Glycopeptides in clinical development: pharmacological profile and clinical perspectives

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Vancomycin and teicoplanin are the two glycopeptides currently used in the clinics for the treatment of multiresistant infections by Gram-positive organisms. The development of resistance in enterococci and staphylococci has stimulated the search for new derivatives with improved activity, particularly against strains resistant to conventional derivatives. Three of these, obtained by hemi-synthesis starting from natural compounds, are now in clinical development (oritavancin and telavancin, as derivatives of vancomycin; and dalbavancin, as a derivative of teicoplanin). The presence of a lipophilic tail on these molecules results in them having a prolonged half-life. It also modifies their mode of action, conferring to them a concentration-dependent bactericidal activity. Their spectrum of activity includes methicillin-susceptible or methicillin-resistant staphylococci, penicillin-resistant pneumococci and enterococci (including vancomycin-resistant strains for oritavancin and telavancin). Ongoing clinical studies are evaluating the efficacy and safety of these molecules for the treatment of complicated skin and soft tissue infections and bactereamia, in a once-daily (oritavancin, telavancin) or once-weekly (dalbavancin) scheme of administration. Despite these remarkable properties, the use of these potent molecules should be restricted to severe infections by multiresistant organisms to limit the risk of selection of resistance.

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Abbreviations

MIC	minimal inhibitory concentration
MRSA	methicillin-resistant *S. aureus*
VISA	vancomycin-intermediate *S. aureus*

Introduction: new glycopeptides in a historical perspective

Discovered soon after penicillin, glycopeptides also act as inhibitors of peptidoglycan synthesis, but at an earlier biosynthetic stage. They bind with a strong affinity and a high specificity to the D-Ala-D-Ala termini of peptidoglycan precursors exposed to the external face of the membrane, preventing the access of transpeptidases and transglycosylases responsible for the reticulation of these precursors [1]. Vancomycin, originally baptized 'old Mississippi mud' as a reminder of its natural source, was the first to be introduced in the clinics in the 1950s. Its use remained confidential until the mid 1970s because of safety issues related to the low purity of the first lots produced, and also because of lack of real medical need. Its spectrum of activity is indeed limited to Gram-positive organisms and a few anaerobes, so that its main indications were infections caused by β-lactamase-producing *Staphylococcus aureus* (for which β-lactamase-resistant penicillins, cephalosporins, and combinations of penicillins with inhibitors of β-lactamases proved safer alternatives), and colitis caused by *Clostridium difficile*. The emergence and rapid spread of methicillin-resistant *S. aureus* (MRSA), which were resistant not only to all β-lactams but also to the main antibiotic classes, renewed the interest in vancomycin and pushed teicoplanin, another natural glycopeptide, onto the European market. Teicoplanin is comparable to vancomycin in terms of activity but presents pharmacokinetic advantages, such as prolonged half-life, allowing for a once-daily administration. The bacterial retort to this increased use of glycopeptides followed three successive waves. First, in the late 1980s, the first glycopeptide-resistant enterococci were described [2]. They rapidly spread in the USA, accounting for 26% of blood isolated in 2000 [3]. The mechanism for this resistance results from their capacity to produce peptidoglycan precursors by an alternative pathway, in which the target of glycopeptides (D-Ala-D-Ala termini of precursors) is replaced by precursors with lower affinity, ending in D-Ala-D-Lac or D-Ala-D-Ser [4]. This mechanism requires the acquisition of a transposon coding for enzymes catalyzing either the formation of the new precursors or the elimination of the native precursors, as well as for glycopeptide-inducible regulatory proteins. Second, in 1996, the first MRSA strain with intermediate susceptibility to vancomycin was isolated in Japan [5]. Vancomycin intermediate *S. aureus* (VISA) or glycopeptide intermediate *S. aureus* strains are now found all over the world. Because of a lack of standard procedures for their diagnosis, considerable controversy subsists regarding their prevalence, which might range from 1% to 20% of all MRSA isolates [6]. Glycopeptide intermediate *S. aureus* are characterized by a thickened cell wall as a consequence of an increased production of precursors ending in D-Ala-D-Ala that can no more be saturated by glycopeptides [7]. Third, three

MRSA strains with a high level of resistance to glycopeptides have been reported since 2002 by the Centers of Disease Control and Prevention in the USA (Morbidity and Mortality weekly reports). These strains have acquired the transposon responsible for glycopeptide resistance in enterococci [8]. Disturbingly, one of these strains was isolated from a patient who was not exposed to vancomycin, but to other antibiotics, which may have provided sufficient selective pressure to promote colonization by vancomycin-resistant enterococci and MRSA, and horizontal gene transfer [9].

