

New Antibiotics Against Multi-Resistant Gram-positive Bacteria



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The emergence of multi-resistance in *Staphylococcus aureus*, *Enterococcus faecium* and *faecalis*, and *Streptococcus pneumoniae* has reinvigorated the search for new antimicrobial classes with good gram-positive bacteria. Fortunately, compared to antibiotics against gram-negative bacteria, these have proven to be comparatively easy to find. Indeed, most of the new classes of antibiotics tend to be agents with activity against gram-positive bacteria only.

The first of these were the oxazolidinones, the lead agent of which, linezolid, is now marketed worldwide. As is common in drug development, the search for new classes often means chemical manipulation of older classes, and this is especially true of glycopeptides, where several new promising agents have emerged. A similar line has been taken with the development of the streptogramin combination, quinupristin-dalfopristin, which was derived from an old oral combination pristinamycin. Most recently, a novel lipopeptide agent which was originally withdrawn from development at a fairly advanced stage, daptomycin, was resurrected, re-evaluated and launched.

Before discussing the new agents, it is worthwhile reviewing what options are still available among the older agents for the treatment of major multi-resistant gram-positive bacteria listed below.

Organism	Multi-resistant type	Agents to which acquired resistance is common	Still available older agents
<i>S. aureus</i>	MRSA	β -lactams, macrolides, lincosamides, tetracyclines, fluoroquinolones, most aminoglycosides	Glycopeptides, rifampin, fusidate sodium, chloramphenicol, folate antagonist combinations*, arbekacin, fosfomycin,
	VISA/VRSA	β -lactams, macrolides, lincosamides, tetracyclines, fluoroquinolones, glycopeptides	Rifampin, fusidate sodium, chloramphenicol, folate antagonist combinations*
<i>E. faecium</i>	VREF	Glycopeptides, β -lactams, aminoglycosides (high-level)	
<i>E. faecalis</i>	VRE	Glycopeptides	Ampicillin/amoxicillin
<i>S. pneumoniae</i>	DRSP	(Penicillin), macrolides, lincosamides, tetracyclines, chloramphenicol,	β -lactams (high dose), ketolides, fluoroquinolones

* resistance is common in some parts of the world

There is quite a range of new compounds that have been developed with good anti-gram-positive activity. In the last year alone at the Interscience Conference on Antimicrobial Agents and Chemotherapy, new classes have been described which inhibit bacterial fatty acid synthesis, β -lactamases, peptidyl deformylase, DNA replication, DNA transcription, and type III protein secretion as well as new β -lactams, novel chemical structures with as yet unknown mechanisms of action, and a host of novel β -lactams, lincosamides, macrolides, ketolides, oxazolidinones, peptides, and quinolones.

The agents discussed in more detail below include only those that are sufficiently advanced in development that they considered truly to be 'on the horizon'.

Lipopeptides

Daptomycin is a lipopeptide antibiotic with a unique mechanism of action involving binding of calcium ions and disruption of the cell membrane. Originally developed by Lilly, development was ceased in the early 1990s when certain toxicities were noted in phase II/III studies. With increasing resistance amongst gram-positives, development was recommenced after the agent was in-licensed by Cubits Pharmaceuticals. The action of daptomycin is calcium dependent, and 50 mg/L is required to be added to broth susceptibility test media to accurately measure its activity. It must be administered intravenously. It is currently approved in the US for complicated skin and skin structure infections involving staphylococci, enterococci and some streptococci. There are indications that it is poorly effective in pneumonia. There are plans to extend the registration of daptomycin to other areas of the world.

There are no other lipopeptides in development.

New glycopeptides

Chemical modification of the glycopeptide nucleus has resulted in the development of several promising new agents, including oritavancin, telavancin and dalbavancin, which are all currently in phase III of development.

Oritavancin

Oritavancin (InterMune, USA) is a semi-synthetic agent related to vancomycin, and with an additional biphenyl derivative side-chain. *In vitro* studies show that oritavancin differs from the older glycopeptides, vancomycin and teicoplanin, in having activity against vancomycin-resistant enterococci, and being rapidly bactericidal. This suggests that it has mechanisms of action additional to that of vancomycin. It is highly protein bound and has a very long elimination half life. Phase III studies have been largely completed, but there are concerns of adverse events from one clinical study and as such the long term prospect of this agent is still unclear.

