Brief Report

Continuation of a Randomized, Double-Blind, Multicenter Study of Linezolid Versus Vancomycin in the Treatment of Patients with Nosocomial Pneumonia

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ABSTRACT

Background: The clinical efficacy and tolerability of linezolid were demonstrated in a previously published, randomized, double-blind, registration study comparing linezolid with vancomycin for the empiric treatment of 396 patients with nosocomial pneumonia.

Objectives: The aims of this study were to obtain additional experience with linezolid and vancomycin in patients with nosocomial pneumonia and to satisfy international regulatory requirements.

Methods: Patients with pneumonia acquired after 48 hours in an inpatient facility were randomly assigned to receive either IV linezolid 600 mg or IV vancomycin 1 g every 12 hours for 7 to 21 consecutive days. Patients also received IV aztreonam 1 to 2 g every 8 hours, which could be discontinued if gram-negative pathogens were not identified. The primary efficacy variables were clinical and microbiologic outcomes in evaluable patients at the follow-up visit 15 to 21 days after the end of therapy. Results from the continuation study were analyzed separately and did not include patients from the previously reported study.

*Members of the Linezolid Nosocomial Pneumonia Study Group are listed in the Acknowledgments.

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Results: A total of 623 patients were enrolled: 321 in the linezolid group and 302 in the vancomycin group. Mean (SD) ages were 63.1 (19.1) years and 61.9 (19.3) years, respectively. Mean (SD) Acute Physiology and Chronic Health Evaluation II scores were 14.1 (5.8) and 14.1 (6.2), respectively. There were no significant differences between the linezolid and vancomycin groups at the follow-up visit in clinical cure rates (114/168 [67.9%] and 111/171 [64.9%]) or microbiologic success rates (47/76 [61.8%] and 42/79 [53.2%]) in evaluable patients (excluding those who had indeterminate or missing outcomes). There were also no significant differences in the rates of all drug-related adverse events (14.0% and 14.0%) or those that occurred in >1% of patients, including diarrhea (3.7% and 3.0%), nausea (0.3% and 1.3%), and rash (0.6% and 1.7%) in the linezolid and vancomycin groups, respectively.

Conclusion: In the population studied, linezolid appeared to be as well tolerated and as effective as vancomycin, each in combination with aztreonam. (Clin Ther. 2003;25:980-992) Copyright © 2003 Excerpta Medica, Inc.

Key words: linezolid, vancomycin, empiric therapy, nosocomial pneumonia.

INTRODUCTION
Nosocomial pneumonia continues to be problematic due to its frequency and associated morbidity and mortality. In addition, the incidence of nosocomial pneumonia due to gram-positive pathogens, including *Staphylococcus aureus* and methicillin-resistant *S aureus* (MRSA), is increasing relative to gram-negative pathogens. These trends create a need for new therapies.

Linezolid is the first of the oxazolidinones, a class of antimicrobial agents that inhibit bacterial protein synthesis by blocking formation of the initiation complex. Linezolid has in vitro and in vivo antibacterial activity against staphylococci, streptococci, and enterococci, including resistant strains such as MRSA, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci. The clinical efficacy and tolerability of linezolid were demonstrated in a double-blind study in which 396 patients with nosocomial pneumonia were randomly assigned to receive either IV linezolid 600 mg or IV vancomycin 1 g every 12 hours, each with concomitant aztreonam therapy. Data from these 396 patients were analyzed for registration purposes in the United States. To obtain additional experience in patients with nosocomial pneumonia and to satisfy international regulatory requirements, we used the same protocol to enroll additional patients in a second study. This brief report summarizes the results of the continuation study.

PATIENTS AND METHODS
This was a continuation of a previously reported, randomized, double-blind, registration study comparing linezolid with vancomycin for the empiric treatment
of patients with nosocomial pneumonia. The design was identical in the 2 studies and is summarized briefly in this paper. The continuation study included investigators from 114 sites in North America, Europe, Israel, South Africa, Australia, and Latin America and enrolled patients from June 21, 1999, through April 28, 2000; 70 of 90 sites (77.8%) from the original registration study participated in the continuation study. The study was approved by the institutional review board for each site, and written informed consent was obtained from all patients or their legally authorized representative.

