

Linezolid in the treatment of Gram-positive prosthetic joint infections

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Objectives: To investigate the clinical efficacy and safety of linezolid in the treatment of Gram-positive prosthetic hip and knee infections.

Materials and methods: A retrospective evaluation of patients hospitalized in the Department of Infectious Diseases of San Martino Hospital in Genoa with the diagnosis of Gram-positive prosthetic joint infection and treated with intravenous and/or oral linezolid. Primary end points were the patient clinical outcome at the end of treatment and at long-term follow-up (up to 12 months after the end of treatment).

Results: Between May 1999 and September 2003, 20 patients with prosthetic joint infection were treated with linezolid. Pathogens isolated were: methicillin-resistant *Staphylococcus aureus* (MRSA), 14 strains; methicillin-resistant coagulase-negative staphylococci, five strains; and *Enterococcus* spp., one strain. The overall duration of treatment was 7.2 ± 2 weeks (range 6–10 weeks). Patients were given intravenous therapy for 3–7 days as inpatients, then were changed as outpatients to oral therapy under weekly laboratory testing. At long-term follow-up (1 year), we observed four cases of failure due to relapsing infections. The other 16 patients treated with linezolid did not need further surgical substitution of prosthesis or surgical joint revision. Linezolid was well tolerated, and no drug-related events leading to discontinuation of treatment were recorded.

Conclusions: Our data indicate that linezolid may be an effective alternative therapy for orthopaedic infections caused by Gram-positive resistant pathogens and that a prospective and comparative evaluation of linezolid in this setting is necessary.

Keywords: *Staphylococcus aureus*, *Staphylococcus epidermidis*, safety, efficacy, hips, knees

Introduction

Prosthetic joint infection of total hip arthroplasty or total knee arthroplasty occurs with an incidence of 1.5–2.5% for primary interventions, but higher rates (2–20%) have been reported after revision procedures.¹ The most common aetiological agents responsible for prosthetic infection are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

The treatment of infections following total joint arthroplasty involves surgery and antimicrobial treatment. Complete removal of all foreign materials is essential, while simple surgical drainage coupled with a finite course of antibiotics is characterized by a high failure rate.² A two-stage re-implantation is considered the standard surgical procedure in the treatment of

septic prosthetic joints. However, when prosthetic removal is not possible or contraindicated, suppressive antibiotic therapy with retention of the functioning joint arthroplasty may be considered.

Linezolid is a recently introduced oxazolidinone compound for the treatment of serious Gram-positive infections. Oral and intravenous administrations of linezolid are completely bioequivalent. The drug has a favourable pharmacokinetic profile and penetrates in high concentrations into osteo-articular tissue.^{3–5} However, clinical experience with linezolid in the treatment of bone and joint infections is limited.^{6,7}

Herein we report on the results of a retrospective study of oral/parenteral linezolid treatment of 20 patients with Gram-positive prosthetic hip and knee infections.

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Patients and methods

We included patients hospitalized in the Department of Infectious Diseases of San Martino Hospital in Genoa with the diagnosis of prosthetic joint infection, treated with intravenous and/or oral linezolid. Diagnosis of prosthetic joint infection was based on clinical symptoms, instrumental data, laboratory findings, and microbiological data. Clinical symptoms considered were pain, local warmth, tenderness, drainage and effusion. Instrumental evaluation included X-rays showing aspecific signs of mobilization of prosthesis or evidence of osteomyelitis, and ^{99m}Tc hexamethylpropyleneamine oxime (HMPAO) leucocyte scans showing signs of inflammation. Laboratory findings suggestive of biological inflammatory syndrome were an elevated erythrocyte sedimentation rate (ESR) ($>20\text{ mm/h}$) and elevated C-reactive protein (CRP) values ($>5\text{ mg/L}$). The diagnosis had to be confirmed by direct examination and cultures of pus obtained from drainage of fistula or joint aspiration. Acute infection was defined by symptoms <30 days in duration, and chronic infection was defined as symptoms >30 days in duration. Early infection was defined as occurrence of infection <2 months after intervention and late infection was defined as occurrence of infection >2 months after intervention.

