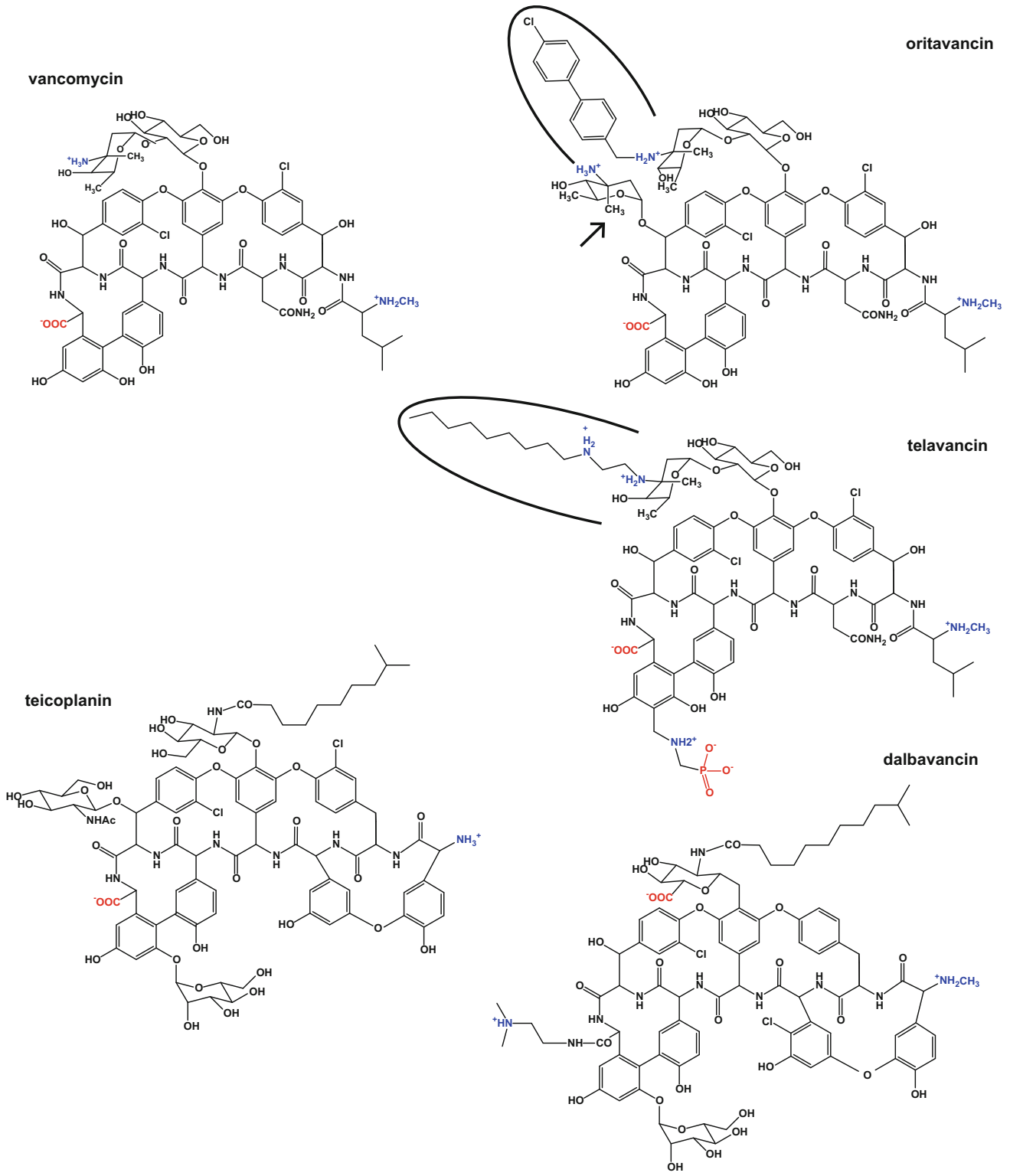

Fig. 1 Chemical structure of new glycopeptides as compared to conventional molecules. Substituents that are positively charged at physiological pH are *highlighted in blue* and those that are negatively charged are *highlighted in red*. The α-carbon atom of each residue is *numbered* in vancomycin. Lipophilic side chains conferring bactericidal character to oritavancin and telavancin are marked by *black arcs*. The additional sugar allowing for cooperative binding in oritavancin is pointed to by a *black arrow*

Fig. 1 for their chemical structures) and are referred to as lipoglycopeptides because they possess an additional lipophilic side chain compared with vancomycin. Among them, telavancin and oritavancin are very innovative, as they show an additional mode of action and a rapidly bactericidal character due to the presence of this lipophilic side chain attached to the disaccharide moiety. On the other hand, dalbavancin, the lipophilic side chain of which is located on the same position as that found in teicoplanin, shows an improved pharmacokinetic profile but the same mode of action as teicoplanin. This review compares the microbiological and pharmacological properties, clinical use, and potential usefulness of these three molecules with those of vancomycin. A PubMed search was performed using the keywords oritavancin (or LY333328), telavancin (or TD-6424), dalbavancin (or BI397). All papers published over the last 5 years were examined. Older papers were also considered if dealing with discovery, pharmacokinetics, pharmacodynamics, mode of action, clinical trials, or toxicity.

2 Discovery and History

2.1 Oritavancin

Oritavancin is a semi-synthetic derivative of the naturally occurring lipoglycopeptide chloroeremomycin. Chloroeremomycin differs from vancomycin by the presence of an additional aminated sugar (4-*epi*-vancosamine) on the amino acid 6 of the cyclic heptapeptide and the replacement of the 4-vancosamine by a 4-*epi*-vancosamine in the disaccharide attached to the aglycone moiety [1]. In oritavancin, the addition of a chlorobiphenylmethyl side chain to this disaccharide is responsible for the amphipathic character of the molecule.

Oritavancin was discovered at Eli Lilly [1] as LY333328 (see Allen [2] for a full history of this molecule). It was selected as a candidate for clinical development in 1994 based on its excellent activity in vitro and in vivo as well as on a favorable pharmacokinetic profile. After Eli Lilly decided to terminate its activities in the field of anti-infective drugs, oritavancin was transferred to InterMune (San Francisco, CA, USA) in 2002, where additional phase I trials were conducted. InterMune also decided to re-focus its activities and sold the molecule to Targanta Therapeutics (Montreal, QC, Canada) in 2006. Many additional in vitro investigations were performed at that time that better documented the mechanism of action of the drug as well as its activity in specific models of infection. Data from additional phase I and II trials suggest that infrequent dosing could be used and effective [3, 4].

In 2008, Targanta submitted new drug applications to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), with a dosing scheme of 1.5–3 mg/kg/day for 3–7 days [5]. These applications were not accepted because of insufficient clinical evidence of efficacy and safety. The Medicines Company (Parsippany, NJ, USA) acquired oritavancin in 2009, completed additional pharmacological investigations, and ran phase III trials with an innovative therapeutic scheme that eventually led to the registration of the drug for the treatment of complicated skin and skin structure infections by both the American and European Agencies in 2014 [6, 7].

2.2 Telavancin

Telavancin is a semi-synthetic derivative of vancomycin, in which a hydrophobic (decylaminoethyl) side chain is added to the disaccharide. A phosphonomethylaminomethyl substituent on the cyclic peptidic core counterbalances to some extent the hydrophobicity brought by this lipophilic side chain. The molecule was named TD-6424 by Theravance [now Theravance BioPharma (San Francisco, CA, USA)] [8]. Remarkably, this small company was able to conduct the preclinical and clinical development of the molecule internally in a streamlined fashion (through strategic collaborations with pharmaceutical companies including Astellas Pharma Inc.) and obtained marketing authorization by the FDA in 2009 for the treatment of complicated skin and skin structure infections and by the EMA in 2011 for the treatment of hospital-acquired pneumonia (see Wenzler and Rodvold [9] for a recent review on the discovery and history of the development of this compound). Telavancin was the first marketed product for this company. In situations where other alternatives are not suitable, the accepted indications in the USA now include both complicated skin and skin structure infections and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus* [10], and in Europe include nosocomial pneumonia, including ventilator-associated pneumonia that is known or suspected to be caused by methicillin-resistant *S. aureus* (MRSA) [11].

