Effectiveness of linezolid over traditional antibiotics in osteomyelitis in adults : a review

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Abstract

Osteomyelitis is rare but complicated and challenging disease, mainly caused by staphylococcus aureus. Although bone is normally resistant to bacterial colonization, some events such as trauma, surgery may disrupt bony integrity and lead to bone infection. Appropriately designed antibiotic regimens are critical to manage the all stages of osteomyelitis. Methicillin, Vancomycin, Fluoroquinolone, clindamycin and so many antibiotics are used. Recently, several newer agents with good activity against causative organisms have been introduced include linezolid, daptomycin, tigecycline, telavancin and ceftaroline. Their roles in the treatment of acute and chronic osteomyelitis are still being evaluated. The best studied of these is linezolid, a bacteriostatic antibiotic. The comparative role of linezolid and other antibiotics in osteomyelitis are thoroughly evaluated in this review article.

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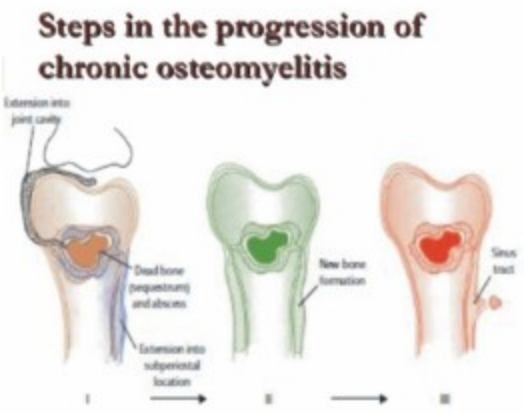
Introduction

Osteomyelitis is one of the oldest disease. When microorganisms are introduced into bones hematogenously, contiguously or from direct inoculation related to foreign body, trauma, osteomyelitis can occur. When bone infection persists for months then referred as chronic osteomyelitis and may be polymicrobial.[1] Osteomyelitis is estimated to affect 2 out of every 10,000 people in United States and around 80% of cases develop it because of open wound.[2] Another study showed that the incidence of osteomyelitis is approximately 13 per 100,000 in children and approximately 90 per 100,000 in adults.[3,4] Early and specific treatment is important in osteomyelitis and identification of causative organisms is essential for antibiotic therapy.[5] The most important consideration for antibiotic selection is spectrum of action. Route of administration by intravenous or oral route is less important than drug levels that are achievable at the site of infection. Intravenous beta-lactam and vanomycin are the treatment of choice for methicillin resistant staphylococcus aureus (MRSA) osteomyelitis. Rifampicin combined with other anti-staphylococcus agents may increase cure rates, especially for device associated infections. Oral fluoroquinolones with beta lactam agents can be used for treatment of gram negative osteomyelitis, but increasing resistance has complicated management of this infection.[6] Successful management requires a combination of targeted antimicrobial therapy and surgical removal of necrotic and devitalized tissue. Consensus recommendation for prolonged (? 6 weeks) antibiotic therapy for most osteomyelitic patients.[7] Antibiotic susceptibility is determined by MIC and susceptibility interpretations are based on achievable serum level . An ideal agent would achieve adequate bone concentration to meet pharmacokinetic and pharmacodynamic targets for bacterial cell death and eradication of infection.[8] Linezolid, approved by FDA in 2000 for MRSA infection like skin and soft tissue infection, diabetic foot ulcer, osteomyelitis.[9] Linezolid has been shown to be clinically useful in the treatment of osteomyelitis, where traditional bactericidal agents have been required.[10] Successful outcomes or cure were reported in several articles.[11-14] The aim of this present work is to provide an effective role of linezolid over traditional antibiotics to treat osteomyelitis.

