High Frequency of Linezolid-Associated Thrombocytopenia and Anemia among Patients with End-Stage Renal Disease

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Background. Data about the efficacy and tolerability of linezolid for the treatment of gram-positive bacterial infections in patients with end-stage renal disease (ESRD) are lacking.

Methods. This retrospective case-control study compared the tolerability and efficacy of linezolid therapy for patients with ESRD and patients with non–end-stage renal disease (NESRD), all of whom had gram-positive bacterial infections.

Results. There were 58 men and 33 women enrolled in the study, with a mean age of 61.5 years (range, 45.4–81.2 years). Among these patients, 28 (30.8%) were receiving hemodialysis at the start of linezolid treatment. The ESRD group had a higher percentage of patients with diabetes mellitus (57.1% vs. 33.3%; P < .029) and an older mean age (±SD) (72.1 ± 10.8 years vs. 56.8 ± 20.4 years; P < .001), compared with the NESRD group. Severe thrombocytopenia (platelet count, <100 × 10^9 platelets/L) and anemia were significantly more frequent in the ESRD group, compared with the NESRD group (78.6% vs. 42.9% [P < .003] and 71.4% vs. 36.5% [P < .003], respectively). The independent risk factors for thrombocytopenia identified by logistic regression analysis were pretreatment disease severity score (odds ratio [OR], 1.34; 95%, confidence interval [CI], 1.13–1.60; P < .001), central catheter–related infection (OR, 4.96; 95% CI, 1.08–22.73; P = .046), and ESRD (OR, 6.14; 95% CI, 1.63–23.26; P = .007). ESRD was the only independent risk factor for anemia (OR, 4; 95% CI, 1.50–10.64; P = .006). Survival analysis for the development of thrombocytopenia or death showed significant differences between patients with ESRD and patients with NESRD (P < .001).

Conclusions. The lower tolerability of linezolid in patients with ESRD, compared with those with NESRD, is evidenced by the higher rates of thrombocytopenia and anemia in the former group. The severity of these conditions necessitates treatment discontinuation for patients with ESRD more often than for patients with NESRD.

Methicillin-resistant Staphylococcus aureus and methicillin-resistant, coagulase-negative staphylococci are common causes of bacteremia among patients undergoing dialysis [1]. The widespread use of vancomycin therapy for patients undergoing dialysis is of concern, because of its association with an increase in the prevalence of vancomycin-resistant enterococci [2]. Linezolid is a new antimicrobial agent with a broad spectrum of activity against virtually all clinically important gram-positive bacteria, including methicillin-resistant S. aureus; methicillin-resistant, coagulase-negative staphylococci; and vancomycin-resistant enterococci [3–7]. Because linezolid is 100% bioavailable, is highly water-soluble, and has good tissue penetration [8], it can be administered in equal doses via the oral or parenteral route [5]. Twice daily dosing at 600 mg has an adequate therapeutic effect, even in critically ill persons. Linezolid is effective therapy for the majority of patients with serious infections caused by S. aureus with reduced vancomycin susceptibility [9] and by vancomycin-resistant enterococci [2]. Clearance of linezolid is not altered for patients with renal dysfunction, including those with end-stage renal disease (ESRD) treated by hemodialysis; therefore, no adjustment of the linezolid dosage is needed [7, 10]. However, serum levels of
Linezolid can decrease to subtherapeutic levels after renal replacement therapy [11].

Linezolid therapy has been associated with myelosuppression, which may result in transient and reversible anemia and thrombocytopenia [12–14]. Renal failure is frequently associated with anemia and higher risks of cardiac failure and mortality. In addition to inappropriate erythropoietin production, uremic toxicity may affect the RBC mass by interfering with both RBC production and life span [15, 16]. Thrombocytopenia is also a common finding in uremic patients, with platelet counts reported to be reduced in 16%–55% of patients [17, 18]. Thus, linezolid treatment for patients with ESRD may exacerbate the development of these preexisting conditions. The aim of this study was to compare the efficacy and tolerability of linezolid treatment between patients with non–end-stage renal disease (NESRD) and patients with ESRD who were receiving hemodialysis.

PATIENTS, MATERIALS, AND METHODS

Patients. This retrospective, case-control study compared the tolerance and efficacy of linezolid therapy between patients with ESRD and patients with NESRD who received treatment for gram-positive bacterial infections at National Taiwan University Hospital (Taipei, Taiwan) from November 2002 through December 2004. In accordance with treatment policy in the hospital, adult patients who had at least 2 of the signs and symptoms of systemic inflammatory response syndrome [19], had infection caused by gram-positive bacteria, had a past medical history of adverse effects (i.e., skin rash and/or thrombocytopenia) due to vancomycin or teicoplanin therapy, or had not responded to vancomycin or teicoplanin treatment for a period of >14 days were indicated for linezolid use. All patients who received linezolid therapy were identified through pharmacy records.

Inclusion criteria were as follows: age of >18 years; adequate respiratory, sputum, or wound pus specimens for Gram stain; adequate samples of blood or wound, urine, or anal swab specimens for microbiological culture, as indicated by clinical signs; and a life expectancy of at least 7 days at the time of treatment. Patients were excluded from the study if they had any of the following conditions: recent clinically significant coagulopathy, known liver disease and a total bilirubin level of >5 times the upper limit of normal, or neutropenia (neutrophil level, <500 × 10^9 neutrophils/L).

Interventions. Linezolid (600 mg every 12 h) was administered intravenously for at least the initial 7 days, with a switch to an oral formulation if resolution of infection-related signs and symptoms was evident. The total duration of linezolid treatment was ≈28 days. For patients with ESRD, one of the twice-daily doses was administered after dialysis treatment on days when dialysis was performed [10]. Concomitant administration of antimicrobial agents to treat infections caused by gram-negative organisms or anaerobes was permitted. Choice of the modality of renal replacement therapy was made by the attending physician on the basis of the clinical characteristics of the patients.

Clinical assessment. Clinical assessments at baseline included medical history, physical examination, and identification of comorbid disease. Comorbid conditions were classified as diabetes mellitus, hypertension, cardiac disease, hepatic disease, oncologic disease, and hematologic malignancy. Patients with liver cirrhosis or abnormal liver function were classified as having hepatic dysfunction. Cancer was defined as an oncologic disorder, and leukemia and lymphoma were defined as a hematologic diseases. Disease severity was compared between patients with ESRD and patients with NESRD using the modified sequential organ failure assessment (mSOFA) [20], which excluded renal function score from the SOFA score.

Microbiological assessment. Specimens were obtained for Gram stain and culture at baseline; during the follow-up period, including at least once during fever; and at the completion of linezolid treatment. All microbiological assessments for this retrospective study were conducted as part of standard care for the patients.

Efficacy evaluation. Criteria for assessing clinical outcome were as follows: cure (defined as resolution of the baseline clinical signs and symptoms of systemic inflammatory response syndrome [19]), failure (defined as persistence or progression of the signs and symptoms of systemic inflammatory response syndrome after at least 5 days of therapy), and death. Outcomes were further classified as cure, failure (defined as an etiology of underlying disease, shock, or infection with gram-negative pathogens), and intermittent cure (defined as recurrent sepsis during the 2-week period after the start of therapy). Microbiological responses were evaluated and classified as follows: success (defined as documented eradication, presumed eradication, or colonization), failure (defined as documented persistence or presumed persistence of infection), and intermittent (defined as recurrent infection with gram-positive pathogens within 2 weeks after eradication) [21].

Safety evaluation. Safety of treatment was assessed for patients who received medication for at least 7 days. This evaluation included hematologic and clinical chemistry analyses, as well as assessment of adverse events. Linezolid therapy was discontinued if thrombocytopenia (platelet count, <100 × 10^9 platelets/L) was detected [12], the duration of vascular access compression at the end of hemodialysis sessions was >15 min, or bleeding (or oozing) at the site of vascular access within 1 h after hemodialysis, gastrointestinal bleeding, or skin ecchymosis was detected [22].

