Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia?

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Received 9 February 2010; returned 14 April 2010; revised 1 July 2010; accepted 2 July 2010

Background: Linezolid therapy has shown high rates of clinical success in patients with osteomyelitis and prosthesis joint infections caused by Gram-positive cocci. Recent studies have demonstrated that linezolid/rifampicin combination therapy prevents the emergence of rifampicin-resistant mutations in vitro. However, linezolid/ rifampicin combination-related haematological and neurological toxicities have not been evaluated.

Objectives: To assess the tolerability of prolonged linezolid/rifampicin combination therapy compared with other linezolid-containing regimens in patients with bone and joint infections.

Methods: We reviewed the medical records of 94 patients who had received linezolid for >4 weeks after bone and joint infections. Anaemia was defined as a ≥2 g/dL reduction in haemoglobin, leucopenia as a total leucocyte count <4×10⁹/L, and thrombocytopenia as a reduction in platelet count to <75% of baseline.

Results: Anaemia was less frequent among patients on linezolid/rifampicin combination therapy than among patients on linezolid alone or in combination with other drugs (9.3%, 44% and 52%, respectively; P<0.01). In multivariate analysis, age and treatment group were independently associated with anaemia. Thrombocytopenia was reported in 44% of patients on linezolid/rifampicin combination therapy, in 48% of patients on linezolid alone and in 57.7% of patients on other linezolid-containing regimens. Age was the only variable associated with thrombocytopenia (P=0.019) in univariate analysis.

Conclusions: Linezolid/rifampicin combination therapy was associated with a significantly reduced incidence of anaemia among patients with bone and joint infections, but it did not have an effect on thrombocytopenia and peripheral neuropathy rates. Linezolid/rifampicin combination therapy was not associated with poor clinical outcomes.

Keywords: oxazolidinone, osteomyelitis, haematological toxicities

Introduction

In early 2000, the US Food and Drug Administration approved the use of linezolid, the first available oxazolidinone agent, for skin and soft tissue infection and staphylococcal pneumonia. Linezolid is active against most Gram-positive multidrug-resistant bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus spp.1–8 It is commonly used to treat bone and joint infection (BJI), because its oral bioavailability is high, its concentration in bone and soft tissues exceeds the MIC for susceptible organisms (<4 mg/L)19–20 and adjustments for renal or hepatic function are not needed. However, its cost and adverse haematological events, such as anaemia and thrombocytopenia,4,17,19–29 often limit its use, especially when it is administered for >28 days. Preclinical and Phase I studies3,7,9,30 have shown that these adverse effects are usually dose dependent and reversible after discontinuation. Nonetheless, some adverse events, namely peripheral neuropathy, optic neuropathy, lactic acidosis and serotonin syndrome, are serious and sometimes irreversible.31–36 Linezolid is metabolized following oxidation of its morpholine ring, resulting in two inactive open-ring carboxylic acid metabolites: the amino-ethoxycetic acid metabolite and
the hydroxyethyl glycine metabolite. Cytochrome P450 does not metabolize linezolid in vitro or in vivo in rats.6

Linezolid/rifampicin combination therapy seems attractive for treating patients with BJI due to meticillin-resistant staphylococci.18,19 Several studies have demonstrated that linezolid/rifampicin combination therapy prevents the emergence of rifampicin-resistant S. aureus strains in vitro.5,8,37,38 In addition, Kim et al.39 have reported that rifampicin induces the expression of P-glycoproteins. These transmembrane proteins operate in organ systems that influence drug absorption (intestate), distribution to the site of action (CNS and leucocytes) and elimination (liver and kidney). The multidrug-resistant MDR1 genotype codes for glycoproteins and polymorphisms that may alter P-glycoprotein function.40–42 For example, subjects who are homozygous for the MDR1 C3435T polymorphism have lower intestinal P-glycoprotein concentrations and higher serum digoxin concentrations. A decreased serum linezolid concentration was recently described in a critically ill patient who was on linezolid/rifampicin combination therapy.43

The aim of the present study was to evaluate the impact of rifampicin use in patients receiving prolonged linezolid therapy for BJI on the clinical outcome and the frequency of antibiotic treatment-related adverse events.

Materials and methods

Study design

We reviewed the medical records of patients who had received linezolid-containing regimens for >4 weeks after BJI and were followed until the scheduled end of treatment. We used a computerized database to identify 99 patients who had received oral linezolid, intravenous linezolid or both, as treatment for BJI between January 2000 and December 2006. Five patients were excluded because their records did not contain haematological follow-up data.

