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REVIEW

Present and Emerging Therapies for the Treatment of Drug-resistant Infections: Focus on Linezolid

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Abstract: Linezolid (trade names Zyvox™, Zyvoxid™ and Zyvoxam™) is a synthetic antimicrobial agent of the family of oxazolidinones, which has been approved for the treatment of vancomycin-resistant *Enterococcus faecium* infections, lower respiratory tract infections, skin and skin-structure infections and diabetic foot infections caused by susceptible bacteria. Its antimicrobial spectrum, which includes Gram-positive cocci and bacteria resistant to other antimicrobials, its favorable pharmacokinetic properties and its safety profile make it an important addition to our therapeutic armamentarium. In this review, we summarize the literature describing linezolid's in vitro characteristics, the clinical experience regarding its approved and off-label clinical uses and its safety and tolerability.

Keywords: linezolid, safety, antimicrobials, oxazolidinones

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Introduction

Oxazolidinones are synthetic antibacterial agents first developed by DuPont Pharmaceuticals in the late 1970s for use in agriculture. By the mid-1980s, more oxazolidinone derivatives potentially useful for human use were released but the early analogues (DuP 105 and DuP 721) proved unsuitable for pharmaceutical development.[1] Investigation was re-initiated by the Upjohn Corporation in the early 1990s, leading to the discovery of linezolid (U-100766), which had promising in vitro and pharmacokinetic properties.[2]

Linezolid (trade names Zyvox™, Zyvoxid™ and Zyvoxam™) was the first oxazolidinone to enter into the market in 2000 in the USA by Amersham Pharmacia (now Pfizer) and subsequently it was approved for use in Europe and in Asia. This represented a landmark in antimicrobial research with linezolid being the first truly novel antibiotic to become approved for clinical use since 1972.[3]

This review outlines linezolid's mechanism of action, *in vitro* antimicrobial activity and pharmacokinetic properties. Also acquired resistance mechanisms developed by certain bacterial species against linezolid are discussed and current clinical experience from its use is summarized in order to define its current place in our armamentarium in the battle against infection.

Mechanism of Action

Linezolid binds to the 23S rRNA of the 50S subunit of the prokaryotic ribosome, preventing it from complexing with the 30S subunit, mRNA, initiation factors and N-formylmethionyl-tRNA.[4,5] Recent elegant studies using X-ray crystallography have determined the crystal structure of linezolid and have elucidated the binding site of the drug on the peptidyltransferase center of the large ribosomal subunit. This site overlaps significantly with the aminoacyl moiety of bound tRNA and stabilizes a distinct conformation of nucleotide U2585.[6] The net result is to block assembly of a functional initiation complex for protein synthesis, thereby preventing translation of the mRNA. This mode of action differs from that of older protein synthesis inhibitors such as chloramphenicol, macrolides, lincosamides and tetracyclines, which allow mRNA translation to begin but then inhibit peptide elongation. This difference is significant in two respects. First, linezolid seems particularly effective in preventing the synthesis of staphylococcal and streptococcal virulence factors (e.g. coagulase, haemolysins, leucocidins, protein A, streptolysin O and DNAase).[7] Second, linezolid has a target that does not overlap with those of other protein synthesis inhibitors; consequently, no cross-resistance with drugs of other classes is exhibited.[8]

In Vitro Antimicrobial Activity

Linezolid demonstrates in vitro activity against most Gram-positive aerobes including *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus* spp., and *Enterococcus* spp. Its activity is maintained irrespective of resistance to other drugs as a consequence of the unique mode of its antimicrobial action. Thus, linezolid is equally active against methicillin-susceptible and -resistant staphylococci including vancomycin-intermediate strains, against vancomycin-susceptible enterococci and those with VanA, VanB or VanC determinants and against pneumococci susceptible or resistant to penicillins and/or macrolides.

Numerous *in vitro* studies have shown that linezolid has narrow, unimodal MIC distributions. The MICs for enterococci, pneumococci, staphylococci and streptococci fall between 0.5 and 4 μg/ml. MIC_{90s} were usually 1 to 2 μg/ml.[9–13] Linezolid has also demonstrated potency against viridans group streptococci, *Clostridium perfringens, Clostridium difficile, Nocardia* spp., *Bacillus* spp., *Corynebacterium* spp., *Listeria monocytogenes*, *Erysipelothrix rhusiopathiae*, *Leuconostoc* spp., *Pediococcus* spp., and *Rhodococcus equi*. For each of these species or species groups, the strains tested were inhibited by <=4 μg/ml of linezolid.[14]

Most Gram-negative organisms are inherently resistant to linezolid (see section on mechanisms of resistance), but MICs of 4–8 μg/ml are seen for many *Bacteroides* spp., *Moraxella catarrhalis* and *Pasteurella* spp.[15]

Linezolid has shown in vitro activity against *Mycobacteria* including *M. avium* complex and *M. bovis*. It is active against *Mycobacterium tuberculosis* irrespective of resistance to other antimicrobial classes. MIC_{90s} of 1 to 8 mg/ml have been reported for 39 MDR *M. tuberculosis* clinical strains.[16]

Susceptibility interpretive criteria proposed by CLSI[17] and EUCAST[18] are shown in Table 1.

Table 1. Interpretative susceptibility criteria for in vitro testing of linezolid, as proposed by CLSI[17] and EUCAST.[18]

	Susceptible/Resistant (μg/ml)			
	***Staphylococcus* spp.**	***Enterococcus* spp.**	***Streptococcus* spp.**	***S. pneumoniae***
CLSI	≤4/–	≤2/≥8	≤2/–	≤2/–
EUCAST	≤4/>4	≤4/>4	≤2/>4	≤4/>4

Linezolid is essentially bacteriostatic, achieving less than a 2 $\log_{10}$ reduction in the count of enterococci and staphylococci over 24 h when tested at 4 × MIC. One group observed a 3–4 $\log_{10}$ reduction in bacterial count over 6 h for pneumococci, and concluded that linezolid was bactericidal against these organisms;[15] another found little or no bactericidal activity for linezolid against viridans or β-haemolytic streptococci.[19] Bactericidal in vitro activity was also observed against *Bacteroides fragilis* and *C. perfringens*.[15]

Metabolism, Pharmacokinetic/ Pharmacodynamic Properties

The pharmacokinetics of linezolid have been extensively studied as part of the clinical development of the agent. Therefore, there is available data from healthy volunteers and patients with stable excretory organ failure as well as from special patient groups.

Linezolid may be assayed in body fluids by HPLC. Available formulations of the agent include an intravenous (iv) form, film-coated tablets and an oral suspension. The recommended dose is 600 mg b.i.d.

Linezolid is well absorbed with a mean absolute bioavailability of ~100% in healthy volunteers. Major pharmacokinetic parameters after multiple i.v or oral doses are shown in Table 2.