2.3 Dalbavancin

Dalbavancin (BI397) is a semi-synthetic derivative from the natural glycopeptide A40926. A40926 differs from teicoplanin by the absence of the acetylglucosamine in the benzylic position, the replacement of the acylglucosamine in position 4 by an acylaminoglucuronic acid, the length of the fatty acid chain, the position of one chlorine atom, and the terminal methylamino group [12]. In dalbavancin, the peptide carboxy group of A40926 has been replaced by a

3,3-dimethylaminopropylamide [13]. Dalbavancin was discovered by Biosearch and out-licensed for North America to Versicor. Both companies then merged to create Vicuron Pharmaceuticals (King of Prussia, PA, USA) and continued to develop the product. Vicuron was acquired by Pfizer in 2005, which pursued the development of dalbavancin to the point where the FDA requested additional clinical data before approval. In 2009, the drug was then acquired by Durata Therapeutics (Chicago, IL, USA), which initiated new phase III trials. The drug was approved by the FDA in 2014 and by the EMA in 2015 for the treatment of complicated skin and skin structure infections [14, 15]. Durata Therapeutics was acquired by Actavis (Parsippany, NJ, USA) in 2014, which commercializes dalbavancin today (see Butler et al. [16] for a review of this history).

3 Activity

3.1 Mechanism of Action and of Resistance for Conventional Glycopeptides

Conventional glycopeptides inhibit the late stages of peptidoglycan synthesis (Fig. 2). Via their aglycone moiety, they establish five hydrogen bounds with the D-Ala-D-Ala termini of pentapeptidic precursors, which by steric hindrance prevents the transglycosylation reaction leading to the extension of the glycan backbone of peptidoglycan as well as the transpeptidation reaction leading to the cross-linking of pentapeptide bridges [17, 18]. This mode of action confers a slowly bactericidal character to vancomycin, which is limited to fast-growing organisms [19]. Resistance to vancomycin has emerged over the years and is mediated by two distinct mechanisms. In *S. aureus*, a thickening of the cell wall confers a so-called VISA (vancomycin-intermediate *S. aureus*) phenotype, with the minimum inhibitory concentration (MIC) typically ranging between 3 and 8 mg/L. This phenotype was first described in 1997 [20]. The underlying mechanism is not yet fully elucidated but it has been associated with mutations in the RNA polymerase gene *rpoB* and in genes that are directly or indirectly involved in the biosynthesis/metabolism of the cell wall, including two-component sensory regulatory systems (for a recent review, see Gardete and Tomasz [21]). In enterococci, high-level resistance is mediated by the occurrence of an alternative pathway for cell wall synthesis. It results from the acquisition of transposon-encoding genes that allow for (a) the hydrolysis of precursors ending in D-Ala-D-Ala and (b) the synthesis of cell wall precursors ending in D-Ala-D-Lac or D-Ala-D-Ser and showing reduced affinity for glycopeptides (see Courvalin [22] for a review). Very few cases of *S. aureus* that have acquired this type of transposon and harbor high-level resistance to vancomycin [vancomycin-resistant *S. aureus* (VRSA)] have been described but they do not seem to spread so far [23].

3.2 Mechanism of Action of Lipoglycopeptides

Because all lipoglycopeptides keep the aglycone moiety of conventional molecules in their structure, they also conserve this primary mode of action. Yet their specific chemical features confer to them additional antibacterial properties. An early work [24] suggested that the interaction between glycopeptides and the D-Ala-D-Ala motif can be enhanced by two mechanisms, namely (a) the formation of homodimers between glycopeptide molecules, which confers a structural rigidity that locks the binding pocket into the correct conformation and may allow for a cooperative binding to the ligand, and (b) the anchoring of the antibacterial in the membrane, which may help to maintain the drug close to its target (see Van Bambeke et al. [25] for a review).

Dimer formation has been shown to occur with oritavancin [1, 26] via the additional 4-*epi*-vancosamine sugar, putting the molecule in a back-to-back orientation and allowing cooperative binding to the ligand. Dalbavancin also strongly dimerizes in solution, and even in the absence of a ligand [27, 28], but via lipophilic side chains. However, in this case, both dimer formation and interaction with cell wall precursors are non-cooperative (the molecule adopting a 'closed' conformation upon ligand binding) and do not contribute to improve the antibacterial activity.

Membrane anchoring has been documented for both oritavancin and telavancin via their lipophilic side chain linked to the disaccharide moiety [29, 30]. Both molecules also cause aberrant septum formation and loss of staining of nascent septal cross walls in electron microscopy, which may result from their effect on cell wall synthesis and/or activation of autolysins [31]. Yet oritavancin shows the unique property of keeping activity against vancomycin-resistant enterococci (VRE) and staphylococci [32].

For telavancin, a specific, high-affinity interaction with lipid II has been demonstrated, leading to membrane depolarization, bacterial lysis, and rapid bactericidal effect [30, 33]. Microarray analyses revealed that after 15 min of exposure to the drug a strong expression of the cell wall stress stimulon (characteristic response to inhibition of cell wall biosynthesis), which was accompanied after 60 min of exposure by an induction of various genes, was also affected by other membrane-depolarizing drugs [34]. These data support a dual mode of action and may explain the bimodal shape of concentration–effect relationships in kill-curve experiments [35].

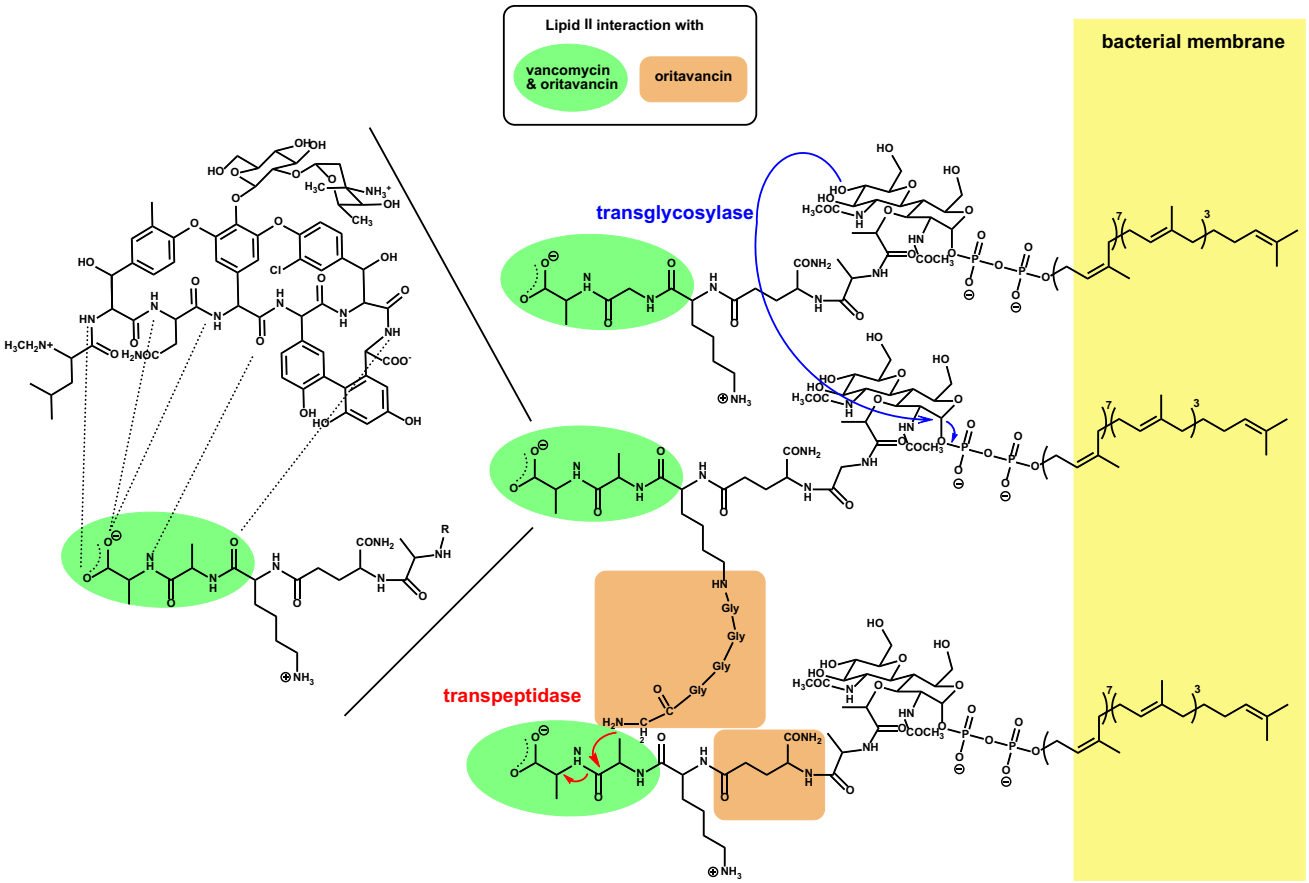

Fig. 2 Illustration of the late stages of peptidoglycan synthesis [transglycosylation (*in blue*) and transpeptidation (*in red*) reactions] and of the way vancomycin and oritavancin interact with the lipid II precursor in order to inhibit these reactions. Vancomycin and new lipoglycopeptides establish 5 hydrogen bounds with the D-Alanyl-D-Alanine extremity of the pentapeptidic terminus of lipid II (*zone highlighted in green*) [17], which leads, by steric hindrance, to an inhibition of the glycan chain extension and, to a lesser extent, of crosslinking between peptidic stems. Oritavancin has additional interactions with the pentaglycyl bridge and the D-iso-glutamine residue in position 2 of the pentapeptide terminus of lipid II (*zone highlighted in orange*) [37], which allow it to be a stronger inhibitor of transpeptidases [38]

Oritavancin also disrupts membrane integrity and causes membrane depolarization both in bacterial cells and liposomes reconstituted from lipids of *S. aureus* [29, 36]. These effects are also related to the capacity of oritavancin to specifically bind to lipid II, with additional interaction sites compared with its precursor chloreremomycin, which can explain its improved activity on vancomycin-resistant strains [37]. Solid-state nuclear magnetic resonance (NMR) studies have indeed shown that oritavancin possesses two binding sites on the lipid-linked disaccharide–pentapeptide monomers in *S. aureus* (D-Ala-D-Ala termini, like vancomycin, but also the pentaglycyl bridging segment via its lipophilic side chain on the dissacharide and components of its aglycon structure). This allows it to inhibit not only transglycosylase activity, and thus precursor chain extension, but also transpeptidase activity, and thus precursor cross-linking [38]. In *Enterococcus faecium*, inhibition of transpeptidase becomes even more prominent due to the preferential interaction of oritavancin with multiple sites on the peptidic bridge [39]. In this case, interaction with D-Ala-D-ala termini becomes marginal, explaining why transglycosylase activity is no longer the primary target of the drug. More importantly, this also rationalizes why oritavancin still exerts activity on vancomycin-resistant strains.

3.3 Spectrum of Activity

Because of their high molecular weight, lipoglycopeptides, like glycopeptides, cannot cross bacterial membranes and the cell wall, meaning that their spectrum of activity is limited to Gram-positive bacteria in which their target is directly accessible. A large number of studies have examined the in vitro activity of these compounds against

collections of Gram-positive clinical isolates, yet many of these studies were performed using broth that was not supplemented by polysorbate-80, which is needed to prevent the adsorption of the drugs to the plastic [40–42]. Table 1 therefore focuses on recent studies that have used the standard procedure currently recommended by the Clinical Laboratory Standards Institute (CLSI), i.e., 0.002 % polysorbate-80 added to the culture medium [43]. Against vancomycin-susceptible staphylococci, streptococci, or enterococci, the three drugs show quite similar MIC distributions and are more potent than vancomycin. Yet a clear-cut correlation between the MICs of vancomycin and of the lipoglycopeptides has been demonstrated, and thus vancomycin MIC can be used as a surrogate for susceptibility to lipoglycopeptides [44–46]. Oritavancin is slightly more potent than the other compounds on enterococci. It is also the only one to keep useful activity against VRE harboring the *vanA* genotype or against VRSA [47]. Teicoplanin, dalbavancin, and telavancin remain active on *vanB*-type resistant strains because they are not inducers for this specific resistance genotype [48, 49]. The MICs are 2–4 dilutions higher against VISA than against MRSA for the three drugs [47, 50, 51].

Like vancomycin, lipoglycopeptides are active on *Clostridia*, including *C. difficile*, with MICs measured in the absence of polysorbate ranging from 0.125 to 2 mg/L for oritavancin [52] (1 dilution lower with polysorbate-80 [53]), 0.25 to 0.5 mg/L for telavancin [54], and 0.125 to 0.5 mg/L for dalbavancin [55]. In addition, oritavancin proved effective against *C. difficile* infection after 4 days of treatment in an in vitro model of human gut [56] and does not induce spore germination or toxin production both in vitro and in vivo [57, 58].

Resistance to lipoglycopeptides has not yet been described in clinics; it is less likely to occur for drugs showing multiple modes of action. In laboratory mutants, a moderate level of resistance to oritavancin in enterococci has been ascribed to the complete elimination of precursors ending in D-Ala-D-Ala during cell wall synthesis, or to the expression of the accessory gene *vanZ*, which also confers resistance to teicoplanin by an unknown mechanism [59]. Mutations in the sensor $VanS_B$ of *Enterococcus faecalis* can also induce low-level resistance to both teicoplanin and oritavancin, which are not inducers of the wild-type $VanS_B$ sensor. Transcriptomic studies of a telavancin-resistant mutant in *S. aureus* revealed multiple changes in gene expression, including upregulation of genes involved in cell wall or fatty acid biosynthesis as well as stress response, and downregulation of genes included in lysine biosynthesis, synthesis of surface proteins, modulin or proteases, and anaerobic metabolism as well as global regulators such as *agr* [60]. These changes are accompanied by a thickening of the cell wall and a decrease in the activity of autolysins, which is reminiscent of what is observed in VISA strains.

3.4 In Vitro Models of Persistent Infections

Staphylococci, which constitute the primary therapeutic target for these drugs, may adopt specific lifestyles associated with the persistent or recurrent character of infection, namely growth within biofilm [61] and intracellular survival [62]. The activity of lipoglycopeptides on these specific types of infections has thus been investigated in appropriate models.

Against static biofilms grown on plastic pegs and made of methicillin-sensitive *S. aureus* (MSSA), MRSA or VISA, oritavancin was effective at minimal biofilm eradication concentrations (MBECs) ranging between 0.5 and 8 mg/L, which are only 1 dilution higher than the MICs [63]. Telavancin activity has been investigated in a wide range of biofilm models, including in vitro static and dynamic models with MSSA, MRSA, VISA, or even enterococci [64–66] as well as animal models (see Chan et al. [67] for an indepth review on this specific topic). Globally speaking, telavancin proves as, or often more, effective than vancomycin thanks to its bactericidal character.

Against intracellular bacteria infecting THP-1 cells (native monocytes or differentiated in macrophages), oritavancin appears to be the most effective of all the antibacterials tested in this model, reaching a true intracellular bactericidal effect (-3 $\log_{10}$ decrease in bacterial counts), as demonstrated against intracellular MSSA [68, 69], MRSA, VISA (including strains collected from a patient with bacteremia) [70], or even small colony variants [71–73]. It also proved synergistic with other bactericidal antibacterials such as fluoroquinolones or rifampicin against small colony variants [74]. This remarkable intracellular activity was attributed to the capacity of oritavancin to accumulate within the lysosomes of cells to exceptionally high levels by a process of adsorptive endocytosis [75]. Telavancin was also more effective than vancomycin in THP-1 cells infected by MSSA, MRSA, or VISA, reaching a bactericidal effect after 3 h; however, its activity was much slower against VRSA, with a bactericidal effect being reached only after 24 h of incubation with concentrations higher than ten times the MIC [35].