Osteomyelitis

When a bacteria adhere to bone by expressing receptors for component of bone matrix (Fibronectin, laminin, collagen and bone siloglycoprotein); the expression of the collagen-binding adhesion permits the attachment of the pathogen to cartilage.[15] During acute infection phagocyte attempt to

combat invading microorganism and in the process generate toxic oxygen radicals and release proteolytic enzymes that may lyse the surrounding tissues.[7] If the infection is not treated, dead neutrophils were accumulate inside the bone, forming an abscess or pocket of pus. Pus spread into vascular channel, raising the intraosseous pressure and impair blood flow. In chronic osteomyelitis, the bone may actually die. So, antibiotic should be started after taking necessary steps.



METHICILLIN AND VANCOMYCIN

Methicillin, an antistaphylococcal penicillin mostly used in osteomyelitis. After isolation of methicillin-resistant strains, glycopeptides particularly vancomycin is preferred extensively. Unfortunately in1996 resistance to this antibiotic has been recognized. It also achieves low bone penetration.[16] The recurrence rate of vancomycin is two times higher than beta-lactam antibiotics.[17] Data suggest that vancomycin is losing its clinical and microbiological potency.[18]

Linezolid

The prevalence of MRSA is increasing and their susceptibility to vancomycin is decreasing.[19] Therefore, linezolid is choiced after considering: potential causative micro-organisms and their corresponding range of MICs (minimum inhibitory concentrations), pharmacokinetic and pharmacodynamic properties, mechanism of action, tolerability, and host toxicity.[20] Some clinical studies are given in Table 2.

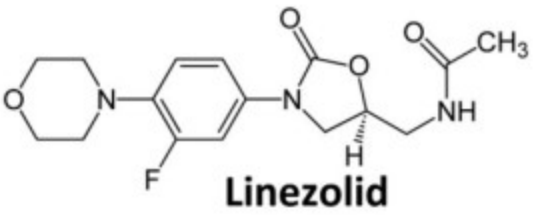


Figure: Chemical structure of Linezolid

Pharmacodynamics

Linezolid belongs to the group of oxazolidinones. It is a synthetic, broad spectrum antibacterial agent available in both oral and parenteral dosage form.[21] It binds to 23s rRNA of the 50s ribosomal subunit and prevent formation of 70s complex, which initiates bacterial protein synthesis.[22]

Pharmacokinetic profile

Linezolid achieve maximum plasma concentration within 1-2 hours and oral bioavailability reaches approximately 100% and demonstrates good bone penetration.[23] It exhibits low protein binding and eliminated via renal and non-renal route.[24] Organisms for which the MIC of linezolid is < 4 µg/ml are considered susceptible, whereas those for which the MIC is = 8 µg/ml are considered resistant.[25] The peak plasma concentration of linezolid significantly surpasses the MIC of enterococci and staphylococci.[26] The pharmacokinetics of different antibiotics including Linezolid are presented in Table 1.[16,27]

Microbiologic activity

Staphylococcus aureus is the most common pathogenic organism recovered from bone followed by pseudomonas aeruginosa, enterobacteriaceae, viridans streptococci,staphylococcus epidermidis, serratia.[28] Mycobacterial and fungal infections have been reported in patients with osteomyelitis, but these are uncommon and generally found in patient with impaired immune function.[29] Linezolid is active against a wide range of gram-positive aerobic bacteria, some gram positive anaerobes and some gram-negative anaerobes. It has good activity against resistant strains of several

gram-positive aerobes such as MRSA, PRP (penicillin resistant pneumococci).[30]

Cost effectiveness of linezolid

Linezolid is a costly medication especially compared to other antibiotic like doxycycline, co-trimoxazole, vancomycin, rifampicin, ciprofloxacin.[31]

Table 1: Pharmacokinetics of antibiotic

Antibiotic	Dose	Peak plasma concentration (µg/ml)	Oral bioavailability	Bone concentration
Ciprofloxacin	750mg	2.6	60-80%	27-48%
TMP/SMX	7-10mg/kg/day	7.4/14.3	90-100%	50%/15%
Linezolid	600mg	18	100%	40-50%
Rifampicin	450-600mg	5-7	70-90%	--------
Clindamycin	450-600mg	5-15	90%	40-67%

Fluoroquinolone

The fluoroquinolones have gained popularity in osteomyelitis in recent years. They achieve bactericidal levels in blood and tissue. The second generation fluoroquinolones like ciprofloxacin, levofloxacin, ofloxacin, lomefloxacin are mostly advisable against gram-negative and some gram-positive organism. The fourth generation fluoroquinolone like moxifloxacin, gatifloxacin has improved streptococcal activity.[33] To prevent emergence of resistance fluoroquinolone is recommended in combined with other agents in osteomyelitis.[34] Some clinical studies are reported in Table-3.

