

# Benefit-Risk Assessment of Linezolid for Serious Gram-Positive Bacterial Infections

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## Abstract

Linezolid is an oxazolidinone, a new class of antibacterial with a unique mechanism of action, namely inhibition of the formation of a functional 70S initiation complex in the 50S bacterial ribosomal subunit. Linezolid is highly active against multidrug-resistant Gram-positive cocci, including meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate and vancomycin-resistant *S. aureus*, and vancomycin-resistant enterococci; its spectrum of activity also includes some anaerobic bacteria.

Linezolid has been studied in several randomized controlled trials for the treatment of patients with community-acquired and nosocomial pneumonia, skin and soft tissue infections (SSTIs), urinary tract infections and bacteraemia. The available evidence suggests that linezolid is at least as effective as vancomycin for patients with nosocomial pneumonia, and there are some retrospective analyses supporting its superiority in comparison with vancomycin for MRSA nosocomial pneumonia, including ventilator-associated pneumonia. Linezolid is more effective than glycopeptides, macrolides and  $\beta$ -lactams for SSTIs. The limited available data for the treatment of patients with bacteraemia suggest that it may be a

better treatment option than vancomycin and  $\beta$ -lactams for these patients, but questions have arisen regarding patients with catheter-related bacteraemias.

Compared with other antibacterials, linezolid is associated with a greater frequency of adverse events, mainly nausea, vomiting, diarrhoea and headaches. Thrombocytopenia also occurs more frequently in patients taking linezolid but there is no increased frequency of anaemia. Other adverse events potentially related to linezolid therapy include fungal infections (moniliasis), hypertension and serotonin-like syndrome, tongue discolouration and taste alterations, dizziness, insomnia, rash and *Clostridium difficile*-related diarrhoea. The majority of adverse events develop after prolonged administration (i.e. >2 weeks) and subside shortly after discontinuation of linezolid. Peripheral or optic neuropathy, another possible adverse effect, is associated with an even longer duration of treatment (3–6 months).

In conclusion, linezolid is an important treatment option for the treatment of patients with multidrug-resistant, Gram-positive bacterial infections. However, in order to reduce the possibility of development of resistance and preserve its activity, the use of linezolid should be restricted to treatment of patients with infections associated with high morbidity and mortality, particularly those caused by multidrug-resistant bacteria.

Linezolid, a drug that belongs to a new class of antibacterials called oxazolidinones, inhibits bacterial growth by binding to the bacterial 23S ribosomal RNA of the 50S subunit and blocking formation of a functional 70S initiation complex, which is essential for the bacterial translation process.<sup>[1–3]</sup> This mechanism of action is not found in any other class of antibacterials currently used for the treatment of Gram-positive infections. Therefore, it has been argued that resistance to linezolid (both cross- and *de novo* resistance) may be unlikely to develop.<sup>[4,5]</sup>

Linezolid is active against a variety of Gram-positive cocci, including staphylococci, streptococci and enterococci.<sup>[6]</sup> Multidrug-resistant strains of the aforementioned cocci (i.e. methicillin- (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant *Enterococcus faecium* and *E. faecalis* (VRE), and penicillin-resistant *Streptococcus pneumoniae*) are also susceptible to this antibacterial.<sup>[6]</sup> Linezolid is bacteriostatic against staphylococci and enterococci, and bactericidal against streptococci. It is also active against anaerobic bacteria including *Clostridium perfringens*, *C. difficile*, *Peptostreptococcus* spp., *Bacteroides fragilis*, *Fusobacterium nucleatum* and *F.*

*meningosepticum*. Finally, it shows limited activity against *Moraxella catarrhalis* and *Haemophilus influenzae*.<sup>[6]</sup>

Linezolid is administered orally or intravenously at a dosage of 600 mg twice daily.<sup>[7]</sup> With this schedule of administration, a 24-hour area under the plasma concentration-time curve over minimal inhibitory concentration (AUC/MIC) ratio of 50 : 100 is achieved, which is usually associated with clinical effectiveness in the treatment of patients with infections due to susceptible bacteria.<sup>[8]</sup> Specifically, having achieved this pharmacodynamic goal, linezolid 600 mg twice daily in humans would be successful against organisms with MICs of up to 2–4  $\mu\text{g/mL}$ .<sup>[8]</sup> Linezolid is 100% bioavailable after oral administration, and the times to peak plasma concentration are 1 and 2 hours after single- and multiple-dose administration, respectively.<sup>[9,10]</sup> Linezolid exhibits good penetration in the lungs,<sup>[11]</sup> skin,<sup>[12]</sup> muscles,<sup>[13]</sup> cerebrospinal fluid<sup>[14]</sup> and bones.<sup>[15]</sup> Its plasma protein binding is approximately 31% (which is concentration independent).<sup>[16]</sup> Its half-life is 5.5 hours<sup>[17]</sup> and it is eliminated through the kidneys and gastrointestinal tract either as the administered form or as metabolites.<sup>[18,19]</sup>

Linezolid was released to the market in 2000. Its primary indications include treatment of patients with complicated and uncomplicated skin and soft tissue infections (SSTIs), community-acquired pneumonia (CAP) and nosocomial pneumonia, and infections caused by VRE.<sup>[7]</sup> Linezolid has also been used to treat other infections caused by Gram-positive cocci, including endocarditis, urinary tract infections, bacteraemia, infections of the CNS, osteomyelitis, infections in neutropenic patients, and tuberculosis caused by multidrug-resistant mycobacteria.

Linezolid is one of the newly available antibacterials that were added to those used traditionally for the treatment of serious Gram-positive infections, i.e. vancomycin and teicoplanin for multidrug-resistant Gram-positive cocci, and broad-spectrum  $\beta$ -lactams, cotrimoxazole (trimethoprim/sulfamethoxazole), clindamycin, aminoglycosides or fluoroquinolones for susceptible micro-organisms. Other new treatment options approved for such infections include quinupristin/dalfopristin, tigecycline and daptomycin, while telavancin, dalbavancin and ceftobiprole have also shown promising results.