Men and women aged ≥18 years with pneumonia acquired after 48 hours in an inpatient facility were eligible for enrollment. Patients had to have at least 2 of the following: cough; purulent sputum; auscultatory findings of pneumonia; dyspnea, tachypnea, or hypoxemia; or isolation of a respiratory pathogen from respiratory, sputum, or blood cultures. Patients also had to have at least 2 of the following: fever; respiratory rate ≥30 breaths/min; systolic hypotension; pulse rate ≥120 beats/min; altered mental status; need for mechanical ventilation; total peripheral white blood cell count >10,000/mm³ or <4500/mm³; or >15% immature neutrophils. Patients had to have radiographic findings of pneumonia, adequate respiratory and sputum specimens for Gram’s stain and culture, and life expectancy of at least 7 days. All patients had sputum or endotracheal suction specimens collected for culture and sensitivity assays. In patients who were intubated, respiratory specimens were obtained by bronchoscopy or another invasive technique (unless blood cultures were known to be positive at study entry).

Exclusion criteria were infection with pathogens resistant to study medication; meningitis, endocarditis, or osteomyelitis; CD4 cell count <200 cells/mm³ secondary to HIV infection; previous antibiotic treatment for >24 hours, unless documented treatment failure or pathogen resistance to previous nonstudy antibiotic therapy was present; liver disease and total bilirubin >5 times the upper limit of normal; and severe neutropenia (<500 cells/mm³).

Patients were randomly assigned to receive either IV linezolid 600 mg or IV vancomycin 1 g, each every 12 hours. Vancomycin dosage adjustments were required for patients with renal impairment and were permitted for other patients according to the local standard of care. To maintain blinding, a research pharmacist or equivalent nonstudy personnel monitored vancomycin dosages. Patients also received IV aztreonam 1 to 2 g every 8 hours, which could be discontinued if gram-negative pathogens were not identified. Treatment was administered for 7 to 21 consecutive days. All study medications were provided by the sponsor (Pharmacia Corporation, Peapack, New Jersey). Patients were not clinically evaluable if they received insufficient therapy (ie, <80% of the prescribed dose).

The primary efficacy variables were clinical and microbiologic outcomes in evaluable patients at the follow-up visit 15 to 21 days after the end of therapy (ie, test of cure). Clinical cure was defined as resolution of baseline signs and
symptoms of pneumonia, with improvement or lack of progression of radiographic findings; failure was defined as persistence or progression of signs and symptoms, administration of nonstudy antibiotic because of lack of efficacy of study drug, or absence of clinical assessments at end of therapy and follow-up. Microbiologic success was defined as documented eradication, presumed eradication, or colonization; failure was defined as documented or presumed persistence, superinfection, or reinfection. Patients had to receive at least 5 days and 10 doses of study drug to be assessed as cured and at least 2 days and 4 doses to be assessed as failed. Patients with missing or indeterminate outcomes were excluded from efficacy analyses.

All patients who received at least 1 dose of study medication were included in the safety analysis. Safety was evaluated throughout the study by the investigator using clinical observations, vital signs, assessment of adverse events (coded by Coding Symbols for Thesaurus of Adverse Reaction Terms terminology), and hematology and chemistry assays. Adverse events were recorded by investigators who were blinded to treatment group; who rated their intensity as mild, moderate, or severe using standard definitions; who rated adverse events as serious or not; and who assessed relationship to study medication.

The target sample size was 238 patients in each treatment group. All statistical tests were 2-sided and performed using SAS version 6.0 (SAS Institute Inc., Cary, North Carolina). \( P \leq 0.05 \) was considered statistically significant. For primary outcomes, 95% CIs were calculated for differences between treatment groups and were considered to be indicative of equivalence if each treatment group had \( \geq 83 \) evaluable patients, the CI included 0, and the lower limit of the CI exceeded \(-20\%\). For comparability of baseline variables, a 1-way analysis of variance fixed-effects model was used for continuous variables and the chi-square test was used for categorical variables.

**RESULTS**

A total of 623 patients with nosocomial pneumonia were enrolled and received at least 1 dose of either linezolid (n = 321) or vancomycin (n = 302). There were no statistically significant differences in baseline characteristics between the 2 groups (Table I) with 1 exception: more patients had multiple-lobe involvement in the linezolid group than in the vancomycin group (56.1% vs 44.3%; \( P = 0.004 \)). \textit{S. aureus} was the most frequently isolated pathogen (65% of isolates), followed by \textit{S. pneumoniae} (11%), \textit{Haemophilus} species (9%), and \textit{Enterococcus} species (5%). Approximately 10% of isolates were other \textit{Staphylococcus} or \textit{Streptococcus} species, \textit{Moraxella catarrhalis} was isolated from 3 patients in the vancomycin group.

