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Leading article

Quinupristin/dalfopristin and linezolid: where, when, which and whether to use?

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The 1980s and 1990s saw the spread of resistant Gram-positive cocci and a lack of new antibiotics directed against them.[1] Concern about this situation has spread to governments and the lay press. Nevertheless, pharmaceutical progress has continued amidst the gloom—a point not yet recognized by the pessimists—and rather a lot of new anti-Gram-positive drugs *are* now progressing. The Table summarizes six drugs to have reached or passed Phase II (proof of efficacy). It excludes antibiotics in laboratory research and Phase I. Also excluded are the new quinolones and ketolides, which may offer new options for the treatment of respiratory infections but have borderline activity against most methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococci.[2,3] Linezolid and daptomycin[4] are members of new chemical classes with new mechanisms of action. Compounds related to quinupristin/dalfopristin and evernimicin (everninomicin)[5] have been used previously as growth promoters for animals; LY-333328[6] is a glycopeptide that retains activity against vancomycin-resistant enterococci and GAR-936[7] is a new tetracycline that evades efflux and ribosomal resistance mechanisms. This article concentrates on quinupristin/dalfopristin, which was recently licensed in the UK, Europe and the USA, and on linezolid, for which licensing is anticipated in 2000. Data on daptomycin,[4] evernimicin,[5] LY-333328[6] and GAR-936[7] have been presented recently elsewhere. Development of evernimicin has recently been suspended, and no other of these compounds seems likely to be licensed within the next year or so.

Quinupristin and dalfopristin are group B and A streptogramins, respectively, which act synergically:[8] quinupristin blocks binding of aminoacyl-tRNA complexes to the ribosome whilst dalfopristin inhibits peptide bond formation and distorts the ribosome, promoting the binding of quinupristin.[8] MICs for most streptococci, pneumococci, staphylococci and *Enterococcus faecium* are from 0.25 to 2 mg/L, but *Enterococcus faecalis* is resistant (MICs usually 16–32 mg/L).[8] Non-fastidious Gram-negative bacteria are impermeable and therefore resistant. Phase III trials demonstrated equivalence to vancomycin or cephazolin in skin and soft tissue infections and to vancomycin in nosocomial pneumonia (aztreonam was added to both arms to cover Gram-negative pathogens).[9] Extensive emergency-use programmes gave impressive results: Moellering[10] reviewed 396 patients with *E. faecium* infections treated worldwide with quinupristin/dalfopristin. Most were severely ill at baseline and were infected with multi-resistant strains. Of 193 who remained clinically evaluable, 142 were cured or improved, and bacterial eradication was achieved in 110 of the 156 evaluable patients. In emergency use against MRSA infections, clinical response rates of 70–75% were seen, and success in severe bone and joint infections was particularly impressive.[11] Against these achievements must be placed significant (*c.* 10%) rates of arthralgia and myalgia, and also the need to administer quinupristin/dalfopristin through a central catheter so as to avoid local venous irritation.[10] In the UK, quinupristin/dalfopristin is licensed for skin and soft tissue infections, nosocomial pneumonia and *E. faecium* infections, 'where no other drug is appropriate'.[12] In the USA, quinupristin/dalfopristin is licensed specifically for the treatment of serious and life-threatening infections caused by susceptible strains of vancomycin-resistant *E. faecium* and for complicated skin and soft tissue infections caused by susceptible pathogens.

