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Linezolid in late-chronic prosthetic joint infection caused by gram-positive bacteria

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ABSTRACT

Linezolid may be an interesting alternative for prosthetic joint infection (PJI) due to its bioavailability and its antimicrobial spectrum. However, experience in this setting is scarce. The aim of the study was to assess linezolid's clinical and microbiological efficacy, and also its tolerance. This was a prospective, multicenter, open-label, non-comparative study of 25 patients with late-chronic PJI caused by Gram-positive bacteria managed with a two-step exchange procedure plus 6 weeks of linezolid. Twenty-two (88%) patients tolerated linezolid without major adverse effects, although a global decrease in the platelet count was observed. Three patients were withdrawn because of major toxicity, which reversed after linezolid stoppage. Among patients who completed treatment, 19 (86%) demonstrated clinical and microbiological cure. Two patients presented with clinical and microbiological failure, and one showed clinical cure and microbiological failure. In conclusion, linezolid showed good results in chronic PJI managed with a two-step exchange procedure. Tolerance seems acceptable, though close surveillance is required.

1. Introduction

Prosthetic joint infection (PJI) is a major health problem of increasing incidence. In chronic and in some acute PJI, removal of hardware is often necessary (Del Pozo and Patel, 2009; Zimmerli et al., 2004), being a 2-step exchange the most common procedure, with success rates around 90% (Jämsen et al., 2009; Zimmerli et al., 2004). Briefly, this technique involves the removal of the infected prosthesis in the first stage, replacement by an antibiotic-loaded cement spacer, administration of systemic antibiotics, and finally the placement of a new prosthesis. The aim is to provide a sterile surgical site for the new arthroplasty.

However, cultures systematically performed at prosthesis reimplantation have demonstrated that sterility is not always guaranteed, as positive results have been found in 6–20% of cases (Bejon et al., 2010; Della Valle et al., 1999; Mont et al., 2000; Murillo et al., 2008). In most of these cases, the isolates are coagulase-negative Staphylococci (CNS) resistant to the antimicrobials used during the previous weeks (Mont et al., 2000; Murillo et al., 2008).

Six weeks of intravenous antibiotic treatment is usually recommended (Del Pozo and Patel, 2009; Hanssen and Spangehl, 2004; Jämsen et al., 2009; Murillo et al., 2008) but the emergence of alternative antimicrobials with good bioavailability may mean that the intravenous route is no longer necessary. It has also been suggested that antibiotics with extended anti-staphylococcal spectrum may be of use in avoiding persistence or superinfection by resistant CNS (Cabo et al., 2011; Murillo et al., 2008).

Linezolid possesses a wide anti-Gram-positive bacteria (GPB) spectrum, including all CNS species, and has 100% bioavailability and good diffusion in bone tissue (Clemmet and Markham, 2000; Rana et al., 2002). These properties may make it a suitable alternative for the treatment of chronic PJI. However, clinical experience with linezolid in this setting is scarce (Rao and Hamilton, 2007; Senneville et al., 2006) and toxicity is a matter of concern (Legout et al., 2010; Rayner et al., 2004; Senneville et al., 2006; Vihn and Rubinstein, 2009).

We undertook a prospective multicentre study of patients with PJI caused by GPB treated with a two-step exchange procedure and therapy with linezolid for 6 weeks. The aims of the present study

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were: 1) to analyze the clinical rate of success and microbiological eradication in patients treated with linezolid; and 2) to assess the safety of this antimicrobial during a 6-week therapy schedule, especially in the elderly population.

2. Patients and methods

2.1. Setting

This prospective, open-label, non-randomized, non-comparative, multicentre study was performed at seven teaching hospitals in Spain between 2007 and 2009. The study was approved by the local ethic committees.

2.2. Study population

Patients undergoing two-steps exchange procedure as treatment of chronic PJI caused by GPB were eligible for this study. These were mainly patients with late-chronic infection according to Tsukayama criteria (Tsukayama et al., 1996), but also patients who underwent salvage therapy for acute infections or relapses.

Clinical diagnosis was based on the presence of typical symptoms and signs, such as joint pain, inflammatory signs, and fistula. Microbiological diagnosis was established from surgical or arthrocentesis samples showing 2 or more positive cultures for the same bacteria with identical antibiogram profile (Atkins et al., 1998). The following baseline characteristics and data were recorded: age, sex, type of prosthesis, Charlson co-morbidity index (Charlson et al., 1987), concomitant treatment, haemogram and biochemistry profile.

The samples obtained during the operation (synovial fluid, periprosthetiic tissue and bone) were seeded in liquid (thioglycolate) and solid media (5% sheep blood, chocolate and MacConkey agar). They were incubated for at least 7 days. Microorganisms and antibiotic susceptibility were identified according to standard criteria (Kloos and Lambe, 1991).