Data on risk factors for primary prosthetic joint infection (rheumatoid arthritis, diabetes mellitus, poor nutritional status, obesity, concurrent urinary tract infection, steroid therapy, malignancy and post-operative surgical site infection) or for revision procedures (prior joint surgery, preoperative infection of teeth, skin or urinary tract) were recorded.

Linezolid was given at the start of treatment intravenously on an inpatient basis, and then orally on an outpatient basis. We also included patients pre-treated with other antibiotic therapies.

Patients were monitored at the end of treatment (within 72 h after the last dose of study medication), and returned for follow-up visits when deemed necessary on clinical grounds and/or every 3 months (up to 12 months after the end of treatment). Clinical outcomes were categorized as follows: 'cure and improvement', resolution of clinical signs and symptoms of infection, eradication of Gram-positive infection, a CRP level below 5 mg/L , reduction in ESR when compared with baseline, and the absence of radiological signs of loosening, pseudarthrosis or dislocation of the artificial joint at follow-up visits; and 'failure', persistence or progression of baseline clinical signs and symptoms of infection, persistence or relapse of positive microbiological culture, progression of baseline infection-related radiographic abnormalities, increase in ESR and CRP, and development of new clinical findings consistent with active infection.

The isolates were identified by standard techniques. MICs of linezolid were determined by Etest (AB Biodisk, Solna, Sweden). Biochemical and haematological analyses were carried out weekly throughout the treatment period.

Results

Between May 1999 and September 2003, 20 patients with prosthetic joint infection were treated with linezolid. Demographic characteristics of the study patients are shown in Table 1. All patients had surgical joint revision or substitution of prosthesis, and either refused further surgical intervention or

Table 1. Demographic and clinical characteristics of the patients

Characteristics	Number of patients (%)
Age (years)	
median	68
range	56–88
Gender	
male	11 (55)
female	9 (45)
Prosthetic joint	
hips	15 (75)
knees	5 (25)
Onset	
early	11 (55)
late	9 (45)
Symptoms	
acute	9 (45)
chronic	11 (55)
Risk factors	
steroid therapy	5 (25)
malignancy	3 (15)
rheumatoid arthritis	6 (30)
diabetes mellitus	4 (20)
prior joint infection	15 (75)
prior joint surgery	15 (75)
surgical site infection	3 (15)
concurrent urinary tract infections	5 (25)

the surgical removal was not feasible. Fifteen patients had previous antibiotic therapy with a combination of rifampicin and ciprofloxacin (11 patients) or glycopeptides (four patients). Reasons for discontinuation of these treatment cycles were *in vitro* resistance to rifampicin and/or ciprofloxacin, clinical relapse, and side effects.

Pathogens isolated were as follows: methicillin-resistant *Staphylococcus aureus* (MRSA), 14 strains; methicillin-resistant coagulase-negative staphylococci, five strains; and *Enterococcus* spp., one strain. All the strains tested were susceptible to linezolid (MIC₉₀ 2 mg/L). Susceptibility profile of staphylococci to other antimicrobial agents was as follows: rifampicin, 15% of strains susceptible; co-trimoxazole, 30%; gentamicin, 84%; ciprofloxacin, 60%; vancomycin and teicoplanin, 100%.

Patients received linezolid 600 mg twice daily intravenously for the first 3–7 days, then orally. The overall duration of treatment was 7.2 ± 2 (range 6–10 weeks).

Assessment of efficacy at the end of treatment showed that all the 20 treated patients achieved clinical and microbiological cure. At long-term follow-up, we observed four cases of failure due to relapsing infections (three strains of MRSA, and one strain of methicillin-resistant coagulase-negative *Staphylococcus*). MICs of linezolid for relapsing isolates were the same as those for initial isolates. The other 16 patients (80%) treated with linezolid did not need further surgical substitution of prosthesis or surgical joint revision.

