Glycopeptides and glycodepsipeptides in clinical development: A comparative review of their antibacterial spectrum, pharmacokinetics and clinical efficacy

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Hemi-synthetic derivatives of glycopeptides have demonstrated bactericidal activity towards Gram-positive bacteria, including vancomycin-resistant strains (oritavancin and telavancin), and a prolonged half-life, allowing for once-daily (oritavancin and telavancin) or once-weekly (dalbavancin) administration. These compounds have proved effective for the treatment of infections caused by multidrug-resistant Gram-positive bacteria, including complicated skin and skin structure infections (oritavancin, telavancin and dalbavancin), bacteremia (oritavancin and dalbavancin) and nosocomial pneumonia. This review compares the antibacterial activity and clinical activity of three glycopeptides, oritavancin, telavancin and dalbavancin, and the natural lipoglycopeptide, ramoplanin, which, being unstable in the bloodstream, is administered orally to treat Clostridium difficile colitis and for digestive tract decontamination. All of these compounds, with the exception of oritavancin, have received Fast Track designation from the FDA because of their clinical efficacy.

Keywords Dalbavancin, MRSA, oritavancin, ramoplanin, telavancin, VRE

Introduction

Glycopeptides are one of the oldest classes of antibiotics, with vancomycin isolated from *Streptomyces orientalis* present in soil in the mid 1950s [1], (see reference [2] for a historical review of vancomycin), and teicoplanin (initially referred to as teichomycin as a reference to its producing organism, *Actinoplanes teichomyceticus*) described approximately 20 years later [3]. Interest in glycopeptides was limited initially, but has increased over recent years because of the evolution of bacterial resistance.

Glycopeptides are characterized by a narrow spectrum of activity, covering essentially Gram-positive bacteria and a few anaerobic organisms (eg, *Clostridium difficile*), toward which they show a bacteriostatic or slowly bactericidal activity. In contrast to β-lactams, they inhibit the early stages of peptidoglycan synthesis (see references [4,5,6••] for reviews of the mechanisms of action of glycopeptides). At the time of vancomycin discovery, β-lactams were efficacious and preferentially employed for the treatment of Gram-positive infections because of their superior safety profile. However, two events returned vancomycin to the forefront. The first event was the demonstration of its high efficacy when administered orally in the management of *Clostridium difficile* colitis arising as a complication of broad-spectrum antibiotic use [7]. The second event was the emergence and rapid spread of methicillin-resistant *Staphylococcus aureus* (MRSA) in the late 1960s [8], for which vancomycin became a first-choice drug [9]. Therefore, it is not surprising that only 15 years later the first cases of resistance to glycopeptides in enterococci were described [10], probably selected by the large oral usage of vancomycin. Of more concern is that, 20 to 25 years after this first threat, glycopeptide resistance emerged in staphylococci, with phenotypes of intermediate (vancomycin-intermediate *S aureus* (VISA) [11]) and high (vancomycin-resistant *S aureus* (VRSA) [12]) levels of resistance. These resistance mechanisms have been elucidated (see references [6••,13,14] for review of resistance mechanisms). However, the extent of the problem remains largely unknown, essentially because of a lack of systematic epidemiological surveys [15••], although it has had at least the merit of renewing interest in the search for new anti-Gram-positive antibiotics [16,17]. Among the novel agents being investigated for the treatment of Gram-positive infections, novel glycopeptide compounds constitute one of the most promising classes [17,18••,19,20]. This review will discuss the salient features of four promising novel glycopeptides and present results from preclinical and clinical studies of these compounds.

Optimizing the pharmacological profile of glycopeptides

Vancomycin has a number of limitations (listed in Table 1), some of which - mainly those related to pharmacokinetic/pharmacodynamic issues - can be dealt with by optimizing vancomycin use. Thus, recent pharmacodynamic studies suggest that the efficacy of vancomycin is best predicted by the AUC/MIC ratio (see reference [21•] for a review), a parameter that can be adjusted by monitoring serum levels. Alternatively, rapid elimination of the drug can be overcome by using continuous infusion as a mode of administration. This would ensure an optimized exposure over time, together with easier adjustment of the dose, while simultaneously reducing the workload of healthcare professionals [22]. Finally, toxicity issues were, before the development of pharmacodynamic concepts [21•,22,23], the main reason for clinical monitoring [24]. They can be avoided by administering appropriate doses. In contrast, resistance issues are more difficult to overcome. Inhibitors of vanA-mediated resistance have been described [25,26], but their activity is quite restricted and interest in the development of these compounds is limited [6].