## 1. Benefit Assessment: Comparison with Alternative Treatment Options

### 1.1 Overview of the Available Evidence from Randomized Controlled Trials

Several randomized controlled trials (RCTs) have been conducted thus far comparing linezolid with another antibacterial for the treatment of patients with Gram-positive infections (table I);<sup>[20-38]</sup> in an additional RCT, two different doses of linezolid were compared.<sup>[39]</sup> The majority of these RCTs enrolled patients with different types of infections, including SSTIs, pneumonia (both CAP and hospital-acquired pneumonia), urinary tract infections and bacteraemia.

A meta-analysis of 12 RCTs<sup>[23-26,28-34,38]</sup> involving 6093 patients has been reported.<sup>[40]</sup> This meta-analysis found that all-cause mortality was similar between patients receiving linezolid and comparator antibacterials (glycopeptides and  $\beta$ -lactams) [odds

ratio (OR) 0.97; 95% CI 0.79, 1.19]. Linezolid treatment resulted in resolution or improvement of symptoms of infection in 86.3% of patients, compared with 81.9% of patients treated with comparator antibacterials. Overall, linezolid was more effective in this respect than comparator antibacterials for the treatment of patients with Gram-positive infections in both intention-to-treat (ITT) [OR = 1.23; 95% CI 1.06, 1.42] and clinically evaluable (OR = 1.41; 95% CI 1.11, 1.81) populations. When data from blinded RCTs only were pooled, linezolid was not more effective than the comparator antibacterials (OR = 1.14; 95% CI 0.95, 1.38). Conversely, when data from non-blinded RCTs only were pooled, linezolid was more effective than the comparators (OR = 1.35; 95% CI 1.08, 1.68). Linezolid was more effective than glycopeptides (OR = 1.51; 95% CI 1.03, 2.22) for all infections combined but not more effective than vancomycin (OR = 1.44; 95% CI 0.90, 2.30) or  $\beta$ -lactams (OR = 1.34; 95% CI 0.99, 1.81).<sup>[40]</sup>

Sub-analyses were conducted according to the site of infection. In patients with SSTIs, linezolid treatment resolved or improved symptoms of infection in 90.3% of patients, while treatment with glycopeptides and  $\beta$ -lactams was successful in 85.7% of patients.<sup>[40]</sup> Linezolid was more effective in this respect than all comparator antibacterials (OR = 1.67; 95% CI 1.31, 2.53), glycopeptides (OR = 2.24; 95% CI 1.12, 4.48) and  $\beta$ -lactams (OR = 1.37; 95% CI 1.00, 1.88). In patients with bacteraemia, linezolid was successful in 81.3% of patients in contrast to 66.4% treated with comparator antibacterials (OR = 2.07; 95% CI 1.13, 3.78). It should be noted that the majority of these bacteraemias were secondary to other infections. Finally, in patients with pneumonia due to Gram-positive infections, linezolid was as effective as comparator antibacterials (74.9% vs 74.8%, respectively; OR = 1.03; 95% CI 0.75, 1.42). There was also no difference between antibacterials when only patients with nosocomial pneumonia were analysed (OR = 1.05; 95% CI 0.75, 1.46). Because of a lack of available data, no further analysis was performed regarding patients with ventilator-associated pneumonia.<sup>[40]</sup>

**Table 1.** Randomized controlled trials (RCTs) comparing linezolid with another antibiotic for Gram-positive infections

| Study (y)                               | Study design | Population  | Regimen 1                       | Regimen 2  | No. of patients (ITT analysis) |
|---|--------------|---|---------------------------------|--|--------------------------------|
| Kohna et al. <sup>[20]</sup> (2007)     | MC, RCT      | Patients with MRSA infections   | IV linezolid 600 mg q12h        | IV vancomycin 1 g q12h   | 100 vs 51                      |
| Jaksic et al. <sup>[21]</sup> (2006)    | DB, MC, RCT  | Febrile neutropenic patients  | IV to PO linezolid 600 mg q12h  | IV vancomycin 1 g q12h   | 304 vs 301                     |
| Jauregui et al. <sup>[22]</sup> (2005)  | DB, MC, RCT  | Hospitalized patients with complicated SSTI   | IV to PO linezolid 600 mg q12h  | IV dalbavancin 1000 mg (day 1) and 500 mg (day 8)  | 571 vs 283                     |
| Sharpe et al. <sup>[23]</sup> (2005)    | RCT          | Hospitalized patients ( $\geq 18$ y) with complicated MRSA SSTI                         | PO linezolid 600 mg q12h        | IV vancomycin 1 g q12h   | 60 vs 59                       |
| Weigelt et al. <sup>[24]</sup> (2005)   | MC, RCT      | Hospitalized patients with suspected or proven complicated SSTI                         | IV to PO linezolid 600 mg q12h  | IV vancomycin 1 g q12h, followed by PO semisynthetic penicillin for confirmed MRSA infections    | 592 vs 588                     |
| Cepeda et al. <sup>[25]</sup> (2004)    | DB, MC, RCT  | ICU patients ( $\geq 16$ y) with Gram +ve infections                                    | IV linezolid 600 mg q12h        | IV teicoplanin 400 mg q12h followed by IV teicoplanin 400 mg q24h                                | 100 vs 102                     |
| Lipsky et al. <sup>[26]</sup> (2004)    | MC, RCT      | Patients ( $\geq 18$ y) with DFI  | IV or PO linezolid 600 mg q12h  | IV ampicillin/sulbactam 1.5–3 g q6h or PO amoxicillin/clavulanate 625 mg q8h or 1 g q12h         | 241 vs 120                     |
| Raad et al. <sup>[27]</sup> (2004)      | Pilot RCT    | Cancer patients ( $>18$ y) with VRE <i>faecium</i> infections                           | IV linezolid 600 mg q12h        | IV quinupristin-dalfopristin 7.5 mg/kg q8h   | 19 vs 21                       |
| Wilcox et al. <sup>[28]</sup> (2004)    | MC, RCT      | Hospitalized patients ( $\geq 13$ y) with Gram + infections                             | IV to PO linezolid 600 mg q12h  | IV or IM teicoplanin 200–800 mg q24h   | 215 vs 215                     |
| Kaplan et al. <sup>[29]</sup> (2003)    | MC, RCT      | Hospitalized children ( $\leq 12$ y) with Gram + infections                             | IV to PO linezolid 10 mg/kg q8h | IV vancomycin 10–15 mg/kg q6–24h, followed by PO appropriate antibacterials (mostly clindamycin) | 215 vs 101                     |
| Wible et al. <sup>[30]</sup> (2003)     | SB, MC, RCT  | Hospitalized patients ( $\leq 17$ y) with uncomplicated SSTI                            | PO linezolid 10 mg/kg q12h      | PO cefadroxil 15 mg/kg q12h or 500 mg q12h if $>12$ y  | 248 vs 251                     |
| Wunderink et al. <sup>[31]</sup> (2003) | DB, MC, RCT  | Patients ( $\geq 18$ y) with HAP  | IV linezolid 600 mg q12h        | IV vancomycin 1 g q12h   | 321 vs 302                     |
| San Pedro et al. <sup>[32]</sup> (2002) | MC, RCT      | Initially hospitalized patients ( $\geq 13$ y) with <i>Streptococcus pneumoniae</i> CAP | IV to PO linezolid 600 mg q12h  | IV ceftriaxone 1 g q12h, followed by PO ceftioxime 200 mg q12h                                   | 381 vs 366                     |

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Table 1. Contd

| Study (y)                                | Study design | Population  | Regimen 1                      | Regimen 2   | No. of patients (ITT analysis) |
|--|--------------|---|--------------------------------|---|--------------------------------|
| Stevens et al. <sup>[33]</sup> (2002)    | MC, RCT      | Hospitalized patients ( $\geq 13$ y) with suspected MRSA infections | IV to PO linezolid 600 mg q12h | IV vancomycin 1 g q12h  | 240 vs 220                     |
| Rubinstein et al. <sup>[34]</sup> (2001) | DB, MC, RCT  | Patients ( $\geq 18$ y) with HAP                                    | IV linezolid 600 mg q12h       | IV vancomycin 1 g q12h  | 203 vs 193                     |
| Cammarata et al. <sup>[35]</sup> (2000)  | RCT          | Hospitalized patients ( $\geq 18$ y) with CAP                       | IV linezolid 600 mg q12h       | IV ceftriaxone 1 g q12h, followed by PO cefpodoxime 200 mg q12h | 381 vs 366                     |
| Cammarata et al. <sup>[36]</sup> (2000)  | SB, RCT      | Outpatients ( $\geq 18$ y) with CAP                                 | IV linezolid 600 mg q12h       | PO cefpodoxime 200 mg q12h                                      | NA                             |
| Duvall et al. <sup>[37]</sup> (2000)     | RCT          | Patients ( $\geq 18$ y) with uncomplicated SSTI                     | PO linezolid 400 mg q12h       | PO clarithromycin 250 mg q12h                                   | 166 vs 166                     |
| Stevens et al. <sup>[38]</sup> (2000)    | DB, MC, RCT  | Hospitalized patients ( $\geq 18$ y) with complicated SSTI          | IV to PO linezolid 600 mg q12h | IV oxacillin 2 g q6h, followed by PO dicloxacillin 500 mg q6h   | 400 vs 419                     |

**CAP** = community-acquired pneumonia; **DB** = double-blind; **DFI** = diabetic foot infections; **HAP** = hospital-acquired pneumonia; **ICU** = intensive care unit; **IM** = intramuscular; **ITT** = intention-to-treat; **IV** = intravenous; **MC** = multicentre; **MRSA** = methicillin-resistant *S. aureus*; **NA** = non-applicable, non-available; **PO** = oral; **qxxh** = every x hours; **SB** = single-blind; **SSTI** = skin and soft tissue infections; **VRE** = vancomycin-resistant enterococcus; + indicates positive.

In the microbiologically evaluable population, linezolid was associated with better resolution or improvement of symptoms than all comparator antibacterials combined (OR = 1.34; 95% CI 1.05, 1.72), glycopeptides (OR = 1.49; 95% CI 1.11, 1.99) and vancomycin alone (OR = 1.41; 95% CI 1.01, 1.98); however, there was no difference in this respect between linezolid and  $\beta$ -lactams (OR = 1.06; 95% CI 0.67, 1.68).<sup>[40]</sup> In addition, linezolid was associated with higher eradication rates for *S. aureus* than all comparator antibacterials (OR = 1.81; 95% CI 1.40, 2.34) and glycopeptides (OR = 2.08; 95% CI 1.51, 2.86), but was not associated with higher eradication rates for MRSA (OR = 1.69; 95% CI 0.84, 3.41) or MRSA strains isolated from patients with nosocomial pneumonia (OR = 1.26; 95% CI 0.54, 2.96). Finally, there was no difference in eradication of enterococcal species (OR = 0.95; 95% CI 0.33, 2.73) or streptococcal species (OR = 0.97; 95% CI 0.55, 1.72).<sup>[40]</sup>

Although meta-analyses are useful for synthesizing results of different studies, they also have limitations, such as the lack of individual patient data or the lack of extractable disaggregated data, which should always be taken into account. Therefore, several issues that have been raised in individual RCTs or *post hoc* analyses of them, which were designed to compare the effectiveness of linezolid with that of other antibacterials for the treatment of patients with Gram-positive infections, are discussed in the following sections.

## 1.2 Community-Acquired Pneumonia

Although linezolid is not highly active against all causative pathogens of CAP, such as atypical pathogens, which are responsible for approximately 30% of pneumonia cases,<sup>[41]</sup> and *H. influenzae*,<sup>[6]</sup> it has been compared with ceftriaxone (1 g twice daily) followed by cefpodoxime (200 mg twice daily) for the treatment of patients with CAP who required hospitalization in an open-label RCT that enrolled 747 patients.<sup>[35]</sup> *S. pneumoniae* was the predominantly isolated pathogen (73% of patients), followed by *S. aureus* (22%), *H. influenzae* (12%) and *M. catarrhalis* (4%); several patients with polymicrobi-

al CAP were enrolled. Linezolid was associated with greater resolution or improvement of symptoms of infection than ceftriaxone/cefepodoxime in the ITT population (83.0% vs 76.4%, respectively;  $p = 0.04$ ) but not in the clinically evaluable (90.8% vs 88.6%, respectively) population of hospitalized patients with CAP. Similar effectiveness was reported for microbiologically evaluable patients in the two groups (89.9% vs 87.1%, respectively). These data suggest that linezolid should not be considered a first-line choice for patients with CAP, given the availability of effective older antibacterials for this infection.

### 1.3 Nosocomial Pneumonia

Two double-blind, multicentre RCTs with similar designs conducted by the same group of investigators have been conducted to study the effectiveness and safety of linezolid for the treatment of patients with Gram-positive nosocomial pneumonia.<sup>[31,34]</sup> In both RCTs, linezolid 600 mg every 12 hours was compared with vancomycin 1 g every 12 hours; aztreonam was added in both groups but discontinued if no Gram-negative bacteria were identified. In the first RCT, 396 patients comprised the ITT population;<sup>[34]</sup> in the second RCT, 623 patients received at least one dose of study medication.<sup>[31]</sup> A dropout rate of approximately 50% was reported for both RCTs. Baseline characteristics (including age, sex, race, Acute Physiology and Chronic Health Evaluation [APACHE] II score, need for ventilator support and days on ventilator before enrolment to the RCTs, chest radiograph and microbiological findings) and treatment duration were similar between the compared treatment groups in both RCTs, except that a more frequent multilobar involvement was found in patients treated with linezolid in one of the RCTs.<sup>[31]</sup> A pathogen was isolated in 43% of patients in the RCT by Rubinstein et al.<sup>[34]</sup> and 61% of patients in the RCT by Wunderink et al.<sup>[31]</sup> Gram-positive cocci were isolated from 45% of these patients in both RCTs, and patients with *H. influenzae* pneumonia were incorporated into this group. *S. aureus* was the most frequently isolated pathogen in both RCTs.

Linezolid and vancomycin were equally effective in resolving or improving the symptoms of nosocomial pneumonia in the clinically evaluable population (66% and 68% for linezolid-treated patients, and 68% and 65% for vancomycin-treated patients, for the two RCTs, respectively).<sup>[31,34]</sup> Although lower, the clinical success rates for the ITT populations were also similar between the compared antibacterials in both RCTs. Microbiological success was not significantly different between linezolid and vancomycin (62% and 68% for linezolid, and 52% and 73% for vancomycin, for the two RCTs, respectively). Eradication rates of all Gram-positive cocci were also similar. Finally, mortality was not different between the compared antibacterials in both RCTs (approximately 20% in both groups of patients in both RCTs). In addition, Rubinstein et al.<sup>[34]</sup> reported that the majority of these deaths in both groups of patients occurred during the follow-up period and “were attributed to the progression or complications of the severe underlying comorbidity”.

Pathogens were isolated from a total of 607 patients enrolled in these two RCTs.<sup>[31,34]</sup> Among them, 339 patients had nosocomial pneumonia due to *S. aureus*, and 160 patients had MRSA pneumonia. These patients were included in a retrospective analysis.<sup>[42]</sup> None of these isolates was resistant to vancomycin; in fact, 90% had an MIC <1 µg/mL. Linezolid was as effective as vancomycin for the treatment of patients (ITT population) with *S. aureus* pneumonia (51.5% vs 43.4%, respectively), but was associated with significantly greater treatment success than vancomycin in patients with MRSA pneumonia (59.0% vs 35.5%, respectively;  $p < 0.01$ ). In addition, Kaplan-Meier analysis for mortality showed that linezolid was associated with non-significantly better survival than vancomycin in patients with *S. aureus* nosocomial pneumonia (78.0% vs 69.8%, respectively), and significantly better survival than vancomycin in the MRSA subset (80% vs 63.5%, respectively;  $p = 0.03$ ). Linezolid administration was not among the predictors of clinical cure among patients with MRSA nosocomial pneumonia in the performed logistic regression

analysis; however, it was a significant predictor of survival in all patients and in the subset of patients with MRSA nosocomial pneumonia.

Data regarding ventilator-associated pneumonia were not reported in these two publications.<sup>[31,34]</sup> However, a retrospective analysis of the combined data from these two RCTs, which included 544 patients with ventilator-associated pneumonia, was performed.<sup>[43]</sup> Among these patients, 264 had a confirmed Gram-positive ventilator-associated pneumonia. Linezolid was associated with a higher, statistically non-significant, clinical cure rate compared with vancomycin in all ventilator-associated pneumonia patients (45.4% vs 36.7%, respectively) and in ventilator-associated pneumonia patients with *S. aureus* infections (48.9% vs 35.2%, respectively). Clinical cure rates significantly favoured linezolid compared with vancomycin in the Gram-positive (53.7% vs 37.7%, respectively;  $p = 0.02$ ) and MRSA (62.2% vs 21.2%, respectively;  $p = 0.001$ ) subsets. Logistical regression analysis showed that linezolid was an independent predictor of clinical cure for all patients, patients with Gram-positive ventilator-associated pneumonia, and patients with MRSA ventilator-associated pneumonia. Kaplan-Meier survival rates favoured linezolid versus vancomycin in the MRSA subset (84.1% vs 61.7%, respectively;  $p = 0.02$ ). On the other hand, Kaplan-Meier survival rates were similar for linezolid versus vancomycin therapy in all patients with ventilator-associated pneumonia (79.1% vs 73.7%, respectively), the Gram-positive subset (80.6% vs 70.8%, respectively), and the *S. aureus* subset (78.2% vs 70.3%, respectively). Logistical regression showed that linezolid was an independent predictor of survival for all patients, patients with Gram-positive cocci ventilator-associated pneumonia and patients with MRSA ventilator-associated pneumonia.

#### 1.4 Complicated Skin and Soft Tissue Infections (SSTIs)

The most recently published study of linezolid for complicated SSTIs was a double-blind, multicentre RCT that compared linezolid 600 mg twice

daily with dalbavancin 1 g on day 1 and 500 mg on day 8.<sup>[22]</sup> Patients were randomized in a 2 : 1 ratio. A total of 854 patients comprised the ITT population. Approximately 23% of patients were not clinically evaluable at the test-of-cure visit. MRSA was the predominantly isolated micro-organism. Linezolid and dalbavancin were equally effective for the treatment of patients with SSTIs (91.2% vs 88.9%, respectively). This was also true for patients with MRSA SSTIs (89% vs 91%, respectively). No differences between treatment groups were reported for patients with specific infections (abscess, cellulitis, surgical wound infections and burns).<sup>[22]</sup>

In another open-label, multicentre RCT, linezolid 600 mg twice daily was compared with vancomycin 1 g twice daily, followed by a semisynthetic penicillin when a susceptible strain was isolated.<sup>[24]</sup> In addition, 37% of linezolid-treated patients and 39% of vancomycin-treated patients also received antibacterials against Gram-negative bacilli. A total of 1200 patients were enrolled in the study, and 1180 comprised the ITT population. Approximately 25% of the ITT population was not considered clinically evaluable. Although the response rate was very high for both regimens, linezolid was more effective than vancomycin for the treatment of patients with SSTIs at the test-of-cure visit (94.4% vs 90.4%, respectively;  $p = 0.023$ ). The same was true for the microbiologically evaluable population (94.5% vs 89.7%, respectively;  $p = 0.022$ ). Linezolid was also more effective for the treatment of patients with major abscesses (98.3% vs 91.1%, respectively;  $p = 0.026$ ) but not for patients with cellulitis or infected surgical wounds. Finally, linezolid was more effective than vancomycin for patients with MRSA SSTIs (88.6% vs 66.9%, respectively;  $p < 0.001$ ), but not for patients with methicillin-susceptible *S. aureus* (84.9% vs 75.3%, respectively;  $p = 0.09$ ) or *S. pyogenes* SSTIs (86.7% vs 94.4%, respectively). Despite the higher cure rates and the earlier change to oral therapy, linezolid was administered for a longer period of time than vancomycin ( $11.8 \pm 4.9$  days vs  $10.9 \pm 5.3$  days, respectively;  $p = 0.004$ ). In a sub-analysis of this RCT, patients with surgical wound infections were further evaluated.<sup>[44]</sup> In this

analysis, linezolid was as effective as vancomycin in the clinically evaluable population but more effective than vancomycin in the microbiologically evaluable population (84% vs 58%, respectively;  $p = 0.0073$ ) and in patients with MRSA infections (87% vs 48%, respectively;  $p = 0.0022$ ).

In a double-blind, multicentre RCT, linezolid 600 mg twice daily was compared with oxacillin 2 g four times daily followed by dicloxacillin 500 mg four times daily for the treatment of patients with complicated SSTIs.<sup>[38]</sup> Patients with MRSA strains were excluded from this RCT. A total of 823 patients were enrolled in the trial and 819 received at least one dose of the compared antibacterials. A large number of dropouts were reported; 600 patients comprised the clinically evaluable population and 294 the microbiologically evaluable population. *S. aureus* was the most commonly isolated pathogen (140 in linezolid patients and 143 in oxacillin/dicloxacillin patients). *Streptococcal* spp. were the second most prevalent isolates (*S. pyogenes* in 41 linezolid patients and 46 oxacillin/dicloxacillin patients, and *S. agalactiae* in 10 linezolid patients and 12 oxacillin/dicloxacillin patients). The effectiveness of both regimens was low in the ITT population (69.8% vs 64.9%, respectively). Linezolid was as effective as penicillins in the clinically evaluable population (88.6% vs 85.8%, respectively) and the microbiologically evaluable population (88.1% vs 86.1%, respectively). Eradication rates were also similar for all groups of isolated Gram-positive cocci.

### 1.5 Diabetic Foot Infections

Although the majority of the RCTs that studied the effectiveness of linezolid for the treatment of patients with SSTIs also included patients with diabetes mellitus, none of them specifically reported the outcomes for diabetic foot infections.<sup>[26]</sup> An open-label, multicentre RCT was designed to study the comparative effectiveness of linezolid 600 mg twice daily and aminopenicillins (sulbactam/ampicillin 1.5–3 g four times daily and amoxicillin/clavulanic acid 625 mg three times daily or 1 g twice daily) for the treatment of diabetic foot infections.<sup>[26]</sup>

Aztreonam could be added in cases of Gram-negative infection in both groups and vancomycin in cases of MRSA infection in the aminopenicillins group. This was the only RCT that allowed enrolment of patients with concomitant osteomyelitis. A total of 371 patients were enrolled in the study; 361 comprised the ITT population. Patients were randomized in a 2 : 1 ratio. Linezolid was more effective – although not statistically significantly so – than aminopenicillins for all SSTIs combined (81% vs 71%, respectively). However, linezolid was more effective for the treatment of patients with infected ulcers (81% vs 68%, respectively;  $p = 0.018$ ) and for patients without concomitant osteomyelitis (87% vs 72%, respectively;  $p = 0.003$ ). There was no difference between the two regimens regarding treatment of patients with osteomyelitis (61% vs 69%, respectively). The clinical cure rates, by baseline pathogen, were similar for the two treatment groups, except that the rate of clinical cure was significantly higher among linezolid recipients infected with *S. agalactiae*. The number of MRSA-infected patients in both groups was small.

### 1.6 Meticillin-Resistant *Staphylococcus aureus* SSTIs

Sharpe et al.<sup>[23]</sup> reported their experience from an open-label, single-centre RCT that enrolled patients with MRSA SSTIs requiring surgical intervention. A total of 117 patients were enrolled in this RCT; 57 were excluded from the final analysis. In this study, linezolid 600 mg twice daily was compared with vancomycin 1 g twice daily. Vancomycin-treated patients were older than those treated with linezolid. Treatment duration was similar between the two treatment groups. Linezolid was more effective than vancomycin in this population (97% vs 43%, respectively;  $p = 0.015$ ); in addition, fewer linezolid-treated patients required amputation (0% vs 23.3%, respectively;  $p = 0.011$ ).

In another multicentre RCT that compared the effectiveness of linezolid 600 mg twice daily with vancomycin 1 g twice daily for known or suspected MRSA infection, 460 patients were enrolled; 224 of these patients had an MRSA infection.<sup>[33]</sup> SSTIs



were the most common infections, followed by pneumonia, urinary tract infections and bacteraemia. In both the ITT and microbiologically evaluable populations, linezolid was as effective as vancomycin for the treatment of MRSA infections (ITT: 56.8% vs 55.0%, respectively; microbiologically evaluable population: 73.2% vs 73.1%, respectively).

Finally, in a recently published RCT in patients with MRSA infections in Japan, 151 patients comprised the ITT population.<sup>[20]</sup> Patients with nosocomial pneumonia, SSTIs and sepsis were included. At the end of treatment, linezolid was as effective as vancomycin in the microbiologically evaluable patients (62.9% vs 50.0%, respectively), but linezolid was associated with higher eradication rates than vancomycin (79.0% vs 30.0%, respectively;  $p < 0.001$ ).

#### 1.7 Vancomycin-Resistant Enterococcal Infections

In a non-comparative, non-randomized, compassionate-use programme, linezolid intravenous (IV) or oral (PO) 600 mg daily for adults, or 10 mg/kg three times daily for children or adults weighing <40 kg, was used for the treatment of patients with serious multidrug-resistant, Gram-positive infections.<sup>[45]</sup> A total of 796 patients were enrolled, from whom 490 VRE *faecium* strains were isolated, comprising 59.2% of the total isolates in the study. Overall, in patients with VRE *faecium* infections, the cure rate in the clinical evaluable population was 81.4%; 5.8% of patients had infections that failed to respond to therapy and 12.8% of patients had indeterminate outcomes. More specifically, the clinical cure rate according to infection site was as follows: urinary tract infections 92%; intra-abdominal infections 91.4%; SSTIs 79.3%; bacteraemia 78%; endocarditis 76.9%; bone infections 75%; and lower respiratory tract infections 75%. The microbiological success rate in patients with VRE *faecium* infection was 86.4%, failure occurred in 12.7%, and the outcome was indeterminate in 0.9%.

In a single-centre, pilot RCT, linezolid IV or PO 600 mg twice daily was compared with quinupristin/

dalfopristin IV 7.5 mg/kg three times daily for the treatment of VRE *faecium* infections in cancer patients.<sup>[27]</sup> Forty patients were enrolled in the trial. Over 90% of patients in both treatment groups had either primary or secondary bacteraemia. More critically ill patients and more patients with pneumonia were enrolled in the quinupristin/dalfopristin group; no other differences between the treatment groups were reported. Linezolid was more effective than quinupristin/dalfopristin for the treatment of Gram-positive infections in cancer patients, but this difference was not statistically significant in both clinically (58% vs 43%, respectively) and microbiologically evaluable (90% vs 71%, respectively) populations. Infection-related mortality was similar in the two treatment groups (16% vs 10%, respectively); all-cause mortality was not reported. Relapse rate was not statistically different between the compared antibacterials (21% vs 10%, respectively).

The efficacy of linezolid in patients with VRE infections was assessed in a multicentre, double-blind RCT.<sup>[39]</sup> This RCT compared the effectiveness of two linezolid doses in the treatment of patients with VRE infections because at the initiation of the study no alternative choice of therapy was available. A total of 145 patients were randomized to treatment with linezolid IV or PO 600 mg twice daily or 200 mg twice daily. The urinary tract was the most frequent site of VRE infections, followed by SSTIs, bacteraemia of unknown origin, peritonitis, intra-abdominal infection, catheter-related infection and pneumonia. The average duration of antibacterial administration was similar in the two groups (15.0 and 16.1 days in the 200 mg and 600 mg groups, respectively). Cure rates were not significantly different between the two groups for all infections combined in the ITT population (67% vs 52%, respectively), as well as at each infection site. However, the microbiological outcome in the clinically evaluable population at follow-up was superior for the linezolid 600 mg group compared with the linezolid 200 mg group (88% vs 62%, respectively;  $p = 0.007$ ). Similarly, success rates favoured the higher linezolid-dose group in microbiologically

evaluable patients (86% vs 59%, respectively;  $p = 0.015$ ).

### 1.8 Paediatric Populations

The results of an open-label, multicentre RCT that enrolled patients aged  $\leq 12$  years with hospital-acquired, Gram-positive infections (pneumonia, SSTIs, bacteraemias or other infections) have been published.<sup>[29]</sup> In this RCT, linezolid 10 mg/kg three times daily was compared with vancomycin 10–15 mg/kg one to four times daily according to dosing recommendations. Patients were randomized in a 2:1 ratio; 316 patients comprised the ITT population. The discontinuation rate was high (approximately 30%). *S. aureus* (including MRSA) and coagulase-negative staphylococci (including methicillin-resistant strains, MRCNS) were the most commonly isolated pathogens. Linezolid was as effective as vancomycin in both ITT (79.1% vs 74.1%, respectively) and clinically evaluable (89.3% vs 84.5%, respectively) populations. Clinical cure rates were also similar in the two groups when specific infections were considered. In addition, clinical cure rates were comparable between linezolid and vancomycin in neonates (84% vs 77%, respectively).<sup>[46]</sup> Treatment duration was similar in the two groups, but IV treatment was shorter in linezolid-treated patients. Success rates were also similar in the microbiologically evaluable population (88.2% vs 87.0%, respectively). Pathogen eradication rates were similarly high in both treatment groups for all isolated groups of pathogens, including MRSA and MRCNS.

Linezolid has also been evaluated in two additional cohort studies for the treatment of children with recurrent otitis media<sup>[47]</sup> and CAP.<sup>[48]</sup> Linezolid was found to be effective in these studies.

### 1.9 Other Infections

In addition to its approved indications, linezolid has been used for the treatment of several other infectious diseases, including bacteraemia,<sup>[40]</sup> infections of the neutropenic host,<sup>[21]</sup> endocarditis,<sup>[49]</sup> urinary tract infections,<sup>[33,45]</sup> bone and joint infections,<sup>[50-52]</sup> infections of the CNS<sup>[53]</sup> and tuberculo-

sis.<sup>[54]</sup> The majority of data regarding these infections (except for bacteraemia and neutropenia) arises from retrospective case series and case reports in which linezolid was usually administered as a rescue drug. These reports support the use of linezolid as an alternative to already approved antibacterials for the treatment of patients with such infections when previous treatments have failed, administration of other antibacterials is prohibited because of allergic reactions or other adverse events, or when IV administration of antibacterials is not feasible or acceptable.