Linezolid was well tolerated, and no drug-related events leading to discontinuation of treatment were recorded. In particular, we did not observe relevant haematological abnormalities, such as anaemia, leucopenia and thrombocytopenia. Only mild to moderate untoward events were observed in three patients, which included diarrhoea, vomiting and decreased appetite.

Discussion

Increasing antimicrobial resistance in Gram-positive pathogens has led to an increased use of glycopeptides which, in turn, has led to the emergence and spread of vancomycin-resistant enterococci, and to the emergence of *S. aureus* with reduced susceptibility to glycopeptides and, most startlingly, of *S. aureus* with high-level resistance to both vancomycin and teicoplanin.⁸ Vancomycin has significant drawbacks which compromise its clinical usefulness. For example, prolonged administration of vancomycin invariably results in the need for extended venous access, monitoring of serum levels and prolonged hospital stay. In the treatment of bone infection, teicoplanin has been found to be particularly convenient, enabling patients to be discharged from hospital while continuing with parenteral therapy given once daily at home.^{9–11} More recently, linezolid has been compared with teicoplanin in the treatment of a variety of Gram-positive infections.^{12,13} Results of a randomized, double-blind study show that linezolid has similar efficacy and safety compared with teicoplanin in critically ill patients.¹² In the treatment of suspected or proven Gram-positive infections, results of a randomized, controlled, open label study show that linezolid is clinically superior, though less tolerated, than teicoplanin.¹³ A recent economic evaluation demonstrated that linezolid had the potential for reducing length of hospital stay and cost when compared with teicoplanin when patients did not have access to outpatient or home parenteral antibiotic therapy (OHPAT), but the potential was non-evident when OHPAT was available.¹⁴

In this study, linezolid was found to be effective and well tolerated in the treatment of Gram-positive prosthetic joint infections.

Long-term antibiotic therapy without any adjunctive surgical intervention is frequently unsuccessful in the treatment of prosthetic joint infections. However, chronic antimicrobial suppression without surgery might be taken into consideration when removal of the prosthesis is not feasible, there are no signs of systemic infection, the prosthesis is not already loose, and when the patient is able to adhere to long-term antibiotic treatment.

To our knowledge, the clinical experience with linezolid for conservative treatment of prosthetic joint infection is extremely limited. In our department, we have already successfully used linezolid in two patients with MRSA prosthetic joint infections.⁶ The efficacy of linezolid in the long-term treatment of a case of methicillin-resistant *S. epidermidis* prosthetic hip infection has also emerged from another report.⁷

Therapeutic options for the treatment of methicillin-resistant staphylococcal infections are limited, and new antimicrobial agents are needed. Linezolid is a recently approved agent for the treatment of these infections. An important advantage of linezolid over glycopeptides is the oral administration that reduces time of hospitalization and increases the compliance, especially when the duration of therapy is considerable, as in the treatment of prosthetic joint infections.

Various adverse events have been associated with linezolid therapy, the most serious of these are bone marrow suppression leading to anaemia, leucopenia and thrombocytopenia, and toxic optic neuropathy resulting in rapid visual loss.^{15,16} Myelosuppression has been reported in patients receiving linezolid for >2 weeks, and the drug at present is not recommended for more than 28 days.¹⁰ However, in a comparative evaluation, linezolid has been used for a longer period in 20 patients with orthopaedic

infections.¹⁷ As the haematological effects were detectable through weekly monitoring and were reversible, the authors conclude that concerns about myelosuppression do not preclude linezolid use for orthopaedic infections requiring long-term therapy. Likewise, we did not observe any serious adverse event related to linezolid use in our patients, where the median duration of linezolid treatment was 7.2 weeks.

Within the limitations of the study design, the data presented here provide a further basis for the clinical use of linezolid in the treatment of prosthetic joint infections. Our data indicate that linezolid may be an effective alternative therapy for orthopaedic infections caused by Gram-positive resistant pathogens and that a prospective and comparative evaluation of linezolid in this setting is necessary.

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