Thus, the design of the new generation of glycopeptides has taken into account the major limitations of vancomycin, to select compounds with a markedly improved pharmacological profile. Efforts have been mainly directed toward the identification of compounds presenting a highly bactericidal activity, including against bacterial strains resistant to conventional glycopeptides, and a prolonged half-life, allowing for infrequent administration. Structure-activity relationships [5,6••,27•,28] have established that the

Table 1. Limitations of vancomycin and possible strategies to overcome them.

Pharmacological property	Vancomycin limitations	Strategies to overcome these limitations
Antibacterial activity	Narrow spectrum of activity	Can be considered as an advantage in non-empiric therapies
	Inactive against VISA, VRSA, and vancomycin-resistant enterococci	Develop inhibitors of resistance mechanisms and design new compounds (multiple and new mechanisms of action)
Pharmacokinetics	Poor tissue distribution and cellular accumulation	Design new compounds (modification of the charge and of the amphipathic character)
	Relatively short half-life (twice-daily administration)	Use continuous infusion, change for teicoplanin and design new compounds with prolonged half-life and/or high protein binding
Pharmacodynamics	Slowly bactericidal	Associate with synergistic antibiotics (aminoglycosides) and design new compounds with multiple and new mechanisms of action
	Low AUC/MIC ratio	Optimize dosages (monitoring peak levels or administering by continuous infusion) and design new compounds with lower MIC and/or higher peak levels
Safety profile	Nephrotoxicity/ototoxicity	Improve purification, monitor serum levels, avoid association with other nephro- or oto-toxic drugs and design new compounds with better safety profile
	Red man syndrome	Monitor serum levels and avoid rapid infusion

AUC area under the curve, **MIC** minimum inhibitory concentration, **VISA** vancomycin-intermediate *Staphylococcus aureus*, **VRSA** vancomycin-resistant *Staphylococcus aureus*.

antibacterial potency of glycopeptides is enhanced by the presence of a hydrophobic side chain comprising an additional sugar or chloride substituent (Figure 1). These features confer new possible interactions with the bacterial surface. Thus, the lipophilic side chain (already present in teicoplanin) can serve to anchor the glycopeptide in the membrane. The presence of an additional chlorine and/or sugar facilitates the formation of homodimers, allowing cooperative binding to the target [4,29]. As a result, additional mechanisms of action have been suggested for these compounds, including a direct inhibition of the activity of enzymes involved in peptidoglycan synthesis, such as transglycosylases [30], an alteration of membrane integrity, or a perturbation of fatty acid synthesis [31••]. These new modes of action may also explain why some of these new glycopeptides maintain activity against strains that are resistant to conventional compounds.

Since the frequent use of oral glycopeptides for *Clostridium* colitis was the probable cause of the emergence of resistance in enterococci, new derivatives have also been specifically developed for this indication [32,33•] so as to preserve other glycopeptides for systemic infections caused by Gram-positive bacteria.

