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Oxazolidinones
A Review

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Abstract

The oxazolidinones represent a novel chemical class of synthetic antimicrobial agents. They exhibit an unique mechanism of protein synthesis inhibition and generally display bacteriostatic activity against many important human pathogens, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. Linezolid, the oxazolidinone which has been selected for clinical development, has near complete oral bioavailability plus favourable pharmacokinetic and toxicity profiles. Results from experimental models of infection and phase II trials reveal linezolid to be highly active *in vivo* against infections due to many common Gram-positive pathogens. The role of linezolid remains to be determined in phase III clinical trials, but it shows great promise as an alternative to glycopeptides and streptogramins to treat serious infections due to resistant Gram-positive organisms. Further modification of the oxazolidinone nucleus may yield agents with even greater potency and with novel spectra of activity.

Since the first report of *Staphylococcus aureus* isolates resistant to penicillin,[1] Gram-positive organisms have developed a host of mechanisms to evade antimicrobial agents. Of particular concern have been the emergence of oxacillin- and glycopeptide-resistant staphylococci,[2-4] glycopeptide-resistant enterococci,[5] and penicillin-resistant *Streptococcus pneumoniae*[6] and viridans streptococci.[7] This increasing resistance among Gram-positive species has been accompanied by their increasing predominance as causes of nosocomial infection. *S. aureus*, coagulase-negative staphylococci (CoNS) and *Enterococcus* spp. represent 3 of the top 5 causes of bacteraemia in hospitalised patients in the US and Canada.[8-10] The widespread emergence of glycopeptide resistance among *Enterococcus* spp., particularly *E. faecium*, has been especially troublesome, since some of these strains have been found to be resistant to all currently available antimicrobial agents.[11]

As a result, new antimicrobial agents are being developed – and old ones re-evaluated – as potential alternatives for the management of infections due to multiply resistant Gram-positive microorganisms. Everninomicins,[12] streptogramins,[13] glycopeptide derivatives,[14] carbapenems,[15,16] daptomycin[17] and the oxazolidinones[18] are all in various stages of development. The oxazolidinones have generated considerable interest recently in anticipation of the release of linezolid (PNU 100766, U 100766) for clinical use.[19] This review focuses on the oxazolidinones, and linezolid in particular, as a promising new class of antimicrobial agents.

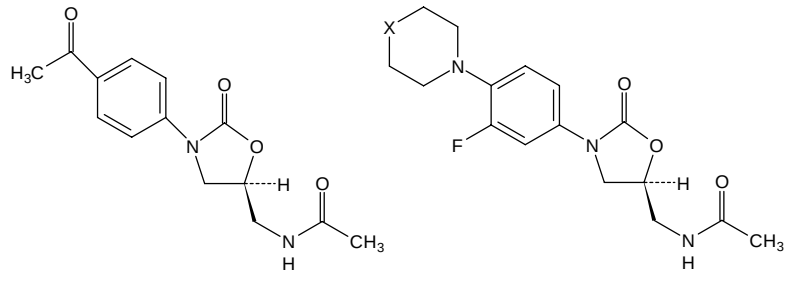
Developed in the late 1980s by scientists at E.I.

du Pont De Nemours and Company,[20] the most promising early oxazolidinones (DUP 721 and DUP 105) have not been further evaluated for clinical use, largely for reasons of toxicity in animal models.[21] Scientists at the Upjohn Company subsequently developed two (*S*)-5-acetamidomethyl-2-derivatives, eperezolid (PNU 100592, U 100592) and linezolid (fig. 1).[22] These compounds have similar *in vitro* activity to the earlier oxazolidinones and were not found to have unfavourable toxicity in Phase I clinical trials. Linezolid was chosen for further clinical development, and is currently in late Phase III clinical trials.