Study population

We collected the following patient demographic data: underlying comorbidities (immunosuppression, diabetes mellitus and alcoholism); osteomyelitis including prosthesis and osteosynthesis infections; microbiological and haematological parameters; surgical treatment; linezolid regimen; treatment duration; and drug-related adverse events. In this study, most of the patients were included before prolonged linezolid-related adverse events had been reported in the literature.18,29 After 2006, because of irreversible neurological disorders associated with linezolid, we limited the prescription of linezolid to 28 days.

Case definition

BJI was defined as the presence of two or more of the following criteria: positive bacterial culture on a joint aspirate or intra-operative sample [more than two intra-operative specimens if bacteria were from skin flora (e.g. coagulase-negative staphylococci, Propionibacterium acnes)]; pathological evidence of acute inflammation; clinical, biological or radiological evidence of infection in the prosthesis or osteomyelitic area.

Microbiological assay

We used API strips (Biomerieux, Marcy l’Etoile, France) to identify intra-operative bacterial samples. Antibiotic susceptibility patterns were interpreted in accordance with the recommendations of the Comité de l’Antibiogramme de la Société Française de Microbiologie (http://www.sfm.asso.fr).

Surgical treatment

The surgical strategy was based on the delay from implantation of the prosthetic joint to onset of infection, the condition of the fracture and the stability of the implant. When the prosthetic joint became infected, surgical options included debridement to preserve the prosthesis; one-stage surgery to replace the prosthesis; two-stage surgery, with or without implantation of a spacer, to replace the prosthesis; and, in some cases, namely major bone destruction or poor bone quality, a Gilderstone hip operation or knee arthrodesis. When an osteosynthesis became infected after the fracture had healed, the device was removed. If the fracture had not healed before infection, the internal device was replaced by an external fixer. Surgeons removed infected necrotic tissue and performed bone biopsies after each detected case of osteomyelitis. In all cases, at least three intra-operative samples were taken after an antibiotic-free period of ≥2 weeks. When sepsis occurred, blood cultures and intra-operative samples were collected immediately.

Medical treatment

Patients were treated with empirical parenteral broad-spectrum antibiotic therapy immediately after the intra-operative samples were taken. An infectious disease physician chose the appropriate 6–12 week treatment based on bacterial susceptibility (as suggested by Zimmerli et al.44) and taking into account any contraindication to a particular antibiotic treatment. No patient received erythropoietin to stimulate red blood cells.

Each patient gave informed consent before initiating a linezolid-containing regimen, because at the time of the study, linezolid was not approved for use for >28 days in France under any circumstance. Patients received information on linezolid-related haematological and neurological disorders, as described in the literature at the time. Patients were treated with linezolid/rifampicin combination therapy when they had infection due to Gram-positive cocci, such as MRSA or methicillin-resistant coagulase-negative staphylococci (CoNS), and when they had no other available therapeutic options (e.g. vancomycin intolerance or contraindication, raised MIC of glycopeptides, contraindications to other susceptible antibiotics or refusal of parenteral therapy). Fluoroquinolones and other broad-spectrum β-lactams were added to treatment regimens in the case of polymicrobial infections.

Safety and tolerance of linezolid-containing regimens

We monitored haematological parameters and adverse events, such as headaches, nausea/vomiting, diarrhoea, anaemia and peripheral neuropathy to assess the tolerability of linezolid-containing regimens. Anaemia was defined as an unexplained ≥2 g/dL reduction in haemoglobin; based on the National Cancer Institute classification, the severity of anaemia was graded as follows: Grade I: 10 g/dL to normal baseline value, Grade II: 8–10 g/dL, Grade III: 6.5–7.9 g/dL and Grade IV: <6.5 g/dL. Leucopenia was defined as a total leucocyte count of <4×10^9/L and thrombocytopenia was defined as a reduction in platelet count to <75% of baseline. The severity of thrombocytopenia was graded as follows: Grade I: >75×10^9/L, Grade II: 50–75×10^9/L, Grade III: 10–50×10^9/L, Grade IV: <10×10^9/L.