Glycopeptides in clinical development

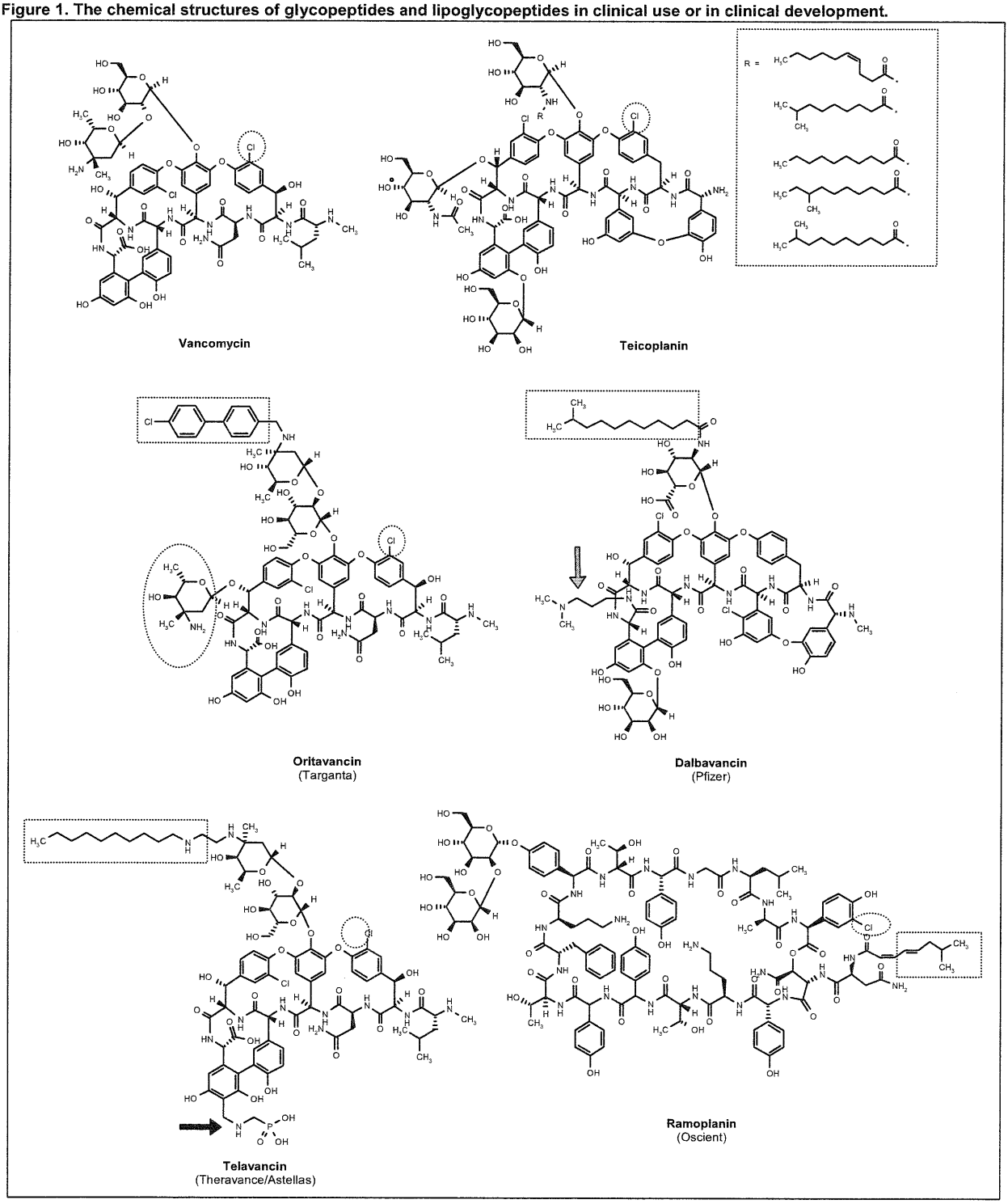
Three glycopeptides are currently undergoing clinical development, namely, oritavancin (Targanta Therapeutics Inc), telavancin (Theravance Inc/Astellas Pharm Inc) and dalbavancin (Pfizer Inc) (see references [6••,18••,19,28] for reviews of these compounds). Ramoplanin (Oscient Pharmaceuticals Corp) is a lipoglycodepsipeptide under evaluation for oral and topical indications [33•]. The main pharmacological properties of these compounds are compared with those of conventional glycopeptides in Table 2.

Oritavancin

Oritavancin (LY-333328; Figure 1) is the *p*-chlorophenylbenzyl derivative of the natural glycopeptide chloroeremomycin, which itself differs from vancomycin by the presence of an additional 4-epi-vancosamine [34], (also see references [6••,28,35•] for reviews of this compound). It was the first clinical candidate of this new generation of glycopeptides, and was identified by Eli Lilly & Co in the late 1990s. Preclinical development and the first clinical trials were conducted by Lilly; however, in September 2001, the company granted worldwide exclusive rights to the drug to InterMune Inc [36], which then subsequently outlicensed oritavancin to Targenta Therapeutics Inc [37]. The more salient features of oritavancin compared with vancomycin are as follows:

