Treatment of Posttraumatic Osteomyelitis with Oral Linezolid

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Purpose. To assess the efficacy and safety of oral linezolid associated with surgery in the treatment of posttraumatic osteomyelitis.
Materials and methods. Monitored prospective study of all patients suffering from posttraumatic osteomyelitis caused by Methicillin-resistant Gram positive cocci treated with elective surgery and linezolid 600 mg every 12 hours from June 2002 to December 2004.
Results. We have used linezolid to treat 9 patients with posttraumatic osteomyelitis. The microorganisms isolated were: Methicillin-resistant *Staphylococcus aureus*, 1; Methicillin-resistant *Staphylococcus epidermidis*, 7. Two patients had an associated infection caused by *Pseudomonas aeruginosa*. Mean duration of treatment was 9.5 weeks (range 6-12). During follow-up 8 patients were found to be clinically cured with fracture stabilization and with no sign of infection. One patient had an infected mal-union. Linezolid was excellently tolerated and in none of the cases it was necessary to discontinue administration due to toxicity.
Conclusions. In our experience oral linezolid associated with surgery can be an excellent option for the treatment of posttraumatic osteomyelitis caused by Methicillin-resistant Gram positive bacteria that do not respond to other antimicrobials or if these are not well tolerated.

Key words: *posttraumatic osteomyelitis, linezolid, Methicillin-resistant Staphylococcus.*

Tratamiento con linezolid oral en osteomielitis postraumáticas

Objetivo. Valorar la eficacia y seguridad de linezolid oral asociado a cirugía en el tratamiento de las osteomielitis postraumáticas.
Material y método. Estudio prospectivo monitorizado de todos los pacientes ingresados en la unidad de infecciones óseas y articulares del hospital con osteomielitis postraumática por cocos grampositivos meticilín resistentes tratados con cirugía programada y linezolid, 600 mg cada doce horas, desde junio de 2002 hasta diciembre de 2004.
Resultados. Hemos tratado con linezolid a nueve pacientes con osteomielitis postraumática. Los microorganismos aislados han sido: un *Staphylococcus aureus* meticilín resistente, un estafilococo coagulasa negativo meticilín resistente, siete *Staphylococcus epidermidis* meticilín resistentes. Dos pacientes han tenido infección asociada con *Pseudomonas aeruginosa*. La duración media del tratamiento ha sido de 9,5 semanas (rango 6-12). En el seguimiento realizado ocho pacientes están clínicamente curados con estabilización de la fractura y sin signos de infección. Un paciente está en situación de pseudoartrosis infectada. El linezolid ha sido tolerado de manera excelente y no ha habido necesidad de suspender la medicación por toxicidad en ningún caso.
Conclusiones. En nuestra experiencia, linezolid oral asociado a cirugía puede ser una excelente opción de tratamiento en osteomielitis postraumática causada por bacterias grampositivas resistentes a meticilina que no respondan a la administración de otros antimicrobianos o que no toleren éstos.

Palabras clave: *osteomielitis postraumática, linezolid, Staphylococcus meticilín resistentes.*

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Post-traumatic osteomyelitis is one of the most severe infections in orthopedic and trauma surgery. Their treatment is based on three Basic pillars: soft tissue management, sterilization of the fracture site and antibiotic therapy[2]. From the microbiological point of view, although these are polimicrobial infections, the most frequently isolated mi-

croorganisms are *Staphylococcus aureus* and *Staphylococcus epidermidis*, which account for 50% of the total[3] and are increasingly resistant to the most frequently used antibiotics like lactamics, glycopeptides, the combination of quinolones or cotrimoxazole and rifampicine[4]. In allergic or glycopeptide-intolerant patients treating these infections is even more challenging. Until the advent of quinupristin-dalfopristin and linezolid there was no antibiotic that was clinically efficient against vancomycin-resistant gram-positive cocci. Linezolid is the first drug in a new family of antibiotics, namely the oxazolidinones, that is active against a wide range of pathogens among which feature methicillin resistant and glycopeptide-resistant cocci. Oxazolidinones act by inhibiting the protein synthesis of bacteria but using a target different from that of other antimicrobials. Indeed, they bind to the 50S5 ribosomal subunit, inhibiting 70S initiation complex formation. Linezolid boasts excellent oral bioavailability (100%)[6] and can reach very high concentrations in musculoskeletal tissues (skin, synovial and bone)[7-9]. These characteristics make linezolid an attractive alternative for trauma-related infections treated traditionally with intravenous or intramuscular antibiotics.

The clinical efficacy of linezolid has been well demonstrated by several clinical studies on nosocomial pneumonia, bacteremia and skin and soft tissue infections[10,11]. Data on more complex infections like osteomyelitis is limited. Clinical use of linezolid in orthopedic infections is based initially on isolated clinical studies12,13 and in the latest published series14-16. To assess the efficacy of linezolid in post-traumatic osteomyelitis we prospectively evaluated all adult patients with post-traumatic osteomyelitis caused by methicillin-resistant gram-positive bacteria admitted to the Department of Bone and Joint Infections of our hospital who were treated with linezolid. All patients treated were clinically and analytically examined every 7 to 10 days until they completed their antibiotic treatment. Given the pathology at hand, all patients continue to be periodically controlled.