The volume of distribution at steady state in healthy adults is 30–50 L. Protein binding is 31% and is not concentration dependent. Adequate to good tissue penetration into skin blister fluids, bone, muscle, fat, alveolar cells, lung extracellular lining fluid and CSF has been documented. In healthy volunteers penetration into cantharidine-induced skin blisters was 104% ± 21% (range 80%–130%) compared with serum.[20] Plasma and lung epithelial lining fluid concentrations were 15.5 ± 24.2 and 64.3 ± 33.1 μg/ml at 4 h and 10.2 ± 2.3 and 24.3 ± 13.3 μg/ml at 12 h, respectively, after multiple oral doses in healthy volunteers. Concentrations in alveolar cells were much lower, with a mean *C*max of 2.2 ± 0.6 μg/ml at 4 h. The mean fluid to plasma ratios for sweat and saliva were 0.55:1 and 1.2:1, respectively[21] and bone, fat and muscle penetration was shown to be at the level of 60%, 37% and 94% of plasma concentration, respectively.[22] In a patient with meningitis, administration of iv linezolid 600 mg b.i.d. produced adequate CSF penetration, with a CSF:plasma ratio of 0.8. On day 5 of treatment CSF levels were 5.36 μg/ml and 3.8 μg/ml, at 5 and 12 h after infusion.[23] In patients with ventricular–peritoneal shunts and noninflamed meninges, the ratio of CSF:plasma concentration was 0.7:1.0 after multiple linezolid doses.[21]

Linezolid is primarily metabolized by nonenzymatic oxidation that produces two major metabolites (PNU-142300 and PNU-142586) and numerous minor ones. None of these has any antibacterial activity. Involvement of the cytochrome P450 (CYP) system in the metabolism of linezolid has not been demonstrated and linezolid neither induces nor inhibits its human CYP isoforms.

Drug elimination takes place by renal and nonrenal routes. Overall, non-renal clearance is 65% of the total clearance of linezolid.[20]

The pharmacokinetics of linezolid are age dependent, with infants and children having greater

Table 2. Mean pharmacokinetic parameters after multiple doses of oral or intravenous linezolid in healthy adults.[20,21]

Dose	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0–12}$ (μg·h/ml)	CL (ml/min)
600 mg po	18.3 ± 6.018	–	0.7 ± 0.3	4.9 ± 1.8	107 ± 41	–
600 mg iv	15.1 ± 2.5	3.7 ± 2.4	0.5	4.8	89.7 ± 31.0	123

Abbreviations: C_{max}, peak serum concentration; C_{min}, trough serum concentration; T_{max}, time necessary to reach the peak plasma concetration; $t_{½}$, serum half life; $AUC_{0–12}$, area under the concentration curve (0–12 h); CL, clearance.

plasma clearance, larger volumes of distribution and corresponding lower serum concentrations and serum AUC.[24] In children, administration of linezolid 10 mg/kg three times daily is required.

No differences were noted between groups of men and women but pharmacokinetic studies have not been performed to date in patients of extreme old age. Nevertheless, dose adjustment in old age is not recommended.[25] Lower but presumably adequate serum levels were observed in obese patients.[26]

Linezolid pharmacokinetics have been studied in patients with mild to moderate liver disease. No statistically significant differences were observed compared with healthy volunteers so no dose modification is recommended in mild to moderate hepatic insufficiency. There are no studies in severe hepatic failure (i.e. Child–Pugh Class C), but as linezolid is metabolized predominantly by a non-enzymic process, impairment of hepatic function would not be expected to alter the pharmacokinetics significantly.[21]

Linezolid pharmacokinetics have been studied in patients with varying degrees of renal insufficiency and no significant differences were noted. Haemodialysis removed 30% of the linezolid dose. Thus, administration of the standard dosage of linezolid, 600 mg every 12 h, is recommended irrespective of the degree of renal insufficiency and should be scheduled after haemodialysis.[27]

Also, penetration of linezolid has been studied into inflamed areas of diabetic foot infection. Tissue/plasma ratios of mean 101.7% produced a mean concentration of 9.6 μg/g, which is greater than those predicted to be effective against MRSA.[28]

The pharmacodynamic characteristics of linezolid have been studied both in animal models and in human studies; $T > MIC$ or $AUC_{24} > MIC$ were found to be the most accurate predictors of in vivo efficacy.[29]

Mechanisms of Resistance

Early in vitro studies have shown that mutational linezolid resistance is extremely difficult to select in vitro against Gram-positive cocci.[8,15] When resistance was ultimately obtained by in vitro passage of staphylococci and enterococci, it was found to be associated with target site mutations to the central loop of domain V of the 23S rRNA, which lies in the 50S ribosomal subunit. Multiple 23S rRNA copies of the genes are present in most species and more than one of these must be altered for resistance to arise, perhaps explaining the difficulty of selection.[30]

Despite the difficulty of in vitro selection, linezolid resistance has emerged during therapy first in enterococci and *S. aureus* and more recently in coagulase-negative staphylococci. Low dose, indwelling lines and devices, protracted therapy and sequestered sites of infection have been identified as risk factors for resistance development.[31,32] Acquired resistance in clinical isolates has been associated with a G2576T mutation in at least two gene copies encoding for 23S rRNA. The MIC level correlates with the number of mutated gene copies.[33] Linezolid-resistant enterococci have emerged sporadically during treatment[31,34] but also as a result of horizontal dissemination among hospitalized patients, irrespective of linezolid exposure.[35–38] Linezolid resistance in *S. aureus* was first described in a sporadic strain in 2001[39] and remains rare.[40] Additionaly to the G2576T mutation, a T2500A mutation in domain V of the 23S rRNA gene and loss of a single copy of the 23S rRNA gene have been identified in a linezolid-resistant *S. aureus* clinical isolate.[41] Recently, nosocomial outbreaks of linezolid-resistant *S. epidermidis* have been described in various institutions[42,43] and the underlying mechanism of resistance was a G2576T mutation[42] or a G2603T mutation[44] or a T2504A mutation[45] in the 23S rRNA gene.

Unfortunately, oxazolidinone resistance mechanisms are not limited to 23S rRNA mutations. Methylation of 23S rRNA (A2503) by the horizontally transmitted Cfr methyltransferase has been described to confer resistance to linezolid as well as phenicols, lincosamides, pleuromutilins, and streptogramin A.[46] Also, ribosomal protein L3 mutations have been identified in *S. aureus* clinical isolates.[47]

Linezolid resistance in *S. pneumoniae* is extremely rare and has been associated with a deletion in the gene encoding ribosomal protein L4.[48]

The ribosomes of *Escherichia coli* are as susceptible to linezolid as those of Gram-positive cocci but, with minor exceptions (see spectrum of activity), Gram-negative bacteria are oxazolidinone resistant most likely because oxazolidinones are excreted by an endogenous AcrAB efflux pump.[49]

In order to prospectively monitor resistance development, multinational surveillance networks have

been organized such as the worldwide Zyvox® Annual Appraisal of Potency and Spectrum Program (ZAAPS). In the 2002–2003 report from the ZAAPS program, near complete activity of the drug was identified against 16060 clinical Gram-positive isolates, with 99.93% of tested isolates being susceptible. Rare linezolid-resistant isolates were identified among enterococci.[50] In the most recent 2008 ZAAPS report, among 6121, eight linezolid-resistant isolates were detected in 7 countries among the enterococci (*E. faecalis* [3] and *E. faecium* [2]) and CoNS (3 *S. epidermidis*). Gram-positive clinical isolates >99.5% were susceptible.[51]

Clinical Studies

Linezolid has been approved for the treatment of vancomycin-resistant *Enterococcus faecium* infections including bacteremia, nosocomial pneumonia caused by methicillin-resistant (MRSA) or methicillin-susceptible *S. aureus* (MSSA), complicated or uncomplicated skin and skin-structure infections and diabetic foot infections without osteomyelitis (in USA only) caused by susceptible bacteria, and community-acquired pneumonia caused by *S. aureus* or *S. pneumoniae*. Linezolid is the first agent approved to treat infections caused by MRSA in 140 years and the second agent (and first oral agent) approved to treat infections caused by vancomycin-resistant enterococci.

