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Forthcoming therapeutic perspectives for infections due to multidrug-resistant Gram-positive pathogens

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Abstract

Multidrug resistance in Gram-positive pathogens emerged as a major therapeutic challenge over two decades ago. The worldwide spread of methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant enterococci and other resistant Gram-positive pathogens had a major impact on antibiotic policies, and prompted the discovery and development of new antibiotics to combat difficult-to-treat infections caused by such pathogens. Several new antibiotics active against multidrug-resistant Gram-positive pathogens have recently been introduced into clinical practice, and the antibiotic pipeline contains additional anti-Gram-positive drugs at an advanced stage of development, including new glycopeptides (dalbavancin, oritavancin, and telavancin), new anti-MRSA β-lactams (ceftobiprole), and new diaminopyrimidines (iclaprim). This article provides a brief overview of these upcoming agents, partially based on the material presented at the ESCMID Conference entitled 'Fighting infections due to multidrug-resistant Gram-positives' (Venice, Italy, 29–31 May 2008) and on the most recent literature.

Keywords: Antimicrobial agents, Gram-positive pathogens, multidrug resistance, review

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Major Resistance Challenges Posed by Gram-Positive Pathogens and Overview of the Anti-Gram-Positive Pipeline

Antibiotic resistance has become a major public health problem on a global scale. Resistance issues are no longer confined to some pathogenic species and to certain healthcare settings, but affect virtually all major bacterial pathogens and all types of epidemiological settings (acute-care hospitals, long-term-care facilities, community), although considerable variability in the epidemiology of resistance can be observed in different geographical and epidemiological settings [1,2 and http://www.rivm.nl/earss/].

In Gram-positive pathogens, multidrug resistance emerged as a major therapeutic challenge in the 1980s [3]. The worldwide spread of methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant enterococci (GRE) and pneumococci resistant to penicillin and macrolides, and the more recent emergence of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) strains, had a major impact on antibiotic policies and prompted an active reaction from the pharmaceutical industry concerning the discovery and development of new antibiotics to combat these strains. Consequently, several new antibiotics active against multidrug-resistant (MDR) Gram-positive pathogens have recently been introduced into clinical practice (e.g. quinupristin–dalfopristin, linezolid, daptomycin, and tigecycline), and the antibiotic pipeline contains additional anti-Gram-positive drugs at an advanced stage of development, including new glycopeptides (e.g. dalbavancin, oritavancin, and telavancin), new anti-MRSA β-lactams (e.g. ceftobiprole and ceftaroline), and new diaminopyrimidines (e.g. iclaprim).

The aim of this review is to provide a brief summary of these upcoming antibiotics active against MDR Gram-positive pathogens, partially based on the the material presented at the ESCMID Conference entitled 'Fighting infections due to multidrug-resistant Gram-positives' (Venice, Italy, 29–31 May 2008) by leading representatives of pharmaceutical companies, and on the most recent literature.

The New Glycopeptides for MDR Gram-Positive Pathogens

Exploitation of the scaffold of the first-generation glycopeptides, vancomycin and teicoplanin, has proved a successful strategy to obtain new glycopeptides with modified pharmacokinetic and pharmacodynamic properties and with enhanced activity against MDR Gram-positive pathogens. Three such derivatives are well advanced in the pipeline, and introduction into clinical practice is expected in the near future.

Dalbavancin

Dalbavancin (Pfizer, New York, USA) is a semisynthetic lipoglycopeptide derived from a teicoplanin analog (Fig. 1), with a mechanism of action similar to that of older glycopeptides [4]. The presence of the lipophilic side chain improves the D-Ala-D-Ala target recognition, and results in significantly lower MICs for staphylococci (including MRSA strains), enterococci, and streptococci, as compared to older glycopeptides. Potent *in vitro* activity is retained against VISA strains and also against VanB enterococci, but whether the latter feature translates into clinical efficacy remains to be confirmed. On the other hand, dalbavancin is poorly active against vancomycin-resistant organisms with a VanA resistance mechanism (Table 1). Against staphylococci (including MRSA), dalbavancin exhibits potent bactericidal activity, with bactericidal rates that are superior to those of the older glycopeptides [5,6]. A low potential for *in vitro* selection of resistance has been documented [5] in preclinical and clinical studies (Goldstein *et al.*, 45th ICAAC, 2005, Abstract L-1577).