Patients were suspected to have developed neuropathy if they demonstrated peripheral nerve dysfunctions such as pain, sensory loss, numbness, and tingling or burning sensations. We used electromyography to confirm neuropathy. We recorded biological values weekly from treatment initiation to the scheduled end of treatment.
Patients discontinued linezolid when they developed a severe adverse event such as severe anaemia (>Grade II), thrombocytopenia (platelets <100 x 10^9/L) or peripheral neuropathy. Patients could receive transfusions if they had haemoglobin values <8 g/dL, symptomatic anaemia or a history of cardiac disease.

**Outcomes**

Patients were considered to have treatment success if there was no clinical, biological or radiological evidence of infection following post-operative treatment. In all other cases, patients were considered to have failed treatment.

**Statistical analysis**

In the first part of the analysis (univariate analysis), we used Pearson’s χ² test to compare qualitative variables (sex, diabetes mellitus, alcoholism, chronic renal failure, immunosuppression, surgical treatment and the presence of anaemia or neuropathy) between patients on prolonged linezolid/rifampicin combination therapy and patients on other linezolid-containing regimens. We used a two-sample t-test to compare continuous variables (pre-therapeutic haemoglobin value; haemoglobin value 1, 2 and 3 weeks after treatment initiation; and haemoglobin value at treatment end).

In the second part of the analysis (multivariate analysis), we performed a logistic regression to identify independent variables associated with anaemia. The significance level was set at P<0.05. The statistical analysis was performed using Stata Software version 7.0.

**Results**

Between January 2000 and December 2006, 99 patients received linezolid-containing regimens for >4 weeks at two separate BJI referral centres in Northern France: the Gustave Dron Hospital in Tourcoing and the Roger Salengro Hospital in Lille. Five patients were retrospectively excluded from the study because their medical records did not contain follow-up data.

A total of 94 patients (65 men, 29 women) were included in the study. There were no significant differences in baseline parameters between treatment groups, except for chronic renal failure, which was more frequent among patients on other linezolid-containing regimens. The baseline characteristics are listed in Table 1. None of the patients in our study received linezolid-containing regimens. We used a two-sample t-test to compare continuous variables (pre-therapeutic haemoglobin value; haemoglobin value 1, 2 and 3 weeks after treatment initiation; and haemoglobin value at treatment end).

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The mean delay from linezolid initiation to the onset of anaemia was 13.4 (SD 8.7) weeks in patients on linezolid/rifampicin combination therapy, compared with 9.5 ± 4.3 weeks in other patients (P=0.001). Fifteen patients who developed anaemia and nine patients with confirmed or suspected linezolid-related peripheral neuropathy discontinued linezolid. Two additional patients with cardiac disease discontinued linezolid because their haemoglobin concentration was <8 g/dL 3 weeks after initiating linezolid. Both of these patients received blood transfusions.

In univariate analysis, chronic renal failure and treatment group were associated with anaemia (P=0.04 and P<0.001, respectively). In the multivariate analysis, 2 variables were independently associated with anaemia: age (hazard ratio (HR): 1.035; 95% confidence interval (CI), 1.005–1.066) and treatment group (HR: 2.884; 95% CI, 1.571–5.294). The area under the receiver operating characteristic (ROC) curve was 0.726 (Table 3, Figure 1).

Thrombocytopenia was reported in 44% of patients on linezolid/rifampicin combination therapy, in 48% of patients on linezolid alone (12/25) and in 57.7% of patients on other linezolid-containing regimens (Table 1). Among the 46 patients who experienced thrombocytopenia (<150 x 10^9/L) with prolonged linezolid treatment, none had serious thrombocytopenia (>Grade I). None of these events led to discontinuation of linezolid. Age was the only variable associated with thrombocytopenia (P=0.019) in univariate analysis. Underlying haematological disease, haematological toxicity related to concomitant medications, iron deficiency, vitamin B12 deficiency and acute bleeding were associated with neither anaemia nor thrombocytopenia.

Nine patients developed peripheral neuropathy without optical involvement. The mean delay from onset of linezolid-containing therapy to peripheral neuropathy was 20.4 (SD 3) weeks. The type of linezolid-containing regimen was not associated with neuropathy (five patients were on linezolid/rifampicin combination therapy and four patients were on other linezolid-containing regimens; P=0.53). Minor adverse events included gastric disorders (n=14; 14.9%) and headaches (n=3; 3.2%).

