The increase in serious gram-positive infections has increased the need for treatment of gram-positive infections in patients with hematologic malignancies. Common gram-positive pathogens exhibit a variety of resistance.

**Introduction**

Changes in patterns of distribution of infectious agents and their resistance to antibiotics are a continual challenge to the treatment of patients with gram-positive infections. Staphylococci (including coagulase-negative staphylococci and *Staphylococcus aureus*) and enterococci account for approximately one-third of all bloodstream infections and up to 50% of nosocomial bloodstream infections.[1] The control of infections caused by these gram-positive and other bacteria is particularly important in patients with hematologic malignancies, whose immune system is unable to mount adequate defense.

Antimicrobial resistance to available antimicrobial agents is a problem for compromised patients. Resistance is a class phenomenon—that is, pathogens resistant to one agent in an antimicrobial class are often resistant to other agents in that class, rendering one or more antibiotics ineffective in any given patient. The identification of antibiotics with new mechanisms of action is therefore important in bypassing established resistance mechanisms.

The oxazolidinones are a new class of antibiotics, chemically unrelated to any currently available antimicrobial agent. Linezolid (Zyvox), a member of this class, has been shown to have an excellent in vitro activity against gram-positive bacteria, including antibiotic-resistant strains.[2] It has recently been tested in clinical studies in non-immunocompromised patients with hospital- and community-acquired pneumonia and in those with skin and soft-tissue infections. Results from these trials are promising and indicate that linezolid may be a safe and effective new option for treating these types of gram-positive infections in patients with hematologic malignancies. This paper presents a review of the properties, clinical efficacy, and safety of linezolid.

**Mechanism of Action of Linezolid**

Linezolid is a synthetic antibiotic that inhibits bacterial translation at the initiation phase of protein synthesis.[3] Linezolid has been shown to bind to ribosomal ribonucleic acid (rRNA) on both 30S and 50S subunits of ribosomes,[4] inhibit the formation of initiation complex during protein synthesis,[5] greatly reduce the length of nascent peptide chains, and decrease the rate of elongation reaction of translation.[4] Both binding site and mode of action are unique among antibiotics known to act on ribosomal protein synthesis (Figure 1).

**In Vitro Activity**

Linezolid has been shown to have in vitro activity against a number of important pathogens, including methicillin-resistant *S aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococci (VRE).[2,6-8] It has been found active against all isolates tested, with minimum inhibitory concentrations (MICs) less than 4 µg/mL or better (range of 1 to 4 µg/mL) (Table 1).[2,6-8] For all vancomycin-susceptible enterococci, staphylococci, and streptococci, the activity of linezolid was comparable to that of vancomycin.[2] For VRE and oxacillin (Bactocil)-resistant staphylococci, linezolid was the most active agent tested when compared with other antibiotics (e.g., penicillin, ampicillin, piperacillin-tazobactam [Zosyn], levofloxacin, [Levaquin]).[2] The break-point for linezolid has been estimated as ≤ 4 µg/mL for staphylococci and 2 µg/mL for streptococci and enterococci. There is no evidence, to date, of rapid resistance development in vitro.[9]

**Pharmacokinetic Characteristics**

Linezolid has been found to be well absorbed after both oral and intravenous administration.[10]
Oral bioavailability of the antibiotic in a normal host is 100%. Although the presence of food may slightly decrease the rate of absorption, it has no effect on the extent of the drug absorbed. (Thus, linezolid may be administered without regard to meals.) Bioavailability in the setting of mucosal disruption secondary to graft-versus-host disease or therapy-associated mucositis is unknown. The drug shows low protein binding (31%) and is eliminated with a half-life of 5 to 7 hours (Table 2). The average steady-state plasma concentrations of the antibiotic following oral administration of 600 mg linezolid every 12 hours remains above MIC concentrations for staphylococci, enterococci, and streptococci (Figure 2).[10]

Steady-state plasma kinetics following oral administration of similar doses in patients with mild or moderate renal compromise has shown no significant differences. Likewise, no change in drug clearance has been observed in patients with mild or moderate hepatic failure. Pharmacokinetic (PK) characteristics in children over age 5 (10 mg/kg/dose q12h) have been found to be similar to that in adults. Thus, PK characteristics appear amenable to adequate dosing with linezolid administration every 12 hours in adults; it appears that the antibiotic can be administered in patients with mild to moderate renal or hepatic disease without kinetic consequences.