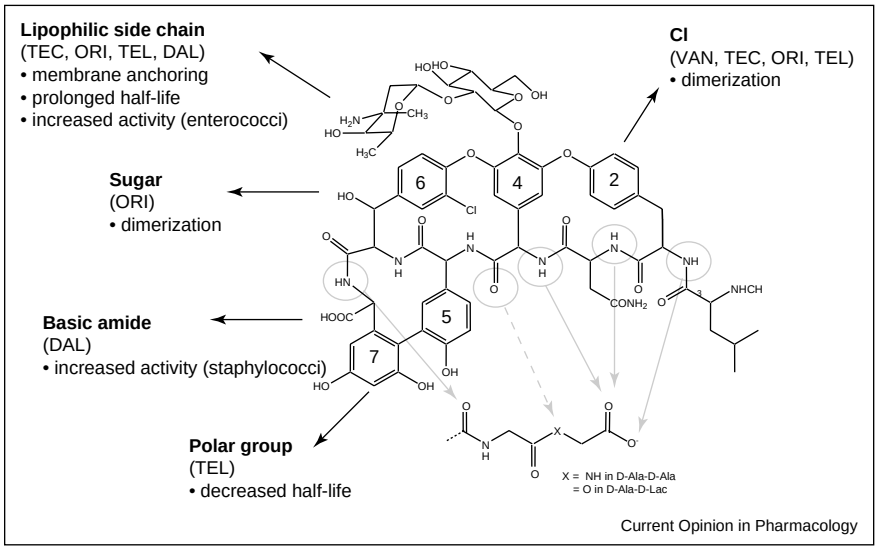
To cope with this preoccupying problem, health authorities published guidelines in 1995, which strictly limit the use of glycopeptides to severe infections by MRSA or to patients allergic to β-lactams [10]. The scientific community and the pharmaceutical industry have reacted by developing new antibiotics, among which are glycopeptides with improved activity against strains resistant to currently in-use glycopeptides. This review examines and compares the properties of the novel glycopeptide molecules in clinical development with those of the conventional glycopeptides, so as to highlight their potential interest in the clinic.

Rational bases for the development of new glycopeptides

Although all glycopeptides share a same basic mechanism of action, detailed structure-activity relationship studies (Figure 1) have demonstrated that some subclasses are more effective than others [11••,12,13]. Key chemical modifications can indeed impart beneficial characteristics to these molecules. Thus, the presence of a hydrophobic side chain —already present in teicoplanin — can serve to anchor the glycopeptide in the membrane, locating it close to its target and potentially causing alteration of the membrane integrity. In addition, the possibility of establishing favorable interactions between disaccharides of adjacent molecules, as well as the presence of chlorine (on ring 2) and an additional sugar (on ring 6), facilitates the formation of homodimers, allowing a cooperative binding to the target [14,15••]. The resulting improvement in the interaction between the glycopeptide molecule and the peptidoglycan precursors is probably, however, not sufficient to explain how some of these derivatives remain active against strains resistant to conventional glycopeptides. Therefore, additional mechanisms of action have been suggested, including direct inhibition of the activity of enzymes involved in peptidoglycan synthesis, such as transglycosylases [16]. However, this does not explain the unusual pharmacodynamic properties of these new glycopeptides, which are characterized by a rapid concentration-dependent bactericidal potency; vancomycin is essentially bacteriostatic.