1. Mechanism of Action

The oxazolidinones are protein synthesis inhibitors.[23-26] Early studies of DUP 721 revealed that this agent inhibits an event preceding translation initiation.[23] Subsequent work by scientists at the Upjohn Company confirmed that linezolid and eperezolid most likely inhibited protein synthesis at a step involving the binding of mRNA to the ribosome at the initiation of translation.[25] Oxazolidinones bind directly to the 50S ribosomal subunit and compete with chloramphenicol, clindamycin, and lincomycin for this binding site.[26] However, unlike chloramphenicol or lincomycin, the oxazolidinones do not inhibit protein synthesis by inhibiting peptidyl transferase or by inhibiting the translation termination reaction.[26] They bind instead to the 50S subunit near to the interface with the 30S subunit, thereby preventing the formation of the 70S initiation complex.[26,27] This represents a unique mechanism of action, and there have been no reports of cross-resistance between oxazolidinones and other antimicrobials that act by inhibiting protein synthesis.[28,29]

In vitro resistance to linezolid and eperezolid is not easily induced. Kaatz and Seo[30] tested 12 strains of methicillin-susceptible and -resistant *S. aureus* and *S. epidermidis* in the presence of twice the minimum inhibitory concentration (MIC) of both agents and found no resistant mutants (spontaneous mutation frequency $<10^{-9}$). Zurenko et al.[28] similarly tested *S. aureus* ATCC 29213 and found no colonies resistant to linezolid or eperezolid at 2-, 4- or 8-fold the MIC of these agents, yielding spontaneous mutation frequencies of $<3.8 \times 10^{-10}$ for eperezolid and $<8 \times 10^{-11}$ for linezolid. Serial passage of *S. aureus* and *E. faecalis* on spiral gradients of linezolid or eperezolid can induce stably elevated MICs,[28-30] and these strains exhibit cross-resistance between the 2 agents.[30] Ribosomes extracted from an eperezolid-resistant *S. aureus* strain bound less eperezolid than ribosomes from a susceptible strain, and in a cell free transcription-translation assay the ribosomal fraction conferred eperezolid resistance.[29] Further evaluation of oxazolidinone-resistant *S. aureus* and *E. faecalis* strains demonstrated resistance to be associated with specific mutations (G2447U and G2528U) in the 23S rRNA gene.[31] For 5 linezolid-resistant *S. aureus* strains (MICs ranging



DUP 721

Eperezolid: X = $NC(O)CH_2OH$
Linezolid: X = O

Fig. 1. Structures of DUP 721, eperezolid and linezolid.

from 4 to 64 mg/L), increasing MICs were associated with an increase in the number of mutant 23S rRNA genes.[31] These data further support the hypothesis that oxazolidinones bind to the 50S ribosomal subunit.

2. *In Vitro* Antibacterial Activity

Eperezolid and linezolid have been tested *in vitro* against a wide range of Gram-positive pathogens. The results of these studies are summarised in table I. Both compounds demonstrate good activity against both methicillin-(oxacillin)-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), inhibiting virtually all strains at concentrations of ≤8 mg/L [MIC inhibiting 90% of strains (MIC_{90}) 1 to 4 mg/L in all studies].[28,32-35] Linezolid and eperezolid are also highly active against CoNS (MIC range, 0.25 to 4 mg/L),[28,32-35] including methicillin-resistant CoNS.

All strains of streptococci tested have been inhibited by ≤4 mg/L of eperezolid or linezolid.[28,32,36,37] Notably, both compounds have excellent potency against both penicillin-susceptible and -resistant *S. pneumoniae* strains (MIC_{90} range, 0.25 to 1 mg/L).

Of particular interest has been the activity of eperezolid and linezolid against the enterococci. Each compound inhibits all enterococcal isolates, regardless of vancomycin resistance pattern, at MICs between 0.5 and 4 mg/L. The nearly 400 isolates tested in published studies include over 250 strains of vancomycin-resistant *E. faecium* (VREF).[28,32,38-40] On the basis of pharmacokinetic data (section 4), a tentative MIC breakpoint for susceptibility for linezolid of ≤4 mg/L[32,41] suggests a role for this new oxazolidinone in the treatment of vancomycin-resistant enterococci.