Hematologic and biochemical abnormalities. Variances in hematologic findings were assessed on at least 3 days during...
Table 1. Demographic and clinical characteristics of patients with end-stage renal disease (ESRD) and patients with non–end-stage renal diseases (NESRD).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NESRD group (n = 63)</th>
<th>ESRD group (n = 28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>40 (63.5)</td>
<td>18 (64.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, years</td>
<td>56.8 ± 20.4</td>
<td>72.1 ± 10.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood urea nitrogen level, mg/dL</td>
<td>27.2 ± 19.9</td>
<td>71.3 ± 31.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum creatinine level, mg/dL</td>
<td>1.2 ± 0.8</td>
<td>4.0 ± 2.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Receipt of intravenous linezolid</td>
<td>43 (68.3)</td>
<td>20 (71.4)</td>
<td>.482</td>
</tr>
<tr>
<td>Duration of linezolid treatment, days</td>
<td>16.7 ± 9.9</td>
<td>15.0 ± 8.8</td>
<td>.438</td>
</tr>
<tr>
<td>Previous vancomycin use</td>
<td>40 (63.5)</td>
<td>20 (71.4)</td>
<td>.632</td>
</tr>
<tr>
<td>Duration of vancomycin treatment before linezolid use, days</td>
<td>13.7 ± 16.1</td>
<td>14.0 ± 17.8</td>
<td>.921</td>
</tr>
<tr>
<td>Overall duration of antibiotic treatment before linezolid use, days</td>
<td>39.4 ± 38.2</td>
<td>32.8 ± 33.8</td>
<td>.434</td>
</tr>
<tr>
<td>Comorbid condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (33.3)</td>
<td>16 (57.1)</td>
<td>.029</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>20 (31.7)</td>
<td>12 (42.9)</td>
<td>.347</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (34.9)</td>
<td>13 (46.4)</td>
<td>.353</td>
</tr>
<tr>
<td>Hepatic disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11 (17.5)</td>
<td>1 (3.6)</td>
<td>.096</td>
</tr>
<tr>
<td>Hematologic malignancy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9 (14.3)</td>
<td>5 (17.9)</td>
<td>.755</td>
</tr>
<tr>
<td>Oncologic disease&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 (19.0)</td>
<td>6 (21.4)</td>
<td>.782</td>
</tr>
<tr>
<td>mSOFA score</td>
<td>3.4 ± 4.1</td>
<td>5.3 ± 3.0</td>
<td>.040</td>
</tr>
</tbody>
</table>

| Coadministered antibiotic(s)                       |                      |                     |       |
| β-lactams                                          | 33 (52.3)            | 20 (71.4)           | .166  |
| Fluoroquinolones                                   | 11 (17.5)            | 4 (14.3)            | 1.000 |
| Fluconazole                                        | 9 (14.3)             | 3 (10.7)            | .749  |

**NOTE.** Data are no. (%) of patients or mean values (± SD). mSOFA, modified sequential organ failure assessment.

<sup>a</sup> Includes patients with liver cirrhosis or abnormal findings of liver function tests.

<sup>b</sup> Includes patients with leukemia or lymphoma.

<sup>c</sup> Indicates patients with solid-organ cancers.

the treatment course, including changes from baseline to the end of treatment and shifts from baseline to the lowest recorded value. For patients who received hemodialysis twice weekly, blood samples were obtained before dialysis. Mean hematologic values were determined for the intent-to-treat population. Anemia was defined as a hemoglobin level of <10 mg/dL, and pancytopenia was defined as thrombocytopenia, anemia, and an absolute neutrophil count of <500 × 10<sup>4</sup> neutrophils/L. For patients with abnormal baseline values, substantially abnormal values were prospectively defined as a hemoglobin level of <75% of the baseline level [23], a platelet count of <75% of the baseline count, and an absolute neutrophil count of <50% of the baseline count [14] detected at any time during the study. Complete blood counts were determined at the start of linezolid treatment and were monitored on at least 3 days during the study period. Abnormal liver function was defined as an aspartate aminotransferase or alanine aminotransferase level that was >5 times the baseline level, as detected by liver function tests.