Clinical studies supporting these approved indications as well as studies describing existing clinical experience on off-label indications will be reviewed.

Skin and Skin-structure Infections (SSSIs)

A summary of relevant randomized comparator-controlled clinical trials (RCT) is depicted in Table 3. Most of these studies have shown non-inferiority of linezolid compared to antistaphylococcal penicillins or most frequently to vancomycin although some studies have shown superiority of linezolid especially in MRSA eradication.[57,60,63]

A meta-analysis[65] of eight randomized controlled trials that reported data on SSSIs revealed that empirical treatment with linezolid was associated with significantly better success than glycopeptides or β-lactams in clinically assessed patients (2,350 clinically assessed patients, OR 1.65 [1.08 to 2.53]). The odds ratio for linezolid superiority was 2.24 (95% CI 1.12 to 4.48) against glycopeptides and 1.37 (95% CI 1.00 to 1.88) against β-lactams. Another recent meta-analysis evaluating six randomized controlled trials of linezolid versus vancomycin for SSSIs concluded that success of empirical treatment was achieved in 89% of linezolid-treated patients and in 86% of vancomycin-treated patients. Empirical treatment of patients with SSSIs with linezolid was associated with significantly better success than vancomycin (1438 clinically assessed patients, OR 1.40, 95% CI 1.01 to 1.95).[66] Finally a meta-analysis evaluating four randomized clinical trials of linezolid versus vancomycin for MRSA hospital-acquired SSSIs was not able to detect a statistically significant difference between the two treatments.[67]

In the study by Wiegelt et al,[57] the mean total duration of treatment was similar in both groups but the mean duration of i.v. treatment was significantly shorter for patients who received linezolid than for those who received vancomycin (4.7 and 11.1 days, respectively; $P = 0.0001$). In another study by Wiegelt et al,[60] the overall mean duration of treatment was longer for patients receiving linezolid (11.8 ± 4.9 vs. 10.9 ± 5.3 days) but i.v. duration was significantly shorter (4.0 ± 2.6 vs. 9.0 ± 5.3 days).

Itani et al[68] compared the health outcomes (other than clinical efficacy and safety) of patients randomized to receive linezolid or vancomycin for cSSSIs in the previously mentioned study by Wiegelt et al.[60] Linezolid treatment was associated with significantly shorter length of stay (all $P < 0.01$), decreased i.v. antibiotic treatment duration (all $P < 0.0001$) and higher discharge rates the first 2 weeks after start of treatment (all $P < 0.05$). The authors concluded that linezolid has the potential to reduce medical resource use for the treatment of cSSSIs. Cost effectiveness studies have shown linezolid treatment to be cost-effective for patients with c-SSSIs when MRSA is a probable cause.[69]

Pneumonia

RCTs evaluating linezolid in comparison with a glycopeptide or a b-lactam for the treatment of pneumonia are summarized in Table 4.

Two retrospective analyses of data from two prospective RCTs for nosocomial pneumonia[70,72] concluded that in the subset of patients with MRSA

Table 3. A summary of clinical studies evaluating the efficacy of linezolid for the treatment of skin and skin structure infections.

Design	Type of infection	Regimen	Successful outcome, *n* (%)	References
Prospective, randomized, comparator-controlled, double-blind, double-dummy, multicenter, multinational	c-SSSIs	LND (600 mg iv then po q12h) or OXA (2g iv q6h) then DICLO (500 mg po q6h)[a] for 10–21 days	CE cure: LZD 264 of 298 patients (88.6%); OXA/DICLO 259 of 302 patients (85.8%) ($P = 0.300$; 95% CI, –2.5 to 8.2) ME cure: LZD126 of 143 patients (88.1%); OXA/DICLO130 of 151 patients (86.1%) ($P = 0.606$; 95% CI, –5.6 to 9.7)	Stevens et al[52]
Prospective, randomized, comparator-controlled, open-label, multicenter, multinational	MRSA infections (230 patients with SSSIs)	LND (600 mg iv or po q12h) or VAN (1g iv q12h)[b] for 7–14 days	ITT cure: LZD 64 of 99 patients (64.6%); VAN 54 of 87 patients (62.1%)	Stevens et al[53]
Prospective, randomized, comparator-controlled open label, multicenter, multinational	Infections caused by Gram-positives in children (0–12 years old) (89 patients with c-SSSIs and 18 patients with c-SSSIs caused by MRSA)	LND (10 mg/kg iv q8h then po) or VAN (10 to 15 mg/kg iv q6 to 24 h)[b,c] for 10–28 days	CE cure: LND 55 of 59 patients (93.2%); VAN 27 of 30 patients (90%) (95% CI, –9.3 to 15.7) MITT in MRSA group cure: LND 9 of 10 patients (90%); VAN 6 of 8 patients (75%) ($P = 0.40$)	Kaplan et al[54]
Prospective, blinded, randomized, comparator-controlled, multinational, multicenter	Unc-SSSIs caused by MRSA in outpatient children (5–17 years old)	LND (10 mg/kg po q12h) or CFD (15 mg/kg po q12h) for 10–21 days	MITT cure: LND 13 of 14 patients (92.9%); CFD 7 of 9 patients (77.8%) ($P = 0.30$; 95% CI, –15.2 to 45.4)	Kaplan et al[55]
Prospective, randomized, blinded, comparator-controlled, multicenter, multinational	Unc-SSSIs caused in outpatient children (5–17 years old)	LND (10 mg/kg po q12h) or CFD (15 mg/kg po q12h) for 10–21 days	CE cure at FU: LND 201 of 221 patients (91%); CFD 189 of 210 patients (90%) ME cure: LND 120 of 134 patients (89.6%); CFD 111 of 125 patients (88.8%)	Wible et al[56]
Prospective, open-label, randomized, comparator-controlled, multicenter, multinational	Surgical site infections	LND (600 mg iv or po q12h) or VAN (1 g iv q12h) for 7–21 days	CE cure: LZD 52 of 53 patients (98%); VAN 47 of 54 patients (87%) ($P = 0.06$; 95% CI, 1.40 to 20.75) ME cure: LZD 41 of 49 patients (84%); VAN 28 of 49 patients (58%) ($P = 0.0073$; 95% CI, 7.97 to 42.71) Microbiological cure in MRSA group: LZD 26 of 30 patients (87%); VAN 14 of 29 patients (48%) ($P = 0.0022$; 95% CI, 16.51 to 60.27)	Wiegelt et al[57]
Prospective, randomized comparator-controlled, open-label, multicenter multinational	Diabetic foot infections	LND (600 mg q12h iv or po) or AMP/SULB (1.5–3 g q6h iv) or AMOX/CLAV (500–875 mg q8–12h po)[d] for 7–28 days	ITT cure: LND 165 of 203 patients (81%), AMP/SULB or AMOX/CLAV 77 of 108 (71%) (95% CI, –0.1 to 20.1) ITT cure in patients without osteomyelitis: LND 87% vs. AMP/SULB or AMOX/CLAV 72% ($P = 0.003$, 95% CI, 4.5 to 25.7)	Lipsky et al[58]