After a median follow-up time of 15.7 ± 9.4 months, the overall treatment success rate was 89.2% (74/83) and did not differ significantly by treatment group (Table 1). Eleven patients (11.7%) were lost to follow-up. Nine patients (9.6%) failed treatment, a mean of 36 ± 26 (range 1–72) months after discontinuation of antibiotic therapy. Eight of these patients underwent a second operation. Preoperative samples showed the presence
Enterococcus faecalis \((n = 1)\), S. aureus \((n = 2)\), CoNS \((n = 3)\), Pseudomonas aeruginosa \((n = 1)\) and Actinomyces spp \((n = 1)\).

One patient refused repeat surgery and instead received oral suppressive antibiotic therapy. None of the organisms recovered from patients who failed treatment were shown to have acquired resistance to rifampicin or linezolid.

**Discussion**

Our results suggest that prolonged linezolid/rifampicin combination therapy is associated with fewer adverse haematological events when compared with other linezolid-containing regimens in patients with BJI. These results confirm those reported by Soriano et al.\(^4\) in 2007. In their study, of 52 patients who received prolonged linezolid treatment for BJI, 17 received linezolid/rifampicin combination therapy. Severe anaemia (i.e., \(8 \text{ g/dL}\)) and thrombocytopenia \((100 \times 10^9/L\) platelets) led 7.7% and 13.4% of patients, respectively, to discontinue

### Table 1. Baseline characteristics and outcomes for 94 patients receiving rifampicin/linezolid combination therapy, linezolid alone or other linezolid-containing regimens

| Characteristics of the study population | Linezolid/rifampicin combination \((n = 43)\) | Linezolid alone \((n = 25)\) | Other linezolid-containing regimen \((n = 26)\) |
|----------------------------------------|------------------------------------------|----------------------------|---------------------------------|
| Mean age, year (range) ± SD            | 56 (28–94) ± 16                         | 53 (25–85) ± 18           | 50 (18–80) ± 18                |
| Gender (M/F)                           | 29/14                                    | 16/9                      | 20/6                           |
| Type of infection, n (%)               |                                          |                           |                                |
| prosthetic joint infection             | 20 (46.5)                                | 8 (32)                    | 11 (42.3)                      |
| osteosynthesis infection               | 8 (18.6)                                 | 8 (32)                    | 8 (30.8)                       |
| diabetic foot infection                | 5 (11.6)                                 | 5 (20)                    | 2 (7.7)                        |
| chronic osteomyelitis                  | 10 (23.3)                                | 4 (16)                    | 5 (19.2)                       |
| Surgical procedure, n (%)              | 30 (69.8)                                | 22 (88)                   | 23 (88.5)                      |
| Underlying disease, n (%)              |                                          |                           |                                |
| diabetes mellitus                      | 12 (27.9)                                | 7 (28)                    | 7 (27.0)                       |
| chronic alcoholism                     | 5 (11.6)                                 | 2 (8)                     | 2 (7.7)                        |
| immunosuppression                      | 3 (7.0)                                  | 3 (12)                    | 3 (7.7)                        |
| chronic renal failure                  | 1 (2.3)                                  | 0 (0)                     | 5 (19.2)*                      |
| Mean duration of linezolid therapy, weeks ± SD | 18 ± 7                                   | 12 ± 8                    | 13 ± 7                         |
| Haematologic values                    |                                          |                           |                                |
| baseline haemoglobin, mean ± SD, g/dL  | 11.6 ± 1.9                               | 11.7 ± 2                  | 11.2 ± 2                       |
| anaemia events,\(^a\) n (%)            | 4 (9.3)                                  | 11 (44)                   | 13 (50)**                      |
| anaemia events leading to linezolid discontinuation, n (%) | 4/4 (100)                              | 6/11 (54.5)               | 5/13 (38.5)                    |
| baseline platelet count, mean ± SD, 10^9/L | 317.078 ± 117.696                      | 340.957 ± 120.986        | 379.818 ± 136.167              |
| thrombocytopenia events\(^b\) n (%)   | 19 (44.2)                                | 12 (48)                   | 15 (57.7)                      |
| thrombocytopenia events leading to linezolid discontinuation, n (%) | 0 (0)                                  | 0 (0)                     | 0 (0)                          |
| Neuropathy events, n (%)               | 5 (11.6)                                 | 1 (4)                     | 3 (11.5)                       |
| Outcomes                               |                                          |                           |                                |
| success, n (%)                         | 37/41 (90.2)                             | 18/21 (85.7)              | 18/21 (85.7)                   |
| failure, n (%)                         | 4/41 (9.8)                               | 2/21 (9.5)                | 3/21 (14.3)                    |
| loss to follow-up, n (%)               | 2 (4.7)                                  | 4 (16)                    | 5 (19.2)                       |
| mean follow-up time, months ± SD       | 15.7 ± 4.5                               | 17.8 ± 7.6                | 13.6 ± 5.4                     |

\(^a\) Anaemia was defined as an unexplained \(\geq 2 \text{ g/dL}\) reduction in haemoglobin.