A preliminary analysis of data from an open-label RCT that included 726 patients with catheter-related bacteraemia and catheter-site infections has been released online by the US FDA.<sup>[55]</sup> In this RCT, patients treated with linezolid had a higher probability of death than patients treated with vancomycin (78/363 patients [21.5%] vs 58/363 patients [16.0%], respectively). Mortality in patients with Gram-positive infections did not differ according to the antibacterial administered. However, mortality was higher in patients receiving linezolid for Gram-negative infections alone (4/15 [26.7%] vs 1/11 [9.1%], respectively), for those with both Gram-positive and Gram-negative infections (16/46 [34.8%] vs 7/39 [17.9%], respectively) and for those in whom no micro-organism was isolated.<sup>[55]</sup>

## 2. Risk Assessment

In addition to relatively common adverse events described for several, if not all, antibacterials, such as vomiting, diarrhoea and rash, linezolid administration has been associated with a series of serious adverse events. Of these, anaemia, leukopenia and thrombocytopenia are most common, but lactic acidosis, optic and peripheral neuropathy, convulsions and serotonin-like syndrome are also noteworthy. In general, these serious adverse events occur either after prolonged linezolid administration ( $>2$  weeks of therapy for myelosuppression or neuropathy) or simultaneous administration with other drugs or foods (e.g. monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and adrenergic drugs or tyramine-containing foods for the development of

serotonin-like syndrome). These adverse effects subside after discontinuation of linezolid.

Several articles investigating the development of adverse events probably or possibly associated with linezolid administration have been published. In a meta-analysis conducted by our team in which 12 RCTs were included,<sup>[40]</sup> we found that linezolid was associated with more adverse events than glycopeptides or  $\beta$ -lactams, but this finding did not reach statistical significance (OR = 1.40; 95% CI 0.95, 2.05). Headaches, diarrhoea, nausea and vomiting of mild to moderate severity were the most commonly reported adverse events. The number of patients who had to be withdrawn from the RCTs because of development of adverse events was equal for those receiving linezolid compared with those receiving glycopeptides or  $\beta$ -lactams (OR = 0.91; 95% CI 0.42, 1.96). There was no difference between the compared treatment groups for development of anaemia (OR = 1.43; 95% CI 0.74, 2.75), but linezolid was associated with significantly more episodes of thrombocytopenia (OR = 11.72; 95% CI 3.66, 37.57).

A pooled analysis that included seven RCTs was published in 2003.<sup>[56]</sup> This meta-analysis was restricted to the assessment of the safety and tolerability of linezolid in comparison with other antibacterials (vancomycin,  $\beta$ -lactams and macrolides). Overall, linezolid was associated with more adverse events than comparator antibacterials (21.7% vs 15.7%, respectively;  $p = 0.001$ ). However, there was no difference between the compared antibacterials in serious adverse events (11.4% vs 10.6%, respectively) or in patients discontinuing the studied antibacterials because of adverse events (2.4% vs 1.9%, respectively). The most common drug-related adverse events associated with both linezolid and comparator agents were diarrhoea (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;  $p = 0.047$ ). Other potentially drug-related adverse events that were reported in  $>0.1\%$  but  $<1\%$  of linezolid-treated patients included abdominal pain, chills, fatigue, fungal infections (moniliasis), localized pain, increase in ALT levels, hyper-

tension, dyspepsia, glossitis, stomatitis, tongue discoloration, eosinophilia, thrombocytopenia, dizziness, insomnia, paraesthesia, pruritus and rash. The rates of *C. difficile*-related complications were similar between linezolid and comparator agents. *C. difficile* was reported in 0.2% of linezolid-treated patients and 0.4% of comparator drug-treated patients. Analyses<sup>[56]</sup> showed essentially no difference between linezolid and comparator antibacterials in the cumulative percentage of patients with outlying haemoglobin, neutrophil or platelet counts over the first 14 days of therapy. However, with longer treatment durations, there appeared to be a small increased risk of decreased platelet counts in linezolid-treated patients compared with the risk for the comparator group, but the difference was not statistically significant.

Linezolid-related haematological adverse effects may not increase in patients receiving chemotherapy for haematological malignancies. An RCT conducted in neutropenic patients, in whom the most common diagnosis was haematological malignancy and treatment was expected to continue for 10–28 days, indicated that myelosuppression is no more likely to occur in patients receiving linezolid than in those receiving vancomycin.<sup>[21]</sup>

Lactic acidosis has also been reported with the use of linezolid. In reported cases, patients experienced repeated episodes of nausea and vomiting.<sup>[57,58]</sup> Convulsions have also been reported: in some of these cases, a history of seizures or risk factors for seizures was present.<sup>[7]</sup>

The association between duration of linezolid administration and development of drug-related adverse events was more evident when the drug was used to treat infections that require prolonged antimicrobial administration. In such cases (i.e. treatment of endocarditis,<sup>[49]</sup> bone and joint infections<sup>[52]</sup> and tuberculosis<sup>[54]</sup>) adverse events were reported to be several-fold higher than in patients with pneumonia or SSTIs. Therefore, complete blood counts once a week are required when linezolid is administered for  $>2$  weeks. Peripheral and optic neuropathy have also been reported in patients treated with linezolid. These adverse effects have occurred primarily in

patients treated for longer than the maximum recommended duration of 28 days; indeed, in many of these patients, treatment durations of 3–6 months were employed.<sup>[59,60]</sup>

Finally, in a review that evaluated the development of adverse events after linezolid administration in children, the authors reported that the most commonly observed adverse events were diarrhoea, vomiting and nausea.<sup>[61]</sup> However, none of these adverse events was more commonly reported in the linezolid group than in comparator antibacterial groups.<sup>[61]</sup>

### 3. Comments

The effectiveness of linezolid has been investigated in several studies. These have shown that linezolid is at least as effective as comparator antibacterials for the treatment of patients with both CAP and nosocomial pneumonia, and is better than comparators for the treatment of patients with SSTIs. In relation to CAP, we believe that the currently available evidence suggests that linezolid should not be used as first-line empirical treatment because it lacks activity against atypical pathogens and Gram-negative bacilli, which are common causes of this infection. In addition, several other treatment options are currently available that are highly effective for such patients.<sup>[62]</sup> Linezolid could be considered as a treatment option in cases of severe CAP but only in addition to  $\beta$ -lactams and/or fluoroquinolones.