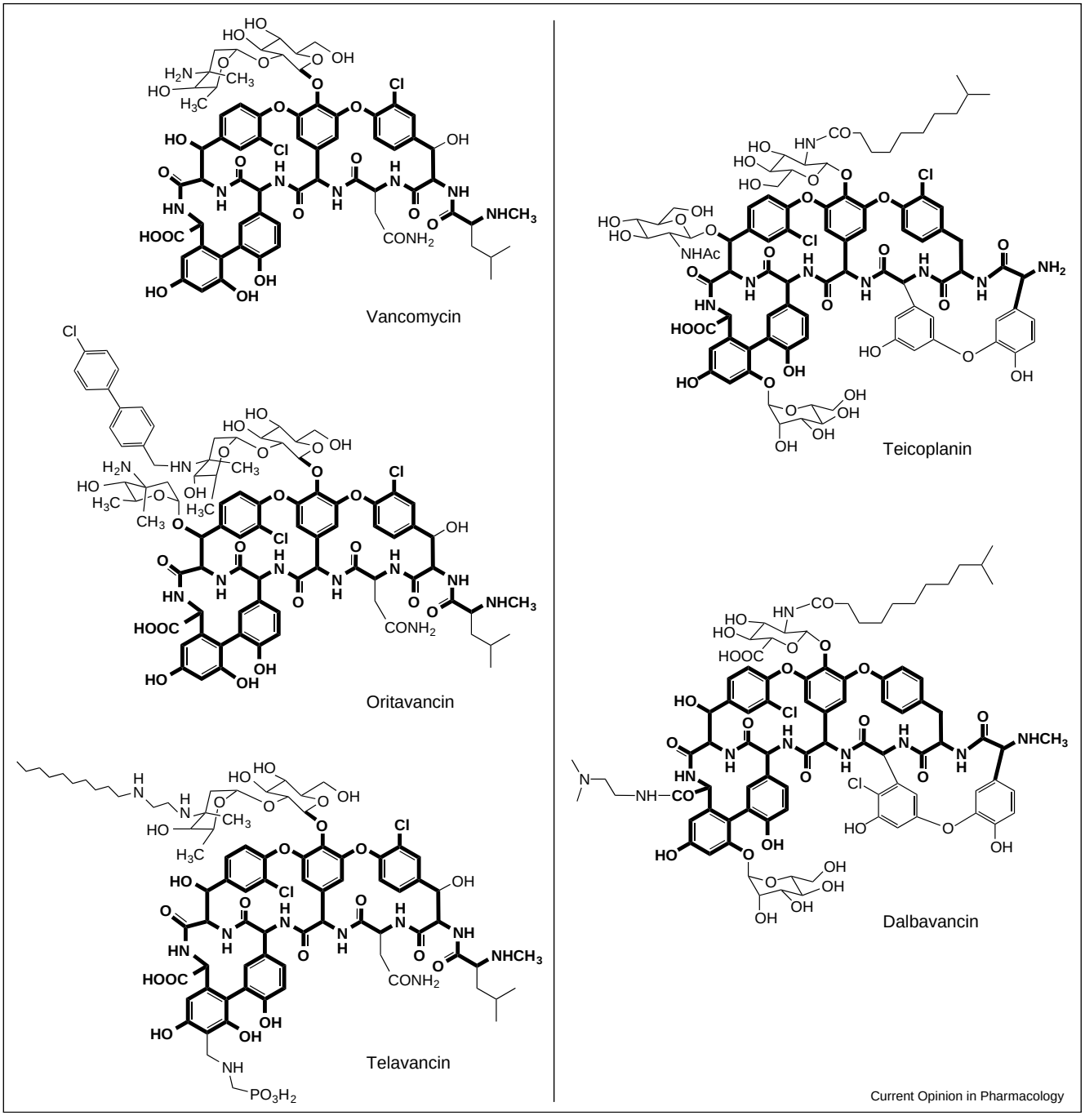
The new physicochemical characteristics of these derivatives do not only modify their pharmacodynamic properties but also drastically alter their pharmacokinetic profile. In particular, the presence of a lipophilic tail confers a high protein binding capacity, which prolongs their half-life in the organism. Among the impressive amount of semi-synthetic derivatives that have been produced and evaluated *in vitro*, only three have been selected for clinical development (Figure 2).

Figure 1



Summarized structure-activity relationship for glycopeptides and the impact on activity and pharmacokinetics of the chemical modifications introduced in teicoplanin (TEC), oritavancin (ORI), telavancin (TEL) and dalbavancin (DAL), as compared to vancomycin (VAN). The figure also shows the interactions established between the glycopeptide molecule and its target in susceptible strains (D-Ala-D-Ala) or in resistant enterococci (D-Ala-D-Lac; the dotted hydrogen bond is missing in this case). Cl, chloride.