- Oritavancin shows rapid and concentration-dependent bactericidal activity, irrespective of the resistance phenotype of the bacterial strains [38]. This property is probably a result of the capacity of the cholorophenylbenzyl side chain to anchor in the membrane, and because of the stronger ability of the drug to form dimers, which cooperatively bind to both D-Ala-D-Ala or D-Ala-D-Lac ending precursors [4]. As a result, oritavancin displays remarkably low MIC values towards Gram-positive organisms (eg, staphylococci, streptococci, enterococci), and most importantly, remains active against strains resistant to conventional glycopeptides, whatever their resistance mechanism.
- Oritavancin has a long half-life, allowing for a once-daily administration, and a prolonged retention in the organism [39]. These properties are best explained by the high protein binding of the drug,

Figure 1. The chemical structures of glycopeptides and lipoglycopeptides in clinical use or in clinical development.



Oritavancin and telavancin are hemi-synthetic derivatives of vancomycin, and dalbavancin is a hemi-synthetic derivative of teicoplanin. Ramoplanin is a mixture of several compounds; the structure of the most abundant (ramoplanin A2) is shown. The figure highlights the molecular elements that confer new properties to glycopeptides. The lipophilic tails (responsible for prolonged half-life and membrane anchoring) are highlighted in dotted rectangles. The additional sugar or chloride favoring homo-dimerization is highlighted in the dotted circle. A black arrow indicates the polar group, which is responsible for shortening the half-life and a gray arrow indicates the basic amide, which increases activity.

Table 2. Pharmacological properties of selected glyco(depsi)peptides.

Pharmacological characteristics	Glyco(depsi)peptide					
	Vancomycin	**Teicoplanin**	**Oritavancin**	**Telavancin**	**Dalbavancin**	**Ramoplanin**
Demonstrated mode of action	Binding to PGN precursors ending in D-Ala-D-Ala and inhibition of cell wall synthesis.	Binding to PGN precursors ending D-Ala-D-Ala and inhibition of cell wall synthesis. Anchoring in the bacterial membrane [29].	Binding to PGN precursors ending in D-Ala-D-Ala or in D-Ala-D-Lac and inhibition of cell wall synthesis. Anchoring in the bacterial membrane [4,105].	Binding to PGN precursors ending in D-Ala-D-Ala and inhibition of cell wall synthesis. Disruption of bacterial membrane integrity. Inhibition of fatty acid synthesis. Inhibition of transglycosylases [31••].	Binding to PGN precursors ending in D-Ala-D-Ala and inhibition of cell wall synthesis. Inhibition of transglycosylases [106]	Direct inhibition of transglycosylases by binding as a dimmer to lipid II [84,85].
***In vitro* activity (μg/ml)**						
MSSA	0.25 to 1.0 [72]	0.25 to 8.0 [72]	0.125 to 1.0 [72]	0.25 to 1.0 [55]	0.03 to 0.5 [72]	0.5 [33•]
MRSA	0.5 to 4.0 [72]	0.125 to 8.0 [72]	0.125 to 4.0 [72]	0.125 to 1.0 [55]	0.06 to 1.0 [72]	0.25 [33•]
VISA	8.0 [6••]	8.0 to 32.0 [6••]	1.0 to 8.0 [6••]	0.5 to 4.0 [60,107]	2.0 [108]	-
enterococci vanco S	0.25 to 2.0 [72]	0.03 to 0.5 [72]	0.06 to 0.25 [72]	0.06 to 1.0 [55]	≤ 0.03 to 1.0 [72]	0.5 [33•]
VRE (VanA)	> 128 [72]	64 to > 128 [72]	0.06 to 1.0 [72]	0.125 to 8.0 [54•]	0.5 to 128 [72]	< 0.007 to 0.5 [109]
VRE (VanB)	8.0 to 128 [72]	0.125 to 8.0 [72]	0.03 to 0.125 [72]	0.125 to 2.0 [54•]	0.02 to 2.0 [72]	-
VRSA	32 to 1024 [110]	-	0.5 [110]	2.0 [54•]	-	-
S pneumoniae peni S	0.125 to 0.5 [72]	0.008 to 0.06 [72]	0.002 to 0.06 [72]	0.008 to 0.03 [55]	0.016 to 0.125 [72]	≤ 0.03 [33•]
S pneumoniae peni R	0.25 to 2.0 [72]	0.016 to 0.125 [72]	0.002 to 0.06 [72]	0.06 [59]	0.008 to 0.125 [72]	0.12 [33•]
Clostridium spp	0.5 to 4.0 [111]	0.064 to 0.5 [111]	0.016 to 2.0 [112]	-	0.125 to 0.5 [111]	0.06 to 2.0 [33•]
Pharmacodynamic profile	Bacteriostatic or slowly bactericidal	Bacteriostatic or slowly bactericidal	Rapidly bactericidal	Rapidly bactericidal	Bactericidal or bacteriostatic depending on the organism [67]	Bactericidal [33•]
Pharmacokinetics						
Protein binding (%)	10 to 55 [113]	90 [114]	90	93 [56]	99 [657	-
Half-life (h)	4 to 8 [113]	83 to 168 [114]	~ 200 [39]	7 to 9 [56]	> 150 [74]	-
Dosages	15 mg/kg bid [113]	6 mg/kg [114]	1.5 to 3 mg/kg [35•]	7.5 to 10 mg/kg [56,63•]	1000 mg on day 1; 500 mg on day 8 [79]	100 to 400 mg tid po [33•]
C_{max} (mg/l)	50 [113]	43 [114]	31 [35•]	88 [56]	325 [74]	-
AUC (mg.h/l)	260 [6••]	550 [6••]	152 [6••]	762 [56]	25790 [74]	-
Clinical indications	Serious infections by β-lactam resistant organisms, or by Gram-positive bacteria in patients allergic to β-lactam, colitis failing to respond to metronidazole, and prophylaxis in specific circumstances [6••].	Serious infections by β-lactam resistant organisms, or by Gram-positive bacteria in patients allergic to β-lactam, colitis failing to respond to metronidazole, and prophylaxis in specific circumstances [6••].	cSSSI by Gram-positive bacteria and Gram-positive bacteremia [35•].	cSSSI by Gram-positive bacteria and hospitally-acquired pneumonia [54•,62,63•].	cSSSI by Gram-positive bacteria and Gram-positive bacteremia [78•].	*C difficile* diarrhea and VRE colonization [33•,93•].
Side effects	Oto- and nephrotoxicity, Red man syndrome and injection-site phlebitis [2,115].	Less frequent oto- and nephrotoxicity, less frequent Red man syndrome and thrombocytopenia [115].	Headache, nausea, sleep disorders and injection-site phlebitis [35•].	Taste disturbance, headache, dizziness, procedural site reaction and nausea [56].	Pyrexia, headache, nausea, oral candidiasis, diarrhea and constipation [68•].	Infrequent GI disorders (diarrhea, abdominal pain, dyspepsia, flatulence, nausea) [93•].