Prospective, randomized, open-label, comparator-controlled, multicenter multinational	Gram-positive infections (240 patients with SSSIs)	LND (600 mg iv or po q12h) or TEICO iv or im for 7–28 days[e]	ITT cure: LND 113 of 117 patients (96.6%); TEICO 103 of 111 patients (92.8%) (95% CI: –2.0 to 9.6)	Wilcox et al[59]
Prospective, open-label, randomized, comparator-controlled, multicenter, multinational	c-SSSIs	LND (600 mg iv or po q12h) or VAN (1 g iv q12h)[a, f] for 7–14 days	CE cure: LZD 436 of 462 patients (94.4%); VAN 394 of 436 patients (90.4%) ($P = 0.023$; 95% CI, 0.53 to 7.48) ME cure: LND 312 of 330 patients (94.5%); VAN 278 of 310 patients (89.7%) ($P = 0.022$; 95% CI, 0.69 to 9.05) MRSA group cure: LZD 124 of 140 patients (88.6%); VAN 97 of 145 patients(66.9%) ($P < 0.001$; 95% CI, 12.38 to 30.97)	Wiegelt et al[60]
Prospective, randomized comparator-controlled, open-label, single-center	c-SSSI caused by MRSA	LND (600 mg po q12h) or VAN (1 g iv q12h) for 7–21 days	Cure at FU: LND 50%, VAN 20% ($P = 0.015$)	Sharpe et al[61]
Randomized, open-label, comparator-controlled, multicenter	Confirmed or suspected MRSA infections (48 patients with c-SSSIs)	LND (600 mg iv or po q12h) or VAN (1 g iv q12h or dose adjusted to renal function)[b] for 7–21 days	Cure: LND 14 of 18 patients (77.8%); VAN 14 of 18 patients (60.0%) (P = 0.32)	Kohno et al[62]
Prospective, randomized, double-blind, comparator-controlled, multicenter	Infections caused by Gram-positives (62 patients with c-SSSIs)	LND (600 mg iv or po q12h) or VAN (1 g iv q12h if age $\leq$ 60 years or 0.75 mg iv q12h if age $>$ 60 years)[a] for 7–21 days	Cure at FU: LND 30 of 33 patients (90.9%); VAN 19 of 24 patients (79.2%) (95% CI, –7.2 to 30.7)	Lin et al[63]
Prospective, randomized, comparator-controlled open-label, multicenter	c-SSSI with or without bacteremia	LND (600 mg iv or po q12h) or VAN (1 g iv q12h)[f,g] for 7–28 days	CE cure: LND 123 of 158 patients (77.8%); VAN 113 of 145 patients (77.9%) (95% CI, –9.4 to 9.3) ME cure: LND 146 of 163 patients (89.6%); VAN 134 of 149 patients (89.9%) ($P = 0.9161$; 95% CI, –7.1 to 6.4)	Wilcox et al[64]

[a]Aztreonam (1–2 g q6–8h) was added if gram-negative coverage was necessary.
[b]Aztreonam or gentamicin was added at the discretion of the physician.
[c]Vancomycin was changed to another appropriate oral antibiotic based on culture results.
[d]Vancomycin (1 g q12h iv, adjusted for renal dysfunction, advanced age, or obesity) could be added to the comparator if MRSA was suspected or confirmed and aztreonam (1–2 g iv q8–12h) could be added in either arm if Gram-negatives were suspected.
[e]Antibiotics to cover for Gram-negative organisms (aztreonam, gentamicin, amikacin, ciprofloxacin, ceftazidime or imipenem) or anaerobes metronidazole) could be added
[f]Patients with documented MSSA infections receiving vancomycin were switched to oxacillin sodium, nafcillin, or flucloxacillin (1–2 g i.v. q6h or to dicloxacillin (500 mg po q6h) after initial vancomycin therapy.
[g]Aztreonam or amikacin was added at the discretion of the physician
Abbreviations: c-SSSIs, complicated skin and skin structure infections; LND, linezolid; OXA, oxacillin; DICLO, dicloxacillin; CE, clinically evaluable patients; ME, microbiologically evaluable patients; VAN, vancomycin; CI, confidence interval; MRSA, methicillin resistant *Staphylococcus aureus*; ITT, intent to treat population; CFD, cefadroxil; unc-SSSIs, uncomplicated skin and skin structure infections; MITT, modified intent to-treat population; FU, follow-up visit; AMP/SULB, ampicillin/sulbactam; AMOX/CLAV, amoxicillin/clavulanic acid; TEICO, teicoplanin.

Table 4. Summary of clinical studies evaluating the efficacy of linezolid in the treatment of pneumonia.

Study design	Type of infection	Regimen	Outcome, *n* (%)	References
Prospective, randomized, comparator-controlled, open-label, multicenter, multinational	MRSA infections (99 patients with pneumonia)	LND (600 mg iv or po q12h) or VAN (1 g iv q12h)[a] for 7–14 days	ITT cure: LZD 20 of 39 patients (51.3%); VAN 16 of 32 patients (50%)	Stevens et al[53]
Prospective, randomized, comparator-controlled open label, multicenter, multinational	Infections caused by Gram-positives in children (0–12 years old) (39 patients with nosocomial pneumonia)	LND (10 mg/kg iv q8h then po) or VAN (10 to 15 mg/kg iv q6 to 24 h)[b,c] for 10–28 days	Cure: LND 9 of 10 patients (90%), VAN 10 of 10 patients (100%) (95% CI, 128.6 to 8.6)	Kaplan et al[54]
Prospective, randomized, open-label, comparator-controlled, multicenter multinational	Gram-positive infections (109 patients with pneumonia)	LND (600 mg iv or po q12h) or TEICO iv or im for 7–28 days[d]	EOT cure: LND 51 of 53 patients (96.2%), TEICO 52 of 56 patients (92.9%) (95% CI, –5.1 to 11.8)	Wilcox et al[59]
Randomized, open-label, comparator-controlled, multicenter	Confirmed or suspected MRSA infections (77 patients with pneumonia)	LND (600 mg iv or po q12h) or VAN (1g iv q12h)[a,e] for 7–21 days	Cure: LND 21 of 35 patients (60%); VAN 9 of 19 patients (47.4%) (P = 0.37)	Kohno et al[62]
Prospective, randomized, double-blind, comparator-controlled, multicenter	Infections caused by Gram-positives (80 patients with pneumonia)	LND (600 mg iv or po q12h) or VAN (1 g iv q12h if age $\leq$ 60 years or 0.75 mg iv q12h if age $>$ 60 years)[f] for 10–21 days	Cure at FU: LND 19 of 26 patients (73.1%); VAN 18 of 33 patients (54.5%) (95% CI, –5.5 to 42.6)	Lin et al[63]
Prospective, randomized, double-blind, comparator-controlled, multicenter, multinational	Nosocomial pneumonia	LND (600 mg iv q12h) or VAN (1 g iv q12h)[c] for 7–21 days	Cure at TOC: LND 71 of 107 patients (66.4%); VAN 62 of 91 patients (68.1%) (95% CI, –14.9 to 11.3)	Rubinstein et al[70]
Prospective, randomized, open-label, comparator-controlled, multicenter, multinational	Community-acquired pneumonia	LND (600 mg iv q12h followed by po)[f] or CTX (1 g q12h) followed by CFD (200 mg q12h)	Clinical cure: LND 83%, CTX/CFD 76.4% (P = 0.04)	San Pedro et al[71]
Prospective, randomized, double-blind, comparator-controlled, multicenter, multinational	Nosocomial pneumonia	LND (600 mg iv q12h) or VAN (1 g iv q12h)[c] for 7–21 days	Cure at FU: LND 114 of 168 patients (67.9%), VAN 111 of 171 patients (64.9%)	Wunderink et al[72]
Randomized, double-blind, double-dummy, multicenter	Gram-positive infections (50 patients with pneumonia)	LND (600 mg iv or po q12h) or TEICO 400 mg q12h for 3 days then 400 mg q24h iv)[b] for 3–28 days	CE cure: LND 15 of 18 patients (83.3%), TEICO 24 of 29 (82.8%) (*P* = 1.00, 95% CI –0.125 to 0.226)	Cepeda et al[73]