Nevertheless, the high accumulation of oritavancin inside eukaryotic cells raises the question of a potential toxicity. In vitro studies have indeed demonstrated the deposition of undigested lipidic material within lysosomes of cells exposed to the drug continuously for 1–3 days [76], but only in conditions generating intracellular concentrations well above those measured in macrophages from patients treated with the drug [77]. Moreover, this effect was reversible upon drug removal [76]. When the exposure

Table 1 Minimum inhibitory concentration distributions of new lipoglycopeptides versus vancomycin against clinically relevant pathogens[a]

Bacterial species	Phenotype	Number of strains	New glycopeptides				Vancomycin			References
			Antibacterial	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	
MSSA (methicillin-susceptible *Staphylococcus aureus*)	All	3245	TLV	≤0.015 to 0.12	0.03	0.06				[40]
	All	1460	ORI	≤0.004 to 0.25	0.03	0.06	≤0.12 to 2	0.5	1	[50]
	All	2958	ORI	≤0.008 to 0.25	0.03	0.06	≤0.12 to 2	1	1	[173]
	All	514	DAL	≤0.03 to 0.25	0.06	0.06	≤0.12 to 2	1	1	[174]
MRSA (methicillin-resistant *S. aureus*)	All	3019	TLV	≤0.015 to 0.25	0.03	0.06	0.25 to 4	1	1	[40]
	All	427	ORI	≤0.004 to 0.25	0.03	0.06	0.5 to 2	1	1	[50]
	All	3376	ORI	≤0.008 to 0.25	0.03	0.06	0.25 to 2	1	1	[173]
	All	522	DAL	≤0.03 to 0.12	0.06	0.06	0.5 to 2	1	1	[174]
	All	61,195	DAL	≤0.008 to 0.25	0.06	0.06	≤0.12 to 4	1	1	[175]
	VAN MIC ≥2	115	TLV	≤0.015 to 0.12	0.06	0.06				[40]
	VAN MIC ≥2	124	ORI	0.015 to 0.25	0.06	0.06				[173]
Staphylococcus epidermidis	All	221	ORI	0.008 to 0.5	0.06	0.12	≤0.12 to 2	1	2	[50]
Coagulase-negative staphylococci (CONS)	All	461	TLV	≤0.015 to 0.12	0.06	0.06	0.5 to 4	1	2	[40]
	All	115	DAL	≤0.03 to 0.25	≤0.03	0.06	0.25 to 2	1	2	[174]
Enterococcus faecalis	All	304	ORI	≤0.004 to 0.5	0.03	0.06	0.25 to 4	1	2	[50]
	VAN-S	325	TLV	≤0.015 to 0.25	0.12	0.12	0.5 to 4	1	1	[40]
	VAN-S	1320	ORI	≤0.008 to 0.25	0.015	0.03	0.25 to 4	1	2	[173]
	VanA	45	ORI	0.03-1	0.25	0.5	>16	>16	>16	[173]
	VanB	19	ORI	≤0.008 to 0.06	0.015	0.03	8 to >16	>16	>16	[173]
Enterococcus faecium	VAN-S	81	TLV	≤0.015 to 0.12	0.03	0.06	0.25 to 4	1	1	[40]
	VAN-S	87	ORI	≤0.004 to 0.03	0.008	0.015	0.25 to 2	0.5	1	[50]
	VAN-S	177	ORI	≤0.008 to 0.03	≤0.008	≤0.008	0.25 to 4	1	1	[173]
	VanA	241	TLV	≤0.015 to >2	1	2	>16	>16	>16	[40]
	VanA	22	ORI	≤0.004 to 0.5	0.008	0.12	32 to >32	>32	>32	[50]
	VanA	600	ORI	≤0.008 to 0.5	0.03	0.12	>16	>16	>16	[173]
	VanB	16	ORI	≤0.008 to 0.03	≤0.008	≤0.008	8 to >16	>16	>16	[173]

Table 1 continued

Bacterial species	Phenotype	Number of strains	New glycopeptides				Vancomycin			References
			Antibacterial	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	
Enterococcus spp.	VAN-S	30	DAL	≤0.03 to 0.12	≤0.03	0.06	0.5 to 2	1	1	[174]
	VanA	24	DAL	0.24 to >4	4	4	>16	>16	>16	[174]
	VanB	2	DAL	≤0.03	≤0.03		>16	>16		[174]
Streptococcus pneumoniae	All	1801	TLV	≤0.015 to 0.06	≤0.015	≤0.015	≤0.12 to 2	1	1	[40]
	Peni-S	216	ORI	≤0.008 to 0.12	≤0.008	0.03				[173]
	Peni-R	86	ORI	≤0.008 to 0.25	0.015	0.06				[173]
Viridans group streptococci (VGS)	All	446	TLV	≤0.015 to 0.06	≤0.015	≤0.015	≤0.12 to 1	0.5	1	[40]
	All	40	DAL	≤0.03 to 0.12	≤0.03	0.06	0.25 to 1	0.5	1	[174]
	Peni-S	216	ORI	≤0.008 to 0.12	≤0.008	0.03				[173]
	Peni-R	86	ORI	≤0.008 to 0.25	0.015	0.06				[173]
Streptococcus pyogenes	All	449	TLV	≤0.015 to 0.12	≤0.015	0.03				[40]
	All	132	ORI	≤0.0005 to 0.5	0.03	0.25	0.25 to 1	0.5	0.5	[50]
	All	155	DAL	≤0.03 to 0.12	≤0.03	≤0.03	0.25 to 0.5	0.25	0.5	[174]
Streptococcus agalactiae	All	393	TLV	≤0.015 to 0.12	0.03	0.06				[40]
	All	153	DAL	≤0.03 to 0.25	≤0.03	0.12	0.25 to 1	0.5	0.5	[174]

DAL dalbavancin, *MIC* minimum inhibitory concentration, MIC_{50} MIC at which 50 % of bacteria are inhibited, MIC_{90} MIC at which 90 % of bacteria are inhibited, *ORI* oritavancin, *Peni-R* penicillin-resistant, *Peni-S* penicillin susceptible, *TLV* telavancin, *VAN* vancomycin, *VanA* VanA phenotype of vancomycin resistance, *VanB* VanB phenotype of vancomycin resistance, *VAN-S* vancomycin susceptible

[a] Limited to studies published from 2012 and July 2015, where lipoglycopeptides where tested in the presence of 0.002 % polysorbate-80 and compared to VAN

of cells was limited to drug amounts for which cellular concentrations were of the same order of magnitude as those measured in patients, no specific sign of intoxication of macrophages was evidenced, including with respect to phagocytic or killing capacities or oxidant species production [77, 78]. Telavancin also caused cellular lipidosis, but to a much lower extent than oritavancin, related to its lower cellular accumulation [79].

4 Pharmacokinetics and Pharmacodynamics

4.1 In Vitro Pharmacodynamics

Oritavancin shows bactericidal activity which is rapid (1 h) against *Streptococcus pyogenes*, MRSA, and VRSA, slower (10–20 h) against daptomycin-resistant *S. aureus,* and VRE and vancomycin-susceptible enterococci (VSE), or even slower (24 h) against VISA in in vitro models of continuous exposure to the drug [80–82]. It was also rapidly (1 h) bactericidal against *Streptococcus pneumoniae* in an in vitro pharmacodynamic model [83]. Moreover, it remains bactericidal against high inocula of vancomycin-susceptible *S. aureus* as well as against hetero-VISA (h-VISA), but not against VISA at a concentration mimicking the free maximum concentration (C_{max}) reached in the serum of patients after a single dose of 1200 mg [84, 85].

Telavancin also proved more rapidly bactericidal against MSSA, MRSA, and h-VISA than against VISA, VRSA, or coagulase-negative *S. aureus* [35, 86]. It remains bactericidal against h-VISA at high inoculum but after a longer

incubation time (16 h) [87]. In an in vitro pharmacodynamic model mimicking human exposure to 10 mg/kg, telavancin was bactericidal after 8 h against h-VISA, linezolid-resistant *S. aureus*, and daptomycin-resistant *S. aureus*, but was bactericidal after 24 h against VISA [88]. In contrast, telavancin is bacteriostatic on *C. difficile* [54].

In sharp contrast, dalbavancin is slowly bactericidal against *S. aureus* and *S. pyogenes*, a 24-h incubation being needed to observe bacterial eradication [89].

Synergy has been demonstrated in vitro between oritavancin and aminoglycosides, β-lactams, linezolid, or rifampin against MRSA or enterococci [90–93] as well as between telavancin and β-lactams, aminoglycosides, or rifampin against MRSA [94, 95], or dalbavancin and oxacillin against MRSA [96].

4.2 Animal Pharmacodynamic Models

Ambrose and coworkers have reviewed the activity of oritavancin in animal models [97]. Oritavancin is as or more effective than comparators (vancomycin, daptomycin) for the treatment of MRSA or *Enterococcus* endocarditis, while at the same time better in preventing relapses [98, 99]. It is also very effective for the treatment of MRSA pneumonia or bacteremia. It is more active than vancomycin against *C. difficile* infection by the oral route in the hamster model and prevents spore germination [57, 58]. A high single dose reduced bacterial burden in a catheter infection by VanA enterococci [100] as well as in pneumonia or in meningitis caused by pneumococci [101, 102]. A single dose is also protective against anthrax in a murine model of spore inhalation [103].

Telavancin activity in animals has also been recently reviewed [104]. In brief, its efficacy and superiority compared with vancomycin or daptomycin has been documented in murine models of bacteremia or pneumonia by MRSA [105, 106], in murine subcutaneous infection models, in rabbit endocarditis caused by MRSA, VISA, or daptomycin non-susceptible staphylococci [107–109], as well as in rabbit meningitis caused by penicillin-resistant pneumococcus [110, 111]. It was equivalent to vancomycin or linezolid in a model of rabbit osteomyelitis caused by MRSA [112].

With respect to dalbavancin, it showed activity in a rat granuloma pouch infection model by MSSA and MRSA [113], in neutropenic murine thigh and lung infection models by *S. aureus* or *S. pneumoniae* [114], in rabbit endocarditis caused by *S. aureus*, including strains with reduced susceptibility to glycopeptides [115], in foreign body infection by MRSA in guinea pigs [116], and in an anthrax inhalation model [117].

4.3 Pharmacokinetics/Pharmacodynamics for Dosing Optimization

In neutropenic mice thigh infection models aimed at determining pharmacokinetic/pharmacodynamic (PK/PD) parameters predictive of efficacy, free area under the concentration–time curve (AUC)/MIC is the best predictor of efficacy for the three drugs, together with the C_{max}/MIC ratio for oritavancin, based on its highly bactericidal character [104, 114, 118, 119].

For oritavancin, its concentration-dependent bactericidal activity combined with its prolonged half-life (see Sects. 4.1 and 4.4) has led to the selection of a 1200 mg single-dose treatment [97], which allows maximization of the C_{max}/MIC and AUC/MIC ratio while at the same time facilitating drug administration. In population pharmacokinetic studies of patients treated with this dose, the C_{max} reaches 138 mg/L (20.7 mg/L for free fraction) and the AUC reaches 1110 mg·h/L (165 for free fraction) after 24 h and 2510 mg·h/L after 576 h [120]. If considering the PK/PD breakpoint of 0.125 mg/L established by both European Committee on Antimicrobial Susceptibility Testing (EUCAST) and FDA for *S. aureus* (Table 2), the fC_{max}/MIC and $fAUC_{24}$/MIC are as high as 165 and 1352 h, respectively, after administration of 1200 mg to humans. Simulating this dose in an in vitro pharmacodynamic model of infection by MRSA generated considerable bactericidal effect [121].

For telavancin, an AUC_{24}/MIC ratio of 219 h has been proposed as the PK/PD target associated with a 1 $\log_{10}$ CFU (colony-forming units) decrease in models of infection by MRSA in neutropenic mice. This value could be achieved in patients with normal renal function receiving a daily dose of 10 mg/kg for MICs $\leq$2 mg/L [122]. It was nevertheless challenged based on inconsistencies in the reported MIC values for the MRSA strain used for this study [123]. Accordingly, a lower susceptibility breakpoint of 1 mg/L had first been selected by the FDA, allowing a target AUC/MIC of 438 to be reached. Yet this breakpoint has recently been revised by both the FDA and the EUCAST to a value of 0.125 mg/L based on the new procedure established by CLSI for determining the MIC in the presence of polysorbate-80 (see Table 2).

For dalbavancin, Monte-Carlo simulations combining pharmacokinetic and MIC data from phase III trials suggest a PK/PD breakpoint of 1 mg/L for staphylococci, allowing a $fAUC_{14days}$/MIC >1000 h to be reached [114, 124], but, again, these were based on MICs determined in the absence of polysorbate-80. The current susceptibility breakpoint is therefore much lower (0.12 mg/L; see Table 2).

Table 2 Current susceptibility breakpoints for new lipoglycopeptides as compared with vancomycin

Antibacterial	Bacterial species	US FDA		EUCAST	
		S≤	*R*≥	*S*≤	*R*>
Vancomycin	Coagulase-negative staphylococci (CONS)	4	32	4	4
	Streptococci (other than *pneumoniae*)	1	NA	2	2
	Enterococci	4	32	4	4
	Other staphylococcal or streptococcal species	2	16	2	2
Oritavancin	Staphylococci	0.12	NA	0.125	0.125
	Streptococci	0.25	NA	0.25	0.25
	Enterococcus faecalis	0.12	NA	0.125	0.125
Telavancin	Staphylococci	0.12	NA	0.125	0.125
	Streptococci	0.12	NA		
	E. faecalis	0.25	NA		
Dalbavancin	Staphylococci	0.12	NA	0.125	0.125
	Streptococci	0.12	NA		

EUCAST European Committee on Antimicrobial Susceptibility Testing, *FDA* Food and Drug Administration, *NA* not applicable (no resistant isolate described so far), *R* resistant, *S* susceptible

4.4 Human Pharmacokinetics and Dosing

The pharmacokinetic profile of the three drugs after administration of registered doses to humans is illustrated in Table 3. As compared with vancomycin, the main characteristic of these drugs is their long half-life, which is related to their high protein binding but also to their capacity to accumulate within eukaryotic cells. The half-life is particularly prolonged (longer than 200 h) for oritavancin and dalbavancin, justifying their administration schedules (single or two doses, respectively). Remarkably, oritavancin shows a distribution volume of 87 L and reaches concentrations in alveolar macrophages as high as 142-fold its serum concentration. Dalbavancin reaches concentrations of 6.3 and 4.1 μg/g in articular tissues 12 h and 4 weeks, respectively, after the administration of 1000 mg. Subsequent administrations of 500 mg per week for 7 weeks did not cause drug accumulation and was well-tolerated, warranting investigation into interest in the use of this drug for the treatment of osteomyelitis [125].

While oritavancin does not require any dose adaptation in cases of impaired renal function, both telavancin and dalbavancin do need an adjustment. In patients with hepatic insufficiency, no dose adjustment is recommended for oritavancin [6, 120] or telavancin [10, 126] for Child-Pugh grades A–B, or for dalbavancin for Child-Pugh grade A [6, 10, 14]. Caution should be exercised in case of more severe dysfunction, as no specific data are available. These drugs cannot be administered to pregnant (class C) or breast-feeding women, or to children. However, a recent phase I, open-label study conducted with dalbavancin on children from 12 to 17 years old concluded that similar plasma exposures were obtained after administration of 1000 mg or 15 mg/kg, with acceptable tolerance [127]. AUC exposures were, however, 30 % lower than in adults who received the same dose, which is consistent with enhanced renal and/or hepatic elimination in healthy adolescents. Other open-label studies focusing on the pharmacokinetics and safety of oritavancin (NCT02134301 [128]) and telavancin (NCT02013141 [129]) in patients younger than 18 or 17 years, respectively, are ongoing.

5 Clinical Efficacy

5.1 Registered Indications

Table 4 shows the main clinical trials that led to the registration of lipoglycopeptides for the treatment of acute bacterial skin and skin structure infections and for hospital-acquired pneumonia (telavancin only). The reader is referred to recent reviews that have examined these studies in details (oritavancin [32, 130], telavancin [131, 132], and dalbavancin [133, 134]).

Globally speaking, and focusing on acute bacterial skin and skin structure infections (a common indication for the three drugs), phase II and III trials concluded that the investigated drug was non-inferior to conventional therapy [vancomycin IV, anti-staphylococcal penicillin, linezolid (with possible oral switch)]. The safety profile was also globally comparable to that of the comparators. A post hoc analysis was recently published for telavancin, in which data from the ATLAS [Assessment of Telavancin in cSSSI (complicated skin and skin structure infection)] trials were reanalyzed taking into consideration the recent guidance from the FDA concerning studies evaluating antibacterials

Table 3 Pharmacokinetics and dosing of new lipoglycopeptides

Parameter	Antibacterial		
	Oritavancin	Telavancin[a]	Dalbavancin[b]
Dosing			
Creatinine clearance >50 mL/min	1200 mg single dose; 3 h infusion [6]	10 mg/kg q24h [10]	1000 mg day 1 + 500 mg day 7 [14]
Creatinine clearance 30–50 mL/min	1200 mg single dose; 3 h infusion [6]	7.5 mg/kg q24h [10]	1000 mg day 1 + 500 mg day 7 [14]
Creatinine clearance 10–<30 mL/min	1200 mg single dose; 3 h infusion [6]	10 mg/kg q48h [10]	750 mg day 1 + 375 mg day 7 [14]
C_{max} (mg/L)	138 [6]	94/108 [10]	287 [14]
AUC_{24} (mg·h/L)	1110 [6]	666/780 [10]	3185 [14]
AUC_{∞} (mg·h/L)	2800 [6]	747/NA [10]	23,443 [14]
Protein binding (%)	85 [6]	90 [10]	93 [14]
$t_{½\alpha}$ (h)	2.29 [6]	8/8.1 [10]	NA
$t_{½\beta}$ (h)	13.4 [6]		NA
$t_{½\gamma}$ (h)	245 [6]		346 [14]
Clearance (L/h)	0.445 [6]	0.97/0.90 [10]	0.015 [14]
V_{ss} (L)	87.6 [6]	10.15/9.31 [10]	7.93 [176]
Macrophages/plasma	142.7[c] [177]	6.67 (24 h) [178]	NA
ELF/serum	4.6[c] [177]	0.7 [179]	NA

AUC_{∞} area under the concentration–time curve from time zero to infinity, *AUC_{24}* area under the concentration–time curve from time zero to 24 h, *C_{max}* maximum concentration, *ELF* epithelial lining fluid, *NA* not available, *qxh* every *x* h, *$t_{½\alpha}$* initial or disposition half-life, *$t_{½\beta}$* terminal elimination half-life in a 2-compartment model, *$t_{½\gamma}$* terminal elimination half-life in a 3-compartment model, *V_{ss}* apparent volume of distribution at steady state

[a] Pharmacokinetic data given for single dose/multiple dose of 10 mg/kg

[b] Pharmacokinetic data for a single dose of 1000 mg

[c] For an 800 mg dose

for acute bacterial skin and skin structure infections that was issued after the performance of these trials (namely, inclusion of patients with lesion size ≥75 cm^2 and exclusion of patients with ulcers or burns) [135]. The adoption of an updated test-of-cure clinical response (≥90 % reduction in lesion size, no increase in lesion size since day 3, and no requirement for additional antibacterialcs/significant surgical procedures) concluded that there was equivalence between telavancin- and vancomycin-treated patients (68.0 vs. 63.3 % cure rates).

Phase II studies determined the optimal dosing regimen as being a single dose of 1200 mg for oritavancin (SIMPLIFI trial [3]), a 1000 mg dose at day 1 followed by a 500 mg dose at day 7 for dalbavancin [136], and a 10 mg/kg daily dose for telavancin (FAST 2 trial [137]). Thus, a possible advantage of oritavancin and dalbavancin resides in their simplified therapeutic scheme, which may even allow their use for home therapy [138, 139].

Telavancin is also indicated for HABP and VABP caused by susceptible isolates of *S. aureus* (including methicillin-susceptible and -resistant isolates), based on the ATTAIN (Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia) phase III trials, which showed non-inferiority to vancomycin for this indication [140]. A secondary objective of the ATTAIN trials was to perform a pooled analysis of the two studies with respect to telavancin superiority compared with vancomycin in patients with pneumonia attributable to MRSA [140]. The clinical response between the two groups was similar, but cure rates were higher in the telavancin group when considering patients with mono-microbial infection due to *S. aureus* (both MRSA and MSSA; 84.2 vs. 74.3 % success rate for telavancin and vancomycin, respectively) or patients infected with strains showing a vancomycin MIC >1 mg/L (87.2 vs. 74.3 % success rate for telavancin and vancomycin, respectively). In contrast, lower cure rates were observed in the telavancin-treated group for patients with mixed infections (66.2 vs. 79.4 % success rate for telavancin and vancomycin, respectively); the difference disappeared if patients who received adequate Gram-negative coverage were considered (66.3 vs. 66.7 % success rate for telavancin and vancomycin, respectively) [141]. Of note, the clinical success of telavancin was also lower than that of vancomycin in the subgroup of patients with severe renal impairment (creatinine clearance <30 mL/min) or pre-existing acute renal failure, including

Table 4 Main clinical trials involving new lipoglycopeptides for their current indications

Phase	Study name and/or ClinicalTrials.gov identifier	Study arm (number of patients; ITT)	Comparator (number of patients; ITT)	Indications	Outcomes	References
II	SIMPLIFI NCT00514527	ORI 1200 mg day 1 (99)	ORI 800 mg day 1 [+400 mg day 5] (100) ORI 200 mg/day for 3–7 days (103)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (15 % margin): • Clinical response at days 21–29	[3]
III	SOLO 1 NCT01252719	ORI 1200 mg day 1 (475)	VAN 1 g or 15 mg/kg bid 7–10 days (479)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (10 % margin): - No spreading or reduction of lesion size measured at 48–72 h, absence of fever, and no need for rescue antibacterials - Clinical cure within 7–14 days - ≥20 % reduction in lesion size at 48–72 h	[159]
III	SOLO 2 NCT01252732	ORI 1200 mg day 1 (503)	VAN 1 g or 15 mg/kg bid 7–10 days (502)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (10 % margin): - No spreading or reduction of lesion size measured at 48–72 h, absence of fever, and no need for rescue antibacterials - Clinical cure within 7–14 days - ≥20 % reduction in lesion size at 48–72 h	[158]
II	FAST 1	TLV 7.5 mg/kg q24h (84)	Antistaphylococcal penicillin 2 g q6h or VAN 1 g q12h (85)	Complicated skin and skin structure infections (major abscess requiring surgical drainage; deep, extensive cellulitis; infected wound or ulcer; infected burn)	Non-inferiority: • Clinical evaluation at EOT and TOC (7–14 days after end of therapy) visits	[180]
II	FAST 2	TLV 10 mg/kg q24h (103)	Antistaphylococcal penicillin 2 g q6h or VAN 1 g q12h (98)	Complicated skin and skin structure infections (major abscess requiring surgical drainage; deep, extensive cellulitis; infected wound or ulcer; infected burn)	Non-inferiority: • Clinical evaluation at EOT and TOC (7–14 days after end of therapy) visits	[137]
III	ATLAS 1 and 2 NCT00091819 NCT00107978	TLV 10 mg/kg q24h for 7–14 days (928)	VAN 1 g q12h for 7–14 days (939)	Complicated skin and skin structure infections (major abscess requiring surgical drainage; deep, extensive cellulitis; infected wound or ulcer; infected burn)	Non-inferiority (10 % margin): • Clinical evaluation at TOC (7–14 days after end of therapy) visits	[156]