The presence of the long lipophilic side chain in the dalbavancin molecule is most probably the reason for its very long half-life of approximately 8 days [7]; this allows for the proposed once-weekly regimen (1000 mg on day 1 and 500 mg after 1 week), which could be very convenient and could allow for earlier patient discharge. The more lipophilic structure also accounts for an intracellular penetration that is superior to that of older glycopeptides (Bulgheroni *et al.*, 44th ICAAC, 2004, Abstract A-1490). Approximately 40% of the dose is excreted unmodified in the urine, and 20% is excreted unchanged in stools. Dose adjustment may not be necessary in subjects with impaired liver function, or in patients with mild to moderate renal impairment (Dowell, ISICEM 2008, Poster P026). Investigation concerning the

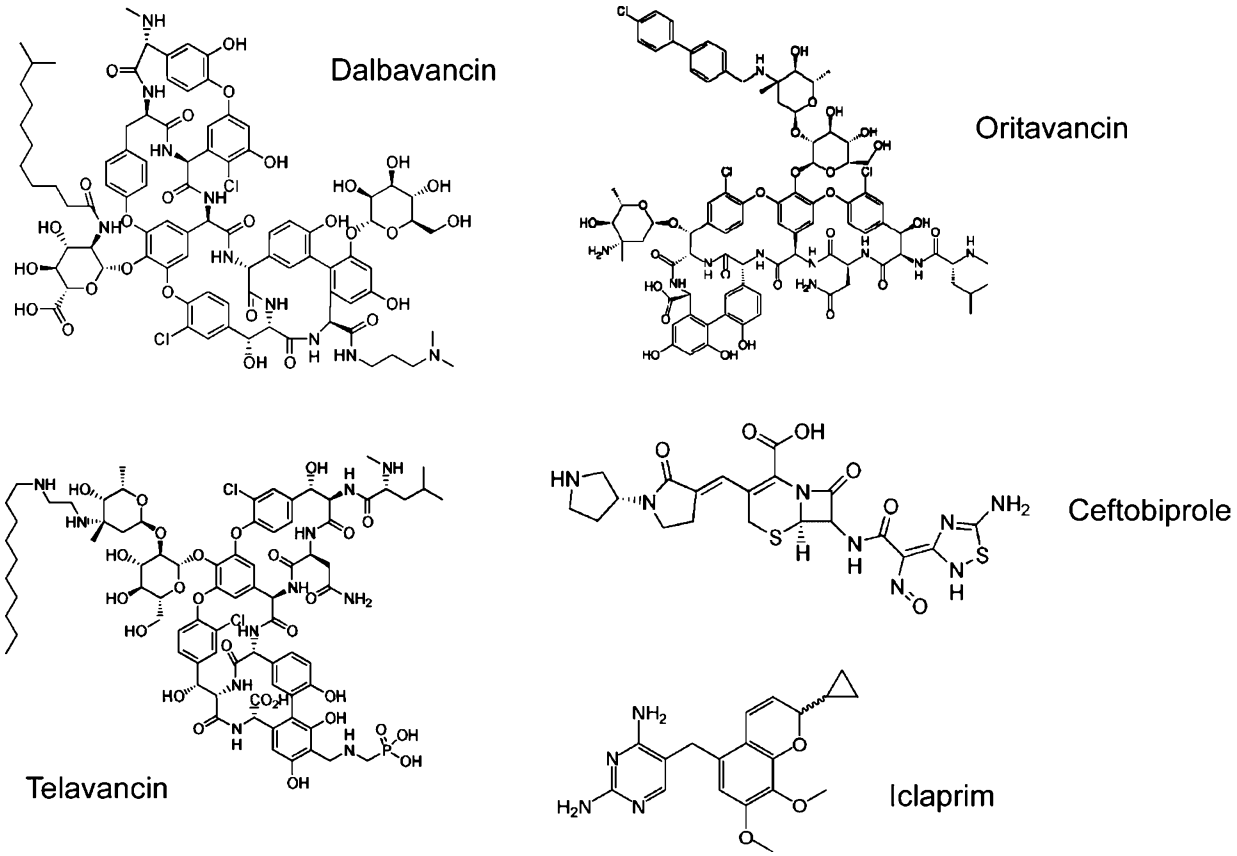

FIG. 1. Structures of the new anti-Gram-positive compounds.

TABLE 1. Antimicrobial activity (MIC_{90} values, mg/L) of the new glycopeptides against Gram-positive pathogens (including strains with clinically relevant resistance traits)

Drug	MSSA	MRSA	hVISA/VISA	Vancomycin-susceptible enterococci	VRE (VanA)	VRE (VanB)	β-Haemolytic streptococci
Dalbavancin	0.06–0.5	0.06–1	1–2	0.06–0.12	≥32	0.12–1	0.015–0.06
Oritavancin	0.12	0.25	1	0.06	1	0.03[a]	0.06
Telavancin	0.25	0.50	1	0.25–0.50	4–8	2	0.25

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; hVISA, heteroresistant vancomycin-intermediate *S. aureus*; VISA, vancomycin-intermediate *S. aureus*; VRE, vancomycin-resistant enterococci.
Data are from [18,32,33]; Grover *et al.*, 47th ICAAC, 2007, Abstract E-1613; Draghi *et al.*, 47th ICAAC, 2007, Abstract E-1615; Draghi *et al.*, 47th ICAAC, 2007, Abstract E-1616; Sahm *et al.*, 47th ICAAC, 2007, Abstract E-1617; and Arhin *et al.*, 47th ICAAC, 2007, Abstract D-242. When different MIC_{90} values have been reported, data are reported as ranges.
[a]Maximum MIC value.

effect of dalbavancin administration on the gut microbiota of healthy subjects showed that it did not select for *Clostridium difficile*, or result in changes of the major anaerobic components or the selection of dalbavancin-resistant aerobic or anaerobic bacteria [8].