Although fewer strains of some less common Gram-positive pathogens have been tested against linezolid and eperezolid, these drugs have demonstrated potency against viridans group streptococci,[32] *Bacillus* spp.,[28,32] *Corynebacterium* spp.,[28,32] *Listeria monocytogenes*,[28] *Erysipelothrix rhusiopathiae*,[42] *Leuconostoc* spp.,[42] *Pediococcus* spp.[42] and *Rhodococcus equi*.[43] For each of these species or species groups, the strains tested were inhibited by ≤4 mg/L of linezolid.

The oxazolidinones are less active against Gram-negative bacteria. Among Gram-negative aerobic bacteria, linezolid and eperezolid have measurable *in vitro* activity against *Moraxella catarrhalis* (MIC_{90}, 4 to 8 mg/L), *Haemophilus influenzae* (MIC_{90}, 4 to 16 mg/L), *Legionella* spp. (MIC_{90}, 8 to >16 mg/L) and *Neisseria gonorrhoeae* (MIC_{90}, 16 mg/L).[28,32,44] Linezolid has also demonstrated activity against *Pasteurella* spp. [including *P. multocida* (MIC_{90}, 2 mg/L)][45] and *Flavobacterium meningosepticum* (MIC_{90}, 4 mg/L).[46] The oxazolidinones are not active (MIC_{90}, >64 mg/L) against Enterobacteriaciae, *Pseudomonas* spp. or *Acinetobacter* spp.[28,32]

Some data suggest *in vitro* activity of the oxazolidinones against *Mycoplasma* and *Chlamydia* spp.[19,42] More data are needed on the activity of linezolid against these common respiratory pathogens, as this information will have implications for the use of the oxazolidinones in the treatment of community-acquired pneumonia.

A limited number of anaerobic bacterial strains have been tested against linezolid and eperezolid.[32,47] In general, the oxazolidinones have demonstrated greater *in vitro* activity against Gram-positive than against Gram-negative anaerobic species (table II).

The oxazolidinones are also active *in vitro* against *Mycobacterium tuberculosis*[28,48] and *M. avium* complex.[49,50] Of particular interest, both eperezolid and linezolid inhibited 5 isolates of multiple drug-resistant *M. tuberculosis* at concentrations of ≤2 mg/L,[28] raising the possibility that these agents may have a future role in the management of these difficult infections. Chemical substitutions may yield additional drugs (e.g. PNU 100480[51,52]) within this class which have useful activity against the mycobacteria.

As is true for most antimicrobials that inhibit bacterial protein synthesis, the oxazolidinones have consistently demonstrated bacteriostatic activity against most species.[20,24,28,32,38] However, Zurenko et al.[28] noted linezolid and eperezolid to have bactericidal activity against *B. fragilis*, *C. perfringens*

Table I. *In vitro* antimicrobial susceptibility results for linezolid and eperezolid tested against the most common Gram-positive pathogens, compiled from prior published studies

Organism (no. represented)	Antimicrobial agent	MIC (mg/L) ranges[a]		Overall MIC (mg/L) range[b]
		50%	90%	
***S. aureus* (685)[28,32-35]**				
oxacillin-susceptible	Eperezolid	1-4	1-4	0.5-8
	Linezolid	1-4	1-4	0.5-8
oxacillin-resistant	Eperezolid	1-4	1-4	0.5-8
	Linezolid	1-4	1-4	0.5-8
Coagulase-negative staphylococci (430)[28,32-35]				
oxacillin-susceptible	Eperezolid	0.5-2	1-2	0.25-4
	Linezolid	0.5-2	1-2	0.25-4
oxacillin-resistant	Eperezolid	0.5-2	1-2	0.5-4
	Linezolid	0.5-2	1-2	0.5-4
β-Haemolytic streptococci (47)[28,32]	Eperezolid	1-2	1-2	0.5-2
	Linezolid	1-2	2-4	1-4
***S. pneumoniae* (454)[28,36,37]**				
penicillin-susceptible	Eperezolid	0.5	0.5	≤0.016-1
	Linezolid	0.5	1	≤0.016-1
penicillin-resistant	Eperezolid	0.25-0.5	0.25-0.5	0.06-1
	Linezolid	0.5-1	1	0.06-4
***Enterococcus* spp. (391)[28,38-40]**				
vancomycin-susceptible	Eperezolid	1-2	2	0.5-4
	Linezolid	1-4	1-4	0.5-4
vancomycin-resistant	Eperezolid	1-2	2	0.5-4
	Linezolid	2-4	2-4	1-4
***Bacillus* spp. (10)[28,32]**	Eperezolid	1	1	0.5-1
	Linezolid	1	1	0.5-1
***Corynebacterium* spp. (21)[28,32]**	Eperezolid	0.25	0.25-0.5	0.25-0.5
	Linezolid	0.5-2	0.5-2	0.25-2