Table 4 continued

Phase	Study name and/or ClinicalTrials.gov identifier	Study arm (number of patients; ITT)	Comparator (number of patients; ITT)	Indications	Outcomes	References
III	ATTAIN 1 and 2 NCT00107952 NCT00124020	TLV 10 mg/kg q24h for 7–21 days (749)	VAN 1 g q12h for 7–21 days (754)	Pneumonia acquired after 48 h in an inpatient acute or chronic care facility or that developed within 7 days after being discharged	Non-inferiority (20 % margin): Improvement or lack of progression of baseline radiographic findings at end of EOT and resolution of signs and symptoms of pneumonia at TOC visit Superiority compared with vancomycin treatment in patients with pneumonia due to MRSA (not met)	[140]
II (open-label)	None	DAL 1 g day 1 + 500 mg day 7 (20)	DAL 1100 mg day 1 (20) or standard of care (21)	Complicated skin and skin structure infections (major abscess, infected ulcer, a major burn deep and extensive cellulitis)	Clinical response at the TOC visit (day 24 for 1-dose DAL, day 34 for 2-dose DAL, and 2 weeks after the last dose for comparators)	[136]
III	None	DAL 1 g day 1 + 500 mg day 7 (571)	LZD 600 mg bid (iv or po) for 14 days (283)	Complicated skin and skin structure infections (major abscesses, major burns, traumatic or surgical wound infections, and deep skin/skin-structure infection) or known or suspected to be caused by MRSA	Non-inferiority (12.5 % margin): • Evaluation of clinical and microbiological responses, both separately and combined, at the EOT and TOC visits	[181]
III	DISCOVER 1 NCT01339091	DAL 1 g day 1 + 500 mg day 7 (288)	VAN 1 g or 15 mg/kg bid for 3 days with possible switch to oral LZD 600 mg bid up to 10–14 days (285)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (10 % margin): • Early clinical response at 48–72 h: cessation of spread of the erythema associated with the infection; temperature ≤37.6 °C	[182]
III	DISCOVER 2 NCT01431339	DAL 1 g day 1 + 500 mg day 7 (371)	VAN 1 g or 15 mg/kg bid for 3 days with possible switch to oral LZD 600 mg bid up to 10–14 days (368)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (10 % margin): • Early clinical response at 48–72 h: cessation of spread of the erythema associated with the infection; temperature ≤37.6 °C	[182]

bid twice daily, *DAL* dalbavancin, *DISCOVER* dalbavancin for infections of the skin compared to vancomycin at an early response, *EOT* end of therapy, *ITT* intent-to-treat, *iv* intravenous, *LZD* linezolid, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ORI* oritavancin, *po* oral, *qxh* every *x* h, *TLV* telavancin, *TOC* test of cure, *VAN* vancomycin

those on hemodialysis [142], but was equivalent for both drugs when excluding these subgroups from the analysis [143]. In Europe, telavancin is therefore not recommended for the treatment of hospital-acquired pneumonia in these circumstances [11].

5.2 Other Types of Infections

The usefulness of these drugs in other potential indications has been examined in small series of patients or even in case reports.

5.2.1 Oritavancin

The pharmacokinetics and pharmacodynamics of oritavancin were evaluated in 55 patients with *S. aureus* bacteremia for both microbiological and clinical responses [144]. Bayesian oritavancin exposure predictions were derived using a validated population pharmacokinetic model for treatments with 5–10 mg/kg of body weight/day; they identified a breakpoint of the percentage of the dosing interval duration for which free-drug concentrations were above the MIC (free-drug % time >MIC) of 22 % for both microbiological and clinical response. Although of interest, this study was performed before the new therapeutic scheme of oritavancin (single dose) was established, limiting its applicability.

5.2.2 Telavancin

Telavancin (10 mg/kg every 24 h, adapted to renal function; see Table 3) was compared with vancomycin or an anti-staphylococcal penicillin in a phase II trial for the treatment of uncomplicated bacteremia, half of the cases of which were related to catheter infections [ASSURE (Telavancin for Treatment of Uncomplicated *S. aureus* Bacteremia) trial] [145]. Of the 60 enrolled patients, only eight (telavancin arm) and nine (comparator arm) were clinically evaluable because they had to fulfill a series of criteria after the administration of the first dose to continue the treatment in order to ensure the non-complicated character of the infection. Comparable cure rates were recorded in the two arms (88 and 89 %), warranting further studies in this indication. Of note, among patients infected by Gram-positive pathogens only enrolled in the two ATTAIN trials, cure rates for the subgroup of bacteremic patients was similar in both treatment groups (41 % for telavancin vs. 40 % for vancomycin), with identical mortality rates [146].

A few case reports have illustrated the efficacy of telavancin in other specific indications. In a patient with endocarditis, linezolid (microbiologically effective but thrombocytopenia developed during the 26 days of treatment) was successfully replaced with telavancin (10 mg/kg/day), with no safety concern after 3 weeks of treatment [147]. The status of another patient who presented with a pacemaker lead infection caused by VISA worsened after successive treatment with vancomycin and daptomycin (8 mg/kg, increased to 10 mg/kg) but she rapidly became non-bacteremic once daptomycin had been replaced with telavancin, with complete cure achieved after 8 weeks of therapy [148]. Following 2 weeks of unsuccessful therapy with a combination of vancomycin and oral rifampicin in a patient with methicillin-resistant *S. epidermidis* prosthetic joint infection following bilateral total knee replacement, the infection was cured with telavancin 10 mg/kg for 6 weeks combined with oral rifampicin [149]. Three patients with osteomyelitis who did not respond to vancomycin therapy were successfully treated with telavancin for 6–10 weeks, with no evidence of recurrence after several months [150]. A fourth patient showed an improved clinical status after 4 weeks of treatment, but his serum creatinine also rose, which justified a switch to tigecycline therapy [150]. Likewise, an 18-year-old male with spina bifida who had chronic osteomyelitis received antibiotherapy with multiple antimicrobials during 133 days. Cure and absence of recurrence were eventually achieved with a regimen consisting of telavancin 750 mg/day for 42 days, meropenem for 50 days, and oral rifampin for 50 days [151].

5.2.3 Dalbavancin

A phase II study compared dalbavancin ($n = 33$; 1000 mg loading dose on day 1 and 500 mg on day 8) with vancomycin ($n = 34$; 1000 mg every 12 h) for the treatment of catheter-related bloodstream infections [152] and concluded that dalbavancin was superior (clinical success rate: 87 vs. 50 %; microbiological success rate: 95.7 vs. 78.6 %). In both arms, success was higher when catheters were removed. Dalbavancin also proved effective for the treatment of catheter-related septic phlebitis caused by MSSA in a single patient eligible for outpatient therapy [153].

6 Safety

6.1 Adverse Events

Safety data with lipoglycopeptides are limited to those of published clinical trials and therefore only concern a few hundred patients. Thus, rare adverse effects may have escaped this analysis and could appear after broad-scale use in real-life patient populations. Therefore, based on the currently available literature, the safety profile of these drugs was globally comparable with that of their comparators in published trials (see Table 5). A few adverse events do, however, need to be highlighted and discussed in more detail.

All three drugs can induce hypersensitivity reactions, with cross-allergy possible with vancomycin. Thus, their use should be considered with caution in patients with a history of allergy to vancomycin and the infusion time should be at least 1 h to avoid red-man syndrome like reactions [131].

The risk of corrected QT (QTc) interval prolongation related to these drugs has been systematically examined in

Table 5 Adverse drug reactions (in % of patients) for new lipoglycopeptides as presented in the product information (compiled from clinical trials in patients with acute bacterial skin and skin structure infections [6, 10, 14])[a]

Adverse reactions	Oritavancin ($n = 976$)	Vancomycin ($n = 983$)	Telavancin ($n = 929$)	Vancomycin ($n = 938$)	Dalbavancin ($n = 1778$)	Vancomycin ($n = 1224$)
Body as a whole						
Rigors			4	2		
Gastrointestinal disorders						
Diarrhea	3.7	3.4	7	8	4.4	5.9
Nausea	9.9	10.5	27	15	5.5	6.4
Vomiting	4.6	4.7	14	7	2.8	3.0
Others: gastrointestinal hemorrhage, melena, hematochezia, abdominal pain					<2	
Nervous system disorders						
Dizziness	2.7	2.6	6	6		
Headache	7.1	6.7				
Taste disturbance			33	7		
General disorders and administration						
Infusion-related reaction					<2	
Infusion-site phlebitis	2.5	1.5				
Infusion-site reaction	1.9	3.5	4	4		
Others: infusion-site erythema, extravasation, induration, edema peripheral	<1					
Immune system disorders						
Hypersensitivity	<1					
Musculoskeletal and connective tissue disorders						
Tenosynovitis	<1					
Myalgia	<1					
Skin and subcutaneous tissue disorders						
Pruritis	<1		6	13	2.1	3.3
Rash	<1				2.7	2.4
Others: urticaria, angioedema, erythema multiforme, leukocytoclastic vasculitis	<1					
Infections and infestations						
Abscess (limb and subcutaneous)	3.8	2.3				
Osteomyelitis	<1					
Respiratory, thoracic, and mediastinal disorders						
Bronchospasm, wheezing	<1					
Metabolism and nutrition disorders						
Hypoglycemia	<1					
Decreased appetite			3	2		
Renal system						
Foamy urine			13	3		
Renal impairment			3	1		
Hepatobiliary disorders						
Hepatotoxicity					<2	
Blood and lymphatic system disorders						
Anemia	<1				<2	
Eosinophilia	<1				<2	
Others: hemorrhagic anemia, leucopenia, neutropenia, thrombocytopenia, thrombocytosis, petechiae					<2	
Investigations						