The clinical efficacy of dalbavancin has been investigated in patients with complicated skin and skin structure infections (cSSSIs) and with catheter-related bloodstream infections. In a large phase III trial involving patients with cSSSIs, including surgical site infections, dalbavancin proved at least as effective as linezolid, as judged by clinical cure rates and microbiological success at the test of cure (14 ± 2 days after the end of treatment). Notably, the MRSA subset accounted for approximately half of the randomized patients [9]. In a small non-blinded trial involving patients with catheter-related bloodstream infections caused by Gram-positive pathogens, a superior clinical response was observed in patients receiving dalbavancin than in those receiving standard vancomycin treatment [10]. Safety and tolerability profiles were overall similar to those of comparators. An additional phase III clinical trial involving patients with cSSSIs is planned to complete the regulatory submission to the EMEA and the FDA.

Oritavancin

Oritavancin (Targanta Therapeutics, Cambridge, MA, USA) (Fig. 1) is a semisynthetic lipoglycopeptide derived from the natural compound chloroeremomycin. The differences with respect to older glycopeptides result in substantial improvements of the pharmacodynamic properties (mediated, at least in part, by dimerization upon target binding), which include the ability to bind depsipeptides (such as D-Ala-D-Lac, present in VanA-type resistant organisms) and to exert an additional mechanism of action that consists of membrane disruption [11] (McKay *et al.*, 46th ICAAC, 2006, Abstract C1-682; Arhin *et al.*, 47th ICAAC, 2007, Abstract C1-1471; Wang *et al.*, 47th ICAAC, 2007, Abstract C1-1474). These properties reflect the microbiological profile of oritavancin, which shows potent activity against major Gram-positive pathogens, including MRSA, VISA and most vancomycin-resistant organisms (Table 1), and, unlike the older glycopeptides, exerts rapid concentration-dependent bacterial killing (McKay *et al.*, 18th ECCMID, 2008, Abstract P-544). Interestingly, oritavancin is also accumulated intracellularly, and exhibits bactericidal activity against intracellular small-colony variants of *S. aureus*, which are known to be involved in some persistent infections (e.g. osteomyelits) (Nguyen *et al.*, 47th ICAAC, 2007, Abstract A-1437; Nguyen *et al.*, 18th ECCMID, 2008, Abtract P-1059). Oritavancin resistance has not yet been described in clinical isolates of *S. aureus*, but moderate increases in oritavancin MICs can be selected for *in vitro* in multistep mutants of VanA and VanB enterococci [12].