bid twice daily, **cSSSI** complicated skin and soft tissue infection, **GI** gastrointestinal, **iv** intravenous, **MRSA** methicillin-resistant *Staphylococcus aureus*, **MSSA** methicillin-susceptible *Staphylococcus aureus*, **peni R** penicillin-resistant, **peni S** penicillin-sensitive, **PGN** peptidoglycan, **po** orally, **tid** three times daily, **vanco S** vancomycin sensitive, **VISA** vancomycin-intermediate *Staphylococcus aureus*, **VRE** vancomycin-resistant *Enterococcus*, **VRSA** vancomycin-resistant *Staphylococcus aureus*.

but also by its exceptional level of cellular accumulation, as demonstrated *in vitro* (in models of cultured phagocytic and non-phagocytic cells [40]) as well as *in vivo* (in alveolar macrophages of volunteers [41]). The later property is a clear advantage for the eradication of intracellular bacteria such as *S aureus,* toward which oritavancin remains bactericidal and among the most active drugs in *in vitro* models of infected macrophages [40,42]. However, this high cellular accumulation may also cause cellular toxicity, as evidenced in cultured cells exposed to the drug, which show morphological alterations characterized by the presence of large vacuoles with heterogeneous content associated with an increase in polar lipid cell content [43]. These observations provide a rationale for revisiting animal safety data in order to establish the potential toxicological significance.

In accordance with these properties, oritavancin proved effective in animal models of pneumococcal meningitis [44,45], catheter infections or endocarditis, including those caused by vancomycin-resistant enterococci [46,47]. Its concentration-dependent bactericidal effect combined with its high protein binding capacity explains why the free C_{max}/MIC value is the best parmacodynamic predictor of its efficacy [48].