On the other hand, use of linezolid for the treatment of nosocomial pneumonia should be considered more often. Several reasons may justify selection of this agent in this context. First, linezolid has a better pharmacokinetic and pharmacodynamic profile than vancomycin, the antibacterial that has been considered the drug of choice for suspected nosocomial pneumonia due to Gram-positive microorganisms. It has been suggested that the vancomycin concentration achieved in the lungs (after administration of the usual dosage of 1 g twice daily) is approximately 20% of that measured in plasma, resulting in a concentration below the MIC for the majority of susceptible pathogens.<sup>[11,63]</sup> In contrast,

mean linezolid concentrations in lung tissue and epithelial lining fluid were reported to be higher than those in blood or plasma.<sup>[11,63]</sup> Second, vancomycin is usually coadministered with other antibacterials (e.g. aminoglycosides or  $\beta$ -lactams such as aztreonam) that may act as antagonists to it.<sup>[64]</sup> Third, use of vancomycin leads to cell death and the release of higher levels of exotoxins and other inflammation inducers to the circulation than linezolid, consequences that may increase the overall severity of the infection.<sup>[65]</sup> Finally, the other currently approved antibacterials for the treatment of Gram-positive infections cannot be used for the treatment of nosocomial pneumonia. Daptomycin activity is inhibited in the lungs by pulmonary surfactant,<sup>[66]</sup> while quinupristin/dalfopristin has not been approved for the treatment of pneumonia although it has been shown to be as effective as vancomycin in an RCT.<sup>[67]</sup> Telavancin, ceftobiprole and tigecycline have been also evaluated in RCTs. Although all were equally effective to their comparator antibacterials in each RCT for the treatment of patients with nosocomial pneumonia, only telavancin was as effective as its comparator regimen for the treatment of patients with ventilator-associated pneumonia.<sup>[68-70]</sup>

Conversely, the currently available evidence, albeit debatable,<sup>[40,71-73]</sup> suggests that linezolid is probably more effective than vancomycin for the treatment of MRSA nosocomial pneumonia, including ventilator-associated pneumonia. However, there was no difference between the two drugs when all pneumonia patients were included in the analyses. Currently, Gram-positive cocci are the leading cause of nosocomial infections,<sup>[74-76]</sup> and the incidence of MRSA infections is increasing.<sup>[77,78]</sup> Therefore, the important question at this point is whether linezolid should replace vancomycin as the empirical treatment option in all patients with nosocomial pneumonia or should it be restricted to those who have several risk factors for MRSA nosocomial pneumonia and those who receive care in hospitals with high MRSA prevalence. In a recent systematic review of outcomes for patients with MRSA or other *S. aureus* ventilator-associated pneumonia, the au-

thors concluded that the presence of meticillin resistance was associated with higher mortality. However, these authors also argued that there is probably no causal relationship between meticillin resistance and mortality, and that the higher mortality may have been attributable to confounders such as severity of underlying diseases, inadequacy of empirical treatment and duration of intensive care unit stay.<sup>[79]</sup>

Linezolid has been shown to be better than comparator antibacterials ( $\beta$ -lactams, glycopeptides and macrolides) for the treatment of patients with SSTIs.<sup>[40]</sup> However, the latter antibacterials were also highly effective for the treatment of SSTIs (90.3% success with linezolid vs 85.7% with comparator antibacterials).<sup>[40]</sup> Furthermore, the RCTs that studied the effectiveness of linezolid for SSTIs excluded patients with the most severe forms, such as gangrene, necrotizing fasciitis and concurrent osteomyelitis, and several of them included only patients with uncomplicated SSTIs (table I). Therefore, there is no good reason to use linezolid as a first-line treatment option for SSTIs and increase the possibility of development of resistance to an antibacterial that is valuable for more severe infections.

Finally, the limited available evidence from RCTs suggests that linezolid is more effective than comparator antibacterials for the treatment of patients with Gram-positive bacteraemia<sup>[40]</sup> but not for patients with MRSA bacteraemia.<sup>[80]</sup> These RCTs did not enrol patients with catheter-related bloodstream infections; rather, patients in these trials had bacteraemias of unknown origin or secondary to other infections. The FDA has released a report file suggesting that linezolid administration is associated with higher mortality than vancomycin in patients with catheter-related blood stream infections; the main difference was observed in patients with Gram-negative bacteremia.<sup>[55]</sup> The FDA committee was not prepared to make any recommendation regarding use of linezolid in the treatment of catheter-related bacteraemias until further analysis of the data had been completed.

There are limited options available for treatment of patients with VRE infections. Clinical suspicion for VRE infection is probably the only unchallenge-

able reason for empirical use of linezolid as a first-line antibacterial choice. The lack of comparative data for infections such as endocarditis or osteomyelitis do not allow us to proceed to recommendations regarding use of linezolid in such patients, although several associations have already incorporated use of this drug into their guidelines.<sup>[62,81]</sup>

Although linezolid has been associated with more adverse events than comparator antibacterials, these were mild to moderate in severity, mainly involved nausea, vomiting, diarrhoea or headache, subsided early after drug discontinuation and were never associated with the death of patients in RCTs. However, physicians should always remember the association between duration of linezolid administration and development of serious adverse events, and monitor complete blood counts at least once a week. In addition, there is evidence that although optic neuropathy usually subsides after discontinuation of linezolid administration, peripheral neuropathy may persist.<sup>[82]</sup> Therefore, close surveillance is warranted when longer treatment duration (>28 days) with linezolid, mainly for off-label indications, is employed.

#### 4. Conclusion

Linezolid is an important, effective and relatively safe treatment option for the treatment of Gram-positive infections. It has a favourable pharmacokinetic profile and surveillance programmes have shown that is highly active against multidrug-resistant, Gram-positive cocci. Its unique mechanism of action suggests that resistance is relatively unlikely to develop, but unwise and uncontrolled prescription will definitely lead to resistant micro-organisms. In order to preserve the role of linezolid in current therapeutics, its use should be limited to specific patient populations (VRE infections, hospitals with high prevalence of MRSA, patients with several risk factors for multi-drug resistant Gram-positive pathogens) and after consideration of data from relevant antimicrobial resistance surveillance studies and hospital infection control programmes.

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