A total of 194 patients (31.1%) discontinued therapy during the treatment period, including 104 patients receiving linezolid and 90 patients receiving van-
Table I. Baseline characteristics of patients with nosocomial pneumonia who received at least 1 dose of linezolid (n = 321) or vancomycin (n = 302).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linezolid</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%)</td>
<td>209 (65.1)</td>
<td>187 (61.9)</td>
</tr>
<tr>
<td>Men</td>
<td>112 (34.9)</td>
<td>115 (38.1)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.1 (19.1)</td>
<td>61.9 (19.3)</td>
</tr>
<tr>
<td>Range</td>
<td>16–93</td>
<td>16–93</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>288 (89.7)</td>
<td>271 (89.7)</td>
</tr>
<tr>
<td>Black</td>
<td>20 (6.2)</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (4.0)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td>Mean (SD) APACHE-II score</td>
<td>14.1 (5.8)</td>
<td>14.1 (6.2)</td>
</tr>
<tr>
<td>Ventilator therapy before enrollment, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 days</td>
<td>159 (49.5)</td>
<td>149 (49.3)</td>
</tr>
<tr>
<td>1–7 days</td>
<td>118 (36.8)</td>
<td>102 (33.8)</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>44 (13.7)</td>
<td>51 (16.9)</td>
</tr>
<tr>
<td>Chest radiographic findings, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple-lobe involvement</td>
<td>176/314 (56.1)</td>
<td>133/300 (44.3)</td>
</tr>
<tr>
<td>Single-lobe involvement</td>
<td>138/314 (43.9)</td>
<td>167/300 (55.7)</td>
</tr>
<tr>
<td>Presence of pleural effusion</td>
<td>98/318 (30.8)</td>
<td>88/302 (29.1)</td>
</tr>
<tr>
<td>Baseline pathogen, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive or <em>Haemophilus</em></td>
<td>104 (32.4)</td>
<td>102 (33.8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>35 (10.9)</td>
<td>39 (12.9)</td>
</tr>
<tr>
<td>Gram-negative only (other than <em>Haemophilus</em>)</td>
<td>55 (17.1)</td>
<td>44 (14.6)</td>
</tr>
<tr>
<td>None</td>
<td>127 (39.6)</td>
<td>117 (38.7)</td>
</tr>
</tbody>
</table>

APACHE-II = Acute Physiology and Chronic Health Evaluation II.

*Data not available for all patients.

†P = 0.004, comparison of lobar involvement versus treatment groups.

†Includes 3 isolates of *Moraxella catarrhalis.*

The most common reasons for discontinuing linezolid were isolation of gram-negative pathogens only and other reasons (38/321 [11.8%]), death (22/321 [6.9%]), and lack of efficacy (15/321 [4.7%]). The most common reasons for discontinuing vancomycin were isolation of gram-negative pathogens only and other reasons (31/302 [10.3%]), lack of efficacy (15/302 [5.0%]), and death (14/302 [4.6%]). There were no clinically relevant differences in reasons for discontinuing treatment between the 2 groups. The mean (SD) duration of treatment was 9.5 (4.5) days in the linezolid group and 9.4 (4.5) days in the vancomycin group.
A total of 345 patients (55.4%) were clinically evaluable: 169 in the linezolid group and 176 in the vancomycin group (Table II). The most common reasons for nonevaluability in the linezolid and vancomycin groups, respectively, were failure to determine clinical outcome within the follow-up window (27.7% and 23.5%), insufficient therapy (23.1% and 20.2%), and noncompliance with treatment (20.6% and 20.5%); some patients had multiple reasons. There were no clinically relevant differences in reasons for nonevaluability between the 2 groups. Clinical cure rates for clinically evaluable patients, excluding patients with missing or indeterminate outcomes, were equivalent between the linezolid and vancomycin groups (114/168 [67.9%] and 111/171 [64.9%], respectively).