Clinical development of the drug has been slowed down by the multiple changes of ownership, so that it is still undergoing phase III clinical development. Published phase II studies have documented the application of oritavancin in *S aureus* bloodstream infections [49]. This open-label, randomized trial showed equivalence between oritavancin (5 to 10 mg/kg, once daily) and comparators (vancomycin [15 mg/kg, twice daily] or a β-lactam) administered for 10 to 14 days. Higher clinical and bacteriological activity was observed in the 10 mg/kg oritavancin cohort. Further pharmacodynamic analysis suggested that the success correlates with the free drug time above the MIC [50]. Phase III studies have examined the safety and efficacy of oritavancin in complicated skin and skin structure infections (cSSSI) caused by Gram-positive organisms, including MRSA. Two randomized, doubled-blind, multicenter clinical trials demonstrated that oritavancin (3 mg/kg, once daily) had equivalent efficacy to vancomycin (15 mg/kg, twice daily) plus cephalexin, but needed shorter treatment duration (maximum of 5 days versus 10 to 14 days for the vancomycin-cephalexin combination) [35•,51,52]. No specific or life-threatening side effects were observed in these studies.

Telavancin

Telavancin (TD-6424; Figure 1), another semi-synthetic derivative of vancomycin, is characterized by a hydrophobic side chain on the vancomsamine sugar (decylaminoethyl) and a phosphonomethylaminomethyl substituent on the cyclic peptidic core [53], which counterbalances to some extent the hydrophobicity of the lipophilic side chain (also see references [18••,19,28,54•] for reviews on telavancin). Specific properties of telavancin that compare with vancomycin or oritavancin, include:

- multiple modes of action, which, most notably, include the depolarization and permeabilization of the bacterial membrane [31••]. This may explain the highly concentration-dependent and rapid bactericidal activity of the drug, including against strains resistant to conventional glycopeptides [55], and the global activity comparable to that of oritavancin.
- a markedly shorter half-life than oritavancin even though it is also highly protein bound [56] and has good tissue penetration [57]. It accumulates to high levels (although these are much lower levels than those achieved by oritavancin) in cultured macrophages, where it displays bactericidal activity against intracellular staphylococci [58]. These differences are probably because of the polar phosphonate substituent, which accelerates drug clearance [53]; however, the drug half-life remains long enough to allow for a once-daily administration, while avoiding the potential drawbacks of prolonged retention in the organism.

The highly concentration-dependent bacterial activity of telavancin has been demonstrated in animal models of thigh or subcutaneous infection, meningitis or endocarditis caused by MRSA or even by VISA [59-61].

In phase II, randomized, double-blind clinical trials of cSSSI, telavancin (10 mg/kg, once daily) produced higher cure and eradication rates than vancomycin when MRSA was the causative organism [62,63•]. Furthermore its safety profile was acceptable [56]. The effect of telavancin on cardiac repolarization was specifically examined, and a QTc interval prolongation of < 4.5 ms was observed, which is shorter than for other antibiotics such as the quinolones [64]. In 2005, telavancin was granted Fast Track designation by the FDA for the treatment of hospitally-acquired pneumonia caused by MRSA or multidrug-resistant *Streptococcus pneumoniae*, as well as of MRSA-associated cSSSI [54].

Dalbavancin

Dalbavancin (BI-397; Figure 1) is a semi-synthetic derivative of the natural glycopeptide A-40926, a teicoplanin analog. It differs from its parent compound by the replacement of the acylglucosamine on amino acid 4 and by the removal of the acetylglucosamine in the benzylic position [65]. Dalbavancin was not the most active in the series, but presented the best tolerability [27•], (also see for references [6••,18••,19,28,66,67,68•] for reviews of dalbavancin). It was discovered by Biosearch Italia SpA and out-licensed to Versicor Inc for the North American market [69]. Biosearch and Versicor merged in March 2003 to form Vicuron Pharmaceuticals Inc [70], which was then acquired by Pfizer in September 2005 [71]. Pfizer is currently pursuing the development of dalbavancin. Two properties differentiate dalbavancin from oritavancin and telavancin:

- Dalbavancin loses activity toward enterococci or staphylococci harboring the vanA gene cluster but

remains extremely active against staphylococci and streptococci [72].