Clinical Efficacy of Linezolid

The clinical efficacy of linezolid has been studied in non-immunocompromised patients with gram-positive infections, including bloodstream infections. Patient populations studied included those with hospital-acquired pneumonia (HAP), community-acquired pneumonia (CAP), those with skin and soft-tissue (SST) infections, and those with documented MRSA or VRE infections from any source.[10]

Linezolid in Hospital-Acquired Pneumonia
In adults with hospital-acquired pneumonia, intravenous linezolid (600 mg every 12 hours) has been compared with intravenous vancomycin (1 g every 12 hours) administered for 10 to 14 days.[10] In all study patients, aztreonam (Azactam) or aminoglycoside antibiotics were given concomitantly to provide coverage against gram-negative bacteria. As in patients with community-acquired pneumonia, clinical outcomes, microbiologic outcomes, and pathogen (S aureus, MRSA,) eradication rates following linezolid treatment were similar to those found with vancomycin administration. An overall efficacy rate of 66% was noted in the linezolid-treated patients, compared to 68% in the vancomycin group. (Figure 3).

Linezolid in Community-Acquired Pneumonia
Two randomized, comparator-controlled, multicenter trials have investigated the efficacy of linezolid (600 mg every 12 hours) in over 1,200 adults with community-acquired pneumonia documented by clinical and radiologic evidence: one in ambulatory patients and another in hospitalized patients. In these studies, clinical outcomes, microbiologic outcomes, and pathogen eradication rates following treatment with 600 mg linezolid every 12 hours were found to be similar to oral cepodoxime (Vantin) (200 mg twice daily) in outpatients, and intravenous ceftriaxone (Rocephin) (1 g twice daily) followed by oral cepodoxime (Vantin) (200 mg twice daily) in hospitalized patients. Figure 4 shows the clinical efficacy of oral and/or parenteral linezolid in patients hospitalized with community-acquired pneumonia.

The overall eradication rates of key pathogens in all patients with community-acquired pneumonia were approximately 90% with linezolid and found to be similar to comparator for S pneumoniae, including a few patients with penicillin-intermediate S pneumoniae (PISP) and penicillin-resistant S pneumoniae (PRSP). In community-acquired pneumonia associated with S pneumoniae bloodstream infection, linezolid has been found to be statistically better than comparator in the microbiologic outcome and eradicated 94% of the pathoge (versus 67% eradication with comparator).

Phase II Pediatric Studies
In phase II, uncontrolled studies in children with community-acquired pneumonia, excellent efficacy has been seen with linezolid treatment (10 mg/kg every 12 hours for 7 to 14 days) in clinical outcome (95%), microbiologic outcome (100%), and overall outcome (100%).[10] A complete eradication of S pneumoniae was achieved in five out of five patients with positive cultures, four of whom had associated bloodstream infection, two with PRSP. Phase III studies in children are ongoing.

Linezolid in Skin and Soft-Tissue Infections
In adults with complicated skin and soft-tissue infections, clinical and microbiologic outcomes in a randomized trial were found to be analogous between linezolid and semisynthetic penicillins (intravenous oxacillin [Baxtoci] followed by oral dicloxacillin). A 91% efficacy rate was observed in patients receiving linezolid, compared to 86% in those receiving the control combination (Figure 5).
The effect of linezolid in adults with uncomplicated skin and soft-tissue infections has been evaluated in two randomized, clarithromycin (Biaxin)-controlled trials, one in the United States and the other in Europe.[10] At the test-of-cure visit, clinical outcomes, microbiologic outcomes, and pathogen (S aureus, Streptococcus agalactiae, Streptococcus pyogenes) eradication rates were found to be similar in the linezolid and clarithromycin groups. A combined efficacy rate of 91% was noted with linezolid treatment and 89% with clarithromycin. S aureus infections were found to dominate in these patients, with 92% and 88% eradication in the linezolid and clarithromycin groups, respectively. S agalactiae and S pyogenes infections, when found, were completely eradicated with linezolid, compared to 80% and 95% eradication of the two pathogens, respectively, with clarithromycin treatment.