Figure 2



Chemical structure of vancomycin, teicoplanin, and their semi-synthetic derivatives currently in clinical development. The core common to these molecules is shown in bold.

Properties of glycopeptides in clinical development

Oritavancin

Oritavancin (LY333328) was obtained by reductive alkylation with 4′chloro-biphenylcarboxaldehyde of the natural glycopeptide chloroeremomycin, which differs from vancomycin by the addition of a 4-epi-vancosamine sugar and the replacement of the vancosamine by a 4-epi-vancosamine [17]. Although oritavancin presents a general spectrum of activity comparable to that of vancomycin, it offers considerable advantages in terms of intrinsic activity (especially against streptococci), and remains

Table 1

In vitro activity (MIC $_{90}$) of glycopeptides against selected target Gram-positive bacteria [32••,48–51].

Bacterial species	Resistance status	MIC $_{90}$ (mg/L)				
		Vancomycin	Oritavancin	Telavancin	Teicoplanin	Dalbavancin
S. aureus	MSSA	1 to 2[a]	1	0.5	1 to 4[a]	0.06 to 0.125
	MRSA	1 to 4[a]	1 to 2[a]	0.5 to 1[a]	2 to 8[a]	0.06 to 0.25
	VISA	8	1 to 8	2		2
	GRSA	>128	0.5	2		
S. epidermidis	MSSE	1 to 2[a]	2	0.5	4 to 8[a]	0.25
	MRSE	2 to 4[a]	1	1	8 to 16[a]	0.25
S. pneumoniae	PenS	0.5	0.008	0.016	0.06 to 0.125[a]	0.03 to 0.06
	PenR	0.25[b] to 0.5[a]	<0.002[b]		0.03[b]	0.03
Enterococcus spp	VanS	1		0.5	0.5 to 1[a]	0.12
	VanA	>128 to >256[a]	1 to 4[a]	4 to 8[a]	>32 to >128[a]	> 128
	VanB	128	0.125		2	1

[a]Range based on MIC$_{90}$ values reported in different studies. [b]MIC $_{50}$ (no MIC$_{90}$ data provided in this study [48]). GRSA, glycopeptide-resistant *S. aureus*; MRSE, methicillin-resistant *S. epidemidis*; MSSA, methicillin-susceptible *S. aureus*; MSSE, methicillin-susceptible *S. epidermidis*; PenR, penicillin resistant; PenS, penicillin susceptible; *spp*, species.

insensitive to the resistance mechanisms developed by staphylococci and enterococci (Table 1). Because the binding affinity of vancomycin and oritavancin to free D-Ala-D-Ala and D-Ala-D-Lac are of the same order of magnitude, the difference in their activity has been attributed to the cooperative interactions that can occur between the drug and both types of precursors *in situ*. This effect is possibly caused by a much stronger ability to dimerize, and the anchoring in the cytosolic membrane of the chlorobiphenyl side chain [15••].

The efficacy of oritavancin has been demonstrated in animal models of meningitis caused by pneumococci susceptible or resistant to β-lactams (even though the concentration in cerebrospinal fluid is only 5% of the serum level) [18,19•]; models of central venous catheter-associated infection by vancomycin-resistant *Enterococcus faecium* [20]; and in models of endocarditis caused by vancomycin-susceptible or -resistant *Enterococcus faecalis* [21]. Pharmacodynamic studies in a neutropenic mouse thigh model of *S. aureus* infection suggest that the parameter that best predicts oritavancin efficacy is the ratio between the free Cmax concentration and the minimal inhibitory concentration (MIC) of the offending organism (free Cmax/MIC) [22••]. Additional favorable pharmacodynamic characteristics include prolonged post-antibiotic effects, and synergy with β-lactams or aminoglycosides [21,23]. Accordingly, oritavancin can be classified as a highly concentration-dependent bactericidal antibiotic with prolonged persistent effects, in the same way as aminoglycosides and, to some extent, quinolones [24]. This pharmacodynamic profile contrasts with that of conventional glycopeptides for which efficacy relies mainly upon the area under the curve/MIC ratio, because they show time-dependent activity and persistent effects [24].

The most salient pharmacokinetic property of oritavancin (Table 2) is its prolonged retention in the organism, which destines it to a once-a-day scheme of administration. The exceptionally long terminal half-life suggests the existence of storage sites within the organism. Studies on cultured macrophages indicate that the drug accumulates slowly (by an endocytic process) but importantly in the lysosomes, from which its efflux is extremely slow [25•]. This explains why it is bactericidal against intracellular forms of *Staphylococcus* or *Enterococcus* infections, but not against cytosolic bacteria such as *Listeria monocytogenes* [25•,26,27]. Corroborating these data, a recent study in volunteers demonstrated that oritavancin reaches high concentrations not only in epithelial lining fluid but also in alveolar macrophages [28].

Oritavancin is currently in phase III of development [29], with two studies in progress published as abstracts only. The first study (double-blind, randomized) is focused on complicated skin and soft tissue infections caused by Gram-positive bacteria, including MRSA, and shows an equivalent clinical success in an intent-to-treat analysis for both arms (oritavancin, 1.5 or 3 mg/kg once daily for 3–7 d; versus vancomycin, 15 mg/kg twice daily for 3–7 d followed by oral cephalexin for up to 10–14 d [30]). The second study is a phase II open-label randomized trial comparing oritavancin (5–10 mg/kg once daily for 10–14 d) with vancomycin (15 mg/kg twice daily) or a β-lactam for 10–14 d in patients with *S. aureus*-associated bacteraemia. Oritavancin was as effective as comparators, with higher clinical and bacteriological success in the 10 mg/kg cohort, and no evidence of increased incidence of side effects [31].

Telavancin

Telavancin (TD-6424) is a semi-synthetic derivative of vancomycin, possessing a hydrophobic side chain on the vancosamine sugar (decylaminoethyl) and a (phosphonomethyl)aminomethyl substituant on the cyclic peptidic core [32••]. The length of the hydrophobic side chain was

Table 2

Pharmacokinetic parameters and pharmacodynamic breakpoints for glycopeptides at doses pertinent of their use in humans (or the foreseen doses for molecules in development).

Parameter (units)	Glycopeptide and dosage				
	Vancomycin [52] (15 mg/kg)	Oritavancin [11••] (3 mg/kg)	Telavancin [53] (7.5 mg/kg)	Teicoplanin [54] (6 mg/kg)	Dalbavancin [55•] (15 mg/kg)
Cmax (mg/L)	20–50	31	89	43	312
Vd (L/kg)	0.3		0.1	0.9–1.6	0.11
Protein binding (%)	10–55	90	90–93	90	98
Terminal half-life (h)	4–8	360	7	83–168	149
AUC (mg.h/L)	260	152	600	550	27103
PD breakpoint based on (free AUC)/MIC ratio[a]	2 (15 mg/kg twice-daily)	0.1 (3 mg/kg) 0.3 (10 mg/kg)	0.5	0.4 (6 mg/kg), 0.8 (12 mg/kg)	4
PD breakpoint based on (free Cmax)/MIC ratio[a]		0.3 (3 mg/kg) 1 (10 mg/kg)	1		0.6

[a]This breakpoint corresponds to the higher MIC for which a free AUC/MIC ratio of 125 or a free Cmax/MIC (for concentration-dependent drugs) of 10 can be reached based on a conventional daily dose (note that for new glycopeptides, these values may be underestimated because the presence of serum proteins does probably not fully impair their activity). AUC, area under the curve; Cmax, maximal concentration in the serum (peak level); PD, pharmacodynamic; Vd, distribution volume.

chosen to reach a compromise between optimized activity against MRSA (8–10 C) and VanA enterococci (12–16 C). Pharmacological studies suggest that the enhanced activity of telavancin on *S. pneumoniae*, *S. aureus* (to a lesser extent), and staphylococci or enterococci harboring the *vanA* gene cluster (Table 1) results from a complex mechanism of action which, on the basis of data obtained with close analogs, involves a perturbation of lipid synthesis [33] and possibly membrane disruption. In contrast to oritavancin, however, no experimental evidence of increased binding to the cell wall precursors or direct inhibition of transglycosylase activity has been found [32••].

The polar substituant introduced on the resorcinol moiety improves the distribution of the molecule in the body and counterbalances the prolonging effect of the lipophilic side chain on the half-life, which is now approximately 7 h and still compatible with a once-daily administration (Table 2). Pharmacodynamic properties include a prolonged post-antibiotic effect and a concentration-dependent bactericidal activity [33]; therefore, one would propose to calculate the pharmacodynamic breakpoint on the basis of the free Cmax/MIC ratio, as done for oritavancin (Table 2). Uniform efficacy in models of infection in immunosuppressed or immunocompetent animals and the absence of major side effects in phase I trials have now pushed this drug to phase II studies (see also Update).