Table 2: Clinical studies of linezolid (600mg) monotherapy in osteomyelitis

No. of patients	Type of infection	Organism	Clinical cure rate	
40	Osteomyelitis	MSSA3, MRSA19 VRE18	90%	Broder et al[35]
53	Osteomyelitis	MRSA21, MSSA6 MRCONS17,	98%	Rod and Hamilton[36]
22	Implant associated Osteomyelitis	MSCoNS2 Enteococci7 Monomicrobial9 polymicrobial13 MRSA10,VRE5	100%	Vercillo et al[37]
55	Chr. Osteomyelits	MRSA25, VRE17 MSSA3, & others	81.8%	Rayner et al[13]

VRE- Vancomycin resistant enterococci
MRCONS-Methicillin resistant coagulase negative staphylococci
MSCONS-Methicillin sensitive coagulase negative staphylococci
Post treatment follow up period was >1 year

But soon after it was approved, the cost savings was appreciated because of its early switching from intravenous to oral therapy.

Adverse events of linezolid

Duration related adverse effects including gastrointestinal disturbances, increases in hepatic enzymes levels, reduction of platelet and hemoglobin are expected. Hematological indices decrease slowly over time and can be detected with the appropriate monitoring of complete blood cell counts during treatment with linezolid.[32]

TMP-SM (Trimethoprim Sulfamethoxazole)

The combination of Trimethoprim-Sulfamethoxazole are bactericidal and having the activity against staphylococcus aureus, pseudomonas aeruginosa, enterobacteriaceae, E.coli and streptococci. A study showed 45% cure rate in osteomyelitis out of 66 patients in double strength of combination.[41] Another study showed 89% cure rate in combination of rifampicin and TMP-SMX.[42] Now- a- days TMP-SMX resistance among staphylococcus aureus isolates are increasing.[43]

Table 3: Clinical studies of Ciprofloxacin (750mg) monotherapy in osteomyelitis

No. of patients	Type of infection	Organism	Clinical cure rate	References
39	Chronic Osteomyelitis	S.aureus19, S.epidermidis2, Gram negative pathogen18	66.7% Staphylococci	Dellomonia et al[38]
31	Chronic Osteomyelitis	Various (S. aureus8)	77% (100% in S. aureus)	Gentry and Rodriguez[39]
14	Chronic Osteomyelitis	Enterobacteriaceae18 Pseudomonas aeruginosa16, S.aureus4	50%	Greenberg et al[40]

Rifampicin

Rifampicin is a broad spectrum, bactericidal antimicrobial agent achieves high intracellular concentration. It has potent anistaphylococcus activity. It is not used alone due to rapid emergence of resistance.[6] Some clinical studies are reported in table-4.

Clindamycin

It is a lincosamide antibiotic, active against most gram positive bacteria. It has been successfully used in osteomyelitis especially in children but rarely in adults.[44] A study showed 42% cure rate out of 12 adult patients.[45] Currently, it is given orally after initial intravenous treatment for 1-2 weeks.[33]

Beta lactam antibiotics

Beta lactam antibiotics like nafcillin, cefazolin, ceftriaxone are less effective in osteomyelitis when used alone. In a study 79% cure rates was found when ceftazidime or nafcillin combinedly used with amikacin.[39]