a Ranges of MIC_{50}s and MIC_{90}s from published studies.

b Overall range of MICs from published studies.

MIC = minimum inhibitory concentration.

and some strains of streptococci, including *S. pneumoniae*. Peters et al.[49] found another investigational oxazolidinone (E 3709-5) to be bactericidal against *M. avium* complex. Against the enterococci, the addition of an aminoglycoside to linezolid or eperezolid did not enhance *in vitro* bacteriostatic activity.[32] There are few additional published data on *in vitro* testing of oxazolidinone-containing antimicrobial combinations.

3. *In Vivo* Antibacterial Activity

The *in vivo* activities of linezolid and eperezolid were investigated in a variety of animal models of bacterial infection by Ford et al.[53] Using a mouse intraperitoneal infection model, both linezolid and eperezolid were comparable in efficacy to vancomycin against MSSA, MRSA and methicillin-resistant CoNS. These oxazolidinones were also very active against penicillin- and cephalosporin-resistant *S. pneumoniae* [dose effective in 50% of animals (ED_{50}) range, 1.8 to 3.8 mg/kg/day] and *S. pyogenes* (ED_{50} range, 5.0 to 5.1 mg/kg/day) in this model. A neutropenic mouse model was used to test linezolid and eperezolid against an aminoglycoside-resistant *E. faecalis* and a VREF strain.[53] Against the *E. faecalis* strain, both eperezolid (ED_{50} 1.3

mg/kg/day) and vancomycin (ED_{50} 0.5 mg/kg/day) were superior in activity to linezolid (ED_{50} 10.0 mg/kg/day), and both eperezolid and linezolid were curative against VREF (ED_{50} range, 12.5 to 24.0 *vs* >100 mg/kg/day for vancomycin). Neither oxazolidinone displayed significant activity *in vivo* against the Gram-negative pathogens *Escherichia coli*, *Klebsiella pneumoniae* or *M. catarrhalis*.

In a mouse model of soft-tissue infection,[53] both linezolid and eperezolid displayed activity against *S. aureus*, although eperezolid was more effective (ED_{50} 12.5 *vs* 39.0 mg/kg/day, with vancomycin ED_{50} 4.7 mg/kg/day). In the *E. faecalis* soft-tissue infection model, both linezolid and eperezolid were comparable to vancomycin, but against *B. fragilis*, only linezolid displayed any activity (ED_{50} 46.3, *vs* >100 mg/kg/day for eperezolid). Combination therapy with eperezolid + gentamicin and linezolid + gentamicin was highly active against a polymicrobic soft-tissue infection model (gentamicin-resistant *S. aureus* and gentamicin-susceptible *E. coli*). The same mixed infection was also cured readily with oxazolidinone + aztreonam combinations.[53]

4. Pharmacokinetic and Pharmacodynamic Profile

The pharmacokinetics of eperezolid and linezolid have been evaluated in randomised, placebo-controlled phase I clinical trials.[54-56] Eperezolid, at the maximum dose tested (2000mg orally 4 times daily), achieved peak and trough serum concentrations of 11.4 mg/L and 4.97 mg/L.[54] This administration schedule thereby achieved trough concentrations greater than the MIC values for most important Gram-positive species.