A total of 159 of all 623 patients (25.5%) were microbiologically evaluable: 76 in the linezolid group and 83 in the vancomycin group. The reasons for nonevaluability in the linezolid and vancomycin groups, respectively, were no baseline pathogen (56.7% and 55.3%), clinical nonevaluability (48.0% and 42.4%), and pathogens resistant to study medications (0.9% and 1.7%); some patients had multiple reasons. There were no clinically relevant differences in reasons for nonevaluability between the 2 groups. Microbiologic success rates were equivalent for microbiologically evaluable patients, excluding patients with missing or indeterminate outcomes, between the linezolid and vancomycin groups, respectively (47/76 [61.8%] and 42/79 [53.2%]) (Table II).

There were no significant differences between treatment groups in any of the subanalyses of clinical and microbiologic outcome (data not shown). When clinically evaluable patients were categorized by baseline Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, the survival rate in the subset with scores of 16 through 19 was significantly higher in the linezolid group than in the vancomycin group (28/28 [100.0%] and 23/29 [79.3%], respectively; P = 0.011; Table II).

All 623 patients received at least 1 dose of linezolid (n = 321) or vancomycin (n = 302) and were included in the safety analysis. There were no significant differences in the rate of individual adverse events, adverse events resulting in discontinuation of study medication, serious adverse events, and deaths between the linezolid and vancomycin groups. Adverse events judged by the investigator to be drug related occurred in 14.0% of patients in each group, with no differences in individual events between groups. Drug-related adverse events reported in >1% of patients in the linezolid and vancomycin groups, respectively, were diarrhea (3.7% and 3.0%), nausea (0.3% and 1.3%), and rash (0.6% and 1.7%). In the linezolid group, there were 3 serious drug-related adverse events, including 1 patient each with rash, thrombocytopenia, and kidney failure. There were 64 deaths (19.9%), and none were judged to be related to linezolid. In the vancomycin group, there were 6 serious drug-related adverse events, including 2
### Table II. Assessment of clinical and microbiologic efficacy.

| Outcome                                           | No. (%) of Patients | Linezolid | Vancomycin | \( p^* \) | 95% CI  \\
|---------------------------------------------------|---------------------|-----------|------------|-----------|--------
| **Clinical cure in intent-to-treat population**   | 135/256 (52.7)      | 128/245 (52.2) | NS         | -8.3 to 9.2 |
| **Clinical cure in clinically evaluable population** | 114/168 (67.9)      | 111/171 (64.9) | NS         | -7.1 to 13.0 |
| **Microbiologic success in microbiologically evaluable population** | 47/76 (61.8) | 42/79 (53.2) | NS         | -6.8 to 24.2 |
| Documented eradication                            | 10/76 (13.2)        | 13/79 (16.5)  |            |            |
| Presumed eradication                              | 37/76 (48.7)        | 27/79 (34.2)  |            |            |
| Colonization                                      | 0/76 (0.0)          | 2/79 (2.5)    |            |            |

Eradication rates for selected pathogens in microbiologically evaluable population:

- *Staphylococcus aureus* 28/52 (53.8) 27/62 (43.5) NS -8.0 to 28.6
- *Methicillin-resistant S aureus* 12/19 (63.2) 10/23 (43.5)
- *Streptococcus pneumoniae* 14/18 (77.8) 12/13 (92.3) NS -38.6 to 9.5

Survival by baseline APACHE-II score in clinically evaluable population:

| APACHE-II score | No. (%) of Patients | Linezolid | Vancomycin | \( p^* \) | 95% CI  \\
|-----------------|---------------------|-----------|------------|-----------|--------
| 0–11            | 57/59 (96.6)        | 58/60 (96.7) | NS         |            |
| 12–15           | 44/53 (83.0)        | 52/55 (94.5) | NS         |            |
| 16–19           | 28/28 (100)         | 23/29 (79.3) | 0.011      |            |
| 20–39           | 16/17 (94.1)        | 17/22 (77.3) | NS         |            |

APACHE-II = Acute Physiology and Chronic Health Evaluation II. Recorded APACHE-II scores ranged from 2 to 36.

*P* value based on a chi-square test.

CI for difference in cure/success rates based on normal approximation.

Denominators exclude patients who had indeterminate or missing outcomes.

Score categories = quartiles from previously reported study.

Denominators exclude patients who were lost to follow-up.

Patients with kidney failure and 1 each with pancreatitis, diarrhea, fever, and hypotension. There were 61 deaths (20.2%), including 3 that were judged to be related to vancomycin in patients who had overwhelming sepsis with kidney failure, pulmonary abscess with acute pancreatitis, and pulmonary edema with antibiotic-associated diarrhea.
As expected in a population of seriously ill patients hospitalized with nosocomial pneumonia, individual patients often had changes in laboratory assay values during the study. However, there were no clinically relevant or statistically significant differences between the treatment groups in either mean laboratory values over time or frequency of substantially abnormal values for any of the hematology or chemistry parameters assayed. For example, regardless of underlying risk factors or relationship to study medication, the occurrence of substantially abnormal hematology values (defined as at least 1 value <75% of the lower limit of normal at some time in the study) was comparable between linezolid- and vancomycin-treated patients, with respective frequencies of 12.6% and 11.6% for hemoglobin; 3.8% and 3.4% for platelets; and 0.6% and 0.7% for white blood cells. In these patients, investigators assessed these laboratory abnormalities for relationship to drug therapy and reported few drug-related adverse events associated with changes in laboratory values. Only 1 report of anemia and 1 report of thrombocytopenia were judged to be possibly related to study medication in linezolid-treated patients.

**DISCUSSION**

The results of this randomized, double-blind study provide additional evidence that linezolid is as effective as vancomycin, each plus aztreonam, in treating patients with nosocomial pneumonia. The clinical cure rates in evaluable patients in this continuation study and the study previously reported by Rubinstein et al. were nearly identical for both linezolid (67.9% and 66.4%, respectively) and vancomycin (64.9% and 68.1%, respectively). The microbiologic success rates in evaluable patients were nearly identical for linezolid (61.8% and 67.9%, respectively); however, those for vancomycin appeared to be lower in this continuation study than in the previously reported study (53.2% and 71.8%, respectively), although the statistical significance of this observation was not assessed.

Both linezolid and vancomycin were well tolerated, as judged by comparable treatment durations, drug discontinuation rates, adverse events, and laboratory assay changes. Although linezolid has been reported to be associated with myelosuppression in some patients receiving long-term treatment, there was no evidence of major hematologic problems in these patients, who were treated for <2 weeks, which is the expected treatment duration for nosocomial pneumonia. Overall survival was similar for linezolid and vancomycin, but there was a difference favoring linezolid in the subset of evaluable patients with baseline APACHE-II scores of 16 to 19 (P = 0.011). An analogous difference was seen in ITT patients with baseline APACHE-II scores of 12 to 15 in the previous registration study (P < 0.038). As expected, these subsets contained small numbers of patients, which were derived by dividing patients enrolled in the registration study into 4 categories. This subanalysis was prospectively defined as a secondary...
The finding of a survival difference favoring linezolid in the subsets of patients with baseline APACHE-II scores in the mid-range categories in these 2 studies, but not in the lowest and highest categories, merits further consideration. When the data from the 2 studies are combined, the database contains >1000 patients with nosocomial pneumonia. A logistic regression analysis of the combined data is in progress to determine whether any measurements of severity of illness identify subsets of patients with nosocomial pneumonia who may have improved outcomes when linezolid is used as empiric therapy.

To avoid duplicating details from the previous paper about the registration study,12 we prepared this article as a brief report and summarized relevant findings. Both the registration and continuation studies were designed to show equivalence between treatment groups and were fully powered to support this objective. The evaluability rate is consistent with the patients' severity of illness and was considered in the statistical calculation of sample size when the study was designed. Furthermore, there was no evidence of a difference between groups in the intent-to-treat analysis.

The optimal method for dosing vancomycin has been debated.17-20 The dosage of vancomycin chosen for both studies, 1 g every 12 hours, is the approved dosage, is the recommended dosage in a standard text,21 and is identical to that used in another randomized study of vancomycin.22 Pharmacokinetic monitoring is often advocated to avoid toxicity or even to improve efficacy, especially when combined with pharmacodynamic modeling,23,24 and our protocol allowed dosage adjustments and pharmacokinetic monitoring according to the local standard of care.

CONCLUSION

In this continuation study, linezolid appeared to be as tolerable and as effective as vancomycin, each in combination with aztreonam, in treating patients with nosocomial pneumonia.

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