However, in that study, MICs were determined using agar-based methods, which function poorly for oritavancin; furthermore, susceptibility breakpoints have not yet been set for oritavancin by either the EMEA or the FDA. Susceptibility and resistance studies in the presence of 0.002% polysorbate-80, now recommended by the CLSI for broth microdilution assays of oritavancin (guideline M100-S18; CLSI, 2008), suggest that the MIC of oritavancin for mutants selected after 20 hours of exposure of *S. aureus* (including MRSA, VISA, and VRSA), enterococci (including both VanA and VanB strains of both *Enterococcus faecalis* and *Enterococcus faecium*) and *Bacillis subtilis* (surrogate for anthrax) does not exceed 1 mg/L [13; Targanta Therapeutics, unpublished data].

Preclinical studies in animal models of staphylococcal and pneumococcal infections showed that AUC/MIC and C_{max}/MIC values are the pharmacokinetic–pharmacodynamic (PK–PD) parameters predictive of *in vivo* efficacy, in agreement with the rapid killing effect observed *in vitro* [14] (Craig and Andes, 44th ICAAC, 2004, Abtract A-1863; Lehoux *et al.*, 47th ICAAC, 2007, Abstract A-49). This feature, along with the long half-life and long-lasting post-antibiotic effect [15], supports once-daily administration.

The clinical efficacy of oritavancin has been investigated in cSSSI patients. In phase III studies, oritavancin given at a

once-daily dose of 200 mg (or 300 mg when body weight was >110 kg) for up to 7 days, followed by an oral placebo, was found to be at least as effective as standard vancomycin treatment followed by oral cephalexin. Notably, effectiveness of oritavancin-based therapy was achieved following a shorter duration of therapy (5.3 vs. 10.9 days), and the percentage of patients who required a discontinuation because of adverse events was significantly lower in the oritavancin arm (Giamarellou *et al.*, 43rd ICAAC, 2003, Abstract L-739a), pointing to a good safety and tolerability profile. Alternative dosages (including single-dose and two-dose regimens) are under investigation. The results from a recently completed phase II study involving patients with cSSSI demonstrate the non-inferiority of oritavancin in both the single-dose and infrequent-dose regimens as compared to the once-daily phase III regimen of oritavancin (http://media.integratir.com/targ/PressReleases/SIMPLIFI_final102208.pdf).

Telavancin

Telavancin (Astellas Pharma, Tokyo, Japan) is a semisynthetic lipoglycopeptide derivative of vancomycin (Fig. 1). As for oritavancin, the structural modification with respect to vancomycin endows the telavancin molecule with a dual mechanism of action, targeting the D-Ala-D-Ala depeptide and the plasma membrane [16] (Lunde *et al.*, 17th ECCMID, 2007, Abstract O256).

This feature results in potent antibacterial activity against Gram-positive pathogens (including MDR strains) in terms of MIC values (Table 1), and in rapid concentration-dependent bactericidal activity that covers MRSA, VISA and VRSA strains [17]. Activity is also retained against linezolid-non-susceptible and daptomycin-non-susceptible staphylococcal strains [18].

Preclinical studies in animal models of infections caused by Gram-positive pathogens showed that the AUC/MIC ratio was the best PK–PD parameter with which to predict efficacy [19]. This behaviour, along with a long half-life (7–9 h) and a long-lasting post-antibiotic effect [20], allows for once-daily dosing. Telavancin is mostly excreted unchanged in the urine, and an extension of the dosing intervals is necessary with creatinine clearance rates lower than 50 mL/min [21].

The clinical efficacy of telavancin has been investigated in patients with cSSSIs and with hospital-acquired pneumonia, including ventilator-associated pneumonia. In phase III studies on cSSSIs, telavancin given at a once-daily dose of 10 mg/kg (with adjustment for reduced creatinine clearance) was found to be at least as effective as standard vancomycin, as judged by clinical cure rates at the test of cure (Corey *et al.*, IDSA 2006, Poster LB-17). The safety profile of telavancin was similar to that of the comparator, and supports the use of telavancin for the treatment of cSSSIs (Corey *et al.*, 44th IDSA, 2006, Abstract LB-17). Similarly, in phase III studies on hospital-acquired pneumonia/ventilator-associated pneumonia, telavancin was found to be at least as effective as the comparator vancomycin (http://www.drugs.com/clinical_trials/theravance-announces-positive-topline-results-phase-3-telavancin-hospital-acquired-pneumonia-program-2913.html), but the results have not been published yet.

The New Anti-MRSA β-lactams

Currently available β-lactams are unable to efficiently inhibit penicillin-binding protein (PBP)2a of methicillin-resistant staphylococci, and they are not clinically useful for the treatment of infections caused by MRSA and methicillin-resistant coagulase-negative staphylococci.

Given the overall efficacy and safety of β-lactam antibiotics, an intensive effort has been made to obtain new β-lactam molecules that are active against methicillin-resistant staphylococci. The most advanced compound in the pipeline is ceftobiprole, and ceftaroline and carbapenems with anti-MRSA activity are at earlier stages of development in the antibiotic pipeline.

Ceftobiprole

Ceftobiprole (Johnson & Johnson, Langhorne, PA, USA) (Fig. 1) is the most advanced anti-MRSA cephalosporin in the pipeline, being already approved for clinical use in some countries (e.g. Canada and Switzerland).

Unlike the β-lactams that are currently available in clinical practice, ceftobiprole binds to, and effectively inhibits, PBP2a of methicillin-resistant staphylococci [22], resulting in MIC values and bactericidal activity that are overall comparable with those observed against methicillin-susceptible *S. aureus* [23,24]. Activity is also retained against VISA and VRSA [25]. Ceftobiprole activity extends to β-haemolytic streptococci (Amsler *et al.*, 46th ICAAC, 2006, Abstract E-116) and pneumococci. In fact, because of its good affinity for penicillin-resistant PBPs of pneumococci, it is the most active cephalosporin against penicillin-resistant pneumococci [26].

Against *E. faecalis*, ceftobiprole exhibits a behaviour more similar to that of ampicillin than to that of other cephalosporins, whereas it does not efficiently inhibit PBP5 of *E. faecium* and is not active against the latter species [24]. Resistance to ceftobiprole in Gram-positive pathogens was found to be very difficult to select *in vitro* after serial passages [25,26] (Banerjee and Chambers, 47th ICAAC, 2007, Abstract C1-844), and ceftobiprole-resistant Gram-positive pathogens were never detected in clinical trials [27,28]. Unlike many

of the new antibiotics active against MDR Gram-positive pathogens (such as linezolid, daptomycin, quinupristin–dalfopristin, and the new lipoglycopeptides discussed above), which show a narrow spectrum of antibacterial activity against Gram-positive pathogens, ceftobiprole has a very broad spectrum of activity, including several Gram-negative pathogens such as the fastidious respiratory pathogen *Haemophilus influenzae*, and *Moraxella catarrhalis*, *Enterobacteriaceae* (except for strains producing extended-spectrum β-lactamases), *Pseudomonas aeruginosa*, and non-MDR strains of *Acinetobacter baumannii* [23].

Preclinical studies in animal models indicated time-dependent PK–PD behaviour, similar to that of other β-lactams, with percentage time over the MIC (%T > MIC) being the PD index for efficacy. Against staphylococci and streptococci, a %T > MIC breakpoint ≥30% (i.e. similar to that of carbapenems) has been calculated for efficacy, whereas for Gram-negative pathogens, the calculated %T > MIC breakpoint is ≥50% (i.e. similar to that of other cephalosporins) [23]. Ceftobiprole is administered as a prodrug, ceftobiprole medocaril, which is rapidly converted to ceftobiprole *in vivo* by plasma esterases. It is primarily excreted unchanged via the kidney [23].

The clinical efficacy of ceftobiprole has been investigated in patients with cSSSIs. In phase III studies on cSSSIs, ceftobiprole at a dose of 500 mg every 12 h was found to be at least as effective as standard vancomycin for infections caused by Gram-positive pathogens, and at a dose of 500 mg every 8 h, it was found to be at least as effective as standard vancomycin ± ceftazidime for infections caused by both Gram-positive and Gram-negative pathogens, including diabetic foot infections, as judged by clinical and microbiological cure rates at test of cure. No major safety issues have been reported during phase III clinical trials with ceftobiprole [27,28].

The New Diaminopyrimidines

Iclaprim (Arpida Pharmaceuticals, Reinach, Switzerland) (Fig. 1) is the only new diaminopyrimidine derivative in an advanced stage of clinical development. Iclaprim is a trimethoprim derivative that targets bacterial dihydrofolate reductase. Owing to its modified structure, iclaprim retains strong inhibitory activity against trimethoprim-resistant dihydrofolate reductase enzymes [29] (Oefner *et al.*, 18th ECCMID, 2008, Abstract O486), which constitute the most important mechanism of acquired resistance against trimethoprim in *S. aureus*. Iclaprim has potent *in vitro* activity against *S. aureus* (including MRSA) and β-haemolytic streptococci (MIC_{90}s: 0.12–0.5 mg/L), and also exhibits good overall activity against penicillin-susceptible pneumococci, some enterococci, *Listeria*, *Legionella* and *Chlamydia*. Iclaprim has moderate activity against *H. influenzae*, *M. catarrhalis* and some *Enterobacteriaceae* [30]. Against Gram-positive pathogens, including MRSA, iclaprim is rapidly bactericidal (Weiss *et al.*, 18th ECCMID, 2008, Abstract P588) and has a post-antibiotic effect of approximately 2–3 h (Hawser *et al.*, 42nd ICAAC, 2002, Abstract F-2029). Selection for resistance *in vitro* by serial passage was found to be very difficult (Hawser *et al.*, 42nd ICAAC, 2002, Abstract F-2028), suggesting a low bacterial propensity for evolution towards iclaprim resistance.

Iclaprim can be administered intravenously or orally (oral bioavailability is approximately 40%) and, together with linezolid, it is the only drug active against MDR Gram-positive pathogens endowed with this interesting feature. Its half-life is approximately 3 h. Iclaprim is metabolized by cytochromes and glucuronidation, and elimination of metabolites is via the urine (about two-thirds) and faeces (about one-third). Dosing does not need adjustment in cases of mild-to-severe or end-stage renal failure. No dose adjustment is needed in cases of mild liver failure, whereas in cases of moderate liver failure, a dose adjustment is indicated. The drug has a large volume of distribution and can accumulate intracellularly, suggesting that it could be used to treat infections caused by intracellular pathogens that are susceptible to iclaprim [30,31].

The clinical efficacy of iclaprim has been investigated in patients with cSSSIs. In phase II and phase III trials, intravenous iclaprim (0.8 mg/kg twice daily) proved to be at least as effective as vancomycin and non-inferior to linezolid, respectively, as judged by clinical cure and microbiological eradication rates, and safety and tolerability profiles were overall very good [31] (Dryden *et al.*, 18th ECCMID, 2008, Abstract P545; Hadváry *et al.*, 18th ECCMID, 2008, Abstract P547; Jones *et al.*, 18th ECCMID, 2008, Abstract P550).

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Transparency Declaration

The authors declare that they have no conflicts of interest in relation to this work.

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