MATERIALS AND METHODS

This is a prospective non-randomized observational study of all adult patients with post-traumatic osteomyelitis caused by methicillin-resistant gram-positive bacteria, treated with linezolid and admitted to our Infections Unit between June 2002 and December 2004.

Patients included in the study received neither vancomycin nor teicoplanin antibiotic treatment for allergies, adverse reactions or lack of previous clinical response. We also included patients who rejected to be hospitalized for four to six weeks for intravenous treatment, those who rejected teicoplanin intramuscular treatment and those who were not susceptible to treatment with other oral antibiotics because of microorganism-resistance. The inclusion criteria were inability to comply with a four-week linezolid treatment and the existence of previous anemia, thrombocytopenia or neutropenia.

Patients were not asked to provide an explicit informed consent in writing since in our hospital this kind of treatment has to be authorized by an infections and pharmacology committee. In addition, treatment with linezolid had been authorized by the Bone Infections Unit of the hospital.

Post-traumatic osteomyelitis was clinically and radiologically diagnosed in all patients. Moreover, multiple intraoperative culture samples were obtained of soft tissues, bone tissues and osteosynthesis materials for all patients. To reduce the error margin, two or more cultures with the same microorganism were needed to come to a decision as to treatment. The lack of response to teicoplanin was defined after the persistence of positive bone cultures after administration of more than one six-week cycle of the drug. Antibiotic treatment with linezolid 600 mg every twelve hours was started intravenously after obtaining the results of the cultures taken during surgery, afterwards oral treatment was substituted for IV administration. The length of treatment in all patients was at least six weeks.

All patients were examined clinically and analytically throughout the period during which they received linezolid every seven to ten days. Analytical controls performed were: complete hemogram, globular sedimentation rate (GSR), C-reactive protein (CRP), glucose, urea, creatinine, aspartate-aminotransferase (AST) and alanin-aminotransferase (ALT). Surgical treatment was planned by the surgeons in the Infections Unit. Patients have been periodically subjected to ambulatory clinical controls since the withdrawal of antibiotic by the medical team of the Infections Unit.

It was determined that those patients who, after a follow-up of at least six months from the withdrawal of antibiotic treatment had no signs or symptoms of infection, normal VSG and PCR values and a healed fracture had achieved a clinical resolution of their condition. Those patients for whom, in addition to the previous requirements, negative bone and/or osteosynthesis material cultures were obtained six months after treatment was discontinued were considered to have attained bone sterilization. Patients with partial remission were those with a healed fracture in whom, on withdrawing the hardware, the culture was positive for the same initial infecting microorganism. Lastly, Therapeutic failure was associated with patients who in addition to not having a healed fracture gave positive bone and/or osteosynthesis material cultures to the initial microorganism.

RESULTS

They are shown in Table 1. Nine adult male patients were treated with linezolid at 600 mg every 12 hours after being diagnosed with post-traumatic osteomyelitis caused by methicillin-resistant gram-positive cocci between June 2002 and December 2004. Mean age was 43 years (range: 23-58 years).

All patients had post-traumatic osteomyelitis: four in the tibia, two in the femur, one in the humerus, one in the ulna and one in the radius. Five of them had osteomyelitis secondary to an open fracture; fracture grading according to the classification by Gustilo was as follows: one grade IIIb open tibial fracture, one grade IIIb open humeral fracture, two grade IIa tibial fractures and one grade IIa radial fracture. The other four patients had post-traumatic osteomyelitis secondary to a closed osteosynthesis. The form of presentation was as follows: two patients had osteomyelitis associated to an osteosynthesis material fracture (cases 2-7), two patients had acute osteomyelitis (cases 3 and 9) and five patients had infected pseudoarthrosis (cases 1,4,5,6,8). Microorganisms causing the infection were: one case of methicillin– resistant *Staphylococcus aureus,* one case of methicillin resistant coagulase negative *Staphyloccocus* and seven cases of methicillin-resistant *Staphylococcus epidermidis*. In two cases there was co-infection associated to *Pseudomonas aeruginosa* (cases 5 and 8). The justifications for treatment with linezolid were: no response to teicoplanin (cases 1 and 5), teicoplanin-intolerance (case 3) and resistance to quinolones and rifampicine, with a preference for oral treatment (cases 2, 4, 6, 7, 8, 9). Patients 5 and 8 received oral ciprofloxacin 750 mg oral every 12 hours as an associated medication for co-infection with *Pseudomonas aeruginosa*. Treatment with intravenous linezolid was not administered for longer than five days in any patient. All patients received at least six weeks' antibiotic treatment with oral linezolid 600 mg oral every 12 hours for a mean of 9.5 weeks (range: 6-12 weeks). The duration of the treatment was defined by the type of osteomyelitis present, the surgery performed and the degree of fracture healing achieved.