Linezolid is an oxazolidinone, an antimicrobial class discovered by DuPont in the 1980s. DuPont's early derivatives were hepatotoxic, but the family was re-investigated in the 1990s by Pharmacia & Upjohn, who studied linezolid and an analogue, eperezolid, in Phase I development programmes.[13] Linezolid had superior pharmacokinetics to

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Table. Present and future options for treatment of Gram-positive pathogens

Agent	Class	Target	Spectrum	Cidal	Status
Quinupristin/dalfopristin	streptogramin	protein synthesis	Gram +ve, not *Enterococcus faecalis*	yes[a]	licensed, EU and USA
Linezolid	oxazolidinone	protein synthesis	Gram +ve	no	licensed in USA; license sought in EU
Daptomycin	peptolide	lipoteichoic acid synthesis (+others)	Gram +ve	yes	Phase III started
Evernimicin (everninomicin)	oligosaccharide	protein	Gram +ve	no	Phase III suspended
LY 333328	glycopeptide	cell wall synthesis	Gram +ve	yes	Phase II completed
GAR-936	glycylcycline (tetracycline)	protein synthesis	broad	no	Phase II

[a]Not bactericidal against $MLS_{B/c}$ strains.

eperezolid, and its development was continued. Oxazolidinones inhibit initiation of protein synthesis by binding to the 50S ribosomal subunit and preventing it from complexing with the 30S subunit, mRNA and initiation factors;[14] this stage of protein biosynthesis has not been exploited previously as an antimicrobial target.

Linezolid has remarkably consistent inhibitory activity against staphylococci, enterococci and pneumococci, with MICs of 1–4 mg/L.[15] It also has moderate activity against *Bacteroides* spp. and *Moraxella catarrhalis* (MIC 8 mg/L), but other Gram-negative bacteria are resistant as a result of endogenous efflux mechanisms. Bactericidal activity is slow or absent. Linezolid can be given orally with virtually 100% bioavailability, or by intravenous injection. A regimen of 600 mg twice daily maintains serum levels above the MICs of Gram-positive cocci throughout the dosage interval.[16]

Several Phase III trials with linezolid are complete, although full publication is still awaited. Linezolid achieved *c.* 90% clinical and microbiological cure rates in skin and soft tissue infections, proving equivalent to clarithromycin for uncomplicated infections and to cloxacillin/dicloxacillin for complicated infections.[17] In community-acquired pneumonia, intravenous, followed by oral, linezolid achieved a cure rate of 90%, and was equivalent to intravenous ceftriaxone followed by oral cefpodoxime.[17] In nosocomial pneumonias—many caused by MRSA—linezolid plus aztreonam was equivalent to vancomycin plus aztreonam, with cure rates of 66–67%.[17] Against MRSA infections, linezolid achieved a clinical cure rate of 63%, compared with 66% for vancomycin: hospital discharge was often earlier for patients in the linezolid arm, owing to the facility to switch to oral therapy (Pharmacia & Upjohn, personal communication). Controlled trials in enterococcal infections are difficult to perform owing to the shortage of effective comparator regimens; in compassionate use Birmingham *et al.*[18] reported an 80% clinical cure rate for bacteraemia caused by vancomycin-resistant *E. faecium*. Noskin *et al.*[19] recorded cure of *E. faecium* bacteraemia in four of five neutropenic patients treated with linezolid, suggesting that the lack of bactericidal activity might not be crucial in this patient group. Nevertheless, more data are needed on efficacy in immunosuppressed patients and for other conditions, notably endocarditis, where bactericidal activity is usually considered mandatory. Intravenous—but not oral—linezolid reduced experimental *S. aureus* vegetations in rabbits.[20] Several endocarditis patients have been treated successfully with linezolid in a compassionate-use programme, but these cases remain unpublished (Pharmacia & Upjohn, personal communication).

The present response to enthusiasm about new antibiotics is often: 'Yes, but resistance will emerge'. In the case of quinupristin/dalfopristin, a tiny proportion of *E. faecium* and *S. aureus* isolates from humans have already acquired the *vatA–E* (previously called *sat*) determinants, which specify dalfopristin acetyltransferases, or *vga* deter-

minants, which determine dalfopristin efflux pumps.[8,21] The occurrence of these mechanisms may reflect previous use of other streptogramins. An oral analogue, pristinamycin, has long been used in France for respiratory infections, and another analogue, virginiamycin, was used until recently as a growth promoter in farm animals. Reflecting this latter usage, substantial rates of resistance to virginiamycin (up to 60%) have been reported among *E. faecium* isolates from animals and food in Denmark,[22] though their spread to humans, as yet, seems minimal.