The following exclusion criteria were applied: impossibility of removing all the components of the prosthetic or one-step exchange procedure; use of cement spacers loaded with vancomycin; need for an antibiotic with anti-GPB activity other than linezolid for more than 7 days; breastfeeding; pregnancy; age less than 18 years; non-controlled hypertension or diseases that could lead to severe hypertension; liver cirrhosis; thrombocytopenia less than 60,000 platelets/μL or anemia of central origin; creatinine clearance less than 20 mL/min; peripheral neuropathy.

2.3. Treatment protocol

Patients underwent a two-step exchange procedure. During the first step surgery, all prosthetic components were removed and a thorough debridement was performed. A cement spacer could be placed in the surgical site; loading with antibiotics other than vancomycin was allowed. Empirical antibiotic therapy was then started. Patients signed written informed consent and linezolid 600 mg every 12 hours, either intravenous or oral, was started within 7 days of the first step surgery. Daily dose was not modified depending on patient's weight or renal function. The co-administration of other antibiotics with no activity against GPB was permitted in patients with polymicrobial infection. Haemogram and biochemistry profiles were performed each week during antimicrobial therapy, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). After a total antimicrobial therapy of 42 days, the reimplantation surgery could be performed. Before placing the new prosthesis and administering prophylactic antibiotics, 4–6 samples were taken from the surgical site and cultured, following a similar protocol as in the first step. Patients were followed up at the outpatient clinic for at least 12 months with prosthesis X-ray, haemogram, and biochemistry profile.

2.4. Outcome definitions

Patients were considered to be clinically cured if there was progressive disappearance of inflammatory signs, significant decrease in CRP, no signs of infection during reimplantation surgery, and no signs of infection due to the same bacteria during follow-up. The need for a new debridement after the first step surgery and before reimplantation was not considered a failure per se. After reimplantation, patients who developed an early post-surgical infection due to different bacteria were not considered to have failed, but to have had a new episode of PJI.

Patients were considered to be microbiologically cured if cultures taken at surgical site during reimplantation were negative. One or more cultures with the same bacteria causing the original infection were required to consider persistence. If 2 or more cultures yielded the same bacteria, but were different from that causing the original episode, it was considered superinfection.

While on therapy with linezolid, patients were interviewed every week for the presence of new symptoms or signs which could be considered an adverse event. Specifically, patients were questioned on whether they had experienced nausea, vomiting, dizziness, abdominal pain, diarrhea, headache, somnolence, paresthesias or other symptoms suggesting neuropathy, blurred vision, hypoacusis, tinnitus, disturbances in the taste or dysgeusia, insomnia, anxiety, behavior disturbances, mood alterations, cough, dyspnea, chest pain, palpitations, arthalgias, myalgias, rashes, pruritus or muco-cutaneous candidiasis. Toxicity was defined as mild if it was transitory or could be managed without stopping linezolid. It was considered to be severe if the life of the patient was exposed to serious risk, if hospitalization needed to be prolonged, or if linezolid had to be withdrawn. Thrombocytopenia was defined as a platelet count less than 100,000 platelets/mm^3 or less than 75% of the baseline count. Anemia was defined as haemoglobin less than 9.0 g/dL or less than 75% of baseline haemoglobin. In order to avoid the interference of blood transfusions during or immediately after surgery, baseline haemoglobin was measured one week after surgery.

Since platelets may behave as acute-phase reactants and may therefore present a progressive decline after surgery, a matched study was performed comparing patients treated with linezolid (cases) and 25 historical controls. These historical controls were patients with chronic-PJI managed at two of the participating hospitals, treated with a 2-step exchange procedure and six weeks of antimicrobial therapy other than linezolid. Cases and historical controls were age and sex-matched.

2.5. Statistical analysis

A per protocol analysis was performed, evaluating the outcome among patients who tolerated linezolid for the programmed schedule. A potential association for the development of AE was evaluated for serveral variables (age, sex, BMI, Charlson score, creatinine and concomitant treatment with pyridoxine or serotoninegic antidepressants) by means of a univariate analysis, using χ^2 or Fisher exact test for categorical variables, and the t test or Mann-Whitney's U test for continuous variables. All analyses were performed using SPSS software (version 15.0).

3. Results

Twenty-five patients were recruited: 20 were women (80%), and the median age was 73 years (range 59–89). Median Charlson-score was 1 (range 0–3), being 0 in 11 (44%) patients. Median body mass index (BMI) was 28.7 kg/m^2 (range 21.3–36.8). Median creatinine