\(^b\) Thrombocytopenia was defined as a reduction in platelet count to \(< 75\% \) of baseline.

\(^*P = 0.04\); \(^**P < 0.001\).

### Table 2. Linezolid regimens in 94 patients with BJI

| Treatment group/regimen | N (%) |
|-------------------------|-------|
| Linezolid/rifampicin combination \((n = 43)\) |       |
| linezolid/rifampicin combination | 36 (83.7) |
| linezolid/rifampicin/fluoroquinolone combination | 7 (16.3) |
| Linezolid alone \((n = 25)\) |       |
| linezolid alone | 25 (100) |
| Other linezolid-containing regimens \((n = 26)\) |       |
| linezolid/fluoroquinolone | 12 (46.1) |
| linezolid/fluoroquinolone/cefepime | 2 (7.7) |
| linezolid/cefepime | 1 (3.8) |
| linezolid/other β-lactams | 2 (7.7) |
| linezolid/other anti-Gram-positive agents\(^a\) | 9 (34.6) |

\(^a\) Clindamycin \((n = 3)\), fosfomycin \((n = 2)\), tetracycline \((n = 1)\), fusidic acid \((n = 1)\), pristinamycin \((n = 1)\), teicoplanin \((n = 1)\).
related neuropathy is currently unknown, and a correlation
between neuropathy and the concentration of linezolid in the
blood has never been shown. In 2003, Lee et al. reported
a case of linezolid-related optic neuropathy and suggested a
mechanism of protein inhibition that might be responsible for
mitochondrial toxicity. More recently, De Vriese et al. reported
the results of an animal model providing direct evidence that
linezolid inhibits mitochondrial protein synthesis. The authors
recommended avoiding prolonged use of linezolid when alterna-
tive treatment options were available. Some authors have
suggested that some individuals may have particular suscepti-
bility to mitochondrial toxicity.47,48

Recent reports have shown that serum linezolid concen-
trations decrease up to 35% in patients who receive rifampicin
and linezolid simultaneously.43,49 The authors suggest that
rifampicin induces a P-glycoprotein that enhances the non-renal
clearance of linezolid. This hypothesis may explain the preventive
effect of rifampicin on bone marrow toxicity in patients receiving
linezolid/rifampicin combination therapy. Soriano et al. used
this mechanism to explain improved haematological tolerance
among patients on linezolid/rifampicin combination therapy. They
did not assess the impact of a hypothetical decrease in
serum linezolid concentrations on clinical and bacteriological
outcomes. In our study, we observed no differences in clinical
success rates between patients treated with linezolid/rifampicin
combination therapy and those treated with other linezolid-
containing regimens. In addition, no acquired linezolid bacterial
resistance was identified in patients treated with linezolid/rifam-
picin combination.

Our study has several limitations: (i) its design is retrospective,
(ii) the study population is small, because of our narrow inclusion
criteria, and (iii) we do not have data on serum linezolid concen-
trations, which could not be assessed during the study period.

In conclusion, linezolid/rifampicin combination therapy for BJI
was associated with better tolerance, especially regarding the
occurrence of anaemia, when compared with other linezolid-
containing regimens. Prolonged linezolid/rifampicin combination
therapy is, however, limited by potentially severe adverse effects
such as peripheral neuropathies and metabolic disorders, which
suggest that this treatment should only be considered in patients
with BJI only when no other alternatives are available.

Acknowledgements
This study was presented in part at the 18th European Congress of
Clinical Microbiology and Infectious Diseases (ECCMID) 2008, Barcelona,
Spain (P824). Thanks to Catherine Sloane for her assistance.

Funding
This study was supported by internal funding. No corporations were
financially involved in this research, either directly or indirectly.

Transparency declarations
None to declare.
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