**Overall Efficacy of Linezolid in VRE Infections**

The efficacy of linezolid in VRE infections was evaluated in a randomized, double-blind study that compared low-dose (200 mg every 12 hours) linezolid with high-dose (600 mg every 12 hours) linezolid in patients 13 years of age or older with VRE-positive cultures.[10] The origin or site of VRE infections was variable, and all patients required two VRE-positive cultures in samples of blood or other fluids (eg, urine, wound, abscess, respiratory secretions, or peritoneal or pleural fluid). Only the higher dose resulted in blood concentrations that were continuously above the MIC of the target pathogen for the entire dosing interval. Patients receiving the higher dosage of linezolid (600 mg every 12 hours) had an 85% cure rate based on overall outcome in microbiologically evaluable patients (Table 3A), a result that was not statistically different from the lower dose.

**Overall Efficacy of Linezolid in MRSA Infections**

In a randomized, multicenter, open-label trial of adult patients with documented MRSA infections, cure rates were found to be comparable between linezolid (600 mg given intravenously every 12 hours followed by 600 mg given orally every 12 hours) and vancomycin (1 gm twice daily given intravenously) in microbiologically evaluable patients (Table 3B). Both groups were treated for 7 to 28 days. Preliminary results in patients with MRSA indicate that linezolid treatment may decrease the length of hospital stay and result in higher numbers of early discharge than those treated with vancomycin.

**Clinical Safety**

Linezolid has been studied in over 2,000 patients in phase III studies.[10] The overall incidence of adverse events with linezolid treatment was found to be similar to that seen with one or more specific comparators in these studies. A total of 56% of patients treated with linezolid and 50% of those treated with comparator agents experienced at least one adverse event during treatment (Table 4). Of these, fewer than half of the patients were identified as having a drug-related adverse event. Approximately 11% of patients in both groups experienced more than one serious adverse event, with hospital-acquired pneumonia being diagnosed in about 1% of patients in both groups. Discontinuation due to drug-related adverse events was noted in about 2% of patients in both linezolid-treated and comparator-treated groups. Diarrhea, nausea, and headache were the most frequently reported (>1%) drug-related adverse events (Table 5).

Although several substantially abnormal hematologic and chemical assays were noted during the study, these were found to be equivalent to those observed for comparator antibiotics. Linezolid treatment was associated with low platelet counts in some patients (2.4% incidence with linezolid versus 1.5% with comparator in phase III trials).[10] However, thrombocytopenia generally did not manifest itself until after 15 days of treatment and was primarily observed in patients who had decreased platelet counts prior to receiving therapy. This may be important for cancer patients with neutropenia who may experience thrombocytopenia. Periodic, complete blood counts with platelet counts should be followed in patients treated with linezolid for more than 2 weeks, in those with preexisting thrombocytopenia, or in those expected to develop thrombocytopenia during therapy.

**Conclusions**

The prevalence of gram-positive infections is increasing both in the United States and Europe (see companion article, Changing Patterns of Infections and Antimicrobial Susceptibilities in Patients with Cancer on page 9) and control of these infections, without imposing selection pressures, is of clinical importance. The efficacy and safety of linezolid are comparable to that of present-day antibiotics used in the treatment of hospital- and community-acquired pneumonia, as well as skin and soft-tissue infections (Table 6). Among patients with intact immune function, linezolid’s unique mechanism of action lessens the likelihood of cross-resistance and provides a true

---

**Note:** The full text is not able to be included in this format due to the limitations of the system. Please refer to the original document for the complete context and information.
addition to the antibiotic armamentarium for the treatment of serious gram-positive infections. Further studies are needed to determine linezolid’s efficacy and safety in immunocompromised patients. Other advantages of linezolid, beside its broad spectrum of gram-positive activity, are its oral and parenteral bioavailability, which may facilitate ambulatory therapy. The oral formulation has promise in the outpatient care of low-risk patients with fever and neutropenia, following appropriate clinical trials.

References:


Source URL:
http://www.physicianspractice.com/review-article/linezolid%E2%80%94-new-option-treating-gram-po sitive-infections

Links: