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Linezolid plus Rifampin as a Salvage Therapy in Prosthetic Joint Infections Treated without Removing the Implant▽

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The aim of this study is to describe our experience with linezolid plus rifampin as a salvage therapy in prosthetic joint infections (PJIs) when other antibiotic regimens failed or were not tolerated. A total of 161 patients with a documented prosthetic joint infection were diagnosed with a PJI and prospectively followed up from January 2000 to April 2007. Clinical characteristics, inflammatory markers, microbiological and radiological data, and antibiotic treatment were recorded. After a 2-year follow-up, patients were classified as cured when the prosthesis was not removed, symptoms of infection disappeared, and inflammatory parameters were within the normal range. Any other outcome was considered a failure. The mean age of the entire cohort (n = 161) was 67 years. Ninety-five episodes were on a knee prosthesis (59%), and 66 were on a hip prosthesis (41%). A total of 49 patients received linezolid plus rifampin: 45 due to failure of the previous antibiotic regimen and 4 due to an adverse event associated with the prior antibiotics. In no case was the implant removed. The mean (standard deviation) duration of treatment was 80.2 (29.7) days. The success rate after 24 months of follow-up was 69.4% (34/49 patients). Three patients developed thrombocytopenia and 3 developed anemia; however, it was not necessary to stop linezolid. Linezolid plus rifampin is an alternative salvage therapy when the implant is not removed.

The use of debridement and prosthesis retention in early postsurgical prosthetic joint infections (PJIs) is an accepted therapeutic approach when the duration of symptoms is <2 to 4 weeks and there are no radiological signs of loosening (20, 22). In the last 15 years, the combination of rifampin with other antibiotics (e.g., fluoroquinolones) has demonstrated a 70 to 90% success rate (1, 3, 11, 21). Failure has been associated with at least one of the following: (i) the type of isolated microorganism (16), mainly methicillin-resistant staphylococci and enterococci, (ii) the need for more than 1 debridement to control the infection, (iii) a high C-reactive protein concentration at the moment of diagnosis (21), and (iv) the antibiotic or combination of antibiotics administered (5). The management of patients who fail while they are on treatment has not yet been well-defined. At present, there are two options: either remove the implant following the one- or two-stage exchange protocol or maintain the prosthesis and switch to an alternative antimicrobial therapy.

Linezolid inhibits bacterial protein synthesis by preventing the fusion of 30S and 50S ribosomal subunits, and it has shown excellent efficacy against Gram-positive cocci, including *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, and streptococci, with a range of MICs of from 0.5 to 4 mg/liter (8). Furthermore, linezolid has a 100% oral bioavailability and reaches high concentrations in musculoskeletal tissues (skin, synovial fluid, and bone) (10). Previous reports on orthopedic implant infections have demonstrated a high success rate with linezolid (2, 17) when it was administered as a part of the first-line therapy. However, the efficacy of this antibiotic when it is administered as a second-line therapy and without removal of the implant has not yet been described.

In 2001, linezolid was included as a second-line therapy in the protocol of University Hospital Virgen de la Arrixaca (Murcia, Spain) for prosthetic joint infections. The aim of the present study was to review the experience with linezolid when it was administered as a second-line therapy after failure or adverse events related to the previous antibiotic regimen when the implant was not removed.

MATERIALS AND METHODS

A total of 161 patients with a documented acute PJI and prospectively followed up from January 2000 to April 2007 in the University Hospital of Virgen de la Arrixaca were included in the study. Acute infections were considered when a diagnosis was made within the first 3 months after joint arthroplasty. The first approach in these cases was not to remove the implant (with or without open debridement) and antimicrobial therapy. Our antibiotic protocol for Gram-positive microorganisms susceptible to fluoroquinolones is ciprofloxacin plus rifampin, and for resistant strains is teicoplanin or trimethoprim plus rifampin. Since January 2001, patients failing or with adverse events associated with this antimicrobial regimen have been switched to oral linezolid at 600 mg/12 h plus rifampin at 300 mg/8 h without removal of the implant. Failure of the antibiotic regimen was considered when fever, purulent drainage, or local inflammatory symptoms persisted or reappeared after more than 10 days on treatment. Clinical characteristics, parameters of inflammatory response, the quantity of purulent drainage through the wound, microbiological and radiological (ecography and bone scintigraphy) data, and outcome after 2 years of follow-up were gathered. The purulent drainage was classified on the basis of the following scores: (i) draining only after local pressure (score = I), (ii) spontaneous draining for less than 8 days (score = II), and (iii) spontaneous draining for ≥8 days (score = III).

