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Linezolid for the treatment of serious gram-positive infections

Summary

- **The rate of resistance of the three most common gram-positive pathogens has increased dramatically in the last decade. In the United States vancomycin resistance in enterococci has risen from less than 1% to 18% exhibiting resistance.[1]**
- **The strength of linezolid comes from its demonstrated ability to handle serious infection for which current therapy is limited (i.e. vancomycin resistant enterococci and methicilin-resistant staphlococcus). However, its efficacy for the treatment of many less serious gram-positive bacterial infections is equal to that of comparator antibiotics.**
- **Linezolid will provide a valuable option for the treatment of patients with serious gram-positive infections resistant to standard therapy. Experience with linezolid is limited to 28-day therapy, mainly in the form of industry run trials and cases of compassionate use.**
- **There is much momentum in the development of therapies for serious gram-positive infections. Only time will tell where linezolid will fit among the new and emerging options.**

The Technology

Linezolid (Zyvox®, Pharmacia & Upjohn) is the first of a new class of antimicrobials, the oxazolidinones.[2] Oxazolidinones are synthetic and structurally unrelated to any agent presently marketed. They inhibit protein synthesis by preventing the formation of protein initiation complex.[3] This represents a novel mechanism of action. Oxazolidinones display a consistent coverage against numerous troublesome pathogens including gram-positive cocci. This coverage may be useful in treating infections caused by multi-drug resistant staphylococci, streptococci and enterococci.[2] Oxazolidinones as a class are bacteriostatic; they restrict the growth and activity of most species of bacteria without actually killing them.3 However, linezolid has demonstrated bactericidal activity against some microbes (e.g. *B. Fragilis, C. perfringens, S. pneumoniae*).[3]

The oral suspension formulation of linezolid contains phenylalanine and therefore must not be taken by individuals with phenylketonuria.

Linezolid is a nonselective inhibitor of monoamine oxidase (MAO). This produces the potential for interaction with adrenergic and serotonergic agents. Caution is advised for patients taking such medications with linezolid.

Pharmacokinetics do not appear to be altered in patients with renal insufficiency or mild to moderate hepatic dysfunction.[4] As approximately 30% of a dose is removed through hemodialysis, linezolid should be given after dialysis.[5]

Regulatory Status

On April 18, 2000 the U.S. Food and Drug Administration approved Zyvox® for the treatment of patients with infections caused by gram-positive bacteria.[6] Pharmacia & Upjohn filed for marketing approval in the United Kingdom under the trade name Zyvoxa in October 2000. As of February 2001, linezolid has not been approved for use in Canada.[7] The literature indicates that comp-assionate use programs for linezolid exist, however the geographical scope of such programs is not clearly defined.[8]

Patient Group

Linezolid is specifically labeled for adults with:

- infections caused by vancomycin-resistant *Enterococcus faecium*, including cases with bacteremia;
- nosocomial pneumonia caused by methicillin-resistant or methicillin-susceptible strains of *Staphylococcus aureus* or penicillin-susceptible stains of *Streptococcus pneumoniae*;
- complicated skin and skin-structure infections caused by methicillin-resistant or methicillin-susceptible strains of *S. aureus* or by *Streptococcus pyogenes* or *Streptococcus agalactiae*;
- uncomplicated skin and skin-structure infections caused by methicillin susceptible strains of *S. aureus* or by *S. pyogenes* and;
- community acquired pneumonia caused by penicillin-susceptible strains of *S. pneumoniae*, including cases with concurrent bacteremia, or methicillin-susceptible strains of *S. aureus*.[9]

Due to concern over the emergence of resistance, Pharmacia & Upjohn have suggested that linezolid be used only after considering of alternatives, especially in the outpatient setting.[10] Information provided by Pharmacia & Upjohn describes unaltered pharmacokinetics following concomitant administration of aztreonam or gentamicin. Concomitant dosing may be required for patients with mixed gram-positive and gram-negative infections.