Much more common than *vat* and *vga* genes among human isolates are the *erm* determinants, which are widespread among Gram-positive cocci.[23] These genes encode mRNA methylases that modify a specific adenine in the 23S rRNA, thereby blocking the binding of macrolides, lincosamides and quinupristin. This mechanism affects quinupristin only if it is expressed constitutively, as in so-called $MLS_{B/c}$ strains. Even then, quinupristin/dalfopristin remains inhibitory, owing to the activity of dalfopristin, but its bactericidal activity is diminished or lost.[8,24] Laboratories should be able to recognize $MLS_{B/c}$ staphylococci since they are resistant to both clindamycin and erythromycin, and the dosage of quinupristin/dalfopristin used to treat infections with such strains may need to be adjusted.[8,12] Reservoirs of linezolid resistance, on the other hand, are unlikely since no analogue has been used previously. Mutational resistance is extremely difficult to select *in vitro*, but was reported in two *E. faecium* vascular catheter infections treated with linezolid in the compassionate-use programme.[25] The mechanism entailed modification of rRNA genes. Bacteria carry multiple copies of these genes and changes to single copies may be recessive, explaining the difficulty in selecting for resistance.

The big question is when to use quinupristin/dalfopristin and linezolid. No antibiotic should be used recklessly, however difficult it appears to be to select for resistance *in vitro*. On the other hand, the attitude that 'All new antibiotics should be locked away', risks stifling innovation whilst denying life-saving treatments. Quinupristin/dalfopristin seems unlikely to be over-used, owing to the need for a central venous access and the incidence of arthralgia and myalgia. It is, however, finding a niche in severely ill patients with vancomycin-resistant *E. faecium* infections, mostly in specialist units. Wider use is likely only if glycopeptide resistance accumulates among MRSA, or if superiority over glycopeptides is shown for some infections. In view of the results obtained with compassionate use, early comparative evaluation against MRSA bone and joint infections is especially desirable.

Linezolid has the potential for wider use, being an oral agent active against all clinically important Gram-positive cocci and with few side effects. It is envisaged that linezolid therapy would be hospital-initiated, but oral administration may allow early discharge with its contingent savings. Skin and soft tissue infections and community and nosocomial pneumonias are likely to be the first indications licensed. Of these, skin and soft tissue infections might have the stronger justification, given: (i) the prevalence of MRSA and vancomycin-resistant enterococci in this setting; (ii) that other likely pathogens are Gram-positive; and (iii) that linezolid is concentrated in the skin structure.[26] Use of linezolid in pneumonia demands confirmation of a Gram-positive pathogen or combination with an anti-Gram-negative agent. Use of linezolid in nosocomial pneumonia does seem appropriate, particularly if the local epidemiology indicates a high risk of MRSA, but prescribing for community-acquired pneumonia does not seem appropriate, except perhaps where multi-resistant pneumococci with high penicillin MICs ($\geq$2 mg/L) have accumulated. More generally, it seems appropriate to consider using linezolid in units and patients where multi-resistant enterococci or staphylococci are documented or likely; but not in units or patients where most of the staphylococci remain susceptible to oxacillin and the enterococci to ampicillin. For severe infections, much still hinges on the question of bactericidal activity, and how essential this is for patients with immunosuppression or endocarditis. These aspects will only be resolved by further clinical experience.

Debates on the use of new anti-Gram-positive agents are sure to intensify as more of the compounds in the Table reach the market, and it is vital that they take place on a basis of science, not knee-jerk restrictions or over-zealous marketing. What is already clear—even with the demise of evernimicin—is that the prospects for the treatment of multi-resistant Gram-positive cocci no longer seem quite so bleak as they were 2 or 3 years ago.

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