Linezolid, however, exhibited superior pharmacokinetics in phase I trials.[55,56] After oral administration, linezolid was rapidly and completely absorbed [bioavailability ≈100%, peak concentration (C_{max}) occurring 1 to 2 hours after administration]. Steady-state C_{max} values were approximately 12 and 18 mg/L after oral doses of 375 and 625mg, respectively, and trough concentrations (C_{min}) during administration of 375mg every 12 hours were above 4.0 mg/L. A parenteral formulation of linezolid has also been tested in humans, and similar steady-state C_{min} values of 3.51 and 3.84 mg/L were seen after 12-hourly intravenous administration of 500 and 625mg, respectively.[56] The elimination half-life ($t_{½\beta}$) for intravenous and oral administration schedules was 4.5 and 5.5 hours, respectively, and C_{max}/area under the concentration-time curve values generally increased in linear fashion with increasing dose.[55,56] Linezolid is cleared by both renal and nonrenal routes, and pharmacokinetics in patients with renal failure suggest that a decrease in linezolid dosage may not be necessary, but that in pa-

Table II. *In vitro* antimicrobial susceptibility results for linezolid and eperezolid tested against the most common anaerobic pathogens

Organism (no. represented)	Antimicrobial agent	MIC (mg/L)[a]		Overall MIC (mg/L) range[a]
		50%	90%	
Bacteroides fragilis (17)	Eperezolid	8	>16	0.5->16
	Linezolid	4	8	0.5-8
Clostridium spp. (not *difficile*) (34)	Eperezolid	2	2	≤0.25-8
	Linezolid	2	4	≤0.25-16
Clostridium difficile (27)	Eperezolid	2	16	1-16
	Linezolid	2	>16	2->16
Peptostreptococcus spp. (36)	Eperezolid	0.5	1	≤0.25-1
	Linezolid	1	2	≤0.25-2
Prevotella spp. (18)	Eperezolid	4	8	1->16
	Linezolid	2	4	0.5-4

a MIC_{50}s, MIC_{90}s and MIC ranges compiled from Jones et al.[32] and Yagi & Zurenko.[47]

MIC = minimum inhibitory concentration.

tients on dialysis, supplemental or postdialysis doses may be required.[57]

Table III provides a summary of the pharmacokinetic characteristics of linezolid in healthy adults. On the basis of these data combined with *in vitro* MIC_{90} values for important Gram-positive pathogens, dosage schedules of 400mg (oral or intravenous) every 12 hours for mild to moderate and 600mg every 12 hours for severe infections have been proposed. In paediatric patients the clearance of linezolid is somewhat higher and $t_{½\beta}$ somewhat shorter (3 to 4 hours) than in adults, and a 10 mg/kg twice daily regimen has been suggested for use in clinical trials.[58]

The pharmacodynamic activities of eperezolid and linezolid have been examined in a mouse thigh infection model.[59,60] For *S. pneumoniae*, time above the MIC was the major predictor of efficacy, and for *S. aureus* there was no parameter correlated with efficacy because of lower rates of *in vivo* killing.[59,60] The *in vivo* postantibiotic effect (PAE) of linezolid was 3 to 4 hours for *S. pneumoniae* and *S. aureus*,[60] whereas the *in vitro* PAE for eperezolid and linezolid against *Staphylococcus* spp. and *Enterococcus* spp. was approximately 0.8 hours.[35] The *in vivo* PAE described by Andes et al.[59,60] lends further support to the proposed twice daily dosage regimen for linezolid.

Table III. Pharmacokinetic characteristics of linezolid

Oral bioavailability	100%
Food effect	Slight decrease in rate but not extent of absorption
Volume of distribution	40-50L
Protein binding	31%
Peak concentration	Occurs 1-2h after PO dose
375mg PO dose	12 mg/L
625mg PO dose	18 mg/L
Trough concentration	
375mg PO q12h	≈4.0 mg/L
500mg IV q12h	3.51 mg/L
625mg IV q12h	3.84 mg/L
Elimination half-life	
PO	5.5h
IV	4.5h
Clearance	100-200 ml/min
renal	30-50 ml/min
nonrenal	70-150 ml/min

IV = intravenous; **PO** = oral; **q12h** = every 12 hours.

5. Therapeutic Trials

Linezolid is now in late phase III clinical trials, and some phase II clinical trial results are available for review.[19,61] Linezolid therapy resulted in cure or improvement in 96% of 204 patients treated for skin and soft-tissue infection, and a favourable microbiological outcome was obtained in 92% of 70 evaluable patients, including many with *S. aureus* and *S. pyogenes* infection.[61] Of 81 patients with community-acquired pneumonia, linezolid therapy resulted in cure or improvement in 98%. When analysed by intention-to-treat, the rate of favourable outcome was 87% in this trial.[19] Notably, microbiological eradication was achieved in all evaluated patients infected with *S. pneumoniae* (n = 25).

Results from a noncomparative, compassionate use linezolid treatment protocol for patients with multidrug-resistant Gram-positive infections have been reported recently.[62] Of 27 patients enrolled, clinical cure was achieved in 63% and microbiological cure in 55.6%. Most of the patients enrolled were infected with vancomycin-resistant *Enterococcus* spp. (n = 20), and the majority had a bacteraemic infection.[62]

Linezolid has also been found effective in eradicating nasal colonisation with *S. aureus*.[63] At doses of 200, 400 or 600mg daily for either 3 or 5 days, linezolid eradicated nasal colonisation in 45 of 48 treated patients (94%), while colonisation persisted in all 8 placebo-treated patients. However, 30 days after therapy 37 of the 48 patients were recolonised with *S. aureus*.[63] Nonetheless, if transient eradication of *S. aureus* nasal colonisation is demonstrated to decrease postoperative infections due to *S. aureus*,[64] linezolid may provide an additional therapeutic option.

Phase III trials currently under way will provide much more information regarding the efficacy of linezolid in the treatment of serious skin, soft-tissue, respiratory tract and bloodstream infections.[19,65]

6. Tolerability

Linezolid is well tolerated after both oral and intravenous administration. Phase I trials have found the most common adverse reactions to be gastrointestinal disturbances (diarrhoea, nausea and tongue discolouration), followed by headache and skin rash.[55,56,63] Overall, adverse effects are seen in approximately 3% of linezolid recipients,[61] and have only rarely required discontinuation of the drug.[61-63] No serious cardiac, respiratory or haematological abnormalities have been reported during phase I or II clinical trials.[55,56,61-63]

Since early oxazolidinones were monoamine oxidase (MAO) inhibitors,[21] concern has been raised about this potential adverse effect. However, *in vitro* testing has revealed linezolid to be a very weak, reversible inhibitor of human MAO,[66] and no clinical evidence of MAO inhibition has been observed during trials to date.[61]

7. Oxazolidinones: Current Status

On the basis of *in vitro* activity and early clinical experience, the oxazolidinones, as represented by linezolid, appear to be a very promising new class of antimicrobial agents. One of the most exciting potential uses for these agents is in the management of resistant Gram-positive infections, including those due to MRSA, methicillin-resistant CoNS, vancomycin-resistant enterococci, and penicillin- or cephalosporin-resistant *S. pneumoniae*. As glycopeptide-intermediate or -resistant *Staphylococcus* spp. infections increase in frequency,[3,4] the activity of linezolid and other oxazolidinones against these strains will be of great interest.

In vitro and pharmacokinetic data also suggest that the oxazolidinones may be extremely useful in the management of mycobacterial infection, including *M. tuberculosis* that is multiply drug-resistant. Chemical modification of the oxazolidinone nucleus[67,68] may yield compounds more potent than linezolid and with novel spectra of activity.

The results of phase III clinical trials will help to define the role of linezolid in the management of lower respiratory tract infections and serious bloodstream infections due to *Staphylococcus* spp. and vancomycin-resistant enterococci. As long as other therapeutic options exist for community-acquired respiratory tract infections and uncomplicated skin and soft-tissue infections, it seems prudent to reserve linezolid for the management of serious or complicated infections due to potentially resistant Gram-positive organisms.

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