Current Treatments

Quinupristin/dalfopristin (Q/D) has been approved for the treatment of gram-positive bacteria resistant to other antibiotics, specifically vancomycin-resistant *Enterococcus faecium* and methicillin-resistant Staphy-lococcus and erythromycin/penicillin-resistant strains of Streptococcus. The drug has no activity against *Enterococcus faecalis*.[11] Q/D is inactive against erythromycin resistant *S. aureus* strains.[12] This poses a limitation as many *S. aureus* strains, both methicillin-susceptible and methicillin-resistant, are innately resistant to erythromycin.[12]

Q/D is contraindicated in patients taking Tacrolimus[13] (an immunosuppressive agent) as well as agents with cytochrome P450 3A4 as metabolites, as it may inhibit cytochrome metabolism and may lead to nephro- or neurotoxicity.

Currently there are no other treatment options for certain serious gram-positive infections as many of these microbes are resistant to traditionally used antibiotics.

Administration and Cost

Linezolid is available in tablet, oral suspension, and injectable formulations. No dosage adjustments are required when switching from IV to oral formulations. All formulations are 100% bioavailable.[14] Linezolid can be taken without regard to meals, food delays absorption but does not affect peak plasma concentrations.[15] Suggested dosing regimen is 400 - 600 mg twice daily depending on the type of infection.[14,16] Treatment should last between 10-28 days depending on the type of infection.[5]

Among injectable formulations, estimates of basic drug cost suggest that linezolid is less costly per daily dose than Q/D but more costly than vancomycin.[17] The oral formulation of linezolid is less costly than the injectable formulation, but still more costly than vancomycin (available only in injectable formulation).[17] Allowing patients to be discharged once they are switched to oral formulations may also reduce hospital costs.

Projected Rate of Diffusion

Gram-positive infections are a common cause of hospital-acquired infections, and bacterial resistance is increasing over time. Therefore, this agent may have a substantial impact on health care and patient outcomes when treating multi-resistant pathogens.

It has been recommended that linezolid be reserved as treatment for infections which do not respond, or are resistant to other available antimicrobials. This suggests that uptake of this product may be great in restricted populations, specifically in methicilin-resistant Staphylococcus (MRS) and vancomycin-resistant Enterococcus (VRE) infections, or in patients intolerant of other therapies.

Concurrent Developments

Quinupristin/dalfopristin (30/70)(Synercid®, Aventis Pharma) is the newest antibiotic available to handle resistant gram-positive infections. It is an injectable streptogramin antibiotic. The two antibiotics work in synergy; dalfopristin inhibits early protein synthesis while quinupristin inhibits late phase protein synthesis.[18] It was approved for use in Canada in April 2000.[7]

There has been much activity in the development of antibiotics for gram-positive infections. LY333328 (Eli Lilly) is a glycopeptide-derivative, which is bactericidal against glycopeptide-resistant enterococci and active against most other important gram-positive bacteria. It is in phase II clinical trials.[19]

Teicoplanin (Targocid®, Aventis Pharma), a glycopeptide, has activity similar to vancomycin. However, resistance has been described in both enterococci and *S. aureus* isolates.[20] Teicoplanin was available in Canada through an emergency drug release program until March 2000. It was discontinued because Synercid®, which targets the same population, was launched (Aventis Pharma: personal communication, 2000 Dec 6).

Development of evernimicin (Ziracin®, Schering-Plough), an oligopeptide with promising early results, has been discontinued due to lack of balance between its efficacy and safety.[21]

Daptomycin (Cidecin®, Cubist) is a novel cyclic lipopeptide, a new class with a new mechanism of action.[22] Intravenous daptomycin is currently in phase III clinical trials.[23]

Ramoplanin (IntraBiotics) is a natural, oral formulation with activity against multidrug resistant gram-positive bacteria (VRE and MRSA) in phase III clinical trials.[24]

The Evidence

Most of the evidence of efficacy of linezolid is in the form of unpublished reports from Pharmacia (two of which have subsequently been published[25,26]). The company conducted eight phase-III randomized controlled trials (RCT) including more than 4000 patients (2191 treated with linezolid). Information provided by Pharmacia (Pharmacia: unpublished data, 2000) details trials that evaluate the efficacy of linezolid in treating pneumonia, skin and soft tissue infections, as well as infections caused by drug-resistant pathogens (MRSA and VRE). Both IV and oral formulations of linezolid were compared to standard treatment. The reports describe five of the eight RCTs as double blind and one as single blind. The remaining two are open-trials. All reports clearly describe the patient population and any inclusion/exclusion criteria.
No explanations are provided for patients not evaluated, however, those who discontinued due to adverse drug events are described. In all cases linezolid was at least as effective in producing a clinical and microbiological cure. The trials showed no statistical difference overall between linezolid and its comparator for clinical or microbiological cure. The microbiological cure for linezolid ranged from ~60-90%.