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Patients were monitored monthly during therapy and every 6 months for 2 years after they completed treatment. The duration of antibiotic treatment in each patient was determined according to the clinical response and normalization of inflammatory markers. At the end of follow-up, patients were classified as being in remission when the prosthesis was not removed and symptoms and signs of infection disappeared, when inflammatory parameters were within the normal range, and radiological studies were negative for infection at the last visit. Failure was considered when it was necessary to remove the prosthesis to control the infection, and relapse was considered when symptoms and signs of infection reappeared after the completion of therapy. Thrombocytopenia during linezolid treatment was considered when the platelet count decreased to less than <100,000 cells/mm^3. Anemia was defined as a decrease of ≥2 g/dl from the baseline hemoglobin concentration.

Descriptive data were expressed as means and standard deviations (SDs). Proportions were compared using the χ^2 test or the Fisher exact test (when necessary), and the quantitative variables were compared by the Mann-Whitney U test. A P value of <0.05 was considered statistically significant. The analysis was performed using SPSS software, version 12.0 (SPSS, Inc., Chicago, IL).

RESULTS

From January 2000 to April 2007, 161 prosthetic joint infections were treated at the University Hospital Virgen de la Arrixaca, of which 45 (27.9%) failed (previous treatment with teicoplanin, ciprofloxacin, or trimethoprim plus rifampin) and 4 developed an adverse event associated with the previous antimicrobial regimen. These 49 patients received linezolid at 600 mg/12 h plus rifampin at 300 mg/12 h by the oral route without removal of the implant. The main characteristics according to the outcome are described in Table 1. The mean (SD) age of the cohort was 64.1 (11.8) years. In 22 cases (44.9%) the infection was in a primary arthroplasty, and the in the rest they were in revision arthroplasties. In 31 cases (63.2%), linezolid was started within the first 30 days after joint arthroplasty and 35 (77.8%) of the cases underwent open debridement without removal of the implant, while 14 were not operated on. Cultures of deep samples (obtained during surgery, by synovial fluid aspiration, or from a deep fistula using a swab) were positive in 28 cases: 22 for methicillin-resistant *Staphylococcus epidermidis* and 6 for methicillin-resistant *Staphylococcus aureus.* All the strains were susceptible to vancomycin and linezolid and resistant to levofloxacin and clindamycin, and 50% and 17% of the *S. aureus* and *S. epidermidis* isolates, respectively, were resistant to co-trimoxazole. The mean (SD) duration of antibiotic regimen was 80.2 (29.7) days, with a range of from 21 to 180 days.

After a 2-year follow-up, the remission rate was 69.4% (34 out of 49 patients), and among those patients who received linezolid due to failure of previous therapy, the remission rate was 66.6% (34 out of 45). A high degree of purulent drainage at the start of linezolid treatment and positive deep cultures were significantly associated with a higher risk of failure.

The most common adverse events were mucocutaneous candidiasis in 6 patients (12.2%) and gastrointestinal discomfort in 6 (12.2%). Three patients (6.1%) developed thrombocytopenia, and 3 developed anemia (6.1%). Two patients received a blood transfusion, but it was not necessary to stop linezolid. No patient had symptoms or signs of peripheral neuropathy.

TABLE 1. Characteristics of patients treated with linezolid as second-line therapy according to outcome after 2 years of follow-up

Characteristic	No. (%) of patients[a]		P[b]
	Success (n = 34)	Failure (n = 15)	
Male sex	14 (50)	7 (26.6)	
Diabetes mellitus	11 (32.3)	5 (33.3)	0.59
Primary arthroplasty	15 (44.1)	7 (46.6)	0.88
Revision arthroplasty	19 (55.9)	8 (53.3)	
Age of implant (days)[c]			0.99
<30	22 (64.7)	9 (60)	
30–90	7 (20.6)	3 (20)	
>90	5 (14.7)	3 (20)	
Type of prosthesis[d]			0.34
Hip	18 (60)	6 (40)	
Knee	12 (40)	9 (60)	
Grade III of drainage[c,d]	5 (14.7)	9 (60)	0.004
Baseline C-reactive protein concn (mg/dl)			
≤5	16 (47)	7 (46.7)	0.77
>5	18 (53)	8 (53.3)	
Reason for switching to linezolid			
Failure (n = 45)	30 (88.2)	15 (100)	
Adverse event (n = 4)	4 (11.8)	0	0.21
Open debridement[c,d]	21 (70)	14 (93.3)	0.08
Microbiology[c,d]			
Culture negative	16 (36.5)	1 (6.6)	0.006[e]
Culture positive for:	14 (31.1)	14 (93.3)	
S. epidermidis (all MR)	11	11	
Methicillin-resistant *S. aureus*	3	3	

[a] The median (SD) ages of the patients in the success and failure groups were 65.3 (11.5) and 62.3 (12.4) years, respectively (P = 0.50). The mean (SD) durations of linezolid treatment were 77.5 (31.9) and 84.4 (26.1) days, respectively (P = 0.45).
[b] Chi-square test or Fisher exact test, as necessary.
[c] At the moment that linezolid treatment was started.
[d] Considering only patients who failed previous treatment (n = 45).
[e] Comparing the outcomes of culture-negative and culture-positive patients.

DISCUSSION

The use of open debridement and antibiotic therapy is an accepted approach in acute prosthetic joint infections. The success rate using rifampin combinations is higher than 70% (21, 23); however, in case of methicillin-resistant staphylococci (including *S. aureus* and *S. epidermidis*), the reported success rate is lower than 50% (5, 9, 15). In these cases there are two options: either remove the implant (one- or two-stage exchange) or switch the antibiotic treatment with or without additional debridement.

Linezolid is an active antibiotic with 100% oral bioavailability, and previous observational experience has shown good results with a success rate of ≥80% (2, 13) as first-line therapy. In the present study, linezolid plus rifampin, as a second-line therapy, showed a success rate of 69.4% (34 out of 49 patients) after 2 years of follow-up. The success rate was similar when only the 45 patients who received linezolid due to failure of the previous regimen were considered (66.6%).

In contrast, the success rate was significantly lower in those patients with grade III purulent drainage (4 out of 15, 35.7%),

although all patients underwent open debridement at the start of linezolid treatment. In this particular situation, removal of the prosthesis is recommended. The success rate was also lower in those patients who underwent open debridement and for whom cultures of deep samples were positive. In this setting, the success rate was 50%, and it was the same for methicillin-resistant *S. aureus* and *S. epidermidis*. Under these circumstances, we consider the success rate to be high enough to recommend linezolid; however, in the future it would be necessary to evaluate whether the results achieved with linezolid could be improved by monitoring the serum concentration. Although linezolid is not a substrate of cytochrome P-450, a recent communication on 16 healthy volunteers showed a 30% reduction in the area under the concentration-time curve (AUC) when linezolid was coadministered with rifampin (6). Therefore, use of this combination requires increasing the linezolid dosages in order to obtain the pharmacodynamic parameter that predicts the efficacy of linezolid (AUC/MIC $>$ 80).

The major concern with linezolid is its safety profile, especially when it is administered for a prolonged period of time. Adverse events are due to mitochondrial toxicity (18) and include hematological disturbances (thrombocytopenia and anemia), peripheral neuropathy, hyperlactacidemia, and metabolic acidosis (4, 7, 14). In our series, the hematological adverse events were uncommon and no neuropathy was observed. This fact could also be attributed to the lower serum concentrations of linezolid when it was combined with rifampin. Indeed, recent data have shown that the coadministration of rifampin was associated with a lower risk of thrombocytopenia (19) and anemia (12), demonstrating a prevalence similar to ours. In contrast, Legout et al. (12) reported peripheral neuropathy in 5 out of 43 patients (11.5%) who received linezolid plus rifampin, while no case of peripheral neuropathy was documented in our series. The reason for this discrepancy could be the duration of linezolid treatment, which was 80 days in our cohort and 126 days in the cohort of Legout et al. (12). In fact, in the study of Legout et al. (12), the mean delay from the onset of linezolid therapy to peripheral neuropathy was 140 days, while in our series only 5 patients received linezolid for more than 120 days (123, 124, 126, 122, and 180 days, respectively).

In conclusion, linezolid plus rifampin is an alternative salvage therapy when the implant is not removed, except in those cases with abundant purulent drainage. Our results suggest that in the future, monitoring of the linezolid serum concentration would improve the tolerance and efficacy of this antibiotic.

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