- Dalbavancin displays an unusually prolonged half-life (6 to 10 days), attributed to high protein binding and retention within the cells [73], and suggestive of the existence of storage compartments. Based on this property, dalbavancin can be administered intravenously once weekly [74].

Animal models of disseminated infection, staphylococcal granuloma pouch, foreign body infection or endocarditis and of pneumococcal pneumonia demonstrated that dalbavancin is as efficacious as comparators at less frequent doses [72,75-77], which is advantage in clinical practice.

In clinical trials, dalbavancin (1 g followed by 500 mg 1 week later) was highly effective in the treatment of SSSI (in phase II and III trials), and catheter-related bloodstream infections (in phase II trials) [68•,78•,79,80]. To date, the observed adverse events are mild and limited [68•,81]. Pfizer has been granted Priority Review status by the FDA for the treatment of MRSA cSSSI [82].

Ramoplanin

Ramoplanin (A-16686, MDL-62198; Figure 1) is a natural compound, usually present as a complex mixture of closely related molecules, produced by *Actinoplanes* spp [83]. It was originally isolated in 1984 by Gruppo Lepetit and was licensed to Oscient Pharmaceuticals in 2001 (see references [18••,19,20,33•,84] for reviews of ramoplanin activity). Ramoplanin's bactericidal activity is a result of the direct inhibition of transglycosylase activity by the drug binding in a dimeric form to lipid II (however, in contrast to glycopeptides, the disaccharide moiety is not required for antibacterial activity) [85,86]. As the lipid II target is located upwards of the targets of conventional glycopeptides in peptidoglycan synthesis, there is no cross-resistance between ramoplanin and vancomycin or teicoplanin [87,88]. Thus, ramoplanin is active against Gram-positive bacteria, including vancomycin-resistant strains, as well as against anaerobes such as *C difficile*. Interest in the development of ramoplanin may have been limited because of its instability in the bloodstream and poor tolerance [18••,84]; however, by taking advantage of its excellent activity against *C difficile* [89,90] and against vancomycin-resistant enterococci [20,91], as well as its high concentration in the feces [33•], ramoplanin is currently in phase III clinical trials for the treatment of *C difficile*-associated diarrhea [92] and for the decolonization of the gastrointestinal tract as a means to prevent vancomycin-resistant enterococci nosocomial infections [93•,94]. Ramoplanin has received Fast Track status from FDA for both indications [95]. However, major concerns remain regarding the use of ramoplanin for these indications as there is a high probability of selecting for Gram-negative bacteria, including multidrug-resistant nosocomial enterobacteriaceae [91], and the possibility of recurrences developing after treatment discontinuation [96].

Conclusion

Glycopeptides are still undergoing active research, with four major approaches being investigated. The first approach involves the continuation of efforts made over more recent years to obtain compounds with additional modes of action and increased activity against strains resistant to conventional compounds. Among investigational compounds, some mannopeptimycins appear promising [97-99]. The second approach involves designing multivalent glycopeptides [100], based on the observation that the self-dimerization of vancomycin enhances its cooperative binding to the D-Ala-D-Ala target. Some of these dimers proved potent against vancomycin-resistant enterococci [101]. The third strategy involves the coupling of glycopeptides to other antibiotics so as to obtain bifunctional antibacterial agents. This is an elegant method of reaching two distinct targets using a single molecule. In the case of glycopeptides, hybridization with β-lactams appears the most rational, based on the topological proximity of the targets of both types of antibiotics [18••]. The last development was unanticipated and arose from the demonstration of the antiretroviral activity of semisynthetic hydrophobic derivatives of glycopeptides [102]. This discovery led to the synthesis of modified glycopeptides showing high activity against HIV or coronaviruses, but devoid of antibiotic action [103,104].

The new glycopeptides discussed in this review offer clear advantages over conventional glycopeptides. The most notable advantages are the highly bactericidal character of telavancin, oritavancin, and to some extent, dalbavancin, against multidrug-resistant MRSA, the ease of administration of dalbavancin, and the restricted indications of ramoplanin. Larger clinical studies (including safety studies) will be helpful to position these compounds in the arsenal of new anti-Gram-positive agents.

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