Eight of the nine patients are at present clinically disease-free and their fractures healed. After the materials were withdrawn, case 4, whose fracture had healed and who showed no signs of infection clinically or in his gammagraphy, presented with a culture positive to the same initial microorganism, methicillin-resistant *Staphylococcus epidermidis* sensitive to linezolid, so a second four-week long oral linezolid cycle was administered at 600 mg every 12 hours; the case has now clinically resolved. Case 8 is again afflicted with a pseudoarthrosis infected by methicillin-resistant *Staphylococcus epidermidis* sensitive to linezolid.

Linezolid was clinically very well-tolerated, with no digestive discomfort reported during treatment. One patient developed a local fungal infection, eczema marginatum, which did not require withdrawing antibiotic treatment and

Table 1. Summary of the patients in our series

Case	Age/ Gender	Initial traumatic injury Posterior infection type	Microorganisms	Weeks of linezolid	Evolution	Last dose of linezolid
1	33/M	Grade IIIb open tibial fracture Infected pseudoarthrosis	Methicillin resistant *Staphylococcus aureus*	6	Clinically healed Bone sterilization	29/08/2003
2	47/M	Grade IIIa open tibial fracture Osteomyelitis associated to the fracturing of osteosynthesis materials	Methicillin resistant coagulase negative *Staphylococcus*	6	Clinically healed	25/07/2003
3	54/M	Closed tibial plateau fracture Acute osteomyelitis	*Staphylococcus epidermidis*	12	Clinically healed	14/05/2003
4	51/M	Closed femoral fracture Infected pseudoarthrosis	*Staphylococcus epidermidis*	12	Clinically healed Partial resolution	26/11/2003
5	40/M	Grade IIIa open humeral fracture Infected pseudoarthrosis	*Staphylococcus epidermidis* + *Pseudomonas aeruginosa*	12	Clinically healed	03/09/2003
6	58/M	Closed ulnar fracture Infected pseudoarthrosis	*Staphylococcus epidermidis*	6	Clinically healed	22/10/2003
7	48/M	Closed femoral fracture Osteomyelitis associated to the fracturing of osteosynthesis materials	*Staphylococcus epidermidis*	8	Clinically healed	28/07/2004
8	34/M	Grade IIIa open tibial fracture Infected pseudoarthrosis	*Staphylococcus epidermidis* + *Pseudomonas aeruginosa*	12	Recurrence of infection	26/02/2004
9	23/M	Grade IIIa open radial fracture Acute osteomyelitis	*Staphylococcus epidermidis*	12	Clinically healed	05/12/2004

was resolved with local treatment. No cases of hematological alterations were detected that required discontinuing the treatment. There was a slight reduction in the platelet count in case 3 (143*103/µl) at the tenth week of treatment, no changes were introduced and the patient recovered once treatment was finished.

DISUSSION

Post-traumatic osteomyelitis is one of the most serious complications in orthopedic and trauma surgery1. Although it is a surgical condition, successful treatment is based on an appropriate surgical management and an adequate antibiotic treatment. For that reason, there is an increasing need of training multi-disciplinary teams capable of approaching this pathology. We present a series of patients with post-traumatic osteomyelitis admitted to our Bone and Joint Infection Unit, where we subjected them first to elective surgery and later to antibiotic treatment with oral linezolid. To date, this is the longest series available for oral linezolid treatment specifically in post-traumatic osteomyelitis.

Other series have been published on the treatment of bone infections with linezolid. Bassetti et al's series[17], specific to joint prostheses, includes 20 patients with a global resolution rate of 80%. In Rayner et al's series[14], which evaluates treatment in a compassionate use program including 55 patients of which 53% had long-bone osteomyelitis, 18% diabetic foot, 14.5% sternal osteomyelitis and 15% vertebral osteomyelitis, the global resolution rate is 82%. The series of Razonable et al[16] comprises 20 patients, of whom only 5 have post-traumatic osteomyelitis, had a global resolution rate of 55%. The series of Rao et al[15], the last series published for osteomyelitis, includes 11 patients of whom 6 have post-traumatic osteomyelitis and the resolution rate is 100%.

Since most of our infections are associated to osteosynthesis materials, the most usual infecting microorganism in our series is methicillin-resistant *Staphylococcus epidermidis,* which is also resistant to quinolones and rifampicin, limiting antibiotic therapy to glycopeptides and linezolid. Eight of the nine patients in our series are at present free of their traumatic and infectious pathology with complete fracture healing and no signs of infection.

Antibiotic treatment with linezolid was perfectly tolerated. Naturally, we encountered the limitations inherent in any prospective study of a short series of only 9 patients. As regards follow-up, even if the follow-up period was longer than 6 months, this is too little for a condition like osteomyelitis, so it may be too soon to draw any hard-and-fast conclusions.

We can conclude that linezolid associated to surgery can be an excellent option to address methicillin-resistant gram-positive cocci-induced post-traumatic osteomyelitis because of its effectiveness vis-à-vis these microorganisms, its ambulatory oral administration, its high tolerance in prolonged treatments and the possibility to associate it to other antibiotics. Broader and longer studies will be necessary to be able to confirm this conclusion.

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