Discussion

Acute osteomyelitis results from bacteremic seeding of bone (19%) and chronic osteomyelitis is generally secondary to open fractures, open wound, bacteremia, and contiguous soft tissue infection. Post traumatic osteomyelitis accounts for as many as 47% of cases.[49] Diabetic patient are at a greater risk of getting this infection. In middle aged, spinal osteomyelitis may be associated with urinary bladder infection. It may occur as a complication of many diseases such as typhoid, syphilis, tuberculosis or sickle cell anemia. Diagnosis is confirmed by radionuclear bone scan. Others are- estimation of erythrocyte sedimentation rate, C - reactive protein level, leucocyte scan, positron emission tomography (PET), musculoskeletal ultrasonography, and technetium-99 bone scintigraphy. The precise cause of infection is determined by culture of blood and bone biopsy.[50] Linezolid has proven to be a valuable addition to the antibiotic

Table 4: Clinical studies of Rifampicin combination therapy in osteomyelitis

Antibiotic regimen	No. of patients	Organism	Clinical cure rate	References
Rifampicin(600mg)+Ofloxacin (200mg)	20	Monomicrobial (15)+Polymicrobial(5)	76.5%	Senneville et al[46]
Rifampicin (600mg)+Levofloxacin (500mg)	7	MSSA(5),Streptococci 1, MScoNS1	86%	Frippiat et al[47]
Rifampicin(900mg)+ Linezolid(600mg)versus Rifampicin(10mg/kg)+ TMP-SXT(8/40mg/kg)	56	MRSA21,MSSA2 MRCoNS18,MSCoNS 3, Others	89.3% versus 78.6%	Nguyen et al[48]

Post treatment follow up period was >2 years

armamentariam against staphylococcus aureus. To date it is the first and only oxazolidinone, which is used to treat staphylococcus aureus osteomyelitis.[51] Rifampicin, vancomycin, clindamycin, fluoroquinolone takes more time for patient discharging . Hepatitis, interstitial nephritis, enterocolitis and QTc prolongation are more common following administration of rifampicin, vancomycin, clindamycin and fluoroquinolone. So dose adjustment must be required. But linezolid can be used safely in patient with liver disease and renal insufficiency. These antibiotics have different dose, different mechanism of action, but all of them have effective role in osteomyelitis. The varying cure rates may be related to variable diagnostic criteria, surgical debridement or duration of follow up. Linezolid has higher cure rates than others. It has post antibiotic effect. It is hopeful that linezolid resistant srains are not established still now. In the past, chronic osteomyelitis was treated parenterally. Now-a-days it is proved that oral therapy is therapeutically equivalent to parenteral therapy.[52] Because of excellent oral bioavailability, linezolid is easier to switch from intravenous to oral formulation with consequent earlier patient discharge and lower in patient costs. Current treatment consists of surgery with prolonged (>6weeks) antibiotic therapy. The goal of success should limit the spread of infection to adjacent healthy bone and tissues and linezolid covers it. Treatment limiting toxicities occurred in one-third of patients. Lactic acidosis, optic neuritis, peripheral neuropathy are rare[53] Most of the adverse effects are reversible upon cessation of therapy and no cross resistance occur to other antibiotics.[54] As osteomyelitis is common in developing countries and recurrence rate is 30%, which might be related to incomplete resection of infected bone or to resistant micro-organism, an accurate antibiotic is necessary.[55] On this ground, this review supports linezolid as a good choice for patient with osteomyelitis.

Conclusion

Acute osteomyelitis could be brought under control with antibiotic, but chronic osteomyelitis is potentially curable. Adequate blood supply is essential for delivery of antibiotic to the chronically infected bone. Surgery is needed to improve the blood supply to the affected bone. Standard of living, hygine and nutrition are important for declining the incidence of osteomyelitis. Attention should always be paid to the adverse reactions that are possibly related to linezolid application. Cost containment issues impact antibiotic stewardship policies and healthcare settings with limited resources. Although not officially accredited for, linezolid seems to be a good alternative in the management of osteomyelitis caused by multiresistant bacteria. So, additional clinical studies are needed to explore better role of linezolid and further research on the cost effectiveness and outcome measurements.

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