Prospective, randomized, open-label, comparator-controlled, multicenter multinational	VAP caused by MRSA	LND (600 mg iv q12h) or VAN (1g iv q12h)[e] for 7–14 days	Microbiologic cure: LND 13 of 23 patients (56.5%), VAN 9 of 19 patients (47.4%) (P = 0.757, 95% CI, –21.1 to 39.4) EOT cure: LND 66.7%, VAN 52.9% (P = 0.375, 95% CI, –16.6 to 44) Day 28 mortality: LND 13.3%, VAN 30% (P = 0.149)	Wunderink et al[74]

[a]Aztreonam or gentamicin was added at the discretion of the physician.
[b]Concomitant antibiotics against Gram-negatives or atypical pathogens or anaerobes were allowed.
[c]Aztreonam (1–2 g q8h) was added to each treatment arm.
[d]Antibiotics to cover for Gram-negative organisms (aztreonam, gentamicin, amikacin, ciprofloxacin, ceftazidime or imipenem) or anaerobes metronidazole) could be added.
[e]Dose was adjusted to renal function.
[f]Aztreonam (1–2g q6–8h) was added if gram-negative coverage was necessary.
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; LND, linezolid; VAN, vancomycin; TOC, test of cure visit; CI, confidence interval; TEICO, teicoplanin; EOT, end of treatment visit; CTX, ceftriaxone; CFD, cefpodoxime; FU, follow-up visit; CE, clinically evaluable patients; VAP, ventilator-associated pneumonia.

pneumonia, initial therapy with linezolid was associated with significantly better survival (80% vs. 63.5%, P = 0.03) and clinical cure rates (59% vs. 35.5%, P < 0.01)[75] and in the subset of patients with MRSA ventilator-associated pneumonia, linezolid treatment was an independent predictor of survival (OR 4.6, 95% CI, 1.5 to 14.8, P = 0.01) and clinical cure (OR 20.0, 95% CI, 4.3 to 92, P < 0.001).[76] The superior efficacy of linezolid was attributed to its good intrapulmonary penetration (see pharmacokinetics above). There is only one RCT designed specifically to study the efficacy of linezolid in MRSA pneumonia[74] but it was limited by a very small number of patients and did not confirm linezolid's superiority (Table 4). The use of linezolid for the treatment of nosocomial pneumonia caused by MRSA was found to be cost-neutral compared with vancomycin because it can be given orally reducing hospital stay (Mullins).[77]

A meta-analysis of seven RCTs evaluated the efficacy of linezolid in comparison to that of vancomycin or b-lactams for the treatment of lower respiratory tract infections. There was no difference in success rates of empirical treatment for pneumonia (74.9% in linezolid-treated patients vs. 74.6% in comparison antibiotic-treated patients) or for nosocomial pneumonia (OR 1.05 [0.75–1.46]). Also there was no difference in bacterial eradication in patients with MRSA pneumonia (OR 1.26, 95% CI 0.54–2.96).[65] Similarly, another meta-analysis of seven RCTs revealed no differences in efficacy between linezolid and vancomycin for the treatment of pneumonia (OR 1.16, 95% CI 0.85 to1.57).[66]

Bacteremia

There is only one RCT designed specifically to study the efficacy of linezolid in bacteremia.[78] Data from this study as well as from studies, which included primary of secondary bacteremias and CRBIs among other types of infections, are shown in Table 5.

A retrospective analysis of case series of patients who received linezolid as salvage therapy for persistent MRSA bacteremia found that the early microbiological response (i.e. negative results for follow-up blood culture within 72 hours) was significantly higher in the linezolid-based salvage therapy group than the comparison group (75% vs. 17%; *P* = 0.006). Adding aminoglycosides or rifampicin to vancomycin was not successful in treating any of the patients, whereas linezolid-based

Table 5. Summary of clinical studies evaluating the efficacy of linezolid in the treatment of bloodstream infections.

Study design	Type of infection	Regimen	Other intervention	Successful outcome, *n* (%)	References
Prospective, randomized, comparator-controlled, open-label, multicenter, multinational	MRSA infections (85 patients with secondary bacteremia or bacteremia of unknown source)	LND (600 mg iv or po q12h) or VAN (1g iv q12h)[a] for 7–14 days		ITT: LND 17 of 33 patients (51.5), VANCO 15 of 32 patients (46.9)	Stevens et al[53]
Prospective, randomized, comparator-controlled open-label, multicenter, multinational	Infections caused by Gram-positives in children (0–12 years old) (80 patients with CRBI and bacteremia of unknown source)	LND (10 mg/kg iv q8h then po) or VAN (10 to 15 mg/kg iv q6 to 24h)[a,b] for 10–28 days		CRBI ITT cure: LND 28 of 33 patients (84.8%) VAN 8 of 10 patients (80%) (95% CI, –22.8 to 32.5) Bacteremia of unknown source ITT cure: LND 19 of 24 patients (79.2%) VAN 9 of 13 patients (69.2%) (95% CI, –20.0 to 39.8)	Kaplan et al[54]
Prospective, randomized, open-label, comparator-controlled, multicenter multinational	Gram-positive infections (65 patients with bacteremia)	LND (600 mg iv or po q12h) or TEICO iv or im for 7–28 days[c]		EOT cure: LND 23 of 26 patients (88.5%), TEICO 17 of 30 patients (56.7%) ($P = 0.009$, 95% CI, 10.2 to 53.4)	Wilcox et al[59]
Randomized, double-blind, double-dummy, multicenter	Gram-positive infections (59 patients with bloodstream infections)	LND (600 mg iv or po q12h) or TEICO 400 mg q12h for 3 days then 400 mg q24h iv)[d] for 3–28 days		CE cure: LND 18 of 22 patients (81.8%), TEICO 26 of 32 (81.3%) ($P = 1.00$, 95% CI, –0.205 to 0.216)	Cepeda et al[73]
Prospective open-label, randomized, controlled, multicenter, multinational	CRBI	LND (600 mg iv q12h) or VANCO (1g iv q12h) for 7–28 days	Removal of all catheters	TOC: LND 70 of 93 patients (75.3), VANCO 59 of 73 patients (80.8) (95% CI, –18.1 to 7.0) ME: LND 82 of 95 patients (86.3), VANCO 67 of 74 patients (90.5) (95% CI, –13.8 to 5.4)	Wilcox et al[78]