Two of the eight studies deal with suspected drug-resistant organisms. One study compared high (600 mg every 12 hours) and low (200 mg every 12 hours) dose linezolid for the treatment of VRE. The high dose was reported to be significantly more effective (microbiologic cure 85.7% high dose versus 58.6% low dose). The other study compared linezolid (IV followed by oral) with vancomycin for suspected MRSA infection. Microbiological cure rates were not significantly different (59.4% linezolid versus 64.2% vancomycin).

Two studies, one comparing linezolid to cephalosporin (IV ceftriaxone followed by oral cefpodoxime) in the treatment of pneumonia, and the other comparing linezolid to oxacillin in the treatment of complicated skin and soft tissue infection,[26] found linezolid superior in eradicating bacteremia (93.3% for linezolid compared to 69.6% for cephalosporin and 85.7% for linezolid compared to 77.8% for oxacillin).

Published case reports and case series from the compassionate use of linezolid suggest that linezolid has a role in the treatment of serious infections. A report of 17 patients (15 with VRE, and two with sensitivity to vancomycin) treated with linezolid showed microbiological cure in 12 patients, the other five died before the completion of treatment. The deaths were not treatment

related.[27] Another non-comparative compassionate use trial of linezolid in 65 patients showed an 83.3% microbiological cure.[28] In this study six patients discontinued due to AE. A case report describes one patient with bacteremia due to VRE infection that was successfully treated with linezolid after failure of treatment with synercid.[29]

Safety and efficacy have not been proven in children less than 18 years of age. Linezolid has been used in a limited number of children, however an appropriate dose has not been established for children.[17] Pediatric trials are ongoing (Aventis Pharma: personal communication, 2001 Mar 5).

Adverse Effects

In the eight clinical studies undertaken by Pharmacia, linezolid was generally well tolerated. The most commonly reported adverse events were diarrhea (3 - 11%), nausea (4 - 10%), and headache (3 - 11%).

Four of seven studies report greater rates of adverse events with linezolid therapy than comparator therapy. There was no difference in rates of AE between linezolid and clarithromycin in a trial of patients with uncomplicated skin and soft tissue infections. Lower rates of discontinuation due to AE were seen in the linezolid arms of two trials, one comparing vancomycin and linezolid in patients with nosocomial pneumonia, and the other comparing linezolid and oxacillin in hospitalized patients with complicated skin and soft tissue infections.

Drug related adverse events (AE) were higher in the linezolid treatment arm of the study comparing linezolid and vancomycin for the treatment of MRSA, however no difference was seen in the number of patients discontinuing treatment due to adverse events. In this study, patients in the linezolid arm were started on an IV formulation and then switched to an oral formulation. Vancomycin is only available in IV formulation. It is postulated that the higher rate of AE may have resulted from the oral formulation of linezolid, as diarrhea and nausea are not uncommon with oral antibiotic therapy.

The trial of high and low doses of linezolid for VRE infections demonstrated a less favourable adverse event profile for the low dose therapy arm. The only AE that was dose dependant was thrombocytopenia.

Reversible thrombocytopenia (low platelet count), dependent on duration of treatment (> 2 weeks), was noted in 2.4% of patients treated with linezolid compared to an average of 1.5% of patients in comparator groups. As with nearly all antibiotics, a diagnosis of Pseudomembranous colitis (mild to life threatening) must be considered in patients who present with diarrhea.

In clinical trial use, there has been no evidence of MAO-B inhibition.

Implementation Issues

No dosage changes are required when switching from IV to oral formulations of linezolid. The availability of oral formulation should facilitate and possibly hasten hospital discharge, which has the potential to reduce hospital costs. The switch from IV to oral formulations may, however, promote inappropriate use of linezolid when another currently available, and possibly less expensive, agent could be used.[30]

This brief was prepared by Laura McAuley, CCOHTA and has been peer reviewed.
References are available online on CCOHTA's website.
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