Dalbavancin

Dalbavancin (Vicuron, USA) is a semi-synthetic agent related to teicoplanin, and therefore technically a lipoglycopeptide. It is also bactericidal more potent than other glycopeptides but does not have predictably good activity against vancomycin-resistant enterococci. It has one of the highest protein binding percentages of any antibiotic, leading to a very long elimination phase (>250 h). Clinical studies are

therefore being conducted with once-weekly dosing. Early published phase III studies suggest activity superior to that of vancomycin. It has recently been submitted to the FDA.

Telavancin

Telavancin (Theravance, USA) is also a lipoglycopeptide. It shares many of the properties of the other new glycopeptides in terms of concentration dependent bactericidal activity, and activity against vancomycin-resistant enterococci. It has a moderate elimination half-life suitable for once-daily dosing, and phase III studies are in progress.

New anti-MRSA cephalosporins

Several cephalosporins with activity against MRSA are in development. Many achieved through a 3-heteroaryl substitution giving the molecule zwitterionic properties. The most advanced appears to be ceftobiprole (BAL5788, Basilea Pharmaceutica, Switzerland), but others include RWJ-54428 (Johnson & Johnson, USA), BMS-247243 (Bristol-Myers Squibb, USA), LB11058 (LG Life Sciences, Korea) and CP6679 (Meiji Seika Kaisha, Japan). Clearly these agents are able to inhibit pbp2a in staphylococci, a prospect that initially seemed unlikely for any β -lactam. However, *in vitro* and early clinical data suggest that these cephalosporins are likely to be effective against MRSA. This may be an important advance, as in general β -lactams have shown better efficacy against staphylococci than glycopeptides. Whether this is true for the new glycopeptides is not clear.

Ceftobiprole

Ceftobiprole is a water-soluble prodrug of BAL9141 that is rapidly converted after injection to the active compound. It is notable for its *in vitro* activity against MRSA and this has been confirmed in animal model studies of pneumonia and endocarditis. As a cephalosporin it retains activity against the common gram-negative bacteria, but has no useful activity against ampicillin-resistant enterococci. It has recently commenced Phase III studies particularly aimed at conditions involving MRSA and DRSP.

New quinolones

Despite several notable failures in the development of quinolones with high activity against gram-positive bacteria, a small number of new agents are continuing to be developed, such as garenoxacin (Schering-Plough, USA) and sitafloxacin (Daiichi, Japan). The former is well advanced, while the latter is just entering phase I studies.

Garenoxacin

Garenoxacin is a new type of quinolone, having one less fluorine atom than conventional fluoroquinolones. For this reason it is often classified as a des-fluoro-quinolone, although it still has two fluorine atoms. The drug continues the trend of recent quinolones in showing high potency against gram-positive bacteria, and being less affected by mutations in the quinolone-resistance determining regions of *Streptococcus pneumoniae*. The agent has completed phase III studies, principally in respiratory tract infections, but was recently dropped from the portfolio of Bristol-Myers-Squibb. It has now been taken up by Schering-Plough in the US. It is still unclear about whether it will be FDA-registered.

Garenoxacin is very active against multi-resistant *S. pneumoniae*, and therefore could be an important addition to the quinolone armamentarium now available for treating respiratory tract infections including community-acquired pneumonia, such as levofloxacin, gatifloxacin, moxifloxacin and gemifloxacin.

Glycylcyclines

The addition of a glycine group to the tetracycline nucleus has resulted in a new class of drugs called glycylcyclines. This has resulted in a spectrum that retains that of the tetracyclines, but now includes a great deal of strains that are tetracycline resistant. The lead compound is tigecycline (Wyeth, USA) which is now under FDA and EMEA consideration. The broad spectrum nature of tigecycline has resulted in it not being targeted during development specifically for resistant gram-positive bacteria, and data are awaited from a range of clinical studies to get information on efficacy against them.

Other agents

Of the other classes of agents under development, the most promising are the peptidyl deformylase inhibitors. A number of compounds have been developed including LBM415 (Novartis and Vicuron, USA), BB-83698 and BB-81384 (Genesoft, USA). These synthetic agents have little activity against gram-negatives, and a novel mechanism of action. Thus, there is no documented resistance amongst gram-positives. None of these have yet reached phase I of development.