[a]Aztreonam or gentamicin was added at the discretion of the physician.
[b]Vancomycin was changed to another appropriate oral antibiotic based on culture results.
[c]Antibiotics to cover for Gram-negative organisms (aztreonam, gentamicin, amikacin, ciprofloxacin, ceftazidime or imipenem) or anaerobes metronidazole) could be added.
[d]Concomitant antibiotics against Gram-negatives were allowed.
Abbrevations: MRSA, methicillin-resistant *Staphylococcus aureus*; LND, linezolid; VANCO, vancomycin; ITT, intent-to-treat population; EOT, end of treatment visit; CRBI, catheter-related bloodstream infections; CE, clinically evaluable population; TEICO, teicoplanin; TOC, test-of-cure visit; ME, microbiologically evaluable population.

therapy gave an 88% salvage success rate ($P < 0.001$). The *S. aureus*–related mortality rate was lower for patients treated with a linezolid salvage regimen than for patients continually treated with a vancomycin-based regimen (13% vs. 53%; $P = 0.030$).[79]

Another retrospective study evaluated patients treated with linezolid (n = 68) or daptomycin (n = 30) for VRE bacteremia. Univariate analyses showed no significant differences between the groups regarding baseline demographic and clinical characteristics,

severity of illness and co-morbidity. Daptomycin was associated with a trend towards a higher mortality rate (26.7% vs. 20.6%), longer median duration of bacteremia (3 vs. 2 days) and higher relapse rate (6.7% vs. 2.9%), but these differences did not reach statistical significance ($P > 0.2$). Microbiological cure rates were 90% for the daptomycin group and 88.2% for the linezolid group ($P = 0.92$).[80]

A pooled analysis of five prospective, RCTs demonstrated that linezolid is associated with outcomes that are not inferior to those of vancomycin in 144 patients with *S. aureus* bacteraemia (53 patients with MRSA). There were no differences between treatment groups in clinical outcome, in microbiological outcome and in survival.[81] In a meta-analysis of 12 RCTs involving 6093 patients, the efficacy of linezolid was compared with glycopeptides or β-lactams. Five RCTs reported outcomes for patients with bacteremia. Overall success of empirical treatment was achieved in 81.3% of linezolid-treated patients and in 66.4% of patients treated with other antibiotics. Empirical treatment with linezolid was associated with better success than glycopeptides or β-lactams (255 clinically assessed patients; OR 2.07, 95% CI 1.13 to 3.78).[65] However, the isolated pathogens were different, their absolute number was small, most of the data came from non-blinded RCTs not allowing any meaningful comparison for the treatment of specific pathogens. Therefore, the authors could not reach any definitive conclusions about the effectiveness of linezolid for the treatment of bacteraemic patients. A recent meta-analysis of RCTs evaluating the efficacy of linezolid and vancomycin in the treatment of various Gram-positive infections included three trials that reported outcomes for patients with bacteremia. Success of empirical treatment was achieved in 76% of linezolid-treated patients and in 78% of vancomycin-treated patients. There was no significant difference in treatment success for bacteremia between linezolid and vancomycin (271 clinically assessed patients, OR 0.88, 95% CI 0.49 to1.58).[66]

Endocarditis

Although linezolid is a bacteriostatic antibiotic, it has been administered in patients with bacterial endocarditis when failure or intolerance to first line regimens had limited the therapeutic options. Relevant experience has been published in the form of case reports and case series studies and has been reviewed by Falagas et al[82] and Munoz et al.[83] Results from published case series are included in Table 6. At present, linezolid is not a standard therapy for endocarditis, although guidelines published by the American Heart Association consider it to be a reasonable alternative for cases of endocarditis caused by multiresistant enterococci.[86]

Central Nervous System Infections (CNS)

Linezolid has been used for the treatment of CNS infections caused by multidrug resistant Gram-positive pathogens because of its adequate CSF penetration. Published case reports were reviewed by Ntziora et al.[87] In most of the reported cases, failure of first line treatment regimens or intolerance to them were the reasons for linezolid use. Overall a success rate of 90.5% was reported for a variety of pathogens (mainly penicillin-non-susceptible *S. pneumoniae*, VRE, *Nocardia* spp and methicillin-resistant staphylococci) and a variety of clinical situations. Currently, linezolid is recommended by the Infectious Diseases Society of America as an alternative for the treatment of methicillin-resistant staphylococcal or vancomycin-resistant enterococcal meningitis (rated B-III).[88]

Bone and Joint Infections (BJI)

The available literature of BJIs consists of case reports and case series studies. A summary of published case series studies is presented in Table 7. Failure or intolerance of first line antimicrobials or isolation of resistant bacteria were the reasons for linezolid use in all of these reports.

In a retrospective case-control study by Papadopoulos et al[99] the efficacy of linezolid for a variety of bone infections with and without prosthetic material was compared to that of various combination regimens commonly used in that institution. Treatment duration was shorter in the linezolid group (6 vs. 20 weeks, $P = 0.001$). There was no statistically significant difference in efficacy at the end of treatment between the two groups but there was a significantly higher relapse rate in the linezolid arm (38% vs. 4%, $P < 0.001$).

Table 6. Summary of clinical studies evaluating the efficacy of linezolid in the treatment of endocarditis.

Study design	Type of infection	Evaluable patients (*n*)	Duration of treatment (days)	Surgical treatment (No. of evaluable patients)	Follow-up	Isolated bacteria (*n*)	Successful outcome, *n* (%)	References
Retrospective non-randomized	Endocarditis (5 in prosthetic valve)	9	14–28	4	7–31 months	*S. aureus* 6, Other 3	9 (100%)	Munoz et al[83]
Prospective, open-label, non-comparative, non-randomized, compassionate use	Endocarditis	40	NA	NA	NA	VREF 22, MRSA 8 Other 10	15 (65.2)	Birmingham et al[84]
Retrospective non-randomized	Serious infections caused by MRSA with reduced vancomycin susceptibility (8 cases with endocarditis)	7	7–49	3	10 weeks to 10 months	MRSA with reduced vancomycin susceptibility 7	3 (42.9%)	Howden et al[85]

Abbreviations: NA, not available; MRSA, methicillin-resistant *Staphylococcus aureus*; VREF, vancomycin-resistant *Enterococcus faecium*.

Overall, the clinical efficacy of linezolid in these case series, which comprised very heterogeneous groups of patients, ranged from 55%–100%. Prospective controlled studies are warranted although there are concerns about potential side effects of long-term use of linezolid in that setting (see section on safety).

Neutropenic Patients

Although linezolid is a bacteriostatic agent it has been evaluated in neutropenic patients for the treatment of Gram-positive bacterial infections. Results from published clinical trials are presented in Table 8. There is only one published RCT, which showed that linezolid was equivalent to vancomycin in terms of clinical efficacy and safety for the treatment of Gram-positive infections in febrile neutropenic patients. Time to defervescence was shorter in linezolid group although post hoc analyses revealed delayed recovery of absolute neutrophil counts for linezolid-treated patients. Mortality was comparable in the two groups but linezolid was associated with fewer drug-related adverse events and fewer cases of drug-related renal failure.[102]

Tuberculosis

Recent small case series have reported clinical and radiographic improvement among patients with intractable multi-drug or extensively-drug resistant tuberculosis (MDR/XDR-TB) whose treatment regimens included linezolid. Park et al prescribed linezolid (600 mg bid for 14 days and then 600 mg/day) for 3–18 months (in addition to 4 more drugs) in 8 patients with XDR or MDR TB and conversion was noted in all patients after 82 ± 47 days. Only one patient developed reversible anemia but four patients developed peripheral neuropathy and two patients optic neuropathy.[103] Koh et al evaluated a dose of 300 mg in 24 patients with MDR/XDR TB and reported that 92% converted after a median of 89 days. Mean duration of linezolid therapy was 359 days and four patients developed peripheral neuropathy but none had hematological side effects.[104] Condos et al reported on seven patients who received linezolid (600 mg bid) for a period of 9–26 months with conversion of 85.7% of them. Two patients developed peripheral neuropathy.[105] von der Lippe et al reported a cohort of ten patients with MDR-TB, seven of whom developed significant side effects necessitating discontinuation

Table 7. Case series studies on the use of linezolid (600 mg bid po or iv) for the treatment of patients with bone or joint infections.

Study design	Type of infection	Evaluable patients (*n*)	Duration of treatment (days)	Surgical treatment (No. of evaluable patients)	Follow-up (months)	Isolated bacteria (*n*)	Successful outcome, *n* (%)	References
Retrospective, non-randomized	Septic joint infections, osteomyelitis (4 patients with bacteremia, 3 patients with prosthetic material)	7	28–78 (median 51)[a]	6	1–10 (median 4.5)	MRSA with reduced vancomycin susceptibility (8)	4 (57.1)	Howden et al[85]
Prospective, non-randomized	Septic joint infections, Osteomyelitis (2 patients with prosthetic material)	11	42–133 (median 56)	NA	17–41 (median 26)	MRSA (5), MRCoNS (4), VRE (1), VSE (1)	11 (100)	Rao et al[89]
Prospective, non-randomized	Osteomyelitis	22	NA	NA	1–18 (median 6.5)	MRSA (11), VRE (5), other (6)	18 (81.8)	Rayner et al[90]
Retrospective, non-randomized	Septic joint infections, osteomyelitis (15 patients with prosthetic material)	20	5–422 (median 32)	20	0.5–25 (median 9.2)	MRSA (8), MRCoNS (9), MSSA (2), VRE (5), VSE (3)[c]	18 (90)[b]	Razonable et al[91]
Prospective, randomized comparator-controlled, open-label, multicenter multinational	Diabetic foot infections (77 patients with osteomyelitis)	60	10–28 (mean 19)	NA	Up to 21 days	NA	LND 27 of 44 patients (61%)[d], b-lactam/ b-lactamase inhibitor 11 of 16 patients (69%)[d,e] (95% CI, –34.3 to 19.5)	Lipsky et al[92]
Retrospective, non-randomized	Osteomyelitis (4 patients with prosthetic material)	20	42–126 (median 65)	10	6–49 (median 36)	MRSA (9), MSSA (2), VRE (2), VSE (2)	11 (55)	Aneziokoro et al[93]
Retrospective, non-randomized	Prosthetic joint infections	20	42–70 (mean 50 ± 14)	20	NA	MRSA (15), MRCoNS (4), VSE (1)	16 (80)	Bassetti et al[94]

(*Continued*)

Table 7. (*Continued*)

Study design	Type of infection	Evaluable patients (*n*)	Duration of treatment (days)	Surgical treatment (No. of evaluable patients)	Follow-up (months)	Isolated bacteria (*n*)	Successful outcome, *n* (%)	References
Retrospective, non-randomized	Chronic osteomyelitis (10 with prosthetic material) and prosthetic joint infections	66	35–252 (median 91)	52	12–36 (median 15)	MRSA (30), MSSA (4), MRCoNS (19), MSCoNS (2), *Enterococcus* spp. (5), other (12)	52 (78.8)[f]	Senneville et al[95]
Retrospective, non-randomized	Chronic osteomyelitis with prosthetic material	22		22	6–34 (mean 22)	MRSA (10), VRE (5)	22 (100)	Vercillo et al[96]
Retrospective, non-randomized	Osteomyelitis and septic joint infections in children 3 months to 14 years old	13	9–36 (mean 20)	11	7.9–39.1 (median 25.4)	MRSA (11), MSSA (1), *Enterococcus* spp. (1), CoNS (1)	11 (84.6)[g]	Chen et al[97]
Retrospective, non-randomized	Chronic osteomyelitis (17 patients with prosthetic material)	28	8–36 (mean 17.8 ± 7.5)	13	24	MRSA (11), MSSA (4), MRCoNS (9), *Enterococcus* (5), other (3)	25 (89.3)[h]	Nguyen et al[98]
Retrospective, non-randomized	Osteomyelitis (2 with prosthetic material) and prosthetic joint infections	34	21–245 (mean 42)	16	2 (median)	MRSA (20), MRSE (7), *E. faecalis* (2)	24 (74%)	Papadopoulos et al[99]

[a]Linezolid monotherapy in 4 of 7 patients.
[b]7 patients received long-term suppressive therapy.
[c]12 patients with polymicrobial infection.
[d]Aztreonam (1–2 g q6–8h) was added if gram-negative coverage was necessary.
[e]Vancomycin (1 g q12h iv) was added if infection with MRSA was suspected or confirmed.
[f]50 patients received combination regimens.
[g]Effective antistaphylococcal antibiotics were used in all 13 patients for a median duration of 23 days (range, 5–41 days) before linezolid.
[h]All patients received also rifampicin [10 mg/kg (max 900 mg) q12h].
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available; MRCoNS, methicillin-resistant coagulase-negative staphylococci; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci; MSSA, methicillin-susceptible *S. aureus*; b-lactam/b-lactamase inhibitor, ampicillin/sulbactam or amoxicillin/clavulanic acid; CI, confidence interval.

of linezolid.[106] In a larger series, 30 patients received a dose of 600 mg for 8–36 months and 73% of them completed treatment with a successful outcome. Six patients developed peripheral or optic neuropathy.[107] Recently, Migliori et al[108] reported 85 patients with MDR/ XDR-TB who were treated with linezolid 600 mg bid or qd. Thirty-two percent required discontinuation of treatment because of side effects. Discontinuation was significantly more frequent among patients receiving the 600-mg bid. Twice-daily administration produced more major side-effects than once-daily dosing, with no difference in efficacy found. The authors concluded that linezolid 600 mg q.d. added to an individualized multidrug regimen may improve the chance of bacteriological conversion, providing a better chance of treatment success in only the most complicated MDR/XDR-TB cases. Its safety profile does not warrant use in cases for which there are other, safer, alternatives.

Safety

The safety of linezolid in adults has been studied in seven comparator-controlled phase 3 clinical trials.[109] Data on the tolerability of linezolid were obtained in 2,046 patients and compared to 2,001 comparator drug-treated patients. Drug-related adverse events were reported for 444 (21.7%) of linezolid-treated patients and for 314 (15.7%) of comparator-treated patients ($P = 0.001$), although drug discontinuation due to adverse events was reported for 2.4% and 1.9% of patients, respectively ($P = 0.23$). Also, there was no statistically significant difference in the percentage of patients who exhibited serious drug-related adverse events or in the mortality among those two groups. The most common drug-related adverse events associated with both linezolid and comparator agents were diarrhea (4.3 and 3.2%, respectively; $P = 0.074$), nausea (3.4 and 2.3%, respectively; $P = 0.036$), and headache (2.2 and 1.3%, respectively; $P = 0.047$).

Abnormalities in hematologic parameters were comparable between linezolid and the comparators. The proportion of patients who developed substantially abnormal hematological values was not statistically significant between the two groups although longer treatment durations (>14 days) were associated with

Table 8. Clinical studies evaluating the efficacy of linezolid in cancer patients.

Study design	Type of infection, *n* (%)	Regimen, duration (mean)	Outcome, *n* (%)	References
Prospective, open label, noncomparative, nonrandomized, compassionate use in febrile neutropenic patients	Bacteremia 93 of 103 patients (90.3%), SSSI, UTI, endocarditis, osteomyelitis	LND (600 mg bid iv or po) for 14 days	ITT cure: 57% CE cure: 79% Mortality: 33%	Smith et al[100]
Prospective, open label, randomized in febrile cancer patients	Infections caused VRE *faecium* (8 neutropenic patients)	LND (600 mg bid iv or po) vs. Q/D (7.5 mg/Kg/8h)	EOT cure: LND 11 of 19 patients (58%), Q/D 9 of 21 patients (43%) ($P = 0.6$) Mortality: LND 3 of 19 patients (16%), Q/D 2 of 21 patients (10%) ($P = 0.7$)	Raad et al[101]
Prospective, double-blind, randomized, comparative, multicenter, multinational in febrile cancer patients	FUO 183 patients (30.2), bacteremia 180 patients (29.8), CRBI 65 patients (10.7), pneumonia, SSSI, UTI, other Neutropenia in 469 of 605 patients (77.5%)	LND (600 mg bid iv) or VAN (1g bid iv) for 10–28 days	ITT: LND 219 of 251 patients (87.3%), VAN 202 of 237 patients (85.2%) ($P = 0.52$, 95% CI ,–4.1 to 8.1)	Jaksic et al[102]

Abbreviations: SSSI, skin and skin structure infections; UTI, urinary tract infections; LND, linezolid; Q/D, quinupristin/dalfopristin; ITT, intent-to-treat population; CE, clinically evaluable population; EOT, end of treatment visit; FUO, fever of unknown origin; VAN, vancomycin; CRBI, catheter-related bloodstream infections; CI, confidence interval.

a small increase in the risk for lower platelet counts in linezolid-treated patients.

The incidence of linezolid-induced thrombocytopenia was estimated to be 2.4% from the original trials.[110] Nevertheless, other studies have reported rates from 7.5%[84] to 48%.[111] Risk factors for thrombocytopenia besides long treatment duration (≥10 days) were lower platelet counts at baseline,[112] renal insufficiency[113] and hematologic malignancies.[101] The incidence of anemia was reported to be 5.4%.[110] In a case control study the onset of anemia was 7.4 weeks after initiation of therapy and predictive factors for this adverse event were age > 58 years and low pretreatment hemoglobin values.[95] Increased susceptibility to anemia was also demonstrated in patients with renal insufficiency.[113] Leucopenia was a rare adverse event occurring in 3.3% of patients in phase III clinical trials and it was fully reversible.[114] Pancytopenia has also very rarely been reported.[115] All hematological adverse events were reversible after drug discontinuation. Weekly evaluation of hematological parameters is advised for all patients receiving >14 days of linezolid treatment.

The postmarketing experience enhanced knowledge about the drug's safety. Lactic acidosis, convulsions, optic and peripheral neuropathy have been reported.

Case reports of peripheral neuropathy include stocking-like and glove-like sensory neuropathy. Optic neuropathy symptoms include loss of color perception, blurred vision and progressive visual loss. Thirty-five cases of peripheral neuropathy, nine cases of toxic optic neuropathy and five cases of combined neuropathy have been reported. Most patients were treated for longer than 28 days.[116] Bell's palsy has also been reported in one patient receiving linezolid for 23 days.[117] After the drug's discontinuation, optic neuropathy was fully or partially reversible after 5 to 9 months[118] and complete resolution of Bell's palsy occurred after 3 months.[117] On the contrary, peripheral neuropathy was only partially reversible.[119]

Lactic acidosis, attributed to linezolid, has been reported in case reports.[119] It is correlated with prolonged treatment, but it was also reported in patients receiving shorter courses of linezolid (1–16 weeks, median 6 weeks).[119,120] Immediate discontinuation of linezolid is recommended usually leading to resolution of hyperlactatemia within 2 weeks (range, 3 days 2 weeks); nevertheless, three fatalities were reported.[119] Patients receiving linezolid should be monitored for signs and symptoms of hyperlactatemia (nausea, vomiting, mental status changes, tachycardia, hypotension) and for the serum level of bicarbonate.

Linezolid is a weak reversible monoamine oxidase (MAO) inhibitor and has the potential to interact with adrenergic and serotonergic agents. In Phase III studies, <30% of linezolid-treated patients and controls received agents that could interact with MAO inhibitors. In these patients, adverse events were generally mild to moderate, with a low overall incidence and similar rates in both linezolid and comparator groups. Hypertension was reported in 0.3% of the linezolid group and in 0.2% of the comparator group.[109] After the drug was approved and marketed several reports documented serotonin syndrome (cognitive dysfunction, hyperpyrexia, hyperreflexia, incoordination) in association with concomitant use of linezolid and serotonin agonists mostly selective serotonin reuptake inhibitors (SSRI).[121,122] Onset of symptoms occurred 1–28 days after initiation of linezolid and most of the cases resolved in 1–9 days after drug discontinuation. Three deaths were reported to be associated with the syndrome.[119,122] In one retrospective survey, the frequency of linezolid-induced serotonin syndrome was less than 3%.[123] Recommendations have been made for a washout period of discontinuing SSRI drugs before linezolid can be administered.[119] FDA released a safety report stating that patients with carcinoid syndrome or patients receiving SSRIs, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine or buspirone should be monitored for serotonin syndrome symptoms and signs and if this is not possible, linezolid should not be administered.[124]

Place in Therapy

Linezolid has offered some important advantages in our therapeutics against serious infections. Its antibacterial spectrum extending to Gram-positive pathogens resistant to one or many classes of antimicrobials, its pharmacokinetic properties characterized by intravenous and excellent oral bioavailability providing opportunity for early oral switch and discharge of the patient as well as no need for dose adjustment in any patient population and its clinical efficacy which is not inferior to studied comparators for a variety of

approved clinical indications and even superior to them for skin and skin-structure infections include some of the major advantages offered by this antimicrobial. Linezolid has been proved easily tolerated by patients and safe in clinical trials although close follow-up is necessary for the possibility of hematological toxicity and especially for neurological toxicity and disturbances of acid-base homeostasis with long-term use beyond approved indications. Bacteriostatic in vitro activity could be a limitation for use in infections thought to require killing antimicrobial activity such as endocarditis. Emerging acquired resistance to linezolid in enterococci and staphylococci mandates for caution and wise use in clinical practice.

In the era of antimicrobial resistance development even in community-acquired infections, a fearful example being CA-MRSA, linezolid becomes an important option for treatment of serious infections caused by Gram-positives, including vancomycin-non susceptible staphylococci and vancomycin-resistant enterococci.

Conflicts of Interest

None.

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