Dalbavancin

Dalbavancin (BI 397) is a semi-synthetic derivative of A40926, a glycopeptide with a structure related to that of teicoplanin [12,34]. As with oritavancin and telavancin, dalbavancin is more active against *S. pneumoniae* than are conventional glycopeptides, and its activity against *S. aureus* is also substantially improved, which was not observed with the semi-synthetic derivatives of vancomycin. However, it is not more active than teicoplanin against enterococci harboring the VanA phenotype of resistance to glycopeptides (Table 1). Dalbavancin is also characterized by a marked bactericidal character [35] and a synergism with penicillin. The pharmacodynamic breakpoint calculated (as for the other bactericidal glycopeptides) on the basis of the free Cmax/MIC ratio is in the same order of magnitude (Table 2). Dalbavancin shows such a prolonged half-life that its plasma concentration exceeds the minimal bactericidal concentration of target organisms even at one week after administration of a single 1000 mg dose; free levels, however, are close to the MICs at these conditions [35,36]. Thus, one can understand that a single dose of dalbavancin significantly reduces the bacterial load in animal models of granuloma pouch infection by MRSA [37], endocarditis by vancomycin-susceptible or -intermediate staphylococci [38], or pneumonia by penicillin-resistant pneumococci [39]. Accordingly, the drug is currently being evaluated in clinical studies using a once-a-week scheme of administration. Pilot phase II trials show an excellent clinical success (> 90 %) in patients receiving 1000 mg dalbavancin at day 1 and 500 mg at day 8 for the treatment of skin and soft tissue infections or catheter-related bloodstream infections by Gram-positive organisms [40•,41].

Conclusions: new glycopeptides in a clinical perspective

New glycopeptides appear as potent molecules with favorable pharmacokinetic and pharmacodynamic properties. If one wishes to avoid the rapid selection of resistance (which has already been obtained *in vitro* [42]), their use should, however, be limited to severe infections by multiresistant organisms [11••], such as septicemia or infections of deep organs, severe skin and soft tissue infections, endocarditis or meningitis, provided efficacy has been demonstrated in correspond-

ing clinical trials. On the basis of pharmacodynamic considerations (Table 2), success rates will be optimal for infections caused by organisms presenting an MIC $\leq$ 0.5–1 mg/L. At the present time, and in the absence of other alternatives, infections by MRSA or methicillin-resistant *Staphylococcus epidermidis* should be preferentially treated with dalbavancin, telavancin (as a potential alternative) and, to a lesser extent, oritavancin. Infections by VISA should be treated with oritavancin rather than telavancin or dalbavancin, whereas infections by vancomycin-resistant *S. aureus* or VanA enterococci should be treated with oritavancin (preferably to telavancin). Infections by pneumococci can be treated with any of these molecules. However, for a definite drug choice, it is necessary to take other factors into account. The pharmacokinetic properties and, in particular, their penetration in the infected compartment are of primary importance if considering the treatment of meningitis, for example [11••]. The safety profile also needs to be further assessed, especially for those molecules that are retained for prolonged times in the organism, even though no major side effects have yet been reported.

Thus, we need to wait and see if the clinical interest in these molecules will measure up to their pharmacological profile. Meanwhile, and based on the experience acquired with these first derivatives, research is still active in exploring new strategies orientated towards other leads [43–45]. In a broader context, pioneer studies suggest other potential pharmacological orientations for this class of drugs. In particular, it has been shown that aglycone derivatives of glycopeptides with hydrophobic substituents display activity against HIV in cell culture models [46,47]. The mechanism of antiviral activity is however not yet elucidated.

Update

Recent work [56] has shown that telavancin is two- to four-fold more active than vancomycin against Gram-positive anaerobic isolates and corynebacteria, with MIC $<$ 1 mg/L (such low MICs were also found for oritavancin and dalbavancin). Safety issues have also been addressed for this drug. In particular, the possibility of prolongation of the QTc was evaluated in healthy subjects, but the mean effect found was $<$ 5 ms, suggesting a minimal risk of cardiac toxicity [57].

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