**Statistical analysis.** Results were expressed as mean values (± SD), unless otherwise specified. The unpaired Student’s t test was used to analyze continuous data, and either χ<sup>2</sup> analysis or Fisher’s exact test was used to analyze categorical data. Statistical analyses were performed with SPSS for Windows, version 10.0 (SPSS). The binomial test of proportions was used to compare incidences between treatment groups. For other between-group comparisons, Fisher’s exact test was used for categorical values, and either Student’s t test or the Mann-Whitney U test was used for mean values.

Survival analysis for patients who died from complications of thrombocytopenia included time to cessation of treatment, time to development of thrombocytopenia, and time to death. Data were censored if, at the end of the follow-up period, the patient had not discontinued linezolid therapy, had not developed thrombocytopenia, or died. The Kaplan-Meier (i.e., product-limit) method was used to estimate survival and to plot time-to-event data. Comparisons between the ESRD and NESRD groups with respect to time-to-event data were made using the Cox proportional hazards model, with graphical and statistical checks for proportionality of hazards. A P value of <.05 was considered to be statistically significant.
RESULTS

Demographic characteristics of patients. A total of 58 men and 33 women were included in the study, with an age of 61.5 years (range, 45.4–81.2 years) (table 1). The duration of linezolid treatment was 16 ± 10 days. A total of 28 patients (30.8%) received dialysis at the start of linezolid treatment. There were no significant differences between patients in the ESRD and NESRD groups with respect to sex, etiology or type of infection, coadministered antibiotics, and duration of other therapy before initiation of linezolid treatment. Most patients (65.9%) had previously received vancomycin. However, the frequency of past vancomycin use was not significantly different between patients in the ESRD group and patients in the NESRD group (table 1). Illness severity scores for the ESRD group were higher than those for the NESRD group (mSOFA score, 5.3 ± 3.0 vs. 3.4 ± 4.1; P = .04).

Efficacy and clinical complications. As shown in table 2, the ESRD group had a significantly higher incidence rate of severe thrombocytopenia (78.6% vs. 42.9%; P = .003) and a significantly lower platelet count (61.5 × 10^9 ± 48.3 × 10^9 platelets/L vs. 148.8 × 10^9 ± 137.4 × 10^9 platelets/L; P < .001). The percentage of patients who developed anemia was also higher in the ESRD group (36.5% vs. 71.4%; P = .003). No difference was found in the incidence of linezolid-related pancytopenia and deterioration of liver function between the 2 groups. There were 14 deaths (50.0% of patients) in the ESRD group and 21 deaths (33.3% of patients) in the NESRD group during the follow-up period (P = .164).

Thrombocytopenia was observed in 49 patients (53.8%). Fourteen (28.0%) of the thrombocytopenic patients with initially low platelet counts (<100 × 10^9 platelets/L) had a platelet count that decreased by at least 25% after the start of linezolid therapy. Thrombocytopenia was observed in 14 patients (50%) in the ESRD group who received linezolid for >10 days. Among patients who developed thrombocytopenia, the periods between the start of treatment and both the development of thrombocytopenia (10.4 ± 4.4 days vs. 13.0 ± 8.0 days; P = .194) and the return to baseline platelet counts (5.0 ± 1.8 days vs. 3.8 ± 1.9 days; P = .112) were not significantly different between patients with ESRD and patients with NESRD. Kaplan-Meier curves for discontinuation of treatment because of thrombocytopenia or death showed significant differences between patients with ESRD and patients with NESRD (P < .001, by the log-rank test) (figure 1).

Factors related to thrombocytopenia and anemia. Patients who developed thrombocytopenia were significantly more likely than patients without thrombocytopenia to have ESRD (22 patients [44.9%] vs. 6 patients [14.3%]; P = .003). The pre-treatment mSOFA score was significantly higher for patients who developed thrombocytopenia than for those who did not (5.51 ± 4.10 vs. 2.24 ± 2.71; P < .001). Thrombocytopenic patients were older than nonthrombocytopenic patients (65.34 ± 18.45 years of age vs. 57.02 ± 19.48 years of age;
patients without anemia. The duration of treatment (17.3 ± 9.0 days vs. 15.3 ± 10.1 days) and mSOFA score (4.8 ± 4.0 vs. 3.3 ± 3.6) were not significantly different between patients with and patients without anemia. Logistic regression analysis revealed that only ESRD was an independent risk factor for anemia (OR, 4; 95% CI, 1.50–10.64; P = .006).

**DISCUSSION**

Linezolid therapy, which is effective against gram-positive bacteria [3–7], has been associated with reversible, time-dependent myelosuppression [24, 25]. In this study, the incidence rate of anemia was higher in the ESRD group than in the NESRD group, despite the lack of statistically significant differences in the baseline characteristics of patients in these 2 groups, all of whom received similar treatment courses and had similar mSOFA scores. Anemia is a frequent complication of renal failure, and its prevalence has been shown to increase with diminishing renal function [23]. In our study, of the patients who received linezolid treatment, more than one-half who had ESRD developed anemia, with ESRD being the only factor that contributed to anemia. The mechanism of linezolid-related anemia has been thought to be inhibition of mitochondrial respiration by inhibition protein synthesis [6, 26]. Determination of whether linezolid therapy has an additional effect on uremic anemia will require further study.

Although anemia is reversible and manageable with transfusions, thrombocytopenia can be a treatment-limiting toxicity, especially for patients undergoing dialysis. The magnitude of the decrease in platelet count is a robust and highly independent predictor of death in analyses that control for severity of illness [27].

We found that a low platelet count was responsible for the premature cessation of linezolid therapy for ~40% of our patients. These findings support those of previous studies that found linezolid therapy to be the cause myelosuppression [14, 28]. In the present study, linezolid was administered for at least 7 days, because of the 7–10-day life cycle of platelets [29]. The incidence of thrombocytopenia in our series (53.8%) was higher than that previously reported in studies of linezolid therapy for treatment of gram-positive bacterial infections (1.5%–32%) [12, 14, 24]. It was suggested that recent treatment with vancomycin increased the risk of thrombocytopenia for patients whose therapy was subsequently switched to linezolid [25], and most (65.9%) of our patients who had received previous vancomycin treatment were switched to linezolid treatment.

The use of different definitions of thrombocytopenia in previous studies makes it more difficult to compare findings from such studies with findings from our study. On the basis of previous reports [14, 25], we defined severe thrombocytopenia as a platelet count that decreased to <100 × 10^9 platelets/L. Grau et al. [30] and Gerson et al. [14] reported that only the pretreatment platelet count is an independent factor related to thrombocytopenia and reported a decreased platelet count for critically ill patients with high illness severity scores. We also considered the effect of a low baseline platelet count by evaluating the lowest platelet count during therapy and the percentage change from the baseline count. One-third of the thrombocytopenic patients in this study had low platelet counts before the start of linezolid therapy. A previous report suggested that substantially low platelet counts occurred most often in patients with underlying hematologic abnormalities [14]. In this study, 14 patients (15.4%) had hematologic malignancy. Thrombocytopenia was previously reported for 32% of patients who received linezolid for >10 days [12], and the mean treatment period for our patients was even longer (16 days). The gram-negative infections were severe in our patients, most of whom had taken several concomitant medications associated with bone marrow suppression. Severe infections may be associated with bone marrow suppression that is independent of therapy.

In this study, the ESRD and NESRD groups had similar infection severity. However, patients with ESRD had a higher incidence of thrombocytopenia and a lower platelet count. ESRD was an independent predictor of thrombocytopenia in our analysis. Previous studies have shown that patients undergoing dialysis are more likely to develop thrombocytopenia [17, 18]. Severe thrombocytopenia or death may occur during linezolid therapy in patients with ESRD, and it often necessitates cessation of linezolid therapy. Heparin is used as anticoagulant during dialysis, but it can induce thrombocytopenia [31]. Although it was impossible to completely exclude heparin therapy as a cause of thrombocytopenia in our patients, the changes in platelet counts correlated more closely with the initiation and discontinuation of linezolid treatment. The interaction between components of blood and membranes that occurs during hemodialysis causes bioincompatible events [32] that may induce platelet activation and decrease the platelet count during hemodialysis [33], and these events are associated with complement activation [34]. Although the mechanism for linezolid-induced thrombocytopenia is not clear, it was suggested that immune-mediated mechanisms were likely [6]. The extents to
which dialysis and linezolid treatment lead to increased platelet consumption or inadequate production and, thus, to further decreases in the count of circulating platelets require further study.

The periods from the start of treatment to both the development of thrombocytopenia and the return to the baseline platelet count were not significantly different between patients with and patients without renal failure. Overall, thrombocytopenia was observed in 50% of the patients with ESRD who received linezolid for >10 days. Because patients with ESRD have a higher incidence rate of severe thrombocytopenia, deviations from normal hematologic findings should be assessed at least every 3 days, especially for patients who have received linezolid for >10 days. We found that patients who have ESRD in conjunction with an ominous disease severity score and central catheter infection were found to be at high risk for development of thrombocytopenia. For any patient with renal failure who develops thrombocytopenia, linezolid treatment should be discontinued.

Pharmacokinetic parameters of linezolid in adults are not altered by hepatic or renal function, age, sex, or disease severity to an extent requiring dose adjustment [11, 35]. A linezolid dosage of 600 mg every 12 h was also adequate for critically ill patients and did not require adjustment for renal function [7, 10, 11]. This finding was based on an increased rate of nonrenal clearance that was observed in these patients as the rate of renal creatinine clearance decreased. This apparent compensatory increase in the rate of nonrenal linezolid clearance could be the result of enhanced drug biotransformation, biliary excretion, decreased absolute bioavailability, or changes in drug distribution [10]. The 2 major metabolites of linezolid (PNU-142586 and PNU-142300) were found to accumulate in patients with renal impairment, especially those with ESRD [10, 36]. In the present study, no significant differences were found in baseline blood counts, duration of treatment, or the duration of the recovery period between the ESRD or NESRD group. Therefore, the clinical significance of metabolite accumulation on platelet destruction in these patients requires further investigation.

Renal replacement therapy is a significant source of elimination of linezolid and its 2 major metabolites in patients with ESRD [10, 11]. Approximately one-third of the administered dose of the drug was removed during hemodialysis [10], which can lead to decreases to subtherapeutic concentrations [10, 11, 37]. However, in our series, microbiological eradication and clinical outcome did not differ between the ESRD and NESRD groups. To our knowledge, this is the first study to evaluate the efficacy of and adverse effects associated with linezolid for treatment of all-cause infection in uremic patients.

In conclusion, the microbiological and clinical efficacy of linezolid therapy is not altered in patients with ESRD, and therefore, no dosage adjustment is required. Profound thrombocytopenia and anemia may occur in uremic patients after initiation of linezolid therapy, which often necessitates discontinuation of treatment. Surveillance for thrombocytopenia should be performed for patients who have ESRD in conjunction with a severe disease assessment and central catheter infection, and surveillance for abnormal hematologic findings should be performed at least every 3 days for patients with ESRD who are receiving linezolid therapy.

**Acknowledgments**

**Potential conflicts of interest.** All authors: no conflicts.

**References**