Table 5 continued

Adverse reactions	Oritavancin ($n = 976$)	Vancomycin ($n = 983$)	Telavancin ($n = 929$)	Vancomycin ($n = 938$)	Dalbavancin ($n = 1778$)	Vancomycin ($n = 1224$)
Alanine aminotransferase increased	2.8	1.5			0.8	0.2
Aspartate aminotransferase increased	1.8	1.5				
Total bilirubin increased	<1					
Hyperuricemia	<1					
Increase in serum creatinine (1.5-fold)			15	7		
Cardiac disorders						
Tachycardia	2.5	1.1				

[a] Vancomycin data are presented on the right of each new glycopeptide for the corresponding trial

healthy volunteers, with negative results reported for oritavancin 800 mg [4] or 1.3-fold the clinical dose of 1200 mg [6], telavancin 7.5–15 mg/kg [154], and dalbavancin 1500 mg [155]. In patients from phase III trials, however, 1.5 % of those patients treated with telavancin for skin infections (vs. 0.6 % of vancomycin-treated patients) and 8 % of those treated for pneumonia (vs. 7 % with vancomycin) experienced QTc interval prolongation of >60 ms or a QTc interval >500 ms, the risk being higher when coadministered with drugs known to prolong the QTc interval or to induce torsades de pointes [10, 140, 156].

For oritavancin, two adverse reactions were more frequent than in the comparator-treated population [157]. First, oritavancin-treated patients were at higher risk of developing osteomyelitis (five cases vs. zero for vancomycin in the SOLO 2 study [158]). These events occurred within 1–9 days after study drug initiation, suggesting that the osteomyelitis may have been pre-existing at the time of study entry. Likewise, elevation of transaminases was more frequent in oritavancin-treated patients in SOLO 1, but it was transient and not reported as serious or as being associated with adverse symptoms related to liver function [159]. Reversible elevation in serum levels of hepatic enzymes was also reported for dalbavancin, especially in patients with underlying conditions affecting liver enzymes such as chronic viral hepatitis of alcohol abuse [14].

With respect to telavancin, two other adverse events of potential concern were evidenced in clinical trials. First, telavancin induces taste disturbance, described as a soapy or metallic taste, in one-third of patients [131]. Second, signs of renal toxicity have been evidenced such as an increase in serum creatinine and foamy urine. However, the latter effect does not necessarily reflect toxicity and could also possibly be due to the renal elimination of hydroxypropyl-β-cyclodextrin present in the formulation as a solubilizing agent [160]. Telavancin should thus be used with caution in patients predisposed to kidney dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension) [10]. Studies in rats suggest that the onset of kidney injury depends on the dose and on the dosing interval (more rapid if a longer dosing interval) [161].

Elevation of hepatic enzymes was more frequently noticed in patients receiving dalbavancin than vancomycin [14]; other adverse effects were comparable.

6.2 Interference with Laboratory Tests and Drug–Drug Interactions

Oritavancin [6] and telavancin [162] may interfere in coagulation testing [aPTT (activated partial thromboplastin time) during 48 h or INR (international normalized ratio) during 24 h] because of their capacity to inhibit the activity of phospholipases included in reagents. An anticoagulant that does not need monitoring may therefore be preferable during antibacterial therapy. This effect has not been reported for dalbavancin [14]. Telavancin also interferes with urine qualitative dipstick protein assays, as well as quantitative dye methods [10].

Studies of interactions with hepatic cytochromes have been conducted. Oritavancin appears to be a weak inhibitor of cytochrome P450 (CYP) 2C9 and 2C19 and a weak inducer of CYP3A4 and 2D6 [6]. A significant risk of bleeding has been reported in patients taking warfarin at the same time. No significant metabolism by hepatic cytochromes or drug interactions related to inhibition or induction of metabolism has been described for both telavancin and dalbavancin [10, 14, 163]. Nor was any pharmacokinetic interaction described when co-administering telavancin with different β-lactam antibacterials [164].

7 Healthcare Costs

As vancomycin is now a generic drug, the drug acquisition cost will obviously be much higher with these novel lipoglycopeptides (see Table 6). However, the cost of MRSA

Table 6 Drug wholesale acquisition cost associated with treatment by new lipoglycopeptides as compared with vancomycin (see *Drugs for MRSA skin and soft-tissue infections* [183] and references cited therein)

Antibacterial	1 vial (mg)	Unit price ($US)	Whole treatment	Total price ($US)
Vancomycin	1000	9.5	2 × 1000 mg × 7–14 days	~133–266
Oritavancin (Orbactiv®)	400	1160	1200 mg	~2900
Telavancin (Vibativ®)	750	309.5	750 mg × 7–14 days	~2167–4333
Dalbavancin (Dalvance®)	500	1490	1000 + 500 mg	~4470

infections is only marginally dependent on the price of the administered drug and mainly reflects the healthcare resources needed to treat the infections, more specifically the length of stay in the hospital, which is in general 1.5–3 times greater than for an MSSA infection [165]. When using the reference drug vancomycin, costs associated with therapeutic monitoring, twice-daily injection or continuous infusion, and prolonged treatment duration need to be taken into account. A cost-effectiveness analysis with telavancin concluded that the treatment cost would be similar for patients from the ATLAS studies treated with vancomycin and telavancin if the acquisition cost of telavancin was approximately 15 times higher than that of vancomycin; the cost effectiveness of telavancin was greater if considering MRSA-infected patients only [166]. The simplified therapeutic scheme of oritavancin, and, to a lesser extent, of dalbavancin, appears to be an appealing solution to the economic burden represented by hospitalization, but the impact of such therapies on global treatment costs needs to be established [32].

8 Conclusion

The pharmacological profile of oritavancin, telavancin, and, to a lesser extent, dalbavancin, demonstrates clear advantages over that of conventional glycopeptides with respect to their bactericidal character (oritavancin and telavancin), activity against vancomycin-resistant strains (oritavancin), or prolonged residence in the organism (oritavancin and dalbavancin). However, this superiority over conventional glycopeptides was not as clear in their clinical evaluation. This discrepancy may be related to the general non-inferiority design of registration studies, the planning and reporting of which is sometimes reported as being suboptimal for anti-infective agents [167]. Moreover, these studies mainly enrolled patients with mid-severity infections [146, 159, 168], against which the comparator is effective, and thus the advantages of more powerful antibacterials do not show through. Thus, superiority trials should be planned in specific indications or situations [169, 170]. Likewise, additional studies in more severe infections as well as clinical experience in real-life situations will possibly help to document these advantages and position these drugs in our current arsenal. At this stage, one can already point out the possibility of using oritavancin or dalbavancin for outpatient therapy, which could contribute to containing costs, improving quality of life, and adherence to the treatment, as well as to reducing adverse reactions related to prolonged intravenous therapy such as thrombophlebitis or catheter-related bloodstream infections [32, 130, 134]. On the other hand, their long half-life asks the question of how to manage adverse effects [133], oritavancin being not extracted by dialysis [171] and dalbavancin only by high-flux dialysers [172]. Thus, among these three drugs, and based on current knowledge of their respective safety profile, the clinician's choice should take into account specific safety concerns, such as a possibly increased risk of osteomyelitis with oritavancin, of nephrotoxicity and QTc interval prolongation with telavancin, and of increased hepatic enzymes with dalbavancin. Also, in this context, dalbavancin may show an advantage by presenting a lower potential for drug interactions or interference in laboratory testing than the other two drugs [134]. As a result, further clinical experience is warranted to better position each of these molecules in our current arsenal and to define their potential in difficult-to-treat infections in which they could reveal all of their advantages.

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Compliance with Ethical Standards

Conflicts of Interest F. Van Bambeke received research grants from Targanta Therapeutics (now The Medicines Company), and Theravance for the performance of in vitro work with oritavancin and telavancin, respectively (most